The Cardiothoracic Surgeon

REVIEW

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Recent advancements in pediatric cardiopulmonary bypass technology for better outcomes of pediatric cardiac surgery

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Abstract

Background: Pediatric cardiac surgery is in itself very enigmatic and individualized. Presently, there has been a slew of new developments aimed primarily toward pediatric cardiopulmonary bypass for safer, patient-centered pediatric cardiac surgery. Still, lot of technological challenges need to be resolved, and their safer application in pediatric and neonate patients requires further refinement.

Main body of the abstract: Considering various significant yet unresolved issues of pediatric cardiac bypass, an exhaustive literature search was done on various internet databases with standard keywords. There are various new recent improvements; as the first oxygenator explicitly designed for neonatal patients; pediatric oxygenators with low prime volumes and surface areas that allow flows up to 2 L/min; pediatric oxygenators with integrated arterial filters; and miniature ultrafiltration devices that allow for high rates of ultrafiltrate removal. These advancements can significantly reduce cardiopulmonary bypass circuit surface areas and prime volumes. These advancements could reduce or eliminate the requirement for homologous red blood cells during or after surgery with reduction or eliminate bypass-related hemodilution, and inflammation. Because of the immaturity of the neonatal hemostatic system, conventional coagulation tests alone are insufficient to guide neonatal hemostatic therapy. Myocardial preservation techniques, safe temperature with duration are still debatable and yet to be fully explored.

Short conclusion: This review is based on Standards for Quality Improvement Reporting Excellence guidelines to provide a framework for reporting new knowledge to find better management strategy for pediatric cardiac cases.

Keywords: Cardiopulmonary bypass, Pediatric cardiac surgery, Goal-directed perfusion, Blood conservation, Myocardial preservation

Background

As quoted by Gillian Jacobs, "Things are never simple when it comes to the human heart", and it is more true if we consider this for complex pediatric heart surgery on CPB. In the pediatric patient population, intracardiac repair requires cardiopulmonary bypass (CPB) and definite specialized perfusion strategies. The development and refinement in the surgical management of complex congenital heart defects under CPB rely on minimizing the possible adverse effects in neonates and infants. The technology has allowed perfusion techniques to evolve and improve the overall survival status. The newer advancements have diversified the clinical setting and focused beyond the survival of neonates and children elected for open-heart procedures. Apart from myocardial preservation, other vital organ protection and postoperative functioning are equally concerned. Our review study based on Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) guidelines highlights the recent advances developed in pediatric cardiopulmonary bypass and perfusion technologies to

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improve the health status of the health status pediatric cardiac patients.

Concerns with recent intervention

Goal-directed perfusion

The concept of goal-directed perfusion (GDP) comes from goal-directed therapy (GDT), which was conceptualized 30 years before. This ensues in the field of emergency medicine by augmenting the oxygen delivery index with a combination of intravenous fluids and inotropes, improved treatment with reduced complications was observed when GDT was applied while treating septic shock patients [1, 2]. Among the first physicians, Dr. William C. Shoemaker 1988, reported the effects of GDT in his publication, when focusing on critical values following high-risk surgery, there is a trend of decreased mortality. To describe the elevated cardiac index levels, oxygen delivery, and maximal oxygen consumption in terms of "supernormal values" seen in the survivors [3]. These studies suggest thinking about oxygenation and cardiac output to the tissues to improve sepsis outcomes rather than maintaining pressures and urine output. The improved oxygen delivery will meet the tissue oxygen demand to prevent anaerobic perfusion. The goal-directed perfusion concept has been reasonably studied in adult cardiac surgical patients by improvising the concept, exhaustively utilized by emergency and critical care departments to strengthen the survival rate of the operating patients. The adult multi-center trial called GIFT has been conducted, which looked at the incidence of renal dysfunction. Moreover, they have found anaerobic perfusion below 280 ml/min/m^2 [4]. Below this critical level of oxygen delivery, renal tissue is at the risk of injury, and above or equal to such levels were independently associated with better patient outcomes. During cardiopulmonary bypass, the commonly used cardiac indexes often underestimate the flow required to deliver oxygen index (DO2i) of 280 ml/min/m^2, especially as hemoglobin (Hb) values decrease. Srey et al.'s made a VA Boston quick reference tool based on goal-directed perfusion concept, so that other perfusion teams can more easily ensure that they are performing goal-directed perfusion, and adequately delivering oxygen during surgeries on CPB. Table 1 calculates and gives us the brief idea that is based on the oxygen content of perfusate, so there may be a need to change CPB pump flows, which is the core concept of goal-directed perfusion (suppose a patient with a Hb of 9.0 g/dl and perfusing BSA of 1.5 m^2 flow of 3.3 l/min is enough to give him adequate flow but if Hb drops to 7.0 g/dl we need to increase the pump flows

