Editorial

Hemolysis during pediatric cardiac surgery: an old issue with renewed concerns

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Hemolysis may be one of the many causes of acute kidney injury (AKI)

Cardiovascular associated acute kidney injury (CVSA-AKI) is a frequent occurrence both in pediatric and adult settings (1,2). After sepsis, cardio-vascular surgery is considered in adult critically ill adults the second most important risk factor of AKI (3). CVSA-AKI is a recently well characterized syndrome, presenting with disparate levels of severity and caused by the complex interaction of multifactorial etiologies (1-3). Well recognized risk factors of pediatric CVSA-AKI are cardiopulmonary bypass (CPB) and surgical procedure duration, younger age, higher surgical risk, preoperative serum creatinine levels, preoperative use of mechanical ventilation and vasoactive drugs (4). In some studies, univentricular anatomy has been identified as a possible clinical variable associated with AKI (4). Neonatal patients, especially preterm, are particularly exposed to the risk of CVSA-AKI (5). Several other factors, such as the nephrotoxic action of some drugs and antibiotics, are furthermore currently emerging (6). As a matter of fact, in all reports, regardless the incidence and severity of renal dysfunction, CPB is clearly identified as one of the most important triggers of post-operative AKI (2,4). During extracorporeal blood circulation, AKI may be secondary to compromised renal perfusion, renal vasoconstriction, loss of pulsatile flow, ischemic injury, low cardiac output and hemodilution (3,4). A milestone study clearly identified oxygen delivery during CPB in adult patients as one of the most significant contributors of postoperative renal damage (7).

In this complex and still incompletely understood pathway of AKI genesis, the release of plasma free hemoglobin (fHb) during CPB is an extensively studied occurrence, frequently associated with tubular injury, which deserves further in depth discussion.

Pathophysiology of CPB associated hemolysis

CPB circuit causes blood to be exposed to plastic surfaces and blood flow interaction with CPB circuit entails shear forces that mechanically break red blood cells and determine the release of fHb into the circulation (8). fHb is physiologically present into circulating bloodstream in the form of tetramer and αβ-subunit heterodimers. αβ-dimers have a molecular size (32 kDa) that eases this molecule to spike vulnerable anatomic sites (e.g., the kidneys and endothelium) (9). There is currently no universally accepted concentration of fHb to exactly define CPB associated hemolysis. Occurrence of hemolysis is typically evident in cases of hemoglobinuria, generally occurring after massive intravascular fHb release. However, fHb is also capable of penetrate endothelial barriers, accessing perivascular spaces and the lymph fluid (9). In the blood stream fHb forms a complex with haptoglobin, is transported to the liver (bypassing the kidneys) where it is metabolized. In the presence of favoring environment (i.e., acid states or when other oxidants are released), free iron is released from heme molecules into the circulation (3) and actively participates to oxygen radical reactions, such as lipid peroxidation and catalyzation of hydroxyl radicals,

with eventual damage to the surrounding tissues. Some fHb also passes the glomerulus barrier, and here releases free iron: at this site, the harmful effect of this oxidant on tubular cells leads to necrotic debris formation, eventually causing, with hemoglobin casts, tubular occlusion (3). This form of tubular sideropathy is eased by aciduric conditions in experimental models (9). Furthermore, uptake of fHb into proximal tubular cells is clearly favored by congested urine flow, and this induces an additional damage to proximal tubular cells (10). The infusion of hemoglobin under alkalinuric conditions protects the kidneys, and urine alkalinization attenuates renal failure in animal model (11). Also, fHb scavenges endothelium-derived nitric oxide, causing a state of reduced circulating nitric oxide: this condition has been hypothesized to cause secondary vasoconstriction with organ hypoperfusion (including kidneys), pulmonary hypertension, platelet activation, increased endothelin-1 expression, and coagulation derangements (9,12). The release of massive fHb together with exhaustion of its scavenging systems may ultimately result in in increased mortality in the most severe cases (12). Sublethal red blood cells damage has also been described: decreased microperfusion and hypoxic red blood cells lead to end organ dysfunction caused by cellular ischemia (8).

How often hemolysis occurs during CPB and its clinical relevance is not fully known.

