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Reviewer A

Ramakrishnan et al describe the approach to neonates undergoing cardiovascular interventions at their institution. Such descriptions help other institutions if their outcomes could be improved. In their overview, the authors describe some fundamental differences that are supposed to distinguish them from the approach of other working groups and which are then held responsible for particularly good postoperative results.

First of all, the results that are to be used to determine the preferred approach:
The working group is to be congratulated that their incidence of AKI is so extraordinarily low.
For comparison, Gist et al. studied 2240 newborns at 22 North American centers in 2019 (NEPHRON data set). Their incidence was 54%. The incidence varied from center to center from a minimum of 27% to a maximum of 86%. 23% of the operations had been performed without CPB. Sasaki et al. subsequently reported that the incidence of AKI in neonates operated on without CPB was as high as 38%. Thus, it can be made clear that the incidence of AKI in neonates after cardiovascular interventions might not be predominantly due to the way CPB is performed.

Response: This information has been added to the text with relevant context.
Changes in the manuscript: The following has been added to the discussion "Acute kidney injury has been noted in neonates even after operations without cardiopulmonary bypass. Multi-institutional data from 22 north American centers revealed an estimated incidence of 54% (ranging from 27% to 86%). A subsequent study also estimated the incidence of acute kidney injury in this cohort to be as high as 38%2. Thus, cardiopulmonary bypass alone may not be a factor in determining the incidence of post cardiac surgical acute kidney injury."

One of the major modifications described in the manuscript is high perfusion flow. Here, the higher oxygen demand of the newborn is sensibly taken into account. The omitted reduction with increasing systemic hypothermia is noteworthy because it is consistent with recent findings of renal oxygen consumption not decreasing with lower temperatures.
However, especially in pediatric patients, we have the problem that venous cannulation of such small patients often causes problems with regard to venous return. In this case, venous congestion in the inferior cavity is not uncommon, which can lead to lower perfusion pressure gradients also with regard to renal perfusion. Here, monitoring by near-infrared spectroscopy is helpful.

However, higher perfusion flow during surgery in neonates is often associated with compromised surgical vision. This particularly affects patients with a pronounced

collateral flow. Such collateral flow affecting the surgical view leads to correspondingly more pronounced cardiotomy suction. A high amount of cardiotomy suction is one of the most important contributors to hemolysis. This is especially true for scenarios in which donor blood units with a longer storage time are used for transfusion. Here, plasma-free hemoglobin would be one of the main causes of AKI and also of impaired tissue perfusion, since free Hb is a potent scavanger of nitric oxide and impairs NO neosynthesis.
The manuscript does not specify whether DHCA is induced in these cases or whether systemic blood flow would be reduced after all. This also applies to the not insignificant number of cases with surgery on the aortic arch (Norwood I, IAA, etc.). Here, it should be explained how the distal perfusion of the descending aorta, namely also the renal perfusion, is preserved or those were operated with DHCA.

Response: DHCA is used in selected cases (some examples include ASD closure during arterial switch operation, aortic arch reconstruction, and selected total anomalous pulmonary venous return repairs). The systemic flows are reduced to 50ml/kg prior to ceasing circulation. This has already been mentioned in the manuscript under the "High flow, high hematocrit strategy-rationale and practice" section.
Changes in the manuscript: The following sentence has been added to the section "High flow, high hematocrit strategy-rationale and practice", for clarity. "In some instances, circulatory arrest is utilized at deep hypothermia to facilitate repair (some examples include ASD closure during arterial switch operation, aortic arch reconstruction, and selected total anomalous pulmonary venous return repairs)

With regard to the quantity of donor blood transfusion (and also the number of donor exposures), the importance of miniaturization of the extracorporeal circuit is pointed out. Consequently, it should be noted that there are also Institutions that enable perfusion without donor blood even in newborns and allow operations without platelet substitution or fresh frozen plasma.

