

essential component of this important regulatory mechanism. Whether baroreceptor function is restricted to renin cells or other cell types within the JGA, and whether proper localization of renin cells within the afferent arteriole directly impacts this function, are questions that remain to be answered. These interesting new observations by Lubkemeier *et al.* lend support to the view that the JGA is an integrated unit whose function depends upon precisely coordinated activity of its component cells. Cx40 gap junctions facilitate the cell-to-cell flow of physiologic information that ensures proper control of renin release for maintenance of fluid homeostasis.

Expression of vascular connexins in the human renal cortex is quite similar to that in rodents,¹⁷ and numerous mutations in human Cx40 have been identified in patients with cardiovascular disease.⁵ Therefore, assessment of the physiologic effects of the Cx40A96S mutation in mice furthers our understanding of renin regulation and BP control in humans. Lubkemeier *et al.* demonstrate, for the first time, that defective regulation of renin in mice lacking functional Cx40 is primarily due to loss of gap junctional coupling in renin-secreting cells. In fact, the patient with the A96S mutation, identified by Gollob *et al.*,⁹ also had hypertension in addition to atrial fibrillation, suggesting a common underlying mechanism. Taken together, these findings bring to light the possibility that mutations in the *Cx40* gene, such as the one modeled in this paper, may contribute to renin-dependent hypertension in humans.

DISCLOSURES

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See related article, “The Connexin40 A96S Mutation Causes Renin-Dependent Hypertension,” on pages 1031–1040.

Pores for Thought: New Strategies to Re-energize Stressed Mitochondria in Acute Kidney Injury

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Ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury (AKI) in both native and transplanted organs. Given that AKI is associated with significant patient morbidity and mortality and the development of long-term chronic kidney disease, there is an urgent need to develop new preventive or treatment strategies to improve outcomes and relieve the financial burden of AKI on health care systems. In this issue of *JASN*, Szeto *et al.*¹ describe a novel agent that is specifically

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targeted to mitochondria and offers substantial protection in a rat model of IR-induced kidney damage; this may represent a significant step forward in the long quest to pharmacologically alter the pathogenesis of AKI.

The renal proximal tubule is densely packed with elongated mitochondria and aerobically metabolizes a range of organic fuels to generate sufficient energy to meet sizeable solute transport demands; however, it has limited anaerobic glycolytic ATP-generating capacity and, as such, is intrinsically vulnerable to hypoxia. Ischemic damage in AKI typically occurs in the outer part of the medulla as a result of the precarious combination of a high-energy demand and relatively low ambient oxygen tension. Sustained ischemia leads to cell death; however, further damage can also occur in potentially viable cells after the reestablishment of blood perfusion as a result of the much-studied phenomenon of IRI.

Extensive research of aerobic tissues revealed that mitochondria play a central role in the mechanisms of cell death in IRI, apparently undergoing a rapid and remarkable transformation from subservient suppliers of ATP to masters of host cell fate. In particular, the opening of a large nonselective channel, called the mitochondrial permeability transition (MPT) pore, in the mitochondrial inner membrane during reperfusion represents a crucial stage, leading to mitochondrial swelling and depolarization, a sustained energetic deficit, and ultimately cell death (for a recent review see reference 2).

Controversies continue about the exact molecular makeup of the pore, but there is a consensus that cyclophilin D (CyP-D) is a key component, and genetic deletion or pharmacologic inhibition of CyP-D is protective in multiple experimental models of IRI, including in the kidney.^{3–6} In addition to the laboratory work, a small clinical trial of patients who underwent primary angioplasty for myocardial infarction reported that cyclosporine (which inhibits CyP-D) reduced infarct size⁷; however, in the kidney, the potential beneficial effects of cyclosporine have to be weighed against its known nephrotoxic actions.

Pharmacologic attempts to inhibit other putative components of the MPT pore during IR may be hampered by the fact that they probably also have important physiologic roles. An alternative nonpharmacologic approach is ischemic preconditioning, whereby repeated short episodes of ischemia before prolonged ischemia seem to prevent MPT pore opening and protect against IR-induced myocardial damage⁸; the clinical benefits of this technique are being evaluated in large multicenter trials.