Studies in pediatric cardiac surgery

Recently, at least three studies have been published carrying interesting novel information about the extent and clinical relevance of fHb release during CPB in pediatric cardiac surgery (13-15). The first, by Kim-Campbell and coauthors, was a prospective study conducted on 60 children (13). Age ranged from about 6 months to about 12 years and, importantly, neonates were excluded from this cohort. During this study, it was showed that levels of fHb increased from about 8 mg/dL before surgery to a maximum peak of 98 mg/dL soon after CPB stop and were significantly associated with CPB duration and change in serum creatinine levels. Restoration of fHb levels occurred in 24 hours. According to KDIGO criteria (16), AKI was diagnosed in about 40% of patients (1/3 of these experienced severe AKI). Interestingly, the association between fHb levels and change in creatinine varied by age and was particularly pronounced in children aged more than 2 years and those with male gender.

The second study, by Mamikonian and coworkers (14), enrolled a slightly smaller (40 patients) and younger (4 days to 4.8 years) cohort. Interestingly, hemolysis was more evident in younger patients with a longer duration of bypass and in those requiring a blood-primed circuit. Moreover average fHb levels were different from the previous study: a baseline fHb level of 51.0 mg/dL (±56.86) was followed by a peak of 146.2 mg/dL (±81.38) immediately after CPB weaning, with a return to baseline over 24 hours. It must be remarked that average CPB duration appeared almost double than Kim-Campbell study and that the case-mix was probably characterized by more complex cases. In fact, also AKI incidence [classified by pRIFLE (17) criteria] appeared to occur in 88% of patients (again about 1/3 were severe cases). In this study, the authors were able to show that in the specific subgroup of patients with fHb above 100 mg/dL for more than 2 hours there was significant and independent risk of developing a severe AKI stage.

The last smallest study on the youngest cohort was conducted by our group in 2014 (15). Twenty-two infants (23% neonates) with a median age of about 100 days were studied. Levels of fHb started from a baseline value of 29 mg/dL, peaked to a maximum level of 109 mg/dL at CPB weaning and returned close to baseline value (35 mg/dL) after 48 hours. During this study, a normalized index of hemolysis was calculated to be about 0.15 (0.09–0.19) g of fHb per 100 L of pumped blood. Other than CPB time, fHb levels appeared to be independently associated with left atrial venting flow. AKI occurred in 10 patients (according to pRIFLE criteria) and 20% reached an "Injury" severity level. FHb levels in the 48 post-CPB hours did not show significant differences between AKI and non-AKI patients. Still, a significant correlation was present between creatinine on first postoperative day and fHb.

Take home messages

Hemolysis has clearly been associated with a number of relevant clinical manifestations. These involve gastrointestinal, cardiovascular, pulmonary systems, as well as clotting disorders (12). Hemoglobinuria and AKI are likely the most frequent clinical consequences of hemolysis. In all cases, the scavenging effect of fHb on circulating nitric oxide has been hypothesized (12). It has been shown that fHb levels above 10 mg/dL may significantly reduce nitric oxide-dependent vasodilation *in vivo* (9,12). Consequently, much of the clinical picture caused by a hemolytic episode is characterized by microcirculatory vasoconstriction and

oxidative stress at endothelial level, further promoting the inflammatory and coagulation cascades. These effects are essentially fHb dose-related and may vary significantly according to the duration and peak of fHb levels into bloodstream. Haptoglobin can bind approximately 70 to 150 mg/dL of fHb (12). FHb concentrations in patients with hemoglobinuria are commonly in the range of 50 to 200 mg/dL and can peak above 1,000 mg/dL during severe hemolytic episodes (12).

It is a matter of fact that all pediatric patients exposed to a CPB circuit experience some level of hemolysis. This is certainly due to blood-circuit interaction and red blood cells exposure to significant shear stress forces. The impact of shear stress varies within the different sites of the CPB circuit but the whole system participates to blood cell rupture, being difficult to exactly analyze the contribution of each section (8). A potentially highly hemolytic component is the arterial cannula, but lower magnitudes of shear stress can be found in almost every segment of the CPB circuit (venous cannulae, oxygenators, reservoirs, suction systems, atrial venting system). Certainly, the roller pumps are the most likely culprits of hemolysis, due to the occlusive action on the raceway tubing and mechanical rupture of red blood cells (8).

