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In Translation

Remote Ischemic Preconditioning for Kidney Protection: GSK3β-Centric Insights Into the Mechanism of Action

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Preventing acute kidney injury (AKI) in high-risk patients following medical interventions is a paramount challenge for clinical practice. Recent data from animal experiments and clinical trials indicate that remote ischemic preconditioning, represented by limb ischemic preconditioning, confers a protective action on the kidney. Ischemic preconditioning is effective in reducing the risk for AKI following cardiovascular interventions and the use of iodinated radiocontrast media. Nevertheless, the underlying mechanisms for this protective effect are elusive. A protective signal is conveyed from the remote site undergoing ischemic preconditioning, such as the limb, to target organs, such as the kidney, by multiple potential communication pathways, which may involve humoral, neuronal, and systemic mechanisms. Diverse transmitting pathways trigger a variety of signaling cascades, including the reperfusion injury salvage kinase and survivor activating factor enhancement pathways, all of which converge on glycogen synthase kinase 3β (GSK3β). Inhibition of GSK3β subsequent to ischemic preconditioning reinforces the Nrf2-mediated antioxidant defense, diminishes the nuclear factor-κB–dependent proinflammatory response, and exerts prosurvival effects ensuing from the desensitized mitochondria permeability transition. Thus, therapeutic targeting of GSK3β by ischemic preconditioning or by pharmacologic preconditioning with existing US Food and Drug Administration–approved drugs having GSK3β-inhibitory activities might represent a pragmatic and cost-effective adjuvant strategy for kidney protection and prophylaxis against AKI.
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BACKGROUND

Acute kidney injury (AKI) is a common and potentially life-threatening complication annually affecting about 2,000 to 3,000 per million population, with two-thirds of cases occurring in intensive care units.[1,2] Common causes of AKI include sepsis, ischemia-reperfusion injury, trauma, and exposure to nephrotoxic agents.[1,2] In examining epidemiologic risk factors, it is apparent that patients with older age, hypovolemia, heart dysfunction, preexisting chronic kidney disease (CKD), and exposure to nephrotoxic medications are more susceptible to developing AKI following diagnostic or therapeutic medical interventions (ie, iatrogenic AKI).[1] Specific medical interventions linked to AKI include intravascular use of iodinated radiocontrast media, administration of nephrotoxic medications, and major surgeries involving cardiopulmonary bypass (CPB) or aortic cross-clamping.[1,2]

In the past 30 years, clinical management of AKI has been principally confined to treatment of symptoms and general supportive care, including fluid resuscitation and kidney replacement therapy. However, these treatments are of limited utility with unsatisfying therapeutic efficacy, given the poor prognosis. Although only a minority of patients with AKI require hemodialysis after the initial hospital discharge, long-term follow-up studies show that the number of patients whose kidney recovery is incomplete has been underestimated and that AKI per se is an independent risk factor for subsequent transition to CKD.[2-4] Therefore, it is imperative to develop a novel, pragmatic, and effective therapy for prophylaxis against AKI in these susceptible patients. Recently, a burgeoning body of evidence from both experimental and clinical studies points to ischemic preconditioning as a promising and feasible approach to kidney protection and prophylaxis against AKI.[5]

CASE VIGNETTE

A 65-year-old man with a history of diabetes and hypertension for more than 30 years presented to the emergency department with unstable angina pectoris. Laboratory testing showed an elevated level of cardiac enzymes and serum creatinine level of 2.1 mg/dL (186 μmol/L; corresponding to estimated glomerular

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filtration rate of 32 mL/min/1.73 m^2 as calculated using the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation[6]), consistent with stage 3 CKD. Urinalysis showed albumin-creatinine ratio of 2.6 mg/mg. The patient underwent urgent coronary angiography, which revealed 90% stenosis of the right coronary artery and 75% stenosis of the left anterior descending branch. An attempt at percutaneous coronary angioplasty of the right coronary artery failed. The patient was referred for surgical coronary artery bypass grafting (CABG) with CPB but was considered to be a poor candidate for surgery because of the high risk for AKI (risk score of 8 using the Thakar model of dialysis risk after cardiac surgery[7]). The patient was subsequently maintained on nonsurgical treatments, including insulin, furosemide, valsartan, metoprolol, amlodipine, acetylsalicylic acid, and lovastatin.

