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Editorial

Renal Dysfunction and Cardiac Surgery: How Can We Study an Undefined Entity?

WHEN THE senior author of this Editorial was completing her anesthesia residency in 1991, we had known for at least a few decades that renal dysfunction after cardiac surgery was a huge problem about which we could do nothing, outside of postoperative diuresis/hemodialysis. Honestly, over the last 30 years, absolutely no real clinical progress has been made—from a 2022 Systematic Review Article, "...there is no effective prophylactic or therapeutic treatment for patients with cardiac surgery-associated acute kidney injury, and renal replacement therapy is the only option to treat severe cases."[1] Acute kidney injury (AKI) remains the most frequent perioperative complication for patients undergoing cardiac surgery, with an incidence ranging from 5% to 42%, depending on the definition of AKI and type of surgery.[1-4] Furthermore, cardiac surgery-associated AKI increases postoperative mortality and increases risk of chronic renal disease, thus increasing healthcare cost.[1-4]

Why has absolutely no progress in intraoperative clinical management been made over the last 50 years? This is especially baffling when one considers the very large number of patients available to study (worldwide, >2 million cardiac surgical procedures are performed each year) and the easy access to preoperative/intraoperative/postoperative blood and urine for investigators to analyze. One major problem in this multifaceted issue is that we still lack scientific consensus on how to define AKI. Thus, herein, we focus on how cardiac surgery-associated AKI has been defined over the years, how such variability complicates interpretation of clinical studies, and how arriving at a modern scientific consensus regarding AKI definition will help us finally appropriately clinically study and solve this problem that has haunted us for half a century.

One of the difficulties in aggregating and understanding results from heterogeneous clinical trials is that until 2004, there was a lack of a standard definition for AKI. The risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria were the first, followed by the Acute Kidney Injury Network (AKIN) definition in 2007.[5,6] Before the RIFLE criteria, the literature was abundant, with reports of >35 different definitions of AKI. Subsequent epidemiologic studies used either the RIFLE or AKIN definitions to classify the severity of AKI. Another major shift occurred in 2012 with the introduction of yet another, more unified, criteria termed "Kidney Disease: Improving Global Outcomes" (KDIGO).[7] The KDIGO guidelines incorporate aspects of both RIFLE and AKIN, and establish consistent criteria for defining AKI in clinical use and research studies. However, inadequacies quickly were apparent. The KDIGO criteria exclusively relies upon serum creatinine and urine output as the foundation to grade the extent of kidney injury. Both variables have obvious inherent limitations; serum creatinine can take 48-to-72 hours to increase after kidney injury, and urine output can be influenced by extrarenal factors (volume status, diuretics, etc.). Furthermore, these dynamic variables are assessed based on baseline kidney function or baseline serum creatinine. Establishing baseline creatinine levels is fraught with controversy, with experts stating that illness/surgery can lead to alterations in steady-state levels of serum creatinine, and accurate measurements should employ several prehospital admission measurements.[8,9] The very foundation of clinical diagnosis of AKI is contentious.

Obviously, by extension, there is no consensus on the definition for cardiac surgery-associated AKI.[4] Researchers and clinicians simply borrow the KDIGO definition for patients undergoing cardiac surgery. However, patients undergoing cardiac surgery have unique considerations that include large fluid shifts, transfusion, the release of inflammatory mediators, hemodilution, and others. Thus, the question remains—can the same definitions for AKI be applied broadly to cardiac and noncardiac surgical patients? A review of the literature can be bewildering, as there are inconsistent results among studies. In a recent large retrospective study (>1,500 patients) comparing different definitions of AKI in cardiac surgery patients (RIFLE *v* AKIN *v* KDIGO), the authors concluded that the RIFLE criteria were the best, with both AKIN and KDIGO lacking sensitivity.[10] This is problematic, as contemporary studies commonly using KDIGO and clinical decisions frequently are based on these criteria. In another recent assessment of AKI after cardiac surgery, researchers found that AKI, as classified exclusively by the KDIGO urine output criteria, was not associated with other biomarkers of renal injury; furthermore this criteria overclassified AKI and did not correlate with patient

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outcomes, suggesting that KDIGO urine output criteria cannot be generalized to patients undergoing cardiac surgery.[11] After realizing the inadequacies in diagnostic criteria, KDIGO held a controversies conference in 2019 with the sole purpose of addressing inconsistencies in the literature.[12] The committee concluded that serum creatinine and urine output are limited grossly; however, there are no viable alternatives that meet rigorous burden of proof.

