Taking a sound approach to acute kidney injury

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ACUTE KIDNEY INJURY (AKI) is the abrupt loss of kidney function leading to the retention of nitrogenous waste products and perturbations in fluid and electrolyte balance. AKI has occurred historically in up to 7% of hospitalized patients and is associated with increased mortality, longer lengths of stay in the hospital, and increased costs of care (4, 12). Due to the aging of the population in the United States, the incidence of AKI has been rising in recent years (1). Difficulty in defining AKI has complicated the study of its pathophysiology. These concerns led to the development of two classification systems, the RIFLE [risk, injury, failure, loss, end-stage renal disease (ESRD)] criteria and the Acute Kidney Injury Network (AKIN) criteria (8, 9), both of which should permit more systemic assessment of AKI in future clinical studies.

The wide variety of causes for AKI further complicates the study of its pathogenesis. AKI can occur in association with administration of contrast dye or other nephrotoxic agents, with rhabdomyolysis and other pigment nephropathies, with infection, and with renal ischemia. Ischemic AKI is a common form of renal damage among hospitalized patients. Sustained underperfusion of the kidney can occur due to hypotension not only in critically ill patients but also in patients undergoing elective surgical procedures, including kidney transplant or coronary artery bypass grafting (CABG). AKI is reported in up to 30% of the two million CABGs performed each year (10). Thus, understanding the mechanisms underlying ischemic AKI to predict and ideally to prevent this outcome is paramount, particularly since the pathological changes that occur in the kidney following AKI increase the risk of developing ESRD (6).

No satisfactory treatments to prevent or reverse ischemic AKI are currently available. Moreover, current markers such as an increased serum creatinine documenting the presence of AKI become abnormal after injury has already occurred such that therapeutic interventions may already be futile when AKI is diagnosed. More sensitive AKI markers such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin that peak sooner in the injury process are under development. No satisfactory treatments to prevent or reverse ischemic AKI are currently available.

In an issue of the American Journal of Physiology-Renal Physiology, Boesen and colleagues (2) describe experiments using noninvasive kidney ultrasound together with a contrast agent conjugated to P-selectin antibody to characterize renal blood flow and vascular P-selectin expression at multiple time points during the reperfusion phase of kidney IRI. The authors find that renal perfusion is still dramatically compromised even at 24 h following apparent reperfusion, confirming that the kidney remains susceptible to hypoxic insult well after resolution of the index ischemic event. With the P-selectin-targeted contrast dye, the authors are able to discriminate cortical and outer medullary vascular expression of P-selectin. They find that vascular expression of P-selectin in the renal cortex rises significantly even at 1 h following ischemic insult. Because alterations in regional blood flow within the kidney could impact P-selectin detection via effects on contrast delivery and/or binding of P-selectin antibody at reduced flow velocities, the authors importantly corroborated their ultrasound findings with direct P-selectin mRNA quantitation in the kidney. The upregulation of a key adhesion molecule in the renal vasculature 1 h following reperfusion reveals once again that pathological changes in the ischemic kidney commence well before serum creatinine and other AKI markers peak, validating the need for this incisive ultrasound tool in AKI research and calling into question conclusions regarding the pathophysiology of AKI based on data collected solely at later time points.

The utility of this imaging tool for the study of ischemic AKI and likely for other forms of progressive renal disease is readily apparent. The approach is noninvasive such that longitudinal study is possible, just as the authors have illustrated (2). In the future, one might assess in real time how blockade or activation of a protein in the renal vascular wall influences renal hemodynamics and thereby discover interventions that could preserve renal blood flow following ischemic injury. Once validated, the approach can be generalized to track interactions with the renal vasculature of any inflammatory cell, mediator, or adhesion molecule to which a relevant, reliable antibody can be produced. The technology may have further applications for pharmacokinetic studies or even attempts to target therapeutics directly to the kidney by tracking the delivery of a drug to the renal vascular endothelium.

The promise of this sound technology comes with several caveats. First, the approach will require validation from several groups with standardization of readouts to simplify interpretation and application. Note that, in humans, renal ultrasound

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F1505
with Doppler for the diagnosis of renal artery stenosis requires considerable expertise, limiting the effective use of this approach to centers with high patient volumes. One can foresee similar operator dependence in the application of any new ultrasound technology. Second, although P-selectin expression is certainly worthy of study in the context of ischemic AKI, a future goal must be to optimize the technology for use with a wide range of adhesion molecules and even circulating cell lineages for a more robust characterization of inflammatory cell diapedesis into the renal parenchyma. Third, as with clinical radiology, this ultrasound technology should complement a range of other approaches such as kidney biopsy or harvest to characterize the relative time courses of vascular dysfunction and epithelial cell changes that are the hallmarks of AKI. Nevertheless, if applied rigorously, this targeted ultrasound technology will generate a wealth of key information and new research questions to elucidate the pathogenesis of ischemic AKI.

GRANTS
This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-087783 and the Research Service of the Department of Veterans Affairs.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS
Author contributions: S.D.C. drafted manuscript; S.D.C. edited and revised manuscript; S.D.C. approved final version of manuscript.

REFERENCES