CrossMark

ORIGINAL ARTICLE

Oxidation Reduction Potential (ORP) is Predictive of Complications Following Pediatric Cardiac Surgery

Amy E. Schmidt[1] · Emily Gore[1] · Kelly F. Henrichs[1] · Grace Conley[1] ·
Charles Dorsey[3] · Kimberly B. Bjugstad[3] · Majed A. Refaai[1] · Neil Blumberg[1] ·
Jill M. Cholette[2]

Abstract Oxidation reduction potential (ORP) or Redox is the ratio of activity between oxidizers and reducers. Oxidative stress (OS) can cause cellular injury and death, and is important in the regulation of immune response to injury or disease. In the present study, we investigated changes in the redox system as a function of cardiopulmonary bypass (CPB) in pediatric patients. 664 plasma samples were collected from 162 pediatric patients having cardiac surgery of various CPB times. Lower ORP values at 12 h post-CPB were associated with poor survival rate (mean $\pm$ SD 167 $\pm$ 20 vs. 138 $\pm$ 19, $p = 0.005$) and higher rate of thrombotic complications (153 $\pm$ 21 vs. 168 $\pm$ 20, $p < 0.008$). Similarly, patients who developed infections had lower ORP values at 6 h (149 $\pm$ 19 vs. 160 $\pm$ 22, $p = 0.02$) and 12 h (156 $\pm$ 17 vs. 168 $\pm$ 21, $p = 0.004$) post-CPB. Patients that developed any post-operative complication also had lower 6 h (149 $\pm$ 17 vs. 161 $\pm$ 23, $p = 0.002$) and 12 h (157 $\pm$ 18 vs. 170 $\pm$ 21, $p = 0.0007$) post-CPB ORP values. Free hemoglobin and IL-6, IL-10, and CRP were not associated with ORP levels. However, higher haptoglobin levels preoperatively were protective against decreases in ORP. Decreased ORP is a marker for poor outcome and predictive of post-operative thrombosis, infection, and other complications in critically ill pediatric cardiac surgery patients. These results suggest that redox imbalance and OS may contribute to the risk of complications and poor outcome in pediatric CBP patients. Haptoglobin may be a marker for increased resilience to OS in this population.

Keywords Blood · Red blood cells · Oxidation reduction potential · Cardiac surgery · Pediatrics · Complications

✉ Amy E. Schmidt
Amy_Schmidt@urmc.rochester.edu

1 Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, 601 Elmwood Ave, Box 608, Rochester, NY 14642, USA

2 Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA

3 Aytu Biosciences, Englewood, CO, USA

Introduction

Oxidation reduction potential (ORP) or Redox is the activity or strength of oxidizers and reducers in relation to their concentration. Oxidizers accept electrons, reducers donate electrons. Similar to acidity and alkalinity, the increase of one is inversely proportional to the other. ORP is measured in millivolts (mV), with no correction for solution temperature. Many enzymatic reactions are oxidation–reduction reactions in which one compound is oxidized and another compound is reduced. The ability of an individual to carry out oxidation–reduction reactions depends on the oxidation–reduction state of the environment, or its reduction potential. Redox affects the solubility of nutrients, especially metal ions. Redox imbalance is caused by an increased production of reactive oxygen species (ROS) and reactive nitrogen species or a decrease in endogenous protective antioxidants. These antioxidant defenses are important for removing free radicals. ROS can initiate cellular tissue damage by modifying lipids, proteins, and DNA. This can compromise cell health and viability. It can also create a cascade of cellular responses that can ultimately result in cell death. Increased redox imbalance caused by overproduction of ROS is typical in a variety of medical conditions, including critical illnesses.

⁂ Springer

A higher ORP measurement is indicative of oxidative stress. Several studies have shown that ORP measurement can be helpful in evaluation of diseases and conditions such as atherosclerosis, diabetes, Alzheimer's disease, myocardial infarction, stroke, sepsis, trauma, and traumatic brain injury (TBI) [1–7]. In these studies, patients with TBI and trauma were found to have higher ORP values as compared to normal healthy individuals indicating a higher level of oxidative stress. Additionally, the ORP levels were found to correlate with the severity of illness, i.e., more severely injured patients had higher ORP values [1, 4, 5]. In a recent study, Bjugstad et al. found that the day 4 capacity for induced oxidative stress (cORP or antioxidant capacity) had prognostic value in patients with TBI [1].

Cardiopulmonary bypass (CPB) has been shown to be associated with increases in inflammatory markers and altered hemostatic status [8–10]. Several of the inflammatory markers released during CPB have been implicated in complications that contribute to organ dysfunction and adverse outcome [11–16]. Notably, blood transfusion, surgical trauma, coagulation and complement activation, and reperfusion injury have been shown to contribute to post-operative inflammation. Cholette et al. performed a prospective, randomized, controlled trial which examined the effect of washing red blood cells (RBCs) and platelets in children undergoing cardiac surgery with CPB. Washed transfusions resulted in decreased inflammatory markers, decreased transfusions, and decreased donor exposures, and were associated with a trend towards reduced mortality [16]. Using samples collected in this study, we explored the prognostic value of ORP as a biomarker for poor outcome and/or complications in children undergoing cardiac surgery with CPB. We describe here the changes in the redox system as a function of cardiac surgery and CPB in pediatric patients.