Table 1 The VA Boston quick reference tool for goal-directed perfusion [5]

BSA (m^2)	*7.0*	*7.3*	*7.7*	*8.0*	*8.3*	*8.7*	*9.0*	*9.3*	*9.7*	*10.0*	*10.3*	*10.7*	*11.0*
1.50	4.2	4.0	3.8	3.7	3.6	3.4	3.3	3.2	3.1	3.0	2.9	2.8	2.7
1.60	4.5	4.3	4.1	4.0	3.8	3.7	3.5	3.4	3.3	3.2	3.1	3.0	2.9
1.70	4.8	4.6	4.4	4.2	4.1	3.9	3.8	3.6	3.5	3.4	3.3	3.2	3.1
1.80	5.1	4.9	4.6	4.5	1.3	4.1	4.0	3.9	3.7	3.6	3.5	3.4	3.3
1.85	5.2	5.0	4.7	4.6	4.4	4.2	4.1	4.0	3.8	3.7	3.6	3.5	3.4
1.90	5.3	5.1	4.9	4.7	4.5	4.3	4.2	4.1	3.9	3.8	3.7	3.6	3.5
1.95	5.5	5.3	5.0	4.8	4.7	4.5	4.3	4.2	4.0	3.9	3.8	3.7	3.6
2.0	5.6	5.4	5.1	4.9	4.8	4.6	4.4	4.3	4.1	4.0	3.9	3.7	3.7
2.05	5.8	5.5	5.3	5.1	4.9	4.7	4.5	4.4	4.2	4.1	4.0	3.8	3.7
2.10	5.9	5.7	5.4	5.2	5.0	4.8	4.6	4.5	4.3	4.2	4.1	3.9	3.8
2.15	6.0	5.8	5.5	5.3	5.1	4.9	4.8	4.6	4.4	4.3	4.2	4.0	3.9
2.20	6.2	5.9	5.6	5.4	5.3	5.0	4.9	4.7	4.5	4.4	4.3	4.1	4.0
2.25	6.3	6.1	5.8	5.6	5.4	5.1	5.0	4.8	4.6	4.5	4.4	4.2	4.1
2.30	6.5	6.2	5.9	5.7	5.5	5.3	5.1	4.9	4.7	4.6	4.5	4.3	4.2
2.35	6.6	6.3	6.0	5.8	5.6	5.4	5.2	5.0	4.8	4.7	4.6	4.4	4.3
2.40	6.7	6.5	6.2	5.9	5.7	5.5	5.3	5.1	4.9	4.8	4.7	4.5	4.4
2.45	6.9	6.6	6.3	6.1	5.9	5.6	5.4	5.3	5.0	4.9	4.8	4.6	4.5
2.50	7.0	6.7	6.4	6.2	6.0	5.7	5.5	5.4	5.1	5.0	4.9	4.7	4.6
2.60	7.3	7.0	6.7	6.4	6.2	5.9	5.8	5.6	5.4	5.2	5.1	4.9	4.7
2.80	7.9	7.6	7.2	6.9	6.7	6.4	6.2	6.0	5.8	5.6	5.4	5.2	5.1
3.0	8.4	8.1	7.7	7.4	7.2	6.9	6.6	6.4	6.2	6.0	5.8	5.6	5.5

