Limb Ischemia Protects Against Contrast-Induced Nephropathy

Joseph V. Bonventre, MD, PhD

Contrast-induced acute kidney injury (CI-AKI), or nephropathy (CIN), is frequently diagnosed in the setting of coronary angiography. The incidence varies in the literature partly related to the differences in diagnostic criteria used for CIN. In a recently published article in Circulation, Maioli et al. 1 used a definition of an increase of ≥0.5 mg/dL over baseline serum creatinine within 3 days of the administration of contrast medium and found an incidence of 12.1% among 1490 patients who had a baseline estimated creatinine clearance of <60 mL/min. It has become increasingly recognized that even mild forms of AKI are associated with adverse short- and long-term outcomes, including onset or progression of chronic kidney disease and more rapid progression to end-stage kidney disease. 2,3 Patients with CIN have an increase in short-term and long-term mortality after adjustments for other comorbidities, whether the renal dysfunction is acute or chronic. 4 Although it has been concluded by many that the development of CIN may identify other comorbidities that are more responsible for the adverse outcomes, there are increasing data from randomized trials that CIN may directly contribute to the increased risk of cardiovascular and renal adverse outcomes. 5 In the previously mentioned study by Maioli et al., 1 the authors reported that persistent renal dysfunction, defined as a relative decrease of creatinine clearance of ≥25% from baseline at 3 months after coronary angiography, occurred in 18.6% of CIN patients. 6 These patients with persistent renal dysfunction had a higher incidence of death at 5 years when compared with those whose renal functional impairment was transient or those who did not develop CIN. In another study, the adjusted odds ratio of sustained decline in kidney function 3 months after coronary angiography was >4-fold in patients who had mild AKI (≥0.3 mg/dL or 50% to 99% increase in serum creatinine) and >17-fold for those with moderate or severe AKI (≥100% increase in creatinine). 6 Experimental models in animals provide pathophysiological explanations for how the effects of acute injury can lead to chronic inflammation, vascular rarefaction, tubular cell atrophy, interstitial fibrosis, and glomerulosclerosis. 7–9 It is therefore very important to avoid the kidney injury associated with contrast administration.

Er et al., 10 in this issue of Circulation, report that remote ischemic preconditioning protects the kidneys against CIN. Preconditioning represents an activation by the organism of intrinsic defense mechanisms to cope with pathological conditions. Ischemic preconditioning is the phenomenon whereby a prior ischemic insult renders the organ resistant to a subsequent ischemic insult. Renal protection afforded by prior renal injury was described exactly one century ago, in 1912, by Suzuki who noted that the kidney became resistant to uranium nephrotoxicity if the animal had previously been exposed to a sublethal dose of uranium. 11 In referring to the work of Suzuki, Aschoff 12 attributed the resistance to uranium toxicity to a resistance of the renal epithelium and proposed this to be a defense mechanism of the kidney. There have been a number of studies over the years demonstrating that preconditioning with a number of renal toxicants led to protection against injury associated with a second exposure to the same toxicant or to another nephrotoxicant. 13 It is not, however, a universal finding that toxins confer resistance to subsequent insults. 14

Zager and colleagues 15 performed experiments evaluating the effects of prior exposure of the kidney to ischemia on subsequent susceptibility to ischemic injury in rats a short time later. Our laboratory created a mouse model in which prior exposure to ischemia protects against a second ischemic insult imposed 8 or 15 days later. 16 Unilateral ischemia was also protective against a subsequent ischemic insult to that kidney, revealing that systemic uremia was not necessary for protection. Unilateral ischemia, however, did not protect the contralateral kidney against ischemic injury 6 or 8 days later. In a subsequent study we found that protection afforded by 30 minutes of ischemic preconditioning (inducing severe functional and histological damage) lasted for at least up to 12 weeks. 17 Some of the cellular processes and signaling mechanisms proposed to explain preconditioning in the kidney and other organs are listed in the Table.

