Acute Kidney Injury in an Infant After Cardiopulmonary Bypass

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Summary: The infant who develops acute kidney injury (AKI) after cardiopulmonary bypass (CPB) surgery presents unique challenges and opportunities to the clinician and to the investigator interested in the study of AKI pathophysiology. Infants do not have many of the comorbid conditions that confound CPB outcome studies of adults. Because the timing of the AKI event is known in this clinical setting, collaboration between cardiology intensivists, nephrologists, and perfusion technologists is essential to minimize the impact of CPB on the kidney. Early institution of ultrafiltration in the operating room and renal replacement therapy in the postoperative period may decrease the proinflammatory milieu and its resultant systemic effects. In addition, early initiation of renal replacement therapy to prevent fluid overload may result in improved infant outcomes.
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Acute kidney injury (AKI) after heart surgery is a relatively infrequent but serious complication in children and infants.[1-8] The few available reports of the literature describe almost exclusively single-center experiences, and conclusions often are biased by center-effect and lack of patient stratification. In children and infants, AKI incidence after heart surgery varies from 2.7% to 24.6%,[5,8] with survival rates ranging from 21% to 80%.[5,6] In most of these reports, AKI was defined by the need for dialysis; consequently, many AKI episodes likely have not been recognized in this setting. The effect of the AKI definition on pediatric AKI epidemiology is discussed more fully in the epidemiology article of this issue of *Seminars in Nephrology* (p. 436).

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PREVENTION OF AKI AFTER CARDIOPULMONARY BYPASS HEART SURGERY IN INFANTS

The clinical phases of AKI after cardiopulmonary bypass (CPB) are characterized by pathologic changes occurring in the clinical course and are determined by preoperative, intraoperative, and postoperative events.[9] The characteristics of the neonatal-infant kidney represent an additional risk factor for the development of AKI under these conditions.

Preoperative Events

First, infants show low glomerular filtration rate (GFR), which is the result of low mean arterial blood pressure and high renovascular resistance. Adequate GFR is maintained by postglomerular, efferent arteriolar vasoconstriction, which mainly is dependent on angiotensin II activity, which is higher than in adults. This results in a higher sensitivity of neonates to the administration of inhibitors of angiotensin-converting enzyme compared with adults.[10] The use of angiotensin-converting enzyme inhibitors in this phase should be regarded with caution.[11] Similarly, the use of prostaglandin synthase inhibitors, such as indomethacin, used to

promote the closure of patent ductus arteriosus, may blunt the vasodilation needed to maintain adequate perfusion of the newborn kidney.

Second, hypoxemia reduces renal blood flow and GFR, and induces hypovolemia, hypotension, and activation of the renin-aldosterone-angiotensin system. Preservation of adequate oxygenation in this phase is crucial.

Third, vasomotor AKI deriving from septicemia usually is part of multiorgan failure. Induced vasoactive mediators (renin-aldosterone-angiotensin system, endothelin, and thromboxane A_2) also may be present in noninfected patients as a consequence of pre-existing congestive heart failure.[12]

Fourth, hypothermia is associated with renal vasoconstriction and a decrease in GFR. Preservation of physiologic body temperature is essential for the infant's renal function.

Fifth, positive pressure ventilation decreases venous return and cardiac output and increases renal sympathetic nervous activity and serum vasopressin levels. In this case, fluid administration that might potentially overcome the problem is hampered by the need for fluid restriction.

Sixth, nephrotoxicity of drugs or of intravenous contrast media in the preoperative period may induce tubular injury.

Intraoperative Events

First, CPB per se may affect renal function both because of hemodynamic changes and because of the activation of immune responses. Hemodynamic changes are determined by the balance between minute oxygen consumption (VO_2) and perfusion pressure during CPB. Minute oxygen consumption is a function of perfusion pressure and, in turn, the nonpulsatile flow of CPB alters the arterial resistance occurring during normal pulsatile flow.[13] Although the exact influence of this on the kidney function of infants is not known, it is likely that CPB itself induces impairment of organ perfusion. This is in agreement with the finding of the association between CPB duration and the risk of AKI in infants.[5]

Second, in infants on CPB, surgical trauma, blood contact with CPB surface, endotoxemia, ischemia, and high levels of free hemoglobin contribute to the initiation or the maintenance of the systemic inflammatory response syndrome. Miniaturization of the CPB circuit[14] and the use of intraoperative ultrafiltration[15] are improvements that could prevent AKI in infants during CPB.