The flow shown (L/min) for a given Body surface area (BSA) and Hb is the minimum required to achieve a DO2i of 280 mL/min/m^2. All values assume 100% arterial saturation and a PaO2 of 200 mmHg. (Proper permission has been taken to reproduce this table from publishers)

[5]. The blood flow (Q) formula was derived from known DO_2 (delivery of oxygen) and CaO_2(oxygen content of the arterial blood):

$$CaO_2 = \left(Hgb \times 1.34\right)\left(SaO_2/100\right) + \left(PaO_2 \times 0.0031\right),$$

$$DO_2 = Q \times 10 \times CaO_2,$$

$$DO_2i = DO_2/BSA,$$

$$280 = Q \times 10 \times Cao_2/BSA,$$

$$Q = 280 \times BSA/\left\{\left(Hgb \times 1.34\right)\left(SaO_2/100\right) + \left(PaO_2 \times 0.0031\right)\right\} \times 10$$

In pediatric cardiac surgical patients undergoing cardiopulmonary bypass, the minimum delivery of oxygen that should be maintained during moderate hypothermia is found to be around 353 ml/min/m^2, which is much higher than the adult value as expected [6]. Furthermore, 340 ml/min/m^2 of nadir oxygen delivery index was found to maintain aerobic respiration in neonates [7]. To track perfusion flow rate as per the HCT to maintain DO_2i specified threshold of 360 ml/min/m^2. It was found that increasing perfusion flow rates in events of low hematocrit (HCT) values, it was unable to maintain the DO2i above the threshold, and packed red blood cell (PRBC) transfusion or ultrafiltration could be considered [8]. Cardiac surgery-related acute kidney injury has been used as a surrogate to tailor the outcomes for goal-directed perfusion. Apart from oxygen delivery, the focus has been on mean arterial pressures during neonatal cardiac surgery because there is no exact standard for maintaining perfusion pressures. An effective strategy for reducing renal dysfunction is to maintain the perfusion pressure above 60% of the normal age-standardized mean arterial pressure in neonates [9]. It is evident that a rise in lactate levels occurs due to the variation of pressures during neonatal bypass procedures and is associated with postoperative mortality. Mean arterial pressure less than 25 mm Hg on CPB leads to a rise in lactate in neonates [10]

Blood conservation

Target hematocrit (HCT)

Pediatric cardiac surgical candidates are frequently exposed to excessive red blood cell (RBC) transfusions [11]. Consequently, several studies have shown an association between increased mortality and RBC transfusions post-cardiac surgery [12, 13]. It is not sure whether the adverse impact of RBC transfusion on the postoperative outcome is because of transfusion itself or unmeasured confounders [14, 15]. RBCs are usually transfused in case of low oxygen-containing perfusate or excessive loss of blood volume. However, PRBC may also be administered in the prime of CPB to maintain the circulating hematocrit to counter the hemodilution, and low hematocrit levels on CPB are found to be deleterious also [16]. Adequacy of RBC transfusion requirement is still uncertain in perfusion practice. Recently, there has been a consensus statement. It has been accepted that the hemoglobin level of 7.0 mg/dl in the corrected pediatric patients and the hemoglobin of 9.0 mg/dl in the uncorrected pediatric patients [17]. But still, it is a vague guideline, and this has not been established in the current pediatric perfusion strategy. The standard pediatric perfusion hemoglobin levels are going high, as it was > 20% in the 1980s and > 25% in the late 1990s and 28–32% after 2016 [18, 19]. There has been a landmark study between two centers with different perfusion practices, and they found that the renal injury is much more minor with high Hb and high pump flows. This study put forward the statement that the minimum HCT on the CPB has to be 32%, and while coming off from the bypass, the high Hb group should have an HCT 43% which is the current pediatric perfusion practice that most of the centers follow.