Materials and Methods

Study Setting

The study was conducted at Golisano Childrens Hospital of the University of Rochester Medical Center (URMC) in Rochester, NY, a tertiary care and community hospital. This study is registered at clinical trials.gov and was conducted with institutional human subjects review board approval (NCT00693498).

Sample Population

Children up to 18 years presenting to URMC for cardiac surgical repair/palliation with CPB were eligible and subjects were enrolled at their pre-anesthesia visit, with

properly witnessed, and documented informed consent. Once enrolled, subjects were divided into groups according to age and the presence of cyanosis, and block randomization was used to randomize subjects to the unwashed or washed transfusion strategy. For additional details of the study, please refer to Cholette et al. [16].

Study Design

All blood products were prestorage leukoreduced, irradiated, and ABO identical without restrictions on storage age. Transfusion of blood products was based upon the standard pediatric cardiac intensive care unit protocol. RBCs were used to prime the CPB circuit for infants weighing less than 10 kg. Citrated blood samples were collected at pre-op, immediately post-CPB, 6 and 12 h after separation from CPB. Steroids were given on CPB to all patients undergoing deep hypothermic circulatory arrest and to all children $\leq$ 6 months old.

Blood Product Washing Procedures

A COBE (Terumo, Lakewood, CO) 2991 Blood Cell Processor was used to wash RBCs and platelets as previously described [16–18]. Following separation and concentration of the RBCs, the supernatant was expressed into a waste bag and two additional washing cycles were repeated by adding normal saline (0.9% NaCl). The platelets underwent a two-wash procedure to remove approximately 95% of the plasma. After washing, platelet units were re-suspended in normal saline.

ORP

Plasma ORP was measured using the RedoxSYS® system as a measure of the electron transfer from reductants (antioxidants) to oxidants under a constant negligible current (static ORP, sORP) and then by increasing the oxidative current (capacity ORP, cORP). The sORP provides a measure of the current balance between all known and unknown oxidants and reductants/antioxidants. As such, higher sORP (in millivolts, mV) suggests a higher level of oxidative stress. The cORP measures the biological sample's ability to withstand an oxidative insult by applying an increasing oxidizing current. This current ultimately exhausts all antioxidants present in the sample. cORP is expressed in microcoulombs (μC). Higher cORP is indicative of more capacity a sample has to mitigate an oxidative insult. While sORP and cORP are related, sORP looks at the current state of oxidative stress and cORP assesses the potential for oxidative stress. Previous studies demonstrated that sORP is linked to the proportion of cysteinylated residues on albumin in serum as measured by

LC–MS [5] and thus may indicate concentrations of oxidized molecules in blood. Higher plasma sORP values have been observed in patients with traumatic brain injury [5, 19], sepsis [3, 6], and in patients with type II diabetes [7].

IL-6 and IL-10

As described previously [16], 2.0 mL whole blood samples were collected in sodium citrate tubes, centrifuged immediately, and the plasma stored at −80° for later IL-6 and IL-10 cytokine quantification. Samples were obtained: 1) in the OR prior to initiation of CPB; 2) once off CPB after the protamine is completed ("post-CPB"); 3) 6 h "post-CPB"; and 4) 12 h "post-CPB". Measurements of IL-6 and IL-10 cytokine levels were determined by a Luminex beadlyte multiplex assay per manufacturer (Millipore Corporation, Billerica MA) instructions. IL-6 and IL-10 levels were quantified for each subject group and the ratio calculated at each time point.

High Sensitivity C-Reactive Protein (CRP)

CRP was measured pre and post-CPB as described previously [16] and on post-operative day (POD) 1-3. CRP testing was performed at the URMC Clinical Laboratories, analyzed by immunoturbidmetric assay (ADVIA 2400 Chemistry System, Bayer Healthcare, Tarrytown, NY).

Clinical Outcome Measures

As described previously [16], patients were monitored daily for clinical complications including: sepsis, active infection, and thrombosis (based on clinical and/or radiographic data).

Statistical Analysis

The data were analyzed and graphed using Statistica (Dell, Inc). Differences in sORP and cORP between the cyanotic and acyanotic patients were analyzed by the Student's t test. Unless indicated otherwise, all graphs are presented as mean $\pm$ SEM. Differences between various time points before and after CPB were analyzed using one way ANOVAs. A p value < 0.05 was considered statistically significant. For clinical outcome data that was normally distributed, t-tests were performed to test for significance. For clinical outcome data that was not normally distributed, and when interleukin levels were compared, Mann–Whitney tests were performed. We did not adjust for multiple comparisons as all secondary analyses are considered exploratory in nature.