Although it is possible in humans that preconditioning can be carried out directly on the kidney (e.g., by inducing ischemia before allograft placement or transiently obstructing the native kidney before a procedure which will result in ischemia 18 ), it is nevertheless more clinically tractable to develop methods in patients in which preconditioning can be induced pharmacologically or by minimally invasive remote ischemic preconditioning protocols. Remote ischemic preconditioning is a therapeutic strategy by which protection can be afforded in one vascular bed by ischemia to another vascular bed in the same organ or a different organ. In 1993...
Table. Factors Implicated as Protective Mediators of Remote Ischemic Preconditioning

<table>
<thead>
<tr>
<th>Adenosine</th>
<th>Nitric oxide</th>
<th>Protein kinase C (PKC)</th>
<th>Extracellular signal-regulated kinase (ERK)</th>
<th>AKT (protein kinase B)</th>
<th>Mitochondrial ATP-sensitive potassium channel (K&lt;sub&gt;ATP&lt;/sub&gt; channel)</th>
<th>Mitochondrial connexin 43</th>
<th>Antioxidants</th>
<th>Hypoxia inducible factors (HIFs)</th>
<th>Heat shock proteins</th>
<th>Sirtuin-1 (SIRT1)</th>
<th>Autophagy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in expression of genes regulating inflammation (cytokine synthesis, leukocyte chemotaxis, adhesion, exocytosis, innate immune signaling pathways)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

it was reported that temporary occlusion of the circumflex artery 4 times for 5 minutes each followed by 5 minutes of reperfusion leads to protection of myocardium in the distribution of the left anterior descending coronary artery after ischemia to that vessel, demonstrating that ischemia in one vascular bed protects tissue in another bed. Since then there have been a large number of studies demonstrating that ischemia to one organ protects against ischemia to another. Patients undergoing elective abdominal aortic aneurysm surgery were randomly assigned to either 2 cycles of intermittent cross clamping of the common iliac artery with 10 minutes of ischemia and 10 minutes reperfusion serving as the remote preconditioning influence. Remote preconditioning resulted in less postoperative myocardial injury, myocardial infarction, and renal impairment.

If the limb is used for preconditioning, ischemia can be carried out reasonably safely thus establishing a highly clinically relevant inexpensive therapeutic approach. A number of studies involving limb ischemia have been performed in animals. Weyer and colleagues evaluated the effects of unilateral or bilateral limb ischemia for 12 minutes of ischemia followed by 12 minutes of reperfusion, or 3 fractionated periods of 4 minutes of ischemia followed by 4 minutes of reperfusion, on kidney injury induced by 25 minutes of ischemia commencing at the end of the preconditioning in the rat. After 24 hours of reperfusion renal function was improved by 30% to 60% in both bilateral preconditioning groups and one unilateral fractionated preconditioning group. Renal tubular histological damage was less in the protected preconditioned groups.

Er et al., in this issue of Circulation, carried out a double-blind study of the role of remote preconditioning on the development of AKI in patients with impaired renal function who received contrast medium for elective coronary angiography. Half of the patients were given 4 cycles of 5-minutes inflation of an upper arm blood pressure cuff followed by 5 minutes of deflation to produce transient and repetitive limb ischemia. In the preconditioning group, standard upper-arm blood-pressure cuffs were inflated to 50 mm Hg above systolic blood pressure whereas in the sham group the cuff was inflated to diastolic pressure levels then deflated to 10 mm Hg. The primary end point was the development of CIN as defined by an increase in serum creatinine ≥25% or ≥0.5 mg/dL above baseline at 48 hours after contrast-medium exposure.

The authors evaluated 100 patients with either baseline serum creatinine >1.4 mg/dL or estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m<sup>2</sup>. Remote preconditioning resulted in protection against CIN. Of 50 patients in the control group, 20 (40%) developed AKI and of 50 patients in the remote ischemic preconditioning group, only 6 (12%) developed AKI. The composite cardiovascular end point (death, rehospitalization, or hemodialysis during a 6-week follow-up period) occurred more often in the control group. All patients in the study received oral N-acetylcysteine, 600 mg twice orally the day before, and the day of, coronary angiography. The patients also received continuous intravenous saline infusion 12 hours before to 12 hours after coronary angiography. The levels of neutrophil gelatinase-associated lipocalin (NGAL) in the urine increased at 24 and 48 hours in both the control and the preconditioned groups with greater increases in NGAL found in the control groups. There was also a greater increase in serum cystatin C in the control group at 24 and 48 hours after the contrast administration. The lower levels of serum cystatin and urinary NGAL are consistent with a protection of GFR and less kidney injury.

