Acute Kidney Injury after Surgery

Where Does the Journey Lead?

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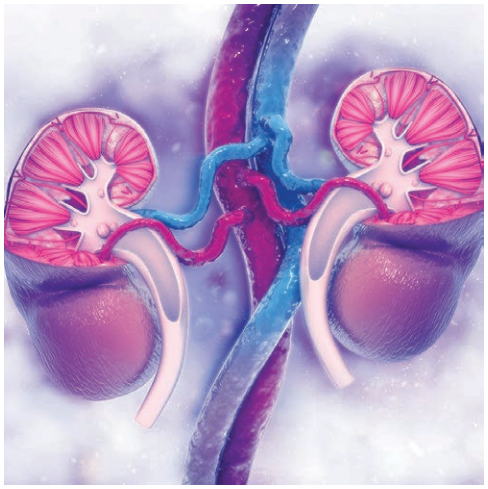
For decades acute kidney injury has been recognized as one of the leading causes of morbidity and mortality during the perioperative period. Along this journey, anesthesiologists, surgeons, and critical care physicians have been exploring strategies to detect acute kidney injury earlier, and to find ways to protect the kidneys from perioperative acute kidney injury. In the current issue of Anesthesiology, a review by Gumbert *et al.* provides a comprehensive update on the pathophysiology, novel diagnostic approaches, and both translational and clinical research findings on preventing or treating acute kidney injury in surgical patients.[1] Nevertheless, it feels as if we are still at the beginning of this journey. Continuing efforts to find better diagnostic approaches to recognize acute kidney injury earlier and to explore early detection strategies and ways to protect the kidneys have to be placed at the forefront in anesthesiology and perioperative medicine.



"[C]ritical areas for our discipline [include]…improved early detection of acute kidney injury and the exploration of molecular pathways that promote the resolution of acute kidney injury in surgical patients."

Historically, the etiology of acute kidney injury has been divided into three categories: (1) prerenal acute kidney injury is caused by a decrease in renal perfusion and probably represents the most common cause of acute kidney injury; (2) intrinsic renal causes (*i.e.,* different nephropathies); (3) postrenal causes of acute kidney injury secondary to inadequate drainage of urine distal to the kidneys. While this definition helps to think through important differential diagnostics for causes of acute kidney injury, it has significant limitations. Frequently, a combination of intrinsic renal disease (such as diabetic nephropathy) and prerenal causes (renal hypoperfusion) may precipitate the event of perioperative acute kidney injury.

The review by Gumbert *et al.* summarizes the data that suggest important findings on the prevention and treatment of acute kidney injury in surgical patients.[1] Therefore, the investigation of therapeutic interventions that have antiinflammatory and/or proresolution effects may be useful in treatment and prevention of acute kidney injury. The authors correctly emphasize the journey and ongoing need for the development of strategies for early diagnosis and novel treatment modalities that should remain at the forefront in anesthesiology and perioperative medicine, and the important role of renal inflammatory disease triggered by surgical intervention and/or renal ischemia induced by direct occlusion or compression of renal arteries (*e.g.,* during cross-clamping of the aorta[2] or during kidney transplantation). Other factors can cause renal ischemia during the perioperative period, including hypovolemia, low cardiac output states, or specific medications that may affect renal autoregulation, and can thereby cause normotensive ischemic acute kidney injury (such as preoperative continuation of angiotensin-converting enzyme inhibitors).[3]

Another disease mechanism that can cause acute kidney injury in surgical patients is related to a systemic inflammatory response syndrome. During systemic inflammatory response syndrome or sepsis, dysregulation of the systemic vascular tone, in combination with renal-specific alterations in microcirculation, represent an important mechanism for perioperative acute kidney injury. Therefore, studies using animal models frequently induce acute kidney injury by clamping of the renal vasculature ("direct" renal ischemia) or by cecal ligation and puncture, causing sepsis-driven acute kidney injury. It has become increasingly important to test novel therapeutic approaches for kidney protection in both ischemic and septic models of acute kidney injury.