Results

A total of 162 pediatric patients undergoing cardiac surgery were enrolled in a randomized controlled trial [16]. They were divided into two groups, one group received washed RBC and platelet transfusions and the other group received standard unwashed products. A total of 17 subjects in each group did not receive any blood product transfusions. The ages of the blood products given to each group were not significantly different. In this study, there were 100 (62%) males and 62 (38%) females with a median age of 7 months (range 2 days–17 years; Table 1). The median weight was 6.75 kg (range 2.2–106.8 kg). Thirty-six (23%) of the patients were neonates that were less than 31 days old. A total of 39 (24%) patients had single ventricle physiology and 78 (48%) had cyanotic cardiac lesions. Of the 162 patients, 31 (19%) had chromosomal abnormalities or syndromes. A total of 30 patients had comorbidities which included a history of a ventriculoperitoneal shunt, G-tube feeding, pulmonary hypertension, bronchopulmonary dysplasia, cleft lip, cleft palate, etc. There were no significant differences in sORP or cORP observed at any time point between patients with and without comorbidities.

There were no significant differences in sORP or cORP values at any time point between the washed and unwashed transfusion groups. Therefore, these two groups were combined in subsequent analyses. No statistically significant differences in cORP between patients that received RBC transfusions and those that did not at any time points. Immediately post-CPB, the mean ($\pm$ SEM) sORP for nontransfused patients was 149 ± 19 and that of transfused patients was 148 ± 17, $p = 0.694$. By 6 h post-CPB, the mean sORP for nontransfused patients was 161 ± 23 and that of transfused patients was 154 ± 10, $p = 0.064$. At 12 h post-CPB, the mean sORP of nontransfused patients was 170 ± 20 as compared to 160 ± 19 in transfused patients, $p = 0.003$. At 12 h post-CPB, a weak correlation was observed between sORP and total RBC volume transfused, $r = -0.15$. As RBC transfusion volume increased, the sORP of the patient decreased.

ORP values were examined as a function of Risk Adjustment for Congenital Heart Surgery (RACHS) score at the different time points. There were no differences in cORP at any time point. There were also no differences in sORP values amongst patients with different RACHS scores pre CPB or immediately post-CPB. At 6 h post-CPB, there were statistically significant differences between patients with a RACHS score of 1 and patients with RACHS scores of 2, 3, 4, and 6 (Fig. 1). Similarly, at 12 h post-CPB, there were statistically significant differences between patients with a RACHS score of 1 as

Table 1 Patient demographics

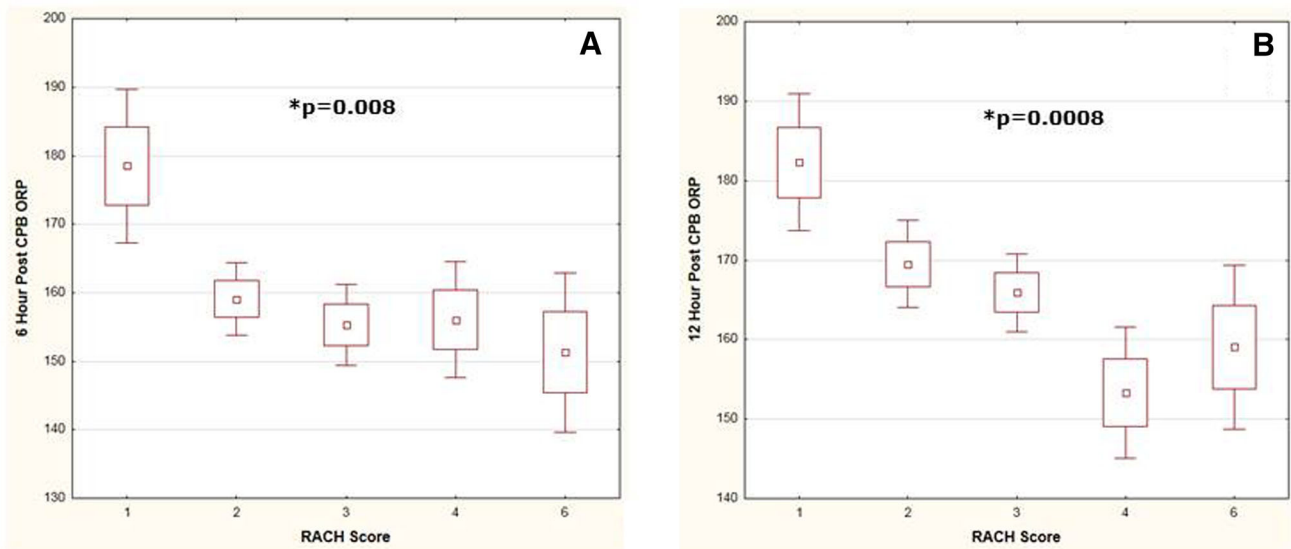|	
Male	100 (62%)
Female	62 (38%)
Median age	7 months (range 2 days–17 years)
Median weight	6.75 kg (range 2.2–106.8 kg)
Neonates (< 31 days old)	36 (23%)
Single ventricle physiology	39 (24%)
Cyanotic cardiac lesions	78 (48%)
Chromosomal abnormalities or syndromes	31 (19%)

Fig. 1 sORP Decreases as RACHS Score Increases. **a** 6 h post-CPB sORP Values. Each rectangle represents the mean ± the standard error (SE) and the error bars represent the mean ± 1.96 SE. **b** 12 h post-CPB sORP values. At both time points, increasing RACHS score is associated with decreased sORP values

compared to the other RACHS scores, with a downward trend in sORP with increasing RACHS score.