Response: We do acknowledge the fact that bloodless neonatal open-heart surgery is possible (Boettcher W, Dehmel F, Redlin M, Sinzobahamvya N, Photiadis J. Cardiopulmonary Bypass Strategy to Facilitate Transfusion-Free Congenital Heart Surgery in Neonates and Infants. Thorac Cardiovasc Surg. 2020 Jan;68(1):2-14. doi: 10.1055/s-0039-1700529. Epub 2019 Nov 3. PMID: 31679152.). Even if the use of blood transfusion cannot be avoided there are means to minimize the use of donor blood (Naguib AN, Winch PD, Tobias JD, Simsic J, Hersey D, Nicol K, Preston T, Gomez D, McConnell P, Galantowicz M. A single-center strategy to minimize blood transfusion in neonates and children undergoing cardiac surgery. Paediatr Anaesth. 2015 May;25(5):477-86. doi: 10.1111/pan.12604. Epub 2015 Jan 12. PMID: 25581204.). However, the trade-off is lower hematocrit which, in our experience, is associated with higher incidence of acute kidney injury and a higher incidence of post-operative bleeding.
Changes in the manuscript: The following has been added to the discussion: "Strategies

have been described to avoid or minimise blood transfusion in neonates undergoing open heart procedures. The trade-off in these strategies has been accepting a lower hematocrit. With our strategy we have been able to minimize the use of donor blood while at the same time maintain a higher hematocrit".

Regarding the non-use of Milrinone, we come to the postoperative course, where the hemodynamic situation of the newborn also influences the AKI. Many patients who are already very severely ill preoperatively do not necessarily improve their circulatory function as a result of the operation or CPB management. They require pharmacological support, either with higher doses of catecholamines or, as a more modern approach, with the help of PDE II inhibitors. Here, I also miss the consistency that occurs in the authors when the hemodynamic situation after CPB is not adequate. Mechanical circulatory assistance such as ECMO (ELCS) is a common form of therapy associated with AKI. Were these patients not considered here?

Response: Patients who needed ECMO were not excluded. ECMO was needed in 1/60 patients (2%).
Changes in the manuscript: None

Has renal replacement therapy, such as peritoneal dialysis, never been used? According to most of the AKI criteria, this would be AKI stage 3.

Response: None of the patients in the published study needed renal replacement therapy (including peritoneal dialysis).
Changes in the manuscript: None

In terms of neurological outcome, it is not only the perfusion flow or the level of Hct that matters. One of the main causes is certainly surgical air embolization due to inadequately deaired cardiac cavities and, in any case, periods of hypocapnia in newborns.
With regard to lactate concentrations, there are several patients before surgery with already elevated concentrations due to their disease and hemodynamics. Others have additional problems like NEC.
In summary, the causes of postoperative complications are certainly also due to certain methods of CPB management. However, an equally large proportion may not be caused by aspects during CPB.
Nevertheless, it seems important to publish a procedure like the one presented here, which obviously shows excellent results.

Reviewer B

This is a nice paper and I enjoyed reading it. However, it is not really scientific. It is more of a journalistic type of article telling us how the authors conduct

cardiopulmonary bypass in babies. Admittedly, it is a very nice way of doing it, and we do the same. In addition, the senior author is a tremendously experienced, very well known and internationally respected paediatric cardiac surgeon, which adds considerable weight to their article, but does not make it scientific. They make several comparisons between their results and those published by others, but the differences could easily be due to many other factors. Still, this is a nice "Opinion Paper", which I think many readers would find interesting.

We thank the reviewer for the comments on our clinical practice review manuscript.

Reviewer C

The authors present a clinical practice review titled "Cardiopulmonary bypass in neonates and infants: advantages of high flow high hematocrit bypass strategy – Clinical practice review" with their stated purpose being to discuss the rationale of their high flow/high hematocrit approach, provide evidence to support its use, and present 15 year outcomes.

Being a clinical practice review, the value of this publication would be for the reader to be able to determine the similarities and differences between institutions and identify changes that can be made to improve patient care and outcomes. Although it is well-written and easy to read, there is not enough information or data to achieve their stated purpose quite yet, which leads to the following comments:

It would be helpful for the authors to report the actual institution/hospital name that is being described here as well as some data to help the reader determine surgical volume, complexity, number of surgeons, and both perfusion and surgeon quality and experience.

Response: We have included the institution details in the manuscript.
Changes in the manuscript: We have added this descriptor in the section titled 'High flow, high hematocrit strategy-rationale and practice': "at LeBonheur CHiuldren's Hospital, Memphis, Tennessee"

2) The data that is being used to support the use of the high flow/high hematocrit strategy is all observational and the authors are overstating when they suggest causation. Even the prior observational study they reference (the reference itself is incorrect and incomplete – please correct it) present associations with univariate analysis that do not consider the "adjuncts" they consider contributory to better outcomes such as lack of milrinone or albumin use, mannitol use, ultrafiltration, cannula size and tubing length, etc. Even just surgical volume of the center, surgeon skill/experience, and bypass duration may also play a large role in outcomes. Unless they present more data than what has been reported previously by this group, it's not clear what this manuscript would add beyond what the authors have already published:
Impact of Different Cardiopulmonary Bypass Strategies on Renal Injury After Pediatric

Heart Surgery. Ann Thorac Surg 2021;111:1374-9

Response: We have updated the citations.
Changes in the manuscript: Updated citations.