Opening of the MPT pore is favored by conditions that occur during IR, including elevated mitochondrial $[Ca^{2+}]$ and oxidative stress.² Ischemia is thought to cause damage to the respiratory chain, so when aerobic metabolism recommences, a burst of excess reactive oxygen species (ROS) is produced as a byproduct of defective electron flux.⁹ The association of oxidative stress with cardiovascular disease has spawned a multimillion-dollar antioxidant supplement industry; however, the effects of these agents have been disappointing in major clinical trials. This may be because ROS have both physiologic and pathophysiologic roles, and a more selective approach might be required. Accordingly, new

generations of antioxidant compounds that specifically accumulate in mitochondria by virtue of either conjugation to a lipophilic cation (MitoQ) or incorporation into a mitochondrially targeted peptide (Szeto-Schiller [SS] peptides) have been developed.¹⁰

MitoQ is protective in rodent models of both type 1 diabetic nephropathy¹¹ and renal transplantation.¹² Szeto *et al.*¹ developed a peptide (SS-31) that has antioxidant properties and specifically targets the inner mitochondrial membrane, and they previously reported its effectiveness in reducing infarct size in the heart after IR.¹³ In this issue of *JASN*, they demonstrate that when given to rats exposed to IR, SS-31 has striking beneficial effects on kidney structure, function, and recovery as measured by important readouts such as serum creatinine, fractional sodium excretion, tubular cell shedding and death, inflammation, vascular congestion, and tubular regeneration.¹

The results reported by Szeto *et al.*¹ are impressive and encouraging; however, the exact mechanisms of action of SS-31 in the kidney are unclear. SS-31 had only a small and temporary beneficial effect on respiratory chain function during reperfusion—as measured in isolated mitochondria provided with complex I substrates—yet had a more marked influence on restoring tissue ATP levels. This disparity raises the possibility that SS-31 may have other actions on respiratory chain function and ATP synthesis beyond modifying complex I activity, or, alternatively, it might somehow reduce cellular ATP consumption. Exposure to SS-31 significantly improves cellular redox state after IR, as measured by changes in markers of oxidative stress; however, it remains to be seen whether this is due to an effect on mitochondrial ROS production or on other ROS or antioxidant-generating pathways. Electron microscopy reveals that SS-31 preserves mitochondrial architecture after IR, consistent with inhibition of MPT pore opening; this effect could be attributable to the demonstrated prevention of oxidative stress, but *in vitro* studies using isolated proximal tubules suggested that MPT pore opening is also influenced by a range of other factors, including concentrations of Ca^{2+} , Mg^{2+} , ADP, and nonesterified fatty acids, and the type of respiratory chain substrate used for oxidative phosphorylation.¹⁴

Even in the absence of MPT pore opening, energetic deficits persist in proximal tubule mitochondria after IR as a result of impaired complex I activity¹⁵ and possibly also to a degree of chemiosmotic uncoupling¹⁶; interestingly, these abnormalities can be ameliorated by supplementation with citric acid cycle intermediates, which are metabolized anaerobically within mitochondria. In the future, resolving the exact mechanisms of action of mitochondrially targeted compounds *in vivo* might be facilitated by the application of advanced imaging techniques that permit direct visualization of mitochondrial function, ROS production, and redox state in intact tissues.¹⁷

The importance of ATP in the pathogenesis of IRI is also nicely demonstrated by the time dependence of cell death pathways in the study by Szeto *et al.*¹: After 30 minutes of ischemia, ATP-dependent apoptosis is prominent, allowing orderly removal of nonviable cells, replacement by proliferation of progenitor cells, and reasonable preservation of archi-

ture. In contrast, after 45 minutes of ischemia, widespread necrotic cell death occurs, leading to acute inflammation, vascular congestion, general structural chaos, and significantly greater functional impairment. These observations suggest the existence of a threshold effect somewhere between 30 and 45 minutes (although this might vary according to cell type, temperature, and age), which probably corresponds to a critical level of intracellular ATP; maneuvers that keep cells on the right side of this line might improve outcomes in IR-induced AKI. Of interest, potential strategies to promote mitochondrial biogenesis and increase oxidative phosphorylation capacity in energetically damaged tissues are emerging.¹⁸

Finally, some important wider issues have to be considered to put the results described by Szeto *et al.*¹ in context. The renal literature contains numerous reports of novel agents that have shown a protective effect in experimental IR-induced AKI but have then subsequently failed to translate into successful clinical therapies.¹⁹ Why is this? First, it could be argued that the rodent models of IR typically used (45 minutes of complete renal artery occlusion) are not representative of AKI in clinical practice^{20,21}; AKI in humans is frequently multifactorial in cause (*e.g.*, drug toxicity, radiocontrast administration, preexisting chronic kidney disease), occurs as a result of impaired rather than absent blood flow,²² and is exacerbated by a lack of timely biomarkers and the failure of physicians to recognize hypovolemia.²³ Furthermore, biopsies from human kidneys exposed to IR (*e.g.*, after transplantation) tend to show epithelial flattening and edema rather than the widespread irreversible cell death observed in rodent models (acute tubular necrosis is probably the most widely used misnomer in nephrology). Last, as in the study by Szeto *et al.*,¹ experimental drugs are often given before the onset of IR, which limits their usefulness to clinical scenarios in which AKI is predictable, such as after major cardiac surgery or organ transplantation. Delivery of therapeutic agents to areas of damage in the renal medulla after IR may be inhibited by persistent arterial vasoconstriction and capillary congestion.²⁴

In summary, mitochondrially targeted antioxidant compounds hold much promise for the prevention of IR-induced damage, and Szeto *et al.*¹ should be applauded for designing a drug with such dramatic experimental effects in the kidney; however, a lot of carefully considered translational work lies ahead if these agents are to migrate from the laboratory to the clinic more successfully than their predecessors in the field. Supposedly, history does not repeat itself, but, sadly, in multiple previous negative AKI trials, it has relentlessly rhymed.