Postoperative Events

First, the degree of cardiac performance plays a central role in the preservation of kidney function after heart surgery. Both persistence of cardiac failure and a residual heart defect or failed correction expose the infant to the risk of AKI. In a case-control series of 61 infants and children who underwent CPB surgery and who were treated with peritoneal dialysis, arterial hypotension and venous hypertension deriving from poor cardiac performance were independent risk factors for AKI development and more important than pre-existing renal failure.[5]

Second, all issues reported as preoperative events may continue to exert a negative influence on renal function postoperatively. In particular, sepsis-associated systemic inflammatory response syndrome may induce multiorgan dysfunction and irreversibly compromise the clinical course. Recently, the association between fluid overload and mortality in critical children treated with continuous renal replacement therapy (CRRT) has been reported.[16,17] Consequently, significant interest has arisen regarding prevention of fluid accumulation and its possible positive influence on mortality. Achievement of a negative fluid balance could be one of the main targets in these patients and can be accomplished by the use of diuretics or by the timely application of dialysis (see later).

MEDICAL MANAGEMENT OF AKI IN INFANTS AFTER HEART SURGERY

As a general rule, hemodynamics and cardiac function optimization are a priority in patients with a congenital heart defect. The low-cardiac-output state (LCOS) consists of an inadequate systemic oxygen delivery to meet the metabolic demands of the organ systems associated with low cardiac output.[18] The LCOS plays an important role after pediatric open-heart surgery, af-

fecting up to 25% of infants between 6 and 18 hours after surgery, and resulting in longer intensive care unit stay and increased mortality.[19] Features of LCOS include tachycardia, poor systemic perfusion, decreased urine output, increased lactate, and reduced mixed venous oxygen saturation. Infants suffering from low cardiac output with decreased kidney perfusion usually are given inotropes (dopamine, milrinone), vasopressors (high-dose dopamine, epinephrine), vasodilators (milrinone, fenoldopam), and diuretics (furosemide) that must be optimized to achieve the best equilibrium between cardiac function (contractility), blood oxygenation (pulmonary flow), and systemic perfusion (kidney, hepatic, gastrointestinal function). Strict clinical observation and constant modification of drug infusion when signs of pulmonary overflow/systemic hypoperfusion occur are the main determinants for successful management of these patients.

Dopamine

Dopamine is the most common drug used in infants after cardiosurgery, at doses ranging from less than 5 mcg/kg/min (stimulation of DA1 receptors), to 5 to 10 mcg/kg/min (stimulation of β1 receptors), up to 20 mcg/kg/min (stimulation of α receptors). Dopamine is titrated after the surgical procedure to achieve adequate mean arterial pressure and systemic perfusion. Renal dopamine receptors (DA1 and DA2) are present in the renal, mesenteric, and coronary vascular beds, but their clinical meaning has been the object of a long-lasting debate. DA receptors appear gradually after birth.[20] Natriuresis in response to DA agonists also is markedly impaired in the newborn.[21] Stimulation of β1 receptors leads to an increase of heart inotropy and chronotropy. Systemic vascular resistances generally are increased by peripheral vasoconstriction induced by stimulation of α1 receptors.[22] The neonatal heart is characterized by the presence of immature adrenergic receptors, with a relatively limited response to catecholamine administration. This is owing to the presence of low receptor density and affinity, to an increase in β2/β1 receptor ratio, to different coupling with intracellular second messengers, and to receptor down-regulation after a few hours of catecholamine administration.[23] For this reason, high doses of dopamine infusion often are required during postoperative LCOS and the potential for peripheral and splanchnic vasoconstriction exists. Nevertheless, in clinical practice the priority usually is given to maintenance of adequate mean arterial pressure to achieve kidney perfusion and possibly preserve renal function.