In a provocative commentary in 2017 in *Lancet*, Barasch et al referred to serum creatinine as "a retrospective marker," essentially too late and insufficient.[13] They highlighted substantial limitations, including its inability to distinguish stage or severity of disease. The authors concluded that the KDIGO criteria did not incorporate the sheer pathophysiologic complexity of renal injury, ignoring contextual, anatomic, and patient characteristics.[13] Current definitions dictate that regardless of patient and clinical circumstances, the same rules apply for determining renal injury (a fallacy, easily challenged by the literature). For instance, in a subanalysis of the Renal Optimization Strategies Evaluation-Acute Heart Failure study of >300 patients, researchers found that worsening renal function (measured by serum creatinine using KDIGO criteria), in the context of patients with heart failure undergoing aggressive diuresis, did not correlate with actual renal tubular injury.[14] The authors concluded that "there is a need to further evaluate how to interpret changes in serum creatinine" in this specific patient population.[14] Additionally, patient-specific factors, such as weight and volume status, may affect urine output. In a recent statement, the KDIGO committee contends that an important question for investigation is how differences in body composition affect urine output.[12]

Although the KDIGO functional parameters are limited signals of renal injury, new real-time biomarkers allow diagnosis to be made earlier. There are several promising biomarkers currently being pursued, each relating to a different aspect of kidney function and corresponding to various mechanisms of injury.[15] Even minor renal injury can be detected days before changes in serum creatinine is observed. In 2012, the combination of the tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 became the first US Food and Drug Administration-approved biomarker for risk assessment of AKI, and subsequently kidney injury molecule 1 was approved. The application of biomarkers into clinical practice is heterogeneous and limited due to cost, lack of global availability, and paucity of implementation trials defining clinical context. However, several encouraging studies, using a biomarker-guided technique for prevention and treatment of AKI after surgery are emerging.[16] An alternative, cost-effective, and reliable biomarker that demonstrates adequate sensitivity and specificity is the renal-resistive index.[17,18] This method assesses arterial blood flow changes on a Doppler ultrasound, and the technique can be employed with a translumbar ultrasound or a transesophageal echocardiography. Pulse-wave Doppler measurements in the interlobular arcuate arteries within the kidney demonstrate high resistive indices in patients with subclinical AKI, suggesting its use as a prognostic tool for the development of postoperative renal injury. Autoregulation in the kidneys is maintained via decreased afferent arteriolar resistance, with prostaglandin signaling, and increased efferent arteriolar resistance, with activation of the renin-angiotensin-aldosterone system. However, this system is overwhelmed easily during cardiac surgery, such that endogenous vasoconstrictors contribute to intrarenal arterial vasoconstriction and impair renal blood flow. Renal blood flow correlates with mean arterial pressure during cardiopulmonary bypass, implying impaired autoregulation. Renal qualitative and quantitative vascular assessment can be incorporated into the routine intraoperative transesophageal echocardiography examination during cardiac surgery. Further clinical trials are needed to define the role of the renal-resistive index in the prognosis, diagnosis, and recovery of renal injury.

Additional future endeavors include the diagnostic evaluation of hepatic vein flow,[19] portal vein flow,[20] and urine oxygen monitoring,[21] as well as artificial intelligence programs designed to identify high-risk patients. Intrarenal venous congestion has been identified as an important mechanism of cardiac surgery-associated AKI. High venous pressures from right heart failure and/or intraabdominal hypertension can lead to deranged and increased variation of velocities in the hepatic vein and portal vein flows, respectively. Hepatic vein waveforms are characterized typically by 4 phases of anterograde S and D waves (with S>D) and retrograde A and V waves. Venous congestion can lead to S<D or a monophasic pattern depending on severity. In a recent prospective study of more than 150 patients, Pettey et al found that there was a correlation between preoperative and immediate postoperative decreased hepatic flow ratios and the subsequent development of AKI.[19] Unlike hepatic vein flow, the portal system normally lacks pulsatility and shows minor variation of velocities during the cardiac cycle. An increase in portal vein pulsatility is observed with inferior vena cava distention from increased central venous pressures, and may serve as an early marker of acute cardiorenal syndrome. Renal hypoxia measurements via real-time urine oxygen monitoring during surgery is yet another exciting new prognostic strategy for AKI.[21] Normally, the renal medulla has high oxygen requirements and a low perfusion state; thus, with impaired autoregulation during cardiopulmonary bypass, there is an oxygen supply/demand mismatch, leading to hypoxic conditions. Urine oxygen monitoring potentially can detect these changes in real time and signal clinicians to provide supportive care. All of these endeavors require further feasibility studies that simultaneously demonstrate efficacy and prognostic value.

The last decade has ushered in tremendous interest and growth in our understanding of perioperative renal injury. However, the translation of ideas into meaningful clinical practice is slow and essentially nonexistent in most institutions. Challenging contemporary notions that form the bedrock principle of our understanding of AKI is an important first step. We must rethink and redefine AKI within the emerging body of evidence that suggests that renal injury is complex, multifactorial, and influenced heavily by patient and clinical context. Current mainstream diagnostic methods are inadequate and fail to reflect the breadth and depth of real-world situations. We are optimistic

that a personalized diagnostic strategy, incorporating multiple methods with emerging technologies and research, will usher in a new era of growth in this field.

Conflict of Interest

None.

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