3) The bulk of this manuscript is written as a summary of the authors' prior work, two of which are not published. It would be more valuable to use this opportunity to review what is established and understood in this space in the field and have a much more mechanistic approach to the discussion of why they think their high flow/high hematocrit strategy is superior to the "conventional" approach. This can inform further studies and also provide a rationale to make others reconsider the "conventional" approach.

Response: The practice of pediatric perfusion is largely based on broad general principles, and institutional preference/experience. In this manuscript we have described our outcomes based on more than a decade of experience of using perfusion techniques that would have been considered non-standard when they were first introduced. Based on the reviewer's suggestions we have attempted to put our practice in perspective based on available literature.
Changes in the manuscript: We have added a section to the discussion 'Overall, there still seems to be a wide variation in the practice of pediatric perfusion. Recent evidence has emerged that a minimum threshold of oxygen delivery is necessary to preserve end organ function(7,33). Our results with high-flow, high-hematocrit strategy has shown promising outcomes with a low incidence of complications. This has also been adopted with modifications by other centers over the years(14,37). Prospective studies with well-defined protocols can further define the safety and efficacy of this approach. These studies can focus on more intense monitoring of end organ perfusion and a more careful evaluation of potential complications to overcome the limitations of a limited retrospective analysis.

4) It is also difficult to determine how the authors determine what is "conventional" because in pediatric cardiac surgery, there are a number of pediatric centers that target a higher cardiac index/blood flow than what they report, which makes their strategy less novel.

Response: Conventional is determined by what is published in contemporary literature, standard textbooks of cardiopulmonary bypass and pediatric cardiac surgery (Principles of Cardiopulmonary Bypass- Gravlee, Comprehensive Surgical Management of Congenital Heart Disease- Jonas, Pediatric Cardiac Surgery- Mavroudis and Backer, Corno AF. What are the best temperature, flow, and hematocrit levels for pediatric cardiopulmonary bypass? J Thorac Cardiovasc Surg. 2002;124(4):856-857. doi:10.1067/mtc.2002.126388, Pouard P, Bojan M. Neonatal Cardiopulmonary Bypass. Seminars Thorac Cardiovasc Surg Pediatric Cardiac Surg Annu. 2013;16(1):59-61. doi:10.1053/j.pcsu.2013.01.010, Whiting D, Yuki K, DiNardo JA. Cardiopulmonary

bypass in the pediatric population. Best Pract Res Clin Anaesthesiol. 2015;29(2):241-256. doi:10.1016/j.bpa.2015.03.006, Hirata Y. Cardiopulmonary bypass for pediatric cardiac surgery. Gen Thorac Cardiovasc Surg. 2018;66(2):65-70. doi:10.1007/s11748-017-0870-1). The strategy described as 'conventional' in our manuscript is based on a review of these publications.

Changes in the manuscript: 'The description of conventional cardiopulmonary bypass is based on what is published in literature(11–14) and in textbooks of cardiopulmonary bypass and cardiac surgery (Principles of Cardiopulmonary Bypass- Gravlee, Comprehensive Surgical Management of Congenital Heart Disease- Jonas, Pediatric Cardiac Surgery- Mavroudis and Backer).'

5) The authors seem to focus on AKI and fluid balance as primary outcome measures. The use of AKIN for renal injury scoring is outdated and they should be using KDIGO. Fluid balance can also be affected by mannitol use, ultrafiltration, etc. which they report as part of their standard practice. AKI is affected by a number of variables including bypass duration, age, gender, inflammation, oxidative injury, hemolysis, etc. At the least, the discussion should suggest how the high flow/high hematocrit strategy can alleviate some of these effects.