Miniaturization

The concept of minimizing the CPB circuit to very short has been the trend in the neonate and pediatric perfusion due to less blood contact with artificial tubing. The priming volume of the circuit can surpass the blood volume of neonates, thus causing severe hemodilution of blood components. Apart from decreasing hemodilution, the miniaturization of the pump circuit reduces the blood-circuit interface, leading to decreased CPB-related inflammation, lowered platelet aggregation, and activation of coagulation. Among the common problems with pediatric perfusion, the pump circuit has to subside the arterial line filter, which took almost 20% of the priming volume. A significant advancement in blood sparing was the availability of new generation oxygenators with integrated arterial line filters (ALFs). Initially, there was skepticism about these oxygenators, but it has been established that they really filter the particulate and gaseous emboli better than standalone units. Integrated ALFs have a primeless filter wrapping around the hollow fiber membrane of the oxygenator, which allows a reduction in prime but increases the surface area of the CPB component. Presently, the newer pediatric oxygenators are coming with a prime volume of 50 ml or less, as shown in Table 2 [20].

Table 2 Characteristics of the neonatal oxygenators [20]

Name	Brand	Integrated ALF	Maximum blood flow (L/min	Priming volume (mL)	Surface area (m2)	Minimum-level in the reservoir (mL)	Biocoating
Quadrox-i Neonatal	Maquet Getinge	Yes	1.5	40	0.38	15	SOFTLINE (polymer coating) BIOLINE (heparin coating)
Capiox FX 0.5	Terumo	Yes	1.5	43	0.50	15	XcoatingTM (amphiphilic polymer)
KIDS D100	LivaNova	No	0.7	31	0.22	10	Phosphorylcholine coating
Affinity Pixie	Medtronic	No	2	48	0.48	20	CORTIVATM (heparin coating) BALANCE® (hydrophilic polymer)
HILITE 1000	Medos	No	1	57	0.39	50	Rheoparin® (heparin coating)

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Even though the priming volume of oxygenators has reached the minimal limit, a majority, i.e. 3/4th of the prime volume, lies in the tubing. The way to reduce the length of tubing is a mass mounting technique to bring the pump head closer to the patient during the pump run. Along with mass mounting, the hard-shell venous reservoir is raised further to decrease the tubing length, and venous return is augmented with vacuum-assisted by many programs. Shorter tubing offers less resistance to blood flow, but such techniques require expertise and a dedicated perfusionist. Extreme miniaturization has been reported, and they have used table mass mounting with sanguineous priming circuitry and have reported operating three neonates with this setup [21]. The other miniaturization technique uses tubing with a minor diameter, such as the 1/8 inch, 3/16 inch, and 1/4 inch tubing usage in neonates. So, by employing these small tubing's priming volumes have reduced to 95 ml [22] and 73 ml [23], as reported by several studies. Most of the infants undergoing cardiac surgery weighing < 5 kg could get benefit from miniaturized and bloodless CPB circuits [24].

Ultrafiltration

Removal of extravascular water along with low molecular weight solutes and inflammatory mediators to concentrate the components of whole blood with the help of filtering membrane is the process called ultrafiltration (UF) or hemofiltration. This popular technique used by most pediatric centers [25] is attached parallel to the CPB circuit with the primary goal of restricting hemodilution. There are multiple ways of doing UF with advantages as shown in Table 3 [26].

There has been a considerable debate between several studies regarding CUF and MUF techniques of hemoconcentration in pediatric cardiac patients [27–31]. Some studies had shown improved left ventricular systolic function when MUF was being used [32]. However, Williams et al. showed no benefit when modified UF was combined with conventional UF in a randomized clinical trial in neonates [27]. Despite that, hemofiltration adjoins the surface activation and lessens the prime volume, so still, advantage excels in infants. Recently, the advancement in hemofilters like Hemocor HPH®Jr (TERUMO Ann Arbor, MI) have a good filtration rate of 30 mL/min and are available with 8 ml of priming volume and surface area of 0.09 m^2 for infants and neonates [28].