ORP values were examined in relation to post-operative complications. Documented post-operative complications included need for extracorporeal membrane oxygenation (ECMO), need to go back on CPB, junctional ectopic tachycardia, hypoxia, complete heart block, need for pacing, need for nitric oxide, and clinically significant bleeding amongst others (excluding thrombosis and infection). A total of 23 patients had post-operative complications not including infection and thrombosis which were analyzed separately. The sORP for patients with and without complications showed no differences either before or immediately after separation from CPB circuit (Table 2). There were statistically significant differences in 6 and 12 h sORP values in patients with and without complications. At 6 h post-CPB, patients with complications had a mean sORP of 149 ± 17 versus 161 ± 23 in those without complications, $p = 0.002$. By 12 h post-CPB, the differences in sORP were increasingly statistically significant ($p = 0.0007$) as patients with complications had a mean

sORP of 157 ± 18 as compared to 170 ± 21 in those without complications.

A total of 15 patients developed thrombosis. There were no significant differences between the cORP or sORP values before or immediately after separation from the CPB circuit. By 6 h post-CPB, patients who later developed a thrombosis had a mean sORP of 149 ± 20 versus 159 ± 22 in those without thrombosis, $p = 0.08$ (Fig. 2). At 12 h post-CPB, patients who subsequently developed thrombosis had a mean sORP of 153 ± 21 versus 168 ± 20 in those without thrombosis, $p = 0.008$.

Twenty-six patients developed infection following cardiac surgery. There were no significant differences in sORP pre or post-CPB in patients who developed infection as compared to those that did not. However, by 6 h post-CPB, patients that went on to develop infection has a mean sORP of 149 ± 19 versus 160 ± 22 in those that did not develop infection, $p = 0.02$ (Fig. 3). This difference in sORP became more pronounced by 12 h post-CPB as those who developed infection had a mean sORP of 156 ± 17 versus 168 ± 21 in those that did not, $p = 0.004$. Day 1 CRP also

Table 2 sORP and Post-op Complications

Time	ORP for patients with no complications (N = 139)	ORP for patients with complications (N = 23)	p Value
Pre CPB	169 ± 25	170 ± 21	0.822
Post-CPB	148 ± 19	153 ± 14	0.199
6 h Post-CPB	161 ± 23	149 ± 17	0.002
12 h Post-CPB	170 ± 21	157 ± 18	0.0007

correlated with subsequent development of infection, $p = 0.008$. IL-10 values at all four time points were found to correlate with subsequent development of infection as did IL-6 values pre and post-CPB, $p < 0.05$. IL-6 values at 6 and 12 h post-CPB did not show any correlation with subsequent development of infection.

There were 78 children in this study with cyanotic heart disease. The sORP values before and immediately after CPB were not statistically different between the patients with cyanotic cardiac defects and those without. By 6 h post-CPB, patients with cyanotic cardiac defects were found to have a mean sORP of 151 ± 21 as compared to a mean sORP of 164 ± 21 in those without cyanotic defects, $p = 0.0002$. This difference in sORP was also observed at 12 h post-CPB, where the sORP for patients with cyanotic defects was 161 ± 20 as compared to 170 ± 21 in those without cyanotic defects, $p = 0.01$.

There was no correlation between IL-6, IL-10, CRP, or free hemoglobin and sORP or cORP at any time point.

Higher haptoglobin levels pre CPB were associated with increased sORP at various time points post-CPB. A total of 8 patients died. Statistically significant differences were observed between the 12 h post-CPB sORP values of patients that survived and patients that died. The mean sORP at 12 h post-CPB of patients that died was 138 ± 19 versus 167 ± 20 in patients that survived, $p = 0.005$.

Discussion

Overall, these data show that lower sORP values in the first 6–12 h post-operatively are associated with poor outcomes. RBC transfusion is associated with decreased sORP values and increased volume of RBC transfusion is correlated with decreasing sORP values. This may be due to the RBC "storage lesion" which includes leakage of potassium and chloride from the RBCs, depletion of 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP), loss of phospholipids and cholesterol as well as exposure of phosphatidylserine (PS), elaboration of lipid mediators, loss of glutathione, autoxidation of hemoglobin to methemoglobin, increased microparticle formation, and disruption of NO-mediated vasodilation [20–23]. The transfused blood is likely lowering the redox potential of the patients' blood resulting in decreased sORP.