Response: The primary difference between AKIN and KDIGO is the duration over which the increase in creatinine occurs. While the increase in creatinine is defined over 48 hours in the AKIN criteria, the increase occurs over 7 days in KDIGO criteria (Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015 Apr 7;10(4):554-61. doi: 10.2215/CJN.01900214. Epub 2015 Feb 3. PMID: 25649155; PMCID: PMC4386245.) AKIN and KDIGO have similar diagnostic accuracy and interstage discrimination in pediatric cardiac surgical patients. KDIGO is better in predicting mortality(Ozcanoglu HD, Öztürk E, Tanıdır İC, Şahin GT, Ozalp S, Yıldız O, Özcan FG, Hatemi A. The comparison of three different acute kidney injury classification systems after congenital heart surgery. Pediatr Int. 2022 Jan;64(1):e15270. doi: 10.1111/ped.15270. PMID: 36239168). Since our patient cohorts had S Cr measured only over a 48-78 hour period and since predicting mortality was not the primary scope of our studies, we had used AKIN criteria. A brief re-analysis of the same cohort with KDIGO criteria did not significantly change the incidence of acute kidney injury.
We agree with the reviewer's comments that AKI is determined by multiple variables. We have added a discussion paragraph addressing this.
Changes in the manuscript: The following has been added to the manuscript. 'The incidence of acute kidney injury, as defined by the KDIGO criteria (25) was 9% (14/155), with 2/155(1.3%) in advanced renal failure or stage 3 renal failure'.

' Acute kidney injury has been noted in neonates even after operations without

cardiopulmonary bypass. There are multiple factors that leads to acute kidney injury

after cardiac surgery. Multi-institutional data from 22 north American centers revealed an estimated incidence of 54% (ranging from 27% to 86%)(34). A subsequent study also estimated the incidence of acute kidney injury in this cohort to be as high as 38%(35). Thus, cardiopulmonary bypass alone may not be a factor in determining the incidence of post cardiac surgical acute kidney injury. However, our own results and studies from other centers do indicate that the way cardiopulmonary bypass is conducted plays an important role in mitigating renal injury(7). A cumulative time spent below the critical oxygen delivery of 350 ml/min/m2 is associated with acute kidney injury after cardiopulmonary bypass in children(7).'

6) Does this high flow/high hematocrit strategy have any complications? For example, if the blood is more "viscous," how is that determined and does this have any impact on things like an increase in hemolysis? Or incidence of thrombus/stroke? The authors suggest this strategy is superior because it provides better end-organ perfusion. Have they looked at any objective markers of perfusion other than lactate to suggest this? SvO2, tissue oxygenation, etc.? Conversely, how does this strategy affect myocardial ischemia reperfusion injury -- having a higher flow and hematocrit when reestablishing perfusion may actually exacerbate this phenomenon. What is the incidence of low cardiac output syndrome? Milrinone is not used but dopamine is initiated prior to separation from bypass. How long is inotropic support required for these patients and what is the frequency and duration of the use of additional support such as epinephrine, dobutamine, later use of milrinone, etc.

Response: We do not routinely test for hemolysis after open heart surgery unless if there is an indication. We looked backed at our data for a cohort of 155 cases (less than 1 year of age only) done between January 2021 to October 2022). There have been no documented cases of post-operative hemolysis. The Vasoactive inotropic score was 5 on the day of operation, 4 on post-operative day 1 and 0 on post-operative day 2 respectively. Most patients had their vasoactives weaned off by post operative day 2. We use arterial blood gases and NIRS monitoring as adjuncts to physical examination to assess adequacy of cardiac output. We use SVO2 very selectively (for example in single ventricle physiology) to define low cardiac output. Based on a combination of lactic acidosis and a worsening base deficit accompanied by down trending NIRS, the incidence of low cardiac output in our most recent cohort was 7.7% (12/155). We do not have a comparison group to say if the incidence of low cardiac output syndrome is higher than conventional perfusion strategies. However, the incidence of low cardiac output syndrome after congenital heart surgery compares favorably with published estimate of 25% (Chandler HK, Kirsch R. Management of the Low Cardiac Output Syndrome Following Surgery for Congenital Heart Disease. Curr Cardiol Rev. 2016;12(2):107-11. doi: 10.2174/1573403x12666151119164647. PMID: 26585039; PMCID: PMC4861938).
The incidence of new onset stroke is less than 1% (1/155). 6/155(3.8%) had new left ventricular dysfunction after surgery. 2/155(1.3%) needed mechanical circulatory support