Cell salvage and residual circuit volume

After discontinuation from CPB, the residual volume left in circuit makes up roughly 14% of the total blood volume of the patient [33] and has a hematocrit of around 60% [20]. Such volume in circuit is either infused or discarded. Hanna D. Golab et al. demonstrated the beneficial effect of cell salvage from the CPB circuit's residual volume in patients weighing < 10 kg [34]. Moreover, in pediatric patients following cardiac

Table 3 Types with advantages of various ultrafiltration (UF) techniques

Type	Timing	Advantages
Conventional UF (CUF)	During CPB	Removes extra water and maintains fluid balance
Zero-balanced UF	Rewarming phase of CPB	Reduce inflammatory cytokines and correct electrolyte and acid-base imbalances.
Modified UF (MUF)	Post-CPB	Limit early postoperative RBCs transfusions

surgery, reinfusion of cleansed RBCs from the residual CPB circuit raises HCT considerably and minimizes postoperative allogeneic RBC transfusion [35].

Anticoagulation

Heparin and anti-thrombin

Anticoagulation effects of heparin are monitored by an activated clotting timer (ACT) and is considered a standard test since its introduction in 1975 by Bull and co-workers. Anticoagulant activity of heparin is served by the body's own anticoagulant cofactor antithrombin (AT) [36]. Heparin works by enhancing AT's anticoagulant effects many folds [37]. The efficacy of heparin is decreased in neonates because of the presence of low levels of anti-thrombin [38]. It takes about 6 months for the normalization of anti-thrombin levels in infants. Other factors such as hemodilution and body temperature changes decrease the effectiveness of heparin [39]. Recently, supplementation of AT before CPB to normalize AT levels in infants has improved heparin anticoagulation during CPB and significantly decreased postoperative bleeding and exposure to blood products [40].

Alternatives of heparin-like Bivalirudin have shown the potential to provide stable anticoagulation. Being a direct thrombin inhibitor does not require anti-thrombin for anticoagulation. The studies have found bivalirudin to be an effective anticoagulant during infant CPB with heparin-induced thrombocytopenia and the first line of choice for extracorporeal circulation [41]. But usages in neonates and pediatric CPB are not well established.

Platelet dysfunction

Impairment in platelet function or decrease in their count can increase the risk of bleeding complications in patients undergoing cardiac surgery [42, 43]. Exposure of cardiopulmonary bypass, hypothermia, hemodilution are some other factors which effect the normalcy of platelets [44, 45]. Different classical methods for assessing platelet functions are clinically identified to help the hemostatic therapy during pediatric cardiac surgery such as light-transmission aggregometry, and multiple-electrode aggregometry (MEA) [46, 47].

B. S. Romlin et al. has studied changes in platelet count and platelet function during and after pediatric cardiac surgery and found that especially in new borns, platelet count, and platelet aggregation are significantly decreased during and immediately after pediatric heart surgery. Moreover, increased transfusion needs are linked to intraoperative platelet dysfunction [48].

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM)

Newer technologies such as TEG and ROTEM, which have recently evolved significantly, use viscoelastic whole blood analyses assessed with whole blood coagulation testing methods and are applied to predict specific blood product usage better. Such tests, however, notify interactions between polymerizing fibrin and platelets and fibrinolysis and show the propagation of coagulation after extrinsic activation. Sirisha Emani et al. used TEG during rewarming phase of CPB to get early results before weaning from bypass. They found TEG may reduce the risk of bleeding while minimizing unnecessary platelet transfusion based on Individualized platelet transfusion therapy during rewarming in pediatric patients [49]. ROTEM was analyzed in 178 neonates and showed significantly reduced postoperative bleeding, RBC transfusions, and ICU stay. Thus, it can be used to tailor the product transfusion in the postoperative period [50]. Sirisha Emani et al. included 511 pediatric patients undergoing complex cardiac operation to study the TEG variables for postoperative bleeding. He summarized that prophylactic platelet transfusion in the OR may reduce bleeding end points in the ICU in patients with TEG MA smaller than 45 mm [51]. Jo Bønding Andreasen et al. mentioned in his study that when targeted transfusion therapy is required to prevent volume overload, RoTEMs can identify hemostatic deficits in children undergoing heart surgery, and the technique should be taken into consideration as an addition to preoperative care for the children [52]. After the development of proper protocol and validation for TEG and ROTEM testing, then only it is possible to incorporate them into mainstream clinical practice of neonates and pediatric cardiac surgery.