Epinephrine

When high doses of dopamine fail to restore adequate perfusion pressure, epinephrine infusion often is required in LCOS. Epinephrine has strong α- and β-adrenergic–receptor activation. At lower doses ($<$0.05 mcg/kg/min), epinephrine increases ventricular contraction, reduces systemic vascular resistance, and increases renal blood flow. As the dose is increased, more prominent vasoconstriction and decrease in renal blood flow is seen. Controversial debate is ongoing about the role of vasopressors in AKI pathophysiology. The respective roles of epinephrine on kidney function under these conditions are unclear. On one hand, vasopressors improve organ perfusion; on the other hand, they have been considered potentially harmful to renal microcirculation.[24,25]

Milrinone

Milrinone is a phosphodiesterase inhibitor that has been shown to increase cardiac output in selected children with LCOS after open heart surgery, most likely as a result of direct myocardial effects as well as pulmonary and systemic vasodilatory properties. A recent multicenter study on prophylactic administration of milrinone showed safety and efficacy in the prevention of clinical features of LCOS in selected infants after heart surgery.[18,19]

Diuretics

Loop diuretics such as furosemide are the most used diuretics in the infant undergoing cardiac surgery.[26] Dosage and administration modality vary from boluses (1 mg/kg every 8 or 12 h) to continuous infusion (up to 10-20 mg/kg/d). The administration strategy has been re-evaluated in light of the results obtained in infants treated

with continuous versus intermittent furosemide after heart surgery. Furosemide continuous infusions may be preferred to bolus administration because it yields comparable urinary output with a much lower dose, fewer hourly fluctuations,[27] and less urinary sodium and chloride wasting.[28] The initial dose of furosemide continuous infusion ranges from 0.1 to 0.2 mg/kg/h. A 3-day trial of 13 post–heart surgery infants and children noted that a mean starting dose of 0.093 was insufficient, and required a significant increase to 1.75 mg/kg/h in 10 of 13 patients. These investigators suggest a starting dose of 0.2 mg/kg/hour and eventual tapering.[29]

Recently, a great amount of interest in the use of dopamine-receptor agonists in post–heart surgery infants has been raised. In a retrospective series of 25 post-CPB neonates, a significant improvement of diuresis was observed with fenoldopam, a selective DA1-receptor agonist, compared with chlorothiazide and furosemide.[30]

RRT OF POST–HEART SURGERY AKI IN INFANTS

The indication for RRT in these patients has changed through the years and the present tendency is that of a wider application of this kind of treatment.[6,8] In our opinion, this evolution has resulted from 2 main causes. Although no clear recommendation is made for the application of RRT in patients without acute renal failure,[31] it is widely accepted that RRT can positively affect the clinical course of multiple organ disease syndrome. Up to 20% of all cases of pediatric multiple organ disease syndrome are represented by children who underwent cardiac surgery.[32] In addition, prevention of fluid accumulation has been associated recently with an improved survival rate in critically ill children.[16] In post-CPB children with AKI, the application of preventive dialysis proposed years ago[5] recently has been associated with very low mortality.[6]

The 2 dialysis modalities most frequently used in infants with post–heart surgery AKI are peritoneal dialysis (PD) and CRRT.