Patients with increasing RACHS score were found to have decreasing sORP values at 6 and 12 h post-CPB. This finding was not unexpected as patients with increasing RACHS score are at higher risk of mortality and poor
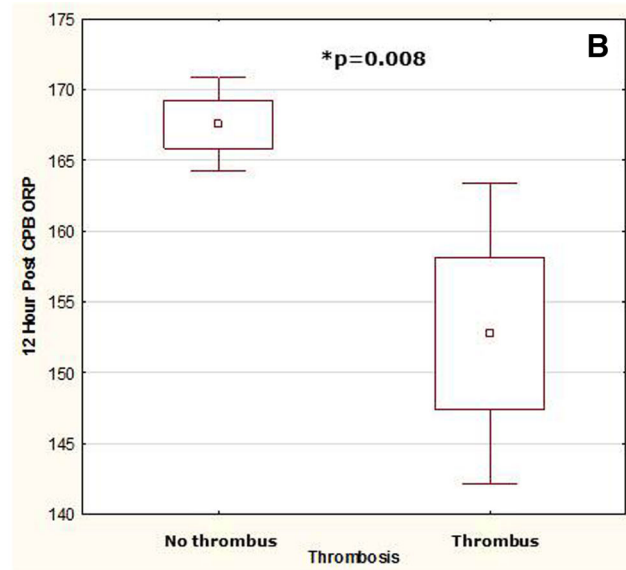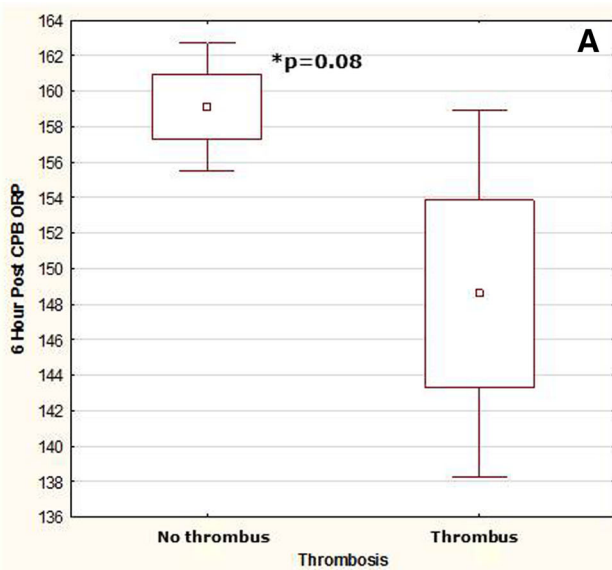

Fig. 2 Thrombosis is Associated with Decreased ORP. **a** 6 h post-CPB ORP Values. Each rectangle represents the mean ± the standard error (SE) and the error bars represent the mean ± 1.96 SE. **b** 12 h post-CPB ORP values. At both time points, development of thrombosis is associated with decreased sORP values
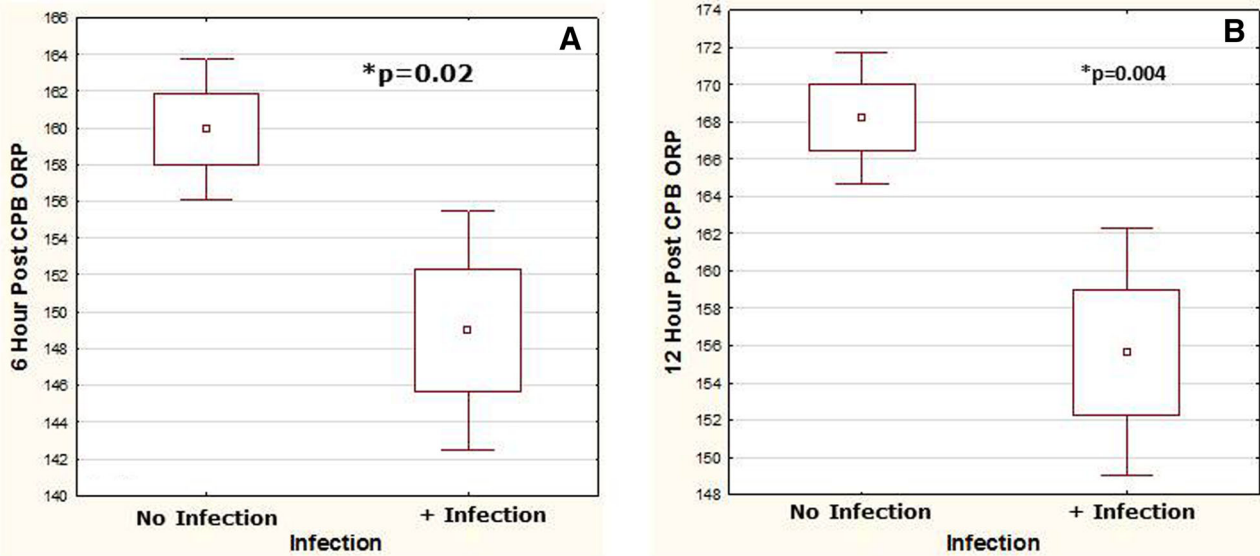
Fig. 3 Infection is Associated with Decreased sORP Values. **a** 6 h post-CPB ORP Values. Each rectangle represents the mean ± the standard error (SE) and the error bars represent the mean ± 1.96 SE. **b** 12 h post-CPB ORP values. At both time points, development of infection is associated with decreased sORP values

outcomes. This finding indicates that these sicker/higher risk patients do not respond as well to the stress of surgery. Patients with lower RACHS score had higher sORP values indicating a favorable stress response that appears to possibly contribute to overall survival.