The study results are very interesting because the protective effects of remote preconditioning suggest an intervention that could be relatively easily applied in routine medical practice. There have been a number of studies examining the potential protective effect of remote preconditioning by cycling of inflation and deflation of blood pressure cuffs on either the arm or leg with varying results. Many of these studies have focused on the heart, but some have been targeted to evaluating kidney protection in patients undergoing cardiac surgery. In the study by Choi et al., 76 patients undergoing complex valvular heart surgery, remote leg ischemic preconditioning (38 patients) did not reduce the degree of renal injury, as reflected by urinary biomarkers, or incidence of AKI, whereas it did reduce myocardial injury and length of intensive care unit stay.

There are, however, a number of issues related to the Er et al., study, which dictate that confirmatory findings will be necessary before considering this approach effective. The number of patients in this pilot study was quite small, and it will become apparent over time whether the results will be confirmed as a second extended RenPro1 Trial will test the effects of remote preconditioning on renal function and cardiovascular mortality and morbidity. One might suspect that repeated episodes of 5 minutes of ischemia at 50 mm Hg above systolic pressure would be not well tolerated by all patients. The incidence of AKI in the control group is higher than a number of reports of patients with chronic kidney disease who are given contrast agents, especially because the patients were all hydrated. This might be explained somewhat by the mean age of 73 years in both control and remote preconditioning group, heart failure in 84%, and diabetes.
mellitus in 64% in both control and treated groups in the RenPro Trial. While the incidence of CIN is consistent with that found by Mehran et al. for the average high risk score of 13 in the RenPro pilot study. In the study by Maioli and colleagues, where the incidence of CIN in 1,490 patients with baseline GFR less than 60 mL/min was 11.5%, the patients had a lower contrast nephropathy risk than the patients in the Er et al study. Er et al used low-osmolar contrast agent (Iohexol) whereas Maioli et al used Iodixanol, a nonionic, dimeric iso-osmolar contrast medium. In a meta-analysis it has been reported that the risk for CIN with intra-arterial administration to patients with renal insufficiency was greater with Iohexol than for Iodixanol.

What might be the mechanism of remote preconditioning–induced protection against CIN? As indicated in the Table, there have been a number of mechanisms implicated as mediators of the protection afforded by remote ischemic preconditioning. One should consider what might be generated by transient muscle ischemia, which could represent a circulating influence that would affect kidney susceptibility to contrast. There is evidence that brief forearm ischemia results in downregulation of proinflammatory genes and upregulation of anti-inflammatory genes in circulating human leukocytes. It is likely that vasodilatory factors are released locally, which may have effects at a distance. It has been reported that transient limb ischemia releases a low-molecular-mass (<15 kDa), hydrophobic, circulating factor that induces protection against ischemia/reperfusion injury across species, is independent of local neurogenic activity, and requires opioid receptor activation for manifestation of protection of cardiac cells. The factors responsible for advantageous effects of remote ischemic preconditioning on the kidney represent a subject that demands more study, particularly because identification of the responsible protective factor(s) would provide a therapeutic approach for prevention of CIN as well as potentially prevention of AKI in other clinical settings.

Sources of Funding
Dr Bonventre is supported by National Institutes of Health grants RC1 DK0864406, R01 DK39773, R01 DK072381, and R01 DK054741.

Disclosures
Dr Bonventre has served as a consultant on acute kidney injury treatment and safety for Genzyme, Cormedix, Gilead, Merck, PTC Therapeutics, Novartis, Johnson and Johnson, and Millennium.

References


**Keywords:** Editorials ■ acute kidney injury ■ cystatin ■ ischemic preconditioning ■ kidney ■ NGAL protein, human