Recent pediatric literature (13-15) confirmed that fHb release during elective surgery with CPB is common and almost always overcomes haptoglobin scavenging capacity. We appraise from these reports that, although some differences can be noted among fHb baseline and peak levels, fHb generally reaches, soon after CPB stop, the moderately severe concentration of about 100 mg/dL and is restored to baseline values in 24 to 48 hours. It is possible that differences between the fHb levels in the described reports may depend on the CPB material, average flow rate and protocols, surgery complexity, need for autologous transfusions and use of suction systems (particularly left atrial venting). Also importantly, the methodology of blood sampling may have a relevant and underestimated role: gentle and relatively slow blood withdrawal is required for fHb dosing, from a smooth and low resistance line, in order not cause red blood cell damage during blood withdrawal. Finally, the clinical sequelae of hemolysis are importantly linked to the duration of fHb peak. Kidneys are particularly at risk for experiencing hemolysis associated dysfunction and this aspect is probably related to cellular damage due to reduced perfusion and epithelial damage secondary to oxidative radical reactions. As a matter of fact, although an association between fHb levels and CVSA-AKI has been shown, this appears to be identified into a multifactorial disease process. In this context, it might be very difficult to appraise the independent role of fHb as a direct cause of renal dysfunction in children. Most of the presented studies report an association (sometimes weak) rather than a direct causative role with AKI. However, given the almost ubiquitous incidence of hemolysis during pediatric CPB, the possibility of an implication of fHb in tubular damage has always to be considered, especially in the most fragile subgroups (i.e., pre-term newborns) and susceptible patients (older and bigger ones, requiring complex procedures with high CPB flow rates, requirement for prolonged suction in the surgical field and large volume of transfusions). Furthermore, evidently, all the conditions exposing children to a prolonged extracorporeal circulation (i.e., extracorporeal membrane oxygenation, ventricular assist devices) may theoretically cause an exponential and extremely prolonged fHb levels peaking (8) with consequent clinical effects.

A call to action

After careful evaluation of the described background, several concepts have to be appraised. First, although common, a short increase of fHb levels, especially if below 50 mg/dL (on the top of haptoglobin scavenging), is hardly associated with relevant clinical effects. According to the presented reports, furthermore, it is possible that AKI secondary to hemolysis is generally transient, with a severity that parallels the temporary fHb levels peaks. However, given its common occurrence, fHb levels should be monitored in the post-operative phase. Currently, standard and widely accepted reference levels of fHb after CPB are not described and fHb dosing is not routine clinical practice in most centers.

In all children undergoing surgery with CPB, and deemed as being at particular risk for a hemolytic episode or for CVSA-AKI, or presenting persistently elevated postoperative fHb levels, some preventive and therapeutic measures must be considered. Pentoxifylline, polyethylene glycol, simvastatin, and inhaled nitric oxide have been described as effective in improving hemorheological properties of red blood cells during CPB (8). The application of auto-transfusion devices is able to significantly reduce the reinfusion of damaged cells into patients' bloodstream (8). Standard hemofiltration during CPB is not able to efficiently clear fHb molecules (60 KDa) and dimers (30 KDa), due to their clearance

cut-off to about 20 KDa. Experience with high cutoff hemofilters (cutoff of 100 KDa) is currently scarce but some indications may be present (18). Some authors have shown that the administration of exogenous haptoglobin may be helpful to decrease the levels of tubular oxidation, suggesting a protective effect on renal function (19). Among the nitric oxide donors' administration, such as inhaled nitric oxide and sodium nitroprusside, inconclusive results have shown that beneficial effects should be balanced with potential side effects of these drugs (8). Urine alkalization is another potentially effective and safe method for the optimization of fHb renal clearance (11). Systemic vasodilation strategies, common during pediatric cardiac surgery, may exert some nephroprotective effects, indirectly related to the resolution and management of the vasoconstrictive effects of fHb release (20). Finally, perfusionists and physicians should also interpret the appearance of hemolysis as an indirect sign for platelets and white blood cells damage: anticoagulation and infection prophylaxis and treatment should be carefully addressed in patients with significant hemolysis.

Conclusions

Hemolysis in children undergoing surgery for congenital heart disease is a well-known and probably underestimated complication due to its insidious clinical effects. Efforts should be made to reduce red blood cells disruption during CPB, and probably the optimization of CPB duration would be the most effective measure to reduce postoperative fHb levels. In those children at highest risk for clinical consequences of hemolysis, especially renal dysfunction, a standard protocol for the assessment, prevention, and treatment of hemolysis appears rational and strongly recommended.

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