Hypothermic strategy

The optimal temperature for pediatric cardiac surgery is debatable and varies depending on the surgical procedure. Hypothermia remains the best approach available to avoid sequelae in the case of CPB-related neurological adverse events according to a key argument in favor of hypothermia [53]/. A recent analysis of North American hospitals revealed significant diversity in systemic temperature management within the same disease/age group, based on four disease scenarios [54]. A meta-analysis in pediatric CPB comparing the benefits of normothermia vs hypothermia could only include 419 participants from 10 eligible trials and found no significant difference in outcomes [55]. The believed pros of hypothermia include reduction of tissue and organ metabolism as well

as the inflammatory response. It can also reduce pump flow, coronary blood return, and improve surgical field visibility.

Nonetheless, hypothermia has a number of disadvantages [56]. It causes a marked inhibition of all enzymatic pathways, including the coagulation cascade, increasing the risk of postoperative bleeding and inducing insulin resistance. Hypothermia interferes with oxygen and glucose uptake in the pediatric brain [57]. It increases organ dysfunction while promoting oxidative stress. Hypothermia increases systemic vascular resistance, blood viscosity, and affects microcirculation. Moreover, it disrupts membrane stability, promoting both capillary leak and postoperative arrhythmias but with rewarming, all of these changes can be reversed.

Acid-base control during hypothermia was a point of contention. The only randomized experiment in newborns to answer this question found no difference in early or midterm neurologic outcomes between alpha-stat and pH-stat after profound deep hypothermic circulatory arrest (DHCA) [58, 59]. However, experimental data backs up the benefits of the pH-stat technique [60]. The cerebral vasodilation effect of increased pCO2 may be especially beneficial in the subgroup of patients with large aorto-pulmonary collaterals, who have been shown to have a higher incidence of neurologic abnormalities and choreoathetosis, and in whom collaterals may cause a reduction in the brain cooling rate.

Near-infrared spectroscopy (NIRS)

The non-invasive technique of NIRS (near-infrared spectroscopy) is used to evaluate oxygen delivery during CPB. Near infrared spectroscopy is increasingly being utilized to correctly quantify end organ perfusion because regional oxygen saturation (rSO2) is a measure of post-extraction oxygen saturation and so indicates the balance between regional DO2 and consumption. (62) Based on abnormal brain magnetic resonance findings and worsened neurodevelopmental outcomes reported in patients with prolonged intraoperative cerebral desaturations, the effective use of NIRS monitoring for cerebral perfusion during pediatric cardiac surgery is now well defined [61, 62]. However, a rSO2 monitoring strategy that focuses solely on the brain is insufficient to assess the amount of oxygen available to organs whose perfusion is controlled by different neuro hormonal mechanisms [63].

The INVOS 5100 (Somanetics, Troy, MI USA) is the cerebral oximeter commercially available in the USA and has been approved for use as a trend monitor of cerebral oxygenation [64]. Tia A. Tortoriello et al. concluded from his study in pediatric patients that SvO2 measured through invasive monitoring correlates with regional cerebral oximetry using NIRS. But given the wide ranges of agreement, it is probable that relying exclusively on the non-invasive measurement of rSO2 will not be sufficient to forecast absolute values of SvO2 for any specific patient. The INVOS 5100 cerebral oximeter's use of near-infrared spectroscopy may be able to detect changes in SVO2, but more research needs to be done in a variety of clinical settings [65].