PD

PD is relatively easy to perform, does not require heparinization or vascular access (often complicated in infants), and generally is well tolerated in hemodynamically unstable patients.[5,33,34] One of the main disadvantages of PD is a relative lack of efficiency in water removal with direct consequences on fluid balance and frequent limitation of parenteral nutrition. Nonetheless, the early application of PD as a measure for fluid overload prevention is presently accepted.[34] In particular, infants with specific risk factors for AKI should be considered for the preventive use of PD. In children undergoing surgery with the Fontan procedure, postoperative unfavorable hemodynamic conditions (high venous pressure) may lead to a high incidence of renal failure.[35] In the last fifteen years, intraoperative placement of a PD catheter in these patients has become a routine procedure in our center.[5,36] An extraordinarily high survival rate was observed (80%) in a group of infants with post–heart surgery AKI in which PD was started much earlier than in other studies (time to PD application after surgery, 5-40 h).[6] Although a very limited experience, this study suggests that prevention of renal failure and/or fluid accumulation may affect survival. PD offers limited depurative performance compared with extracorporeal techniques.[37] Moreover, in post–heart surgery infants, high dialysate volumes to increase PD clearance lead to modifications of atrial, mean pulmonary artery, and systemic pressure.[38] For this reason, a PD prescription of 10 mL/kg dwell volume, with continuous 1-hour cycles (5 minute fill, 45-minute dwell, and 10-minute drain), is prescribed commonly.[6,39,40] Recent debate has occurred regarding the potential beneficial effect of removing other solutes such as inflammatory mediators via dialytic therapies.[41] Pilot data reveal measurable levels of proinflammatory cytokines in peritoneal fluid after CPB in neonates[42] and a renoprotective influence of PD related to proinflammatory cytokine removal in post–heart surgery newborns.[43]

CRRT

Both ultrafiltration and solute clearance occur rather slowly in patients undergoing PD. Con-

sequently, PD may not be the optimal modality for patients with severe volume overload who require rapid ultrafiltration, or for patients with severe life-threatening hyperkalemia who require rapid reduction of serum potassium. Moreover, the amount of ultrafiltration often is unpredictable because of the impaired peritoneal perfusion in hemodynamically unstable patients such as post–heart surgery infants. In such conditions, the ultrafiltration capacity of PD may not cope with the desired amount of fluid removal and, if scarce, it is obligatorily dedicated to patient's weight loss rather than to the balance of nutrition intake with subsequent risk of malnutrition in hypercatabolic patients. These limitations of PD explain the increased use of extracorporeal dialysis in critically ill pediatric patients[44] and in post–heart surgery infants.[45] These children generally are treated with CRRT, which provides both fluid and solute re-equilibration and proinflammatory mediator removal. Commercially available circuits with reduced priming volume together with monitors providing an extremely accurate fluid balance have rendered CRRT feasible in infants.[46,47] Further details regarding the technical considerations required for providing CRRT to infants can be found in the Technical Aspects article in this issue of *Seminars in Nephrology* (p. 488).

Infants undergoing CPB show 2 unique features with respect to exposure to a proinflammatory state. First, post–heart surgery infants are most exposed to the risk of water accumulation, AKI, and inflammation owing to the nature of hemodilutional, hypothermic CPB and to the massive exposure of blood to the artificial surface of CPB.[48-51] Second, the exact moment of the renal-inflammatory injury (ie, CPB initiation) is known.[52] Cardiac surgery patients receive ultrafiltration during CPB preventively with the filter placed in parallel with the CPB circuit to remove inflammatory mediators from the beginning of their generation. This strategy may exert beneficial effects on hemodynamics, metabolism, and inflammation in the postoperative period.[51]

A highly specialized patient with respect to this general description is the infant with AKI and an extracorporeal membrane oxygenation treatment (ECMO). In this case, the CRRT circuit is placed in parallel and countercurrent to the ECMO circuit. The blood into the CRRT circuit runs in the opposite direction with the one in the ECMO circuit, with its arterial side connected to the circuit after the pump. The venous side is connected to the bladder, which collects patient venous return. With this set-up the CRRT circuit receives the blood after the ECMO pump, a positive pressure segment, and it returns it to the ECMO bladder where the pressure is close to zero. Although his configuration may cause minimal recirculation, it results in the safest provision in an ECMO circuit.[53] Recent data detail experience with 2 different subgroups of children: one group that required hemofiltration alone and a second group that required hemofiltration and ECMO.[54] Not surprisingly, the investigators identified a higher mortality rate in those patients requiring continuous venovenous hemofiltration and ECMO compared with those patients requiring hemofiltration alone. The investigators promoted the concept that certain therapies should be reserved for experienced teams.

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