Changes in the manuscript: We have modified the following section in the manuscript: The lactate clearance, calculated as (initial lactate-delayed lactate)*100/initial lactate as described by Ladha et.al with a cut-off greater than 10% indicating adequate lactate clearance (24) was 12% in the first 6 hours and 28% in the first 24 hours. The incidence of acute kidney injury, as defined by the KDIGO criteria (25) was 9% (14/155), with 2/155(1.3%) in advanced renal failure or stage 3 renal failure. This included patients who needed extracorporeal life support (2/155-1.3%). None of the patients needed renal replacement therapy (including peritoneal dialysis). The adequacy of cardiac output is mainly determined by physical examination, serial lactate levels, arterial blood gas (base deficit) and end-organ function (Urine output, serum creatinine, near infra-red spectroscopy, liver function tests). Mixed venous oxygen saturations are measured when the adequacy of cardiac output is equivocal. The incidence of persistent or new onset low cardiac output in our cohort was 7.7% (12/155). This compares favorably with the 25% incidence of low cardiac output reported in literature(26). The median vasoactive inotropic score (VIS) was 5(Interquartile range 3.5) on the day of surgery, 4 (interquartile range 8) on post operative day one and 0(interquartile range 6) on post-operative day 2). Most patients in our cohort were off inotropes within 48 hours to 72 hours after surgery. There was no documented incidence of hemolysis. The incidence of new post-operative stroke was less than 1% (1/155) and 6/155(3.8%) showed evidence of post-operative ventricular dysfunction that subsequently resolved. Primary chest closure was achieved in 140/155 (90%) with all open chests in the STAT 4/5 categories. The low lactate levels in the peri-operative period, adequacy of lactate clearance, low VIS, low incidence of low cardiac output syndrome and preservation of end-organ function attests to the success of our bypass strategy.

7) The lack of a true comparison group to determine the benefits of this strategy is a real limitation in this report. Because determinants of pediatric cardiac surgery outcomes are multifactorial and in no small part determined by surgical complexity and surgeon skill, it unfortunately makes it difficult to make any conclusions from any of the observational studies that are cited here.

Response: We do acknowledge the limitations of our study. It is true that determinants of outcomes in pediatric cardiac surgery are multifactorial. Our strategy provides excellent results in our experience and probably can be used by centers who have a high incidence of acute kidney injury.
Changes in the manuscript: None

Reviewer D

We thank the authors for their study which addresses important finding in the field of pediatric cardiac surgery and cardiac critical care. The paper add value to our understanding of the best strategy of CPB for pediatric patients.

Please provide clarifications for the following points:

Line 75, (cardiac output times hematocrit), please explain this and provide a reference.

Response: The oxygen delivery is a product of the cardiac output and the oxygen carrying capacity of the blood (Hayward A, Robertson A, Thiruchelvam T, Broadhead M, Tsang VT, Sebire NJ, et al. Oxygen delivery in pediatric cardiac surgery and its association with acute kidney injury using machine learning. J Thorac Cardiovasc Surg. 2023;165(4):1505–16.). The oxygen carrying capacity of the blood is determined by the hematocrit and the oxygen saturation. Since the oxygen saturation is maintained at 100% during cardiopulmonary bypass, the hematocrit plays a predominant role in determining oxygen delivery in addition to the flow.
Changes in the manuscript: (cardiac output times hematocrit) has been modified to (cardiac output times oxygen carrying capacity).

Line 102, the authors justify the use of their strategy based on the senior author's experience in adult experience. We appreciate the senior author's experience and his contribution to the field, however, as authors know, adult central nervous system is dramatically different compared to neonates and children CNS. Some readers may see this as weakness point in this argument. Please edit or remove.

Response: We did not attempt to justify the use of our strategy based on the adult experience. This line was included to give an insight into how this idea came to the senior author's mind which then led to a thoughtful change in clinical practice, the results of which we have published and presented.
Changes in the manuscript: None

Line 134: please provide more details about the definition of the immediate post-operative period. The authors reported that Milrinone is not used in the ICU after surgery which is very rare in our field.

Response: The immediate post-operative period is defined as the first 24 to 48 hours after the operation.
Changes in the manuscript: The line has been modified for clarification.
….in the immediate post-operative period (usually the first 24 to 48 hours)

Line 135: Same comment as above, if you avoid Albumin, what is the fluid of choice that you use for resuscitation after surgery.

Response: The fluid of choice is either fresh frozen plasma or packed red blood cells, depending on the hematocrit or crystalloids like normal saline.
Changes in the manuscript: The following line has been added at the end of the discussion on albumin.
'We prefer to use fresh frozen plasma or crystalloids like normal saline for volume replacement, or packed red blood cells if the hematocrit is low.'

Line 144: The author reports that one of the main outcomes of their strategy is decreasing the incidence of AKI and advanced renal failure. Please provide your definition of both.