Myocardial preservation

Based on principle for ideal myocardial preservation, intracellular and extracellular types of Cardioplegia solutions were developed and tested. Intracellular solutions are histidine–tryptophan–ketoglutarate (HTK) branded as Custodiol, University of Wisconsin (UW), and Euro-Collins. UW, and Euro–Collins solutions were originally used as preserving agent for intra-abdominal organ transplantation and has now been used mainly for heart preservation during transport. Currently, very few cardiac centers use them for cardiac surgical procedures. Histidine–tryptophan–ketoglutarate (HTK) or Bretschneider's cardioplegia solution is easy to use and may give a long cardioprotective time in adult patients but in some studies, this solution was considered to cause myocardial edema and hemodilution. This hemodilution is prone for blood transfusions, electrolyte disturbances, and cardiac arrhythmias [66]. A recent study has suggested that single-dose cold histidine–tryptophan–ketoglutarate may not be adequate for children undergoing arterial switch operation [67].

Extracellular cardioplegia solutions are the following: St. Thomas no. 1 and no. 2, and del Nido. St. Thomas has been promoted at St. Thomas Hospital in London since 1976. In 1981, an improved formula emerged—St. Thomas no. 2 (Plegisol, Abbott Laboratories, North Chicago) was developed. Del Nido cardioplegia was initially developed for pediatric interventions. It is a low-glucose hyperpolarizing crystalloid solution delivered in a combination of 1:4 with autologous blood.

The contention between different cardioplegic solutions (del Nido vs blood-based St. Thomas) for neonates and the pediatric population is still there, and it is debatable which has more favorable outcomes. Myocardial preservation has been a burning topic since the concept emerged from the heart's diastolic arrest for open-heart surgery. The randomized controlled studies were done in pediatric heart surgery patients to compare the safety and effectiveness of del Nido cardioplegia with blood-based St. Thomas Hospital. No difference in myocardial function was found except for the fact that Del Nido is more conveniently used [68]. The del Nido was initially meant for the pediatric population, but now its use has been extended to adults. The more extensive clinical trial showed no significant difference in myocardial protection

for adult and pediatric cardiac patients compared to del Nido cardioplegia with St. Thomas cardioplegia. The additional advantage of del Nido cardioplegia was shorter aortic cross-clamp time and decreased rates of arrhythmia and defibrillation [69]. Cardioplegia is still a matter of institute protocol. Every center has its own method of practice; however, single-dose cardioplegia has been the preferred standard for decades due to ease and uninterrupted surgery over multi-dose cardioplegia.

Nitric oxide on bypass

Nitric oxide (NO) is an endogenous anti-inflammatory mediator and is essential to regulate endothelial function and microvascular inflammation [70]. NO's addition to pediatric bypass may improve myocardial function and modulates the inflammatory pathway. A predictable drop in cardiac output is seen most frequently in post-pediatric cardiac surgery [71]. The use of nitric oxide during the procedure reduces the low cardiac output in these children [72]. Another clinical trial studied a group of 40 neonates undergoing the Norwood procedure, and they showed NO decrease troponin levels [73]. This needs a further extension and multi-center randomized clinical trials to see the possible benefits of NO for neonate and pediatric cardiac surgery.

The defective endogenous generation of nitric oxide by the pulmonary endothelium complicates pulmonary artery hypertension (PAH) in congenital heart disease (CHD). Additionally, children have increased activity of phosphodiesterase type 5 postoperatively, that is enhanced by cardiopulmonary bypass. Inhaled nitric oxide (iNO), phosphodiesterase (PDE) type 5 inhibitors (sildenafil), prostacyclin analogs (epoprostenol), endothelin-receptor antagonists (bosentan), and inodilators (milrinone) are some of the pharmaceutical treatments for the management of pulmonary artery hypertension [74].