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In addition to the interface between ischemia, inflammation, and infection, more recent studies have focused on the role of molecular resolution programs in perioperative inflammation. The resolution of inflammation is considered to be a process separate from inflammation, where specific repair programs with specialized proresolving mediators such as lipoxins, resolvins, and protectins,[4] but also microRNAs,[5] purinergic signaling events,[6] or stabilization of hypoxia-inducible transcription factors, stimulate key resolution responses that ultimately lead to the resolution of inflammation and restoration of kidney function. For example, studies in patients undergoing abdominal aortic aneurism surgery show that profiles of proinflammatory mediators and proresolving mediators have different temporal relationships and highlight that those programs are important in the resolution of inflammation in patients.[7] Indeed, a very recent study in animal models of perioperative inflammation indicate that simultaneously blocking the ensuing proinflammatory response (*e.g.,* by ketorolac treatment) and activating endogenous resolution programs (by treatment with resolvins RvD2, RvD3, and RvD4) before surgery may enhance proresolution programs, while at the same time eliminating micrometastases and reducing tumor recurrence.[8]

There are many different pathways that have been shown to promote the resolution of injury in the kidneys, including specialized proresolving mediators, purinergic-signaling events, or pharmacologic strategies to enhance hypoxia signaling. In this regard, some exciting clinical progress has been made quite recently. Several translational studies in animals have shown a protective role of the transcription factor "hypoxia-inducible factor" in acute kidney injury. For example, deleting the transcription factor hypoxia-inducible factor in the vasculature of the kidneys aggravates ischemic renal injury dramatically, while treatment with pharmacologic hypoxia-inducible factor activators provides kidney protection. In the past decade, orally available hypoxia-inducible factor activators have been developed by pharmacologic companies that promote the stabilization of hypoxia-inducible factors by blocking their degradation pathway through the inhibition of hypoxia-inducible factor prolyl hydroxylases. These prolyl hydroxylase inhibitors have recently been tested in patients and were found to have a great safety profile. In July 2019, two randomized phase 3 clinical trials were published showing great safety and efficiency of the orally available prolyl hydroxylase inhibitor roxadustat in the treatment of anemia in chronic kidney disease.[9] This is exciting for the field of perioperative acute kidney injury prevention, and hopefully studies to investigate the efficiency of orally available hypoxia-inducible factor activators in surgical patients for acute kidney injury prevention will be performed in the near future. These studies are in line with the current review[1] that suggests such investigations. This is an example of how new therapeutic approaches could be effective in promoting the resolution of acute kidney injury in surgical patients. It also highlights how close we could be with translating novel basic research findings of acute kidney injury prevention into the treatment of surgical patients.

While acute kidney injury occurs frequently in surgical patients, and even subclinical forms of acute kidney injury are associated with increased mortality and prolonged length of hospital stay, it is particularly difficult to diagnose acute kidney injury in the perioperative period. As described in detail in the review by Gumbert *et al.,*[1] all current clinical definitions of acute kidney injury rely predominantly on two diagnostic criteria: urine output and plasma creatinine levels. While urine output can be easily traced in most surgical patients, we are aware that many factors affect urine output in the perioperative period that are independent of the presence or absence of acute kidney injury. A decrease in urine output during anesthesia and surgery is a very poor predictor of postoperative acute kidney injury. In many instances, patients experience low urine output during the perioperative period without developing acute kidney injury. Similarly, measurements of creatinine levels do not allow for an early recognition of acute kidney injury, as glomerular filtration rate changes of more than 50% from baseline must occur before a rise in serum creatinine levels will be encountered. As discussed in more depth Gumbert *et al.,*[1] many efforts have been undertaken to enhance early detection by acute kidney injury, including the use of multiple biomarkers. While some of the initial enthusiasm over specific acute kidney injury biomarkers has somewhat faded, the combined bedside measurements of acute kidney injury biomarker panels may be quite informative.

The current review on perioperative acute kidney injury highlights many areas of recent progress that are ultimately targeted to prevent or treat acute kidney injury in surgical patients. [1] While we have made some progress on this journey, I believe, based on this review, that the two most critical areas for our discipline lie within the introduction of improved early detection of acute kidney injury and the exploration of molecular pathways that promote the resolution of acute kidney injury in surgical patients, and their translation from basic research into clinical practice. It is important to keep in mind that anesthesiologists have a great advantage over many of our colleagues from nephrology or emergency medicine. Patients who come to the emergency room for acute kidney injury usually present with the disease process already fully established. In contrast, patients for elective surgery usually present without acute kidney injury.

There may be a high risk of developing acute kidney injury in the perioperative period due to the type of surgery or the comorbid state of the individual patient. It is often much easier to prevent acute kidney injury than it is to treat acute kidney injury once it has developed fully. Unfortunately, some of our prophylactic means to decrease the risk for acute kidney injury—such as renal dopamine or high doses of furosemide treatment—have failed the proof of time. However, pretreatment of high-risk patients for acute kidney injury with proresolvin mediators or

hypoxia-inducible factor activators could be the next destination of the acute kidney injury journey in perioperative medicine.

Competing Interests

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