Perfusion-induced acute kidney injury: A litany of uncertainty and frustration

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Litany is defined as a “tedious recital or repetitive series,” and synonyms include “a lengthy enumeration or a sizable series of trials.” This seems to be an appropriate word to describe investigations of acute kidney injury (AKI) after cardiopulmonary bypass (CPB). Just within the last year, there have been publications almost too numerous to count related to AKI and CPB. Table 1 gives a partial list of these publications that address mechanisms and interventions aimed at discovering causes and reducing incidence of postoperative AKI after CPB. It is symptomatic of the diversity and confusion surrounding AKI and CPB that published reports suggest that 3 of the interventions listed in Table 1 (atrial natriuretic peptide, remote ischemic preconditioning, and diuretic therapy) have opposite effects on AKI incidence after CPB. The article by Ranucci and coauthors²⁴ published in this issue of the *Journal* undoubtedly adds to this litany, and probably adds to the frustration as well.²⁴

One of the factors that may affect this litany of uncertainty and frustration is the heterogeneity (substitute “confusion”) surrounding the definition of AKI, especially after CPB. Expert panels propose at least 3 different consensus criteria on AKI, each with its own idiosyncrasies and with its own acronym (RIFLE [Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease], AKIN [Acute Kidney Injury Network], and KDIGO [Kidney Disease: Improving Global Outcomes]). Despite efforts at standardization, multiple AKI definitions continue to be used in clinical trials. Further problems arise in investigation of AKI after CPB because of end point definitions.²⁵ There is always a trade-off in defining testable outcomes with either high clinical relevance or high event rates. There are strict outcome measures, such as renal replacement therapy after CPB, and liberal outcome measures, such as serum creatinine elevations. More liberal end points often surface in smaller trials, whereas strict end points are common in larger studies.

Heart-kidney interactions.

Central Message

There are many missing pieces to the causes and remedies of acute kidney injury after cardiopulmonary bypass. Perfusion interventions may help limit acute kidney injury after reperfusion.

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Ranucci and coauthors²⁴ have included some difficult choices in their study design. They were interested in the effect of increasing oxygen delivery on postoperative AKI. They chose to use the AKIN algorithm as one measure of post-CPB AKI. This algorithm relies on measures of serum creatinine and urinary output to create 3 categories of AKI with increasing levels of creatinine and decreasing levels of urine output (AKIN groups 1 through 3). For assessment of postoperative AKI, Ranucci and coauthors²⁴ refined the AKIN outcome definitions into 2 subgroups by combining AKIN groups 2 and 3. This compromise in the outcome measures undoubtedly relates to their relatively small sample size and the infrequency of advanced AKI, as represented by AKIN levels 2 and 3, in the study group. Ranucci and coauthors²⁴ developed a randomized trial that used what they call “goal-directed perfusion” (GDP) in the treatment arm, with the aim of maintaining oxygen delivery (DO_2) at greater than $280 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. They found a significant improvement in the AKIN level 1 group but not in the AKIN level 2 and 3 group when maintaining DO_2 in the target range. Importantly, the only group with GDP-related benefit was the group with the least significant AKI (AKIN stage 1). Patients with stage 2 or 3 AKIN did not have any benefit from GDP. There were very few patients with stage 2 or 3 AKI in the study group, however, and this limited sample size makes it very likely that there is a type 2 error in the assessment of this negative finding. Because of this limited sample size of patients with stages 2 and 3 of renal dysfunction, it is not appropriate to suggest that GDP has no effect on AKI in AKIN groups 2 and 3. The

TABLE 1. Literature reports on interventions that limit acute kidney injury during cardiopulmonary bypass, from a brief review of articles published in 2017

Things that may reduce AKI after CPB
<ul style="list-style-type: none"> • High HDL may improve AKI rates¹ • Prophylactic furosemide infusions during and after CPB improve AKI rates² • Dexmedetomidine during CPB improves AKI rates³ • Peritoneal dialysis in children⁴ • Optimization of KDIGO “bundle” (reduce hyperglycemia, optimize hemodynamics, avoid nephrotoxic drugs)⁵ • Atrial natriuretic peptide⁶ • Remote ischemic preconditioning during CPB^{7,8}
Things that worsen AKI rates after CPB
<ul style="list-style-type: none"> • Hydroxyethyl starch prime may worsen⁹ • Transfusion of red blood cells increases risk of AKI¹⁰
Things that did not affect AKI after CPB
<ul style="list-style-type: none"> • Ascorbic acid¹¹ • Levosimendan¹² • Bicarbonate¹³ • Remote ischemic preconditioning¹⁴⁻¹⁶ • Atrial natriuretic peptide¹⁷ • Preoperative β-blocker¹⁸ • Allogeneic mesenchymal stem cells¹⁹ • Statin therapy²⁰ • Spironolactone after CPB²¹
Things proposed but not tested
<ul style="list-style-type: none"> • Small interfering RNA²² • Hyperoxygenation during CPB²³

AKI, Acute kidney injury; CPB, cardiopulmonary bypass; HDL, high-density lipoprotein; KDIGO, Kidney Disease: Improving Global Outcomes.

statistical power of this negative observation is quite low, and it is likely that this negative observation is not meaningful. Further research with a larger study group is therefore necessary to make meaningful observations about patients who have AKIN level 2 or 3 renal dysfunction develop after CPB.

It is possible that the significant impact of optimizing DO₂ during CPB on post-CPB AKI underestimates the true relationship between DO₂ and AKI. One of the means of optimizing DO₂ is to transfuse red blood cells during CPB. Some studies, however, suggest that this type of transfusion may actually increase the risk of AKI.¹⁰ Transfusion and GDP thus may represent a competing risk/benefit relationship, with transfusion fostering AKI while GDP limits AKI, at least in the most common subgroup of patients with AKIN 1 level AKI. Much more work needs to be done to define the importance of perfusion-related interventions in alleviating post-CPB AKI. Ranucci and coworkers²⁴ have attempted to tackle a difficult problem with the science of a randomized trial, but there are still more questions than answers about the relationship between CPB and AKI. The frustration and uncertainty of postoperative AKI persists even in the face of this randomized trial.

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