Patients with cyanotic cardiac defects were found to have much lower sORP values at 6 and 12 h post-CPB as compared to patients without cyanotic defects. This was not unexpected as cyanotic cardiac defects alter the blood oxygenation and redox balance. Additionally, patients with any post-operative complication were found to have statistically significantly lower 6 and 12 h post-CPB sORP values as compared to those patients without complications. Specifically, patients who developed infection and/or thrombosis also had significantly decreased sORP values at 6 and 12 h post-CPB. Finally, the 12 h post-CPB sORP values for patients that died was significantly decreased as compared to those patients that survived. Interestingly, higher haptoglobin levels pre CPB were associated with increased sORP at various time points post-CPB. Thus, higher levels of haptoglobin preoperatively appear to possibly be protective against decreases in sORP and poor outcome. These data indicate that patients who have complications, fatal or not, do not develop robust responses to the oxidative stress of CPB and surgery.

Previously, Cholette et al. found that washing RBC and platelets transfused to children undergoing open heart surgery reduced post-operative inflammatory biomarkers [16]. Similarly, other studies have found that higher IL-6 levels are associated with greater illness severity, longer

length of hospital stay, sepsis, and death [24]. IL-6 levels are known to rise following CPB and correlate with post-operative morbidity [12, 25–27]. Moreover, in pediatric patients following CPB, post-operative IL-6 levels correlate with length of inotropic support, mechanical ventilation, and increased oxygen requirement, and patients undergoing the most complex surgeries have the highest levels of IL-6 [12, 25]. IL-10 is an anti-inflammatory cytokine, stimulates the compensatory anti-inflammatory response syndrome, with elevated levels correlating with adverse clinical outcomes including multiple organ dysfunction, sepsis, and mortality [28–33]. IL-10 levels have been shown to rise following pediatric cardiac surgery with CPB [12, 26, 27]. Bilgin et al. studied the effect of leukocyte-depleted RBC transfusions on post-operative inflammatory mediators and post-operative complications in 346 adults undergoing cardiac valve surgery and found increased concentrations of IL-6 and IL-12 in patients receiving leukocyte-containing RBCs, and higher interleukin levels were measured in those subjects developing post-operative infections and multiple organ dysfunction. Multivariate analysis showed an association between elevated IL-6 concentration and multiple organ dysfunction and hospital mortality [34].

Although the 6 and 12 h post-CPB sORP was found to be significantly decreased in patients that subsequently developed infections, the decreasing sORP at these time points served as an overall indicator of poor outcome and mortality and was not a specific indicator of one specific finding. Day 1 CRP levels and all four time points of IL-10

values were statistically significant indicators of subsequent development of infection, with increased levels being associated with infection development. Similarly, increased pre and immediate post-CPB IL-6 levels were also associated with subsequent infection development. Notably, there were no correlations between IL-6, IL-10, or CRP and sORP or cORP at any time point.

Overall, these findings indicate that decreased sORP in pediatric patients having cardiac surgery is associated with poor outcomes: infection, thrombosis, and mortality. Patients who survived and did well were found to have an oxidative stress response or increase in sORP post-CPB that gradually decreased over time. In some circumstances, a redox imbalance in favor of oxidative stress can be beneficial [35–37] and failure or a delay in engaging the redox system to oxidative stress may be an important indicator of outcome [38]. Similar findings have been observed in patients with sepsis. Cowley et al. found that septic patients had decreased ORP as compared to normal controls and that the ORP remained low in septic patients who died and returned to normal in patients that survived [39].

This study has several limitations. Patient samples were only consistently drawn for up to 12 h post-CPB. Samples from later time points might have been valuable in further monitoring of the sORP. Similarly, the short term measurements of interleukin levels are a limitation of this study. Additionally, testing of the transfused blood for sORP and cORP might have added clarity to the effect of transfusion on the patients' redox potential.

Conclusions

In this study, lower sORP values serve as a marker for poor outcome and are predictive of development of thrombosis, infections, and other complications in critically ill pediatric cardiac surgery patients. Notably, a decrease in sORP values is not specific for any one outcome, but the failure to generate a timely oxidative stress response could result in a worse outcome or complication. These results suggest that redox imbalance indicating oxidative stress may contribute to the risk of complications and poor outcome in pediatric CPB patients. Haptoglobin may be a marker for increased resilience to oxidative stress in this population and RBC transfusions may exacerbate oxidative stress. Additional studies are needed to evaluate the possible predictive value of ORP for poor outcome or complications in critically ill children and adults. Although CRP, IL-6, and other markers are helpful in measuring or predicting inflammation and infection, there are few biomarkers at present that are broadly indicative of poor outcome and/or impending complications. If validated in other studies, ORP may serve

as additional marker to predict a higher risk of thrombosis, infection, or other complications, thus allowing earlier detection and potentially improved outcome through therapeutic intervention.

Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Bjugstad KB, Rael LT, Levy S, Carrick M, Mains CW, Slone DS, Bar-Or D (2016) Oxidation–reduction potential as a biomarker for severity and acute outcome in traumatic brain injury. Oxid Med Cell Longev 2016:6974257. https://doi.org/10.1155/2016/6974257
2. Bar-Or D, Bar-Or R, Rael LT, Brody EN (2015) Oxidative stress in severe acute illness. Redox Biol 4:340–345. https://doi.org/10.1016/j.redox.2015.01.006
3. Bar-Or D, Carrick MM, Mains CW, Rael LT, Slone D, Brody EN (2015) Sepsis, oxidative stress, and hypoxia: are there clues to better treatment? Redox Rep 20:193–197. https://doi.org/10.1179/1351000215Y.0000000005
4. Rael LT, Bar-Or R, Mains CW, Slone DS, Levy AS, Bar-Or D (2009) Plasma oxidation-reduction potential and protein oxidation in traumatic brain injury. J Neurotrauma 26:1203–1211. https://doi.org/10.1089/neu.2008-0816
5. Rael LT, Bar-Or R, Salottolo K, Mains CW, Slone DS, Offner PJ, Bar-Or D (2009) Injury severity and serum amyloid A correlate with plasma oxidation-reduction potential in multi-trauma patients: a retrospective analysis. Scand J Trauma Resusc Emerg Med 17:57. https://doi.org/10.1186/1757-7241-17-57
6. Spanidis Y, Goutzourelas N, Stagos D, Kolyva AS, Gogos CA, Bar-Or D, Kouretas D (2015) Assessment of oxidative stress in septic and obese patients using markers of oxidation–reduction potential. In Vivo 29:595–600
7. Spanidis Y, Mpesios A, Stagos D, Goutzourelas N, Bar-Or D, Karapetsa M, Zakynthinos E, Spandidos DA, Tsatsakis AM, Leon G, Kouretas D (2016) Assessment of the redox status in patients with metabolic syndrome and type 2 diabetes reveals great variations. Exp Ther Med 11:895–903. https://doi.org/10.3892/etm.2016.2968
8. Levy JH, Tanaka KA (2003) Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 75:S715–S720
9. Gessler P, Pretre R, Hohl V, Rousson V, Fischer J, Dahinden C (2004) CXC-chemokine stimulation of neutrophils correlates with plasma levels of myeloperoxidase and lactoferrin and

contributes to clinical outcome after pediatric cardiac surgery. Shock 22:513–520

10. Edmunds LH (1998) Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 66:S12–S16 **discussion S25-8**

11. Allen ML, Hoschtitzky JA, Peters MJ, Elliott M, Goldman A, James I, Klein NJ (2006) Interleukin-10 and its role in clinical immunoparalysis following pediatric cardiac surgery. Crit Care Med 34:2658–2665. https://doi.org/10.1097/01.CCM.0000240243.28129.36

12. Madhok AB, Ojamaa K, Haridas V, Parnell VA, Pahwa S, Chowdhury D (2006) Cytokine response in children undergoing surgery for congenital heart disease. Pediatr Cardiol 27:408–413. https://doi.org/10.1007/s00246-006-0934-y

13. Holmes JHT, Connolly NC, Paull DL, Hill ME, Guyton SW, Ziegler SF, Hall RA (2002) Magnitude of the inflammatory response to cardiopulmonary bypass and its relation to adverse clinical outcomes. Inflamm Res 51:579–586

14. Hirai S (2003) Systemic inflammatory response syndrome after cardiac surgery under cardiopulmonary bypass. Ann Thorac Cardiovasc Surg 9:365–370

15. Gando S, Nishihira J, Kemmotsu O, Kobayashi S, Morimoto Y, Matsui Y, Yasuda K (2000) An increase in macrophage migration inhibitory factor release in patients with cardiopulmonary bypass surgery. Surg Today 30:689–694. https://doi.org/10.1007/s005950050041

16. Cholette JM, Henrichs KF, Alfieris GM, Powers KS, Phipps R, Spinelli SL, Swartz M, Gensini F, Daugherty LE, Nazarian E, Rubenstein JS, Sweeney D, Eaton M, Lerner NB, Blumberg N (2012) Washing red blood cells and platelets transfused in cardiac surgery reduces postoperative inflammation and number of transfusions: results of a prospective, randomized, controlled clinical trial. Pediatr Crit Care Med 13:290–299. https://doi.org/10.1097/PCC.0b013e31822f173c

17. Kalmin ND, Brown DJ (1982) Platelet washing with a blood cell processor. Transfusion 22:125–127

18. Vesilind GW, Simpson MB, Shifman MA, Colman RE, Kao KJ (1988) Evaluation of a centrifugal blood cell processor for washing platelet concentrates. Transfusion 28:46–51

19. Rael LTB-OR, Kelly MT, Carrick MM, Bar-Or D (2015) Assessment of oxidative stress in patients with an isolated traumatic brain injury using disposable electrochemical test strips. Electroanalysis 27:2567–2573