Sunny Kesvani et al. has evaluated the efficacy of intravenous sildenafil in patients with moderate-to-severe pulmonary hypertension undergoing corrective surgery for CHDs. Study has shown that perioperative administration of intravenous sildenafil provides a well-tolerated, practical, and potentially effective treatment for PAH and improve PO2: FiO2 ratio after surgical correction [75].

Inflammation and cardio pulmonary bypass

Artificial surface, blood air contact, different blood flow patterns, and CPB circuit with surgical trauma result in the activation of systemic inflammatory response and the development of systemic inflammatory response syndrome (SIRS) [76]. To overcome systemic inflammation, many methods have been followed. Most common among them is pharmacological treatment with perioperative steroid administration. The addition of corticosteroids, as mentioned in a recent meta-analysis, has produced a major impact on postoperative fluid balance but has no impact on the mortality and morbidity in complex pediatric cardiac surgical patients [59]. To mitigate the harmful effects of CPB by corticosteroids, there is wide variability in practice in the case of pediatric cardiac patients [77].

Besides following the interleukins and cytokines for inflammation, the new direction has focused on dysbiosis. Over time, it has been noted that children with complex heart diseases tend to have different pro-inflammatory bacteria in the gut even before the surgery, which are more of an infectious organism and can invade the mucosa at the time of lower immunity. A pioneering study has found an increase in the incidence of pro-inflammatory gut bacteria in children, which possibly contributes to SIRS [78].

Another completely different way of looking at inflammatory pathways in pediatric perfusion technology is to investigate plasma proteins and their functions. Several techniques have been developed to analyze whole plasma proteome and organ proteome by different methods. Now we can detect variation in the protein fractions at various disease levels, and in each disease, plasma protein changes in different patterns. In the future, we can possibly identify proteins that are markers for a particular disease or situation or those causing the disease effect and can be used as targeted therapy [79, 80]. Apart from proteome studies, recently, metabolic fingerprinting of infants undergoing CPB has been done. They found that non-survivors and subjects requiring longer intensive care unit stay showed distinct changes in metabolism. Aspartate and methyl nicotinamide are small molecules that tend to spike post-CPB, and this trend in such children has a sicker course [81, 82].

Conclusions

This review article explores the various aspects and recent developments to develop and refine institutional protocols on (SQUIRE 2.0) guidelines. As with perfusion technology advancement, it is critical to review and assess the use of earlier procedures on a frequent basis. Most newer approaches, which are typically created primarily based on adult CPB validation, usually overlook the pediatric and neonate's particular physiology and require robust testing in this different and fragile population. Because of the vast volume and blood contact surface area differences between the CPB circuit and the infant, pediatric CPB is a different domain, with hemodilution, inflammatory activation, and coagulation, unlike

any other age group. Future approaches point toward "goal-directed" and customized CPB management focusing on multi-organ protection for this age group. The best way to counterbalance the need to get better research on the safety and efficacy of novel CPB techniques for the neonatal and pediatric period is to use multi-institutional databases and scientific analysis.

Abbreviations

CPB: Cardiopulmonary bypass; SQUIRE 2.0: Standards for Quality Improvement Reporting Excellence; GDP: Goal-directed perfusion; GDT: Goal-directed therapy; Hb: Hemoglobin; HCT: Hematocrit; RBC: Red blood cell; ALF: Arterial line filter; UF: Ultrafiltration; ACT: Activated clotting time; TEG: Thromboelastography; ROTEM: Rotational thromboelastometry; DHCA: Deep hypothermic circulatory arrest; NIRS: Near-infrared spectroscopy; NO: Nitric oxide; SIRS: Systemic inflammatory response syndrome.

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Authors' contributions

YS, AD, and RS initially planned this concept and design. YS, AD, and AV collected and assemble data after researching the literature. Data analysis and interpretation done by YS, AD, and RS. Manuscript writing was done by all authors and jointly edited. All authors have made substantial contributions and contributed equally in the article's preparation. The requirements for authorship as stated have been met, and that each author believes that the manuscript represents honest work. All authors have read and approved the manuscript.

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