DISCLOSURES

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Differential Outcomes Between Dialysis Modalities: Purely a Reflection of Selection Bias?

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Cardiovascular morbidity and mortality among patients receiving lifesaving dialysis far exceeds that of the age-adjusted general population. Over the last several decades, there have been ongoing debates and numerous investigations seeking to identify the ideal dialysis modality for individual end-stage renal disease (ESRD) patients. Despite a paucity of evidence to support the use of one modality over another, the prevalence rates of peritoneal dialysis (PD) have declined in the United States to a current level of 7%.¹ In the era of bundled dialysis payments, health care reform, and pay-for-performance, there is a heightened interest in identifying the most cost-effective interventions associated with the best clinical outcomes. Home dialysis modalities are cost-effective, but do they improve clinical outcomes?

While the annual payer costs for patients treated with peritoneal dialysis are lower compared with hemodialysis, it remains unknown which modality is associated with the best clinical outcomes. Several recent studies have identified an early survival advantage associated with the use of PD *versus* hemodialysis (HD) among incident ESRD cohorts, while others have either failed to identify a survival difference or have identified poorer outcomes associated with PD *versus* HD.^{2–6} However, considering the known selection bias introduced by patients and physicians in choosing the appropriate dialysis modality, comparisons of outcomes between dialysis modalities inevitably is limited by unmeasured prognostic differences between groups at baseline. While a randomized controlled trial is necessary to solve the differential findings in observational studies, an initial attempt at a trial was not successful.⁷ Thus, observational studies with robust statistical methods are the only feasible alternative.

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In this issue of *JASN*, Perl *et al.* compare outcomes between PD and HD among a Canadian cohort of incident ESRD patients, with the HD patients stratified by dialysis access.⁸ The authors speculate that patients initiating HD with an arteriovenous fistula or graft (AVF/AVG) *versus* a catheter would be more similar to patients starting dialysis with a PD catheter, thus minimizing selection bias. They also hypothesize that the previously identified early survival advantage associated with PD *versus* HD would be attenuated in a comparison that controlled for vascular access. This study included 38,512 patients incident to dialysis between 2001 and 2008 who were registered in the Canadian Organ Replacement Register. Approximately 19% of patients started PD, and, of those who started on HD, only 21.4% initiated dialysis with an AVF or AVG. Similar to prior studies, PD patients in this cohort had lower overall comorbidity compared with HD patients, including a lower prevalence of diabetes mellitus, coronary artery disease, peripheral vascular disease, malignancy, and pulmonary disease.

Overall, 1-yr adjusted mortality was higher with HD compared with PD; however, when patients were stratified by dialysis access type, the increased mortality was limited to HD patients with a catheter. Among patients who started HD with an AVF/AVG *versus* PD, 1-yr adjusted mortality was equivalent between HD and PD (hazard ratio 0.9, 95% CI 0.8 to 1.1). However, 5-yr adjusted mortality was lower among HD patients with an AVF/AVG relative to PD patients (HR 0.80, 95% CI 0.80 to 0.90). Among patients who started HD with a catheter *versus* PD, 1-yr and 5-yr adjusted mortality was higher among HD-catheter patients *versus* PD patients. However, after the first year, HD-catheter patients had similar mortality risk to PD patients.

In further sensitivity analyses including the use of marginal structures models, which adjusted for propensity scores for selection of dialysis modality and probability of renal transplantation, the results were robust. In prespecified subgroup analyses, nearly all subgroups had improved 5-yr survival associated with HD with an AVG/AVF *versus* PD, while there was decreased survival among those with HD with a catheter *versus* PD.

These findings provide new insights into outcomes associated with different dialysis modalities. Only patients who have been under the care of a nephrologist and have planned for dialysis initiation will have dialysis access in place (whether a PD catheter or AVG/AVF), which makes comparisons between these groups reasonable. Furthermore, the use of a catheter *versus* AVF/AVG is known to be associated with higher infectious complications and higher mortality, and may bias toward worse early outcomes with HD, as suggested by prior observational studies. Thus, the analysis by Perl *et al.* appears to be a reasonable approach to compare outcomes between dialysis modalities while minimizing the inherent selection bias between groups.

However, cautious interpretation and application of these findings should be considered. This is a secondary analysis in which patients were allocated to one dialysis modality for a reason, whether it was patient or physician selection or other possibly unmeasured risk factors. While this study attempts to minimize these differences by minimizing pre-ESRD care as a confounder, residual unmeasured confounding likely exists. Despite over 50 years of