Response: Acute kidney injury was defined by the AKIN criteria (Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015 Apr 7;10(4):554-61. doi: 10.2215/CJN.01900214. Epub 2015 Feb 3. PMID: 25649155; PMCID: PMC4386245.). AKIN stage 3 corresponded to advanced renal failure.
Changes in the manuscript: The appropriate references have been cited in the manuscript.

Line 140: Please provide a table which delineates the outcomes for your strategy vs the traditional strategy. It will be easier for the reader to appreciate the improved outcome of the high flow strategy. I understand that some of the reported outcomes in this paper, have already been reported and published.

Response: Thank you for this suggestion. We have added a table.
Changes in the manuscript: Table 3 has been added to the manuscript.

Line 167: please provide a reference to explain this phenomena, higher hematocrit decreases the bleeding.

Response: This is based on the senior author's observations and does not have a reference
Changes in the manuscript: None

Line 197: the author conclude that low lactate levels attests to the success of the bypass strategy, the language of this conclusion is strong. At this level of analysis and due to the different pathophysiology (single ventricle, bi-ventricle) of the included patients, it is hard to use the lactate as a marker of success. Especially the median number. The authors could have used the peak, time to clear lactate which are used in prior studies. Also, other outcomes like the VIS and time to wean off vasopressors will be important and can be of an additional value of this report.

Response: We collected additional data from the 155 infants who had undergone open heart surgery between January 2021 and October 2022, and performed some additional analysis. We specifically looked at the peak lactate and time to clear lactate. We also looked at the VIS and time to wean off vasoactives and have made appropriate additions to the manuscript as described below.
Changes in the manuscript: The lactate clearance, calculated as (initial lactate-delayed lactate)*100/initial lactate as described by Ladha et.al with a cut-off greater than 10% indicating adequate lactate clearance (24) was 12% in the first 6 hours and 28% in the

first 24 hours. The incidence of acute kidney injury, as defined by the KDIGO criteria (25) was 9% (14/155), with 2/155(1.3%) in advanced renal failure or stage 3 renal failure. This included patients who needed extracorporeal life support (2/155-1.3%). None of the patients needed renal replacement therapy (including peritoneal dialysis). The adequacy of cardiac output is mainly determined by physical examination, serial lactate levels, arterial blood gas (base deficit) and end-organ function (Urine output, serum creatinine, near infra-red spectroscopy, liver function tests). Mixed venous oxygen saturations are measured when the adequacy of cardiac output is equivocal. The incidence of persistent or new onset low cardiac output in our cohort was 7.7% (12/155). This compares favorably with the 25% incidence of low cardiac output reported in literature(26). The median vasoactive inotropic score (VIS) was 5(Interquartile range 3.5) on the day of surgery, 4 (interquartile range 8) on post operative day one and 0(interquartile range 6) on post-operative day 2). Most patients in our cohort were off inotropes within 48 hours to 72 hours after surgery.

Reviewer E

The Authors reported their experience with the high flow/high hematocrit cardiopulmonary bypass in pediatric patients, with excellent results.

Being myself one of the introducers of this strategy for pediatric cardiopulmonary bypass more than 20 years ago, I believe that the manuscript will be extremely useful for the readers involved in the management of this group of patients.

Most of the Reviewers made very appropriate comments, all to improve the quality of the manuscript.

As the Editor, I have to agree that the input of the message transmitted by this study will be much enhanced by a revision of the structure of the text.

The Authors have given very well all the pathophysiological reasons behind their strategy, which make a lot of sense.

The fact that the "conventional" management was introduced for the comfort of the surgeon, in terms of better exposure by reducing the number of cannulas and the amount of blood in the operatory field, revealed in the results that the conduction far from the "physiological" values of flow, temperature and hematocrit, was characterized by a large number of complications in an unacceptable percentage of pediatric patients.

To better substantiate the choice of their strategy, as suggested by many Reviewers, the Authors should seriously consider to modify their text, adding more scientific data, possibly presenting the patient population in a Table rather in the text, adding more preoperative and postoperative information such as the clinical categories of the children related to their conditions and the subsequent ICU management, with the VasoActive Inotropic Score (already requested by all serious journals), the incidence and type of neurological complications, and all other available clinical details.

Response: Thank you for the comprehensive review. We have made the necessary changes to the manuscript to strengthen the message.

Changes in the manuscript: Changes made as described in the response to the reviewers.

This will substantially improve the quality of the manuscript, and therefore the strength of the message transmitted to the readers.
In any case the Authors have to be acknowledged for their efforts to improve the outcomes in this difficult group of patients.