Although not currently standard of care, remote ischemic preconditioning may prove very helpful for patients like the one presented. In future clinical practice, the approach to this patient might change. After induction of anesthesia for CABG surgery, this patient might undergo 4 cycles of a 5-minute period of upper-arm ischemia, brought about placing a 9-cm blood pressure cuff around the upper arm and inflating it to a pressure 50 mm Hg greater than his systolic blood pressure. Each period of ischemia would be followed by a 5-minute period of reperfusion induced by deflation of the blood pressure cuff. Remote ischemic preconditioning would occur in the anesthetic room during patient monitoring and placement of intravascular and bladder catheters. Immediately after the remote ischemic preconditioning protocol is completed, the patient would undergo CABG surgery with an anticipated significant reduction in the risk for AKI.

PATHOGENESIS

Ischemic preconditioning is an innate tissue adaptation whereby brief episodes of ischemic insult to a tissue or solid organ make both local and remote organs more resistant to a later prolonged exposure to the same or other injuries.[8] The concept of ischemic preconditioning was first advanced in 1986 by Murry et al,[9] who described a protective effect of repeated brief episodes of coronary artery ischemia-reperfusion on a subsequent myocardial infarction induced by sustained occlusion of the coronary artery in dogs. Before the introduction of ischemic preconditioning, Zager et al[10] had already made a similar observation in the kidney, namely that in rats, prior exposure of the kidney to ischemia confers protection against additional ischemic kidney insults. It has been known for almost a century that a previous sublethal heavy metal exposure renders the kidney resistant to the additional injury.[11]

More recently, studies have demonstrated that brief ischemia imposed even on nontarget organs, most commonly the limbs, exerts a protective effect on remote solid organs (eg, heart, lung, kidney, or intestine) against injuries associated with ischemia and with other insults, including toxicants, hemorrhagic shock/resuscitation, and iodinated radiocontrast media.[12] Limb ischemic preconditioning achieved by cycling between inflating and deflating blood pressure cuffs on either the arm or leg is a cost-free, straightforward, and attractive protocol. This technique has been reproducibly shown to attenuate acute injuries in the heart and other organs, including the kidney.[13] A meta-analysis by Wever et al[14] examined a total of 58 experimental studies of the effect of ischemic preconditioning (including limb ischemic preconditioning) in animal models of AKI and concluded that ischemic preconditioning has a protective effect on AKI induced by ischemia-reperfusion injury. Ischemic preconditioning successfully prevents reductions in kidney function as assessed by serum creatinine and serum urea nitrogen levels and also minimizes kidney histologic damage. Moreover, the kidney-protective properties of ischemic preconditioning seem to be most effective in animals when the ischemic preconditioning stimulus is applied 24 hours before the ischemic injury (late window of protection).[14]

In an effort to evaluate the safety and effectiveness of ischemic preconditioning in humans, 13 randomized controlled trials (1,334 participants) have been completed to date in patients at risk for AKI following cardiac or vascular interventions. In 11 of the 13 trials (1,216 participants), limb ischemic preconditioning was found to reduce the risk for AKI compared with the control group (risk ratio, 0.70; 95% confidence interval, 0.48-1.02).[15] A substantial trend toward statistical significance suggests that limb ischemic preconditioning might be beneficial for the prevention of AKI, although more adequately powered trials are still needed to validate its effectiveness.[15]

The kidney-protective effect of limb ischemic preconditioning seems more pronounced in patients who are at high risk for AKI. This is supported by the recent Renal Protection (RenPro) Trial[16] in which 100 adult patients with stable angina pectoris were recruited for elective coronary angiography using the contrast agent iohexol, a nephrotoxic iodinated radiocontrast media. This group of patients also had preexisting CKD and thus was at increased risk for developing superimposed AKI.[16] A total of 26 patients developed contrast-induced AKI, 6 (12%) in the limb ischemic preconditioning group and 20 (40%) in the control group. Multivariable analysis suggested limb ischemic preconditioning as a strong independent contributor to prevention of contrast-induced AKI.[16]

Notwithstanding the positive findings obtained in most of the clinical and animal studies, a few clinical trials[17-21] have demonstrated no benefit of ischemic preconditioning in preventing AKI. The conflicting results may be attributable to confounding variables such as ischemic preconditioning protocols and patient characteristics. To date, the optimal protocol for remote ischemic preconditioning to trigger organ protection in humans remains unknown, but at least in rats, 3 or 4 (not 1 or 2)