20. Donadee C, Raat NJ, Kanias T, Tejero J, Lee JS, Kelley EE, Zhao X, Liu C, Reynolds H, Azarov I, Frizzell S, Meyer EM, Donnenberg AD, Qu L, Triulzi D, Kim-Shapiro DB, Gladwin MT (2011) Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation 124:465–476. https://doi.org/10.1161/CIRCULATIONAHA.110.008698

21. Yalcin O, Ortiz D, Tsai AG, Johnson PC, Cabrales P (2014) Microhemodynamic aberrations created by transfusion of stored blood. Transfusion 54:1015–1027. https://doi.org/10.1111/trf.12361

22. Hess JR (2010) Red cell changes during storage. Transfus Apher Sci 43:51–59. https://doi.org/10.1016/j.transci.2010.05.009

23. Stapley R, Owusu BY, Brandon A, Cusick M, Rodriguez C, Marques MB, Kerby JD, Barnum SR, Weinberg JA, Lancaster JR Jr, Patel RP (2012) Erythrocyte storage increases rates of NO and nitrite scavenging: implications for transfusion-related toxicity. Biochem J 446:499–508. https://doi.org/10.1042/BJ20120675

24. Sullivan JS, Kilpatrick L, Costarino AT Jr, Lee SC, Harris MC (1992) Correlation of plasma cytokine elevations with mortality rate in children with sepsis. J Pediatr 120:510–515

25. Gessler P, Pfenninger J, Pfammatter JP, Carrel T, Baenziger O, Dahinden C (2003) Plasma levels of interleukin-8 and expression of interleukin-8 receptors on circulating neutrophils and monocytes after cardiopulmonary bypass in children. J Thorac Cardiovasc Surg 126:718–725

26. Eggum R, Ueland T, Mollnes TE, Videm V, Aukrust P, Fiane AE, Lindberg HL (2008) Effect of perfusion temperature on the inflammatory response during pediatric cardiac surgery. Ann Thorac Surg 85:611–617. https://doi.org/10.1016/j.athoracsur.2007.10.062

27. Schroeder VA, Pearl JM, Schwartz SM, Shanley TP, Manning PB, Nelson DP (2003) Combined steroid treatment for congenital heart surgery improves oxygen delivery and reduces postbypass inflammatory mediator expression. Circulation 107:2823–2828. https://doi.org/10.1161/01.CIR.0000070955.55636.25

28. Hietbrink F, Koenderman L, Rijkers G, Leenen L (2006) Trauma: the role of the innate immune system. World J Emerg Surg 1:15. https://doi.org/10.1186/1749-7922-1-15

29. Mokart D, Capo C, Blache JL, Delpero JR, Houvenaeghel G, Martin C, Mege JL (2002) Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer. Br J Surg 89:1450–1456. https://doi.org/10.1046/j.1365-2168.2002.02218.x

30. Seekamp A, Jochum M, Ziegler M, van Griensven M, Martin M, Regel G (1998) Cytokines and adhesion molecules in elective and accidental trauma-related ischemia/reperfusion. J Trauma 44:874–882

31. Giannoudis PV, Smith RM, Perry SL, Windsor AJ, Dickson RA, Bellamy MC (2000) Immediate IL-10 expression following major orthopaedic trauma: relationship to anti-inflammatory response and subsequent development of sepsis. Intensive Care Med 26:1076–1081

32. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA (2000) Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. Crit Care Med 28:2591–2594

33. Harris MC, D'Angio CT, Gallagher PR, Kaufman D, Evans J, Kilpatrick L (2005) Cytokine elaboration in critically ill infants with bacterial sepsis, necrotizing enterocolitis, or sepsis syndrome: correlation with clinical parameters of inflammation and mortality. J Pediatr 147:462–468. https://doi.org/10.1016/j.jpeds.2005.04.037

34. Bilgin YM, van de Watering LM, Versteegh MI, van Oers MH, Brand A (2010) Effects of allogeneic leukocytes in blood transfusions during cardiac surgery on inflammatory mediators and postoperative complications. Crit Care Med 38:546–552. https://doi.org/10.1097/CCM.0b013e3181c0de7b

35. Scudellari M (2015) The science myths that will not die. Nature 528:322–325. https://doi.org/10.1038/528322a

36. Rael LT, Bar-Or R, Kelly MT, Carrick MM, Bar-Or D (2015) Assessment of oxidative stress in patients with an isolated traumatic brain injury using disposable electrochemical test strips. Electroanalysis 27(2567–2573):37

37. Watson JD (2014) Type 2 diabetes as a redox disease. Lancet 383:841–843. https://doi.org/10.1016/S0140-6736(13)62365-X

38. Zhi L, Hu X, Han C (2014) Biphasic changes (overreduction and overoxidation) of plasma redox status and clinical implications in early stage of severe burns. J Crit Care 29:1063–1068. https://doi.org/10.1016/j.jcrc.2014.06.013

39. Cowley HC, Bacon PJ, Goode HF, Webster NR, Jones JG, Menon DK (1996) Plasma antioxidant potential in severe sepsis: a comparison of survivors and nonsurvivors. Crit Care Med 24:1179–1183