Remote Ischemic Preconditioning and Renoprotection: From Myth to a Novel Therapeutic Option?

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ABSTRACT
There is currently no effective prophylactic regimen available to prevent contrast-induced AKI (CI-AKI), a frequent and life-threatening complication after cardiac catheterization. Therefore, novel treatment strategies are required to decrease CI-AKI incidence and to improve clinical outcomes in these patients. Remote ischemic preconditioning (rIPC), defined as transient brief episodes of ischemia at a remote site before a subsequent prolonged ischemia/reperfusion injury of the target organ, is an adaptational response that protects against ischemic and reperfusion insult. Indeed, several studies demonstrated the tissue-protective effects of rIPC in various target organs, including the kidneys. In this regard, rIPC may offer a novel noninvasive and virtually cost-free treatment strategy for decreasing CI-AKI incidence. This review evaluates the current experimental and clinical evidence for rIPC as a potential renoprotective strategy, and discusses the underlying mechanisms and key areas for future research.


Ischemic preconditioning (IPC), transient brief episodes of ischemia before a subsequent prolonged ischemia/reperfusion injury, has been shown to reduce the extent of organ damage. IPC can be induced locally when the preconditioning stimulus is applied to the same organ or tissue incurring the ischemic injury. The concept of IPC was introduced in 1986 by Murry et al., who first described the cardioprotective effect of multiple brief ischemic episodes before subsequent sustained ischemic insult in dogs with myocardial infarction.1

However, this protection not only acts locally but can also protect distant tissues, a phenomenon known as remote IPC (rIPC). rIPC was first demonstrated in cardiac tissue in which brief episodes of myocardial ischemia and reperfusion applied to one vascular territory reduced the infarct size of the adjacent tissue that had not undergone any preconditioning.2 rIPC has primarily been applied to the myocardium as a target organ, but subsequent studies showed that brief ischemia induced in nontarget tissue, most commonly in the limb or arm, confers protection at a remote site such as the brain, lung, kidney, intestine, or skeletal muscle.3–5 rIPC causes a similar degree of tissue protection, as does IPC.6

Kidneys are one of the major organs of interest for clinical application of rIPC. Due to their high energy demand and complex microvascular network, kidneys are especially sensitive to ischemic injury, which is a major pathophysiologic basis of acute renal dysfunction, including contrast-induced AKI (CI-AKI), in patients with pre-existing heart disease.2,8 Accordingly, experimental and clinical evidence suggests that rIPC might be an effective tool to protect kidneys from ischemic injury. In this regard, we and others recently demonstrated that rIPC may offer a novel noninvasive and virtually cost-free treatment strategy to decrease acute renal impairment incidence in patients undergoing cardiac catheterization.5,9 This article evaluates the current evidence for rIPC as a potential renoprotective strategy and discusses its possible clinical applications.

POTENTIAL MECHANISMS IN rIPC

The underlying mechanisms of rIPC are very complex and not yet fully defined. It has been hypothesized that rIPC predominantly involves systemic multifactorial anti-inflammatory, neuronal, and humoral signaling pathways, which may differ in response to various ischemic stimuli and are likely to interact with each other (Figure 1).

Signal Transduction Pathways
As reviewed in more detail elsewhere,10 considerable interest has focused on the role of protein kinases (PKs) as the key
point of convergence for a range of preconditioning triggers, including adenosine, bradykinin, and opioids. Armstrong et al. were the first to identify PKC as a potential mediator of ischemia-induced protection. The current concept of signal transduction in IPC suggests activation of the signaling cascades through the phosphoinositide 3-kinase/Akt/endothelial nitric oxide synthase (NOS)/cyclic guanosine monophosphate/PKG pathways, eventually leading to the opening of the ATP-dependent mitochondrial potassium (K\text{ATP}) channel, which is believed to be a downstream target of PKG/PKC activation. The activated mitochondrial K\text{ATP} channels have the ability to limit the opening of mitochondrial permeability transition pores, thus causing a marked improvement in cell survival.

Nitric oxide (NO) is emerging as an important cytoprotective agent and may play a pivotal role in rIPC both as a trigger and mediator of rIPC. Supporting evidence for the role of NO in mediating the protection against ischemic injury comes from experiments showing that inhibition of NOS isoforms by the nonselective NOS inhibitor L-NAME (NG-nitro-L-arginine methyl ester hydrochloride) results in abrogation of the protective effects of IPC.

In addition, IPC was shown to induce NOS expression with a subsequent increase in the NO oxidation products nitrite and nitrate. Similarly, infusion of L-NAME before hind limb rIPC abolished its protective effects against subsequent abdominal adipocutaneous ischemia.

**Neuronal and Humoral Pathways**

Involvement of neuronal pathways is mostly based on the finding that blockade of the autonomic ganglion reversed the cardioprotective effects of rIPC when the preconditioning ischemic insult is performed via mesenteric artery occlusion. This concept appears to also apply to the rIPC-associated neuroprotection in cerebral tissue, as was recently demonstrated. In addition, adenosine receptors, particularly the subtype A1, have been implicated as the mediators of neuroprotection in rIPC, likely through increased production of specific antioxidants and NO.

**Anti-Inflammatory Pathways**

Some studies suggested that protective effect of rIPC may be due to the beneficial anti-inflammatory or antioxidant effects, including decreased extracellular levels of noxious metabolites, such as protons and lactate. In support of this concept, rIPC reduced neutrophil activation through expression of neutrophil CD11b and platelet neutrophil complexes. Moreover, all three key kinases involved in TNF synthesis, mitogen-activated protein kinase (MAPK) – activated protein kinase 2, MAPK kinase kinase 2, and MAPK kinase kinase 8, were suppressed, whereas ischemic preconditioning activated TNF-R1, which promotes the production of manganese SOD, a strong antioxidant and protector against reactive oxygen species. The suppression of anti-inflammatory genes extended to proapoptotic, chemotactic, and cell adhesion molecules that promote cellular extravasation. Other immunologic changes include the suppression of genes encoding key proteins involved in cytokine synthesis, leukocyte chemotaxis, adhesion, migration, exocytosis, innate immunity signaling pathways, and apoptosis.

**CONTRAST-INDUCED NEPHROPATHY: INCIDENCE, PATHOPHYSIOLOGY, AND THERAPY**

Contrast agents are being widely utilized in diagnostic and interventional procedures, resulting in increased incidence of contrast-induced renal impairment. CI-AKI after cardiac intervention is associated with significant morbidity and mortality, with an in-hospital mortality
rate of 20% in unselected patients and a 1-year mortality rate of up to 66% in patients with acute myocardial infarction and renal dysfunction.34–36

CI-AKI, defined most commonly as an increase in serum creatinine by >25% or >0.5 mg/dl (>44 μmol/L) above baseline within 48 days after administration of contrast agents in the absence of an alternative etiology, is one of the most common causes of hospital-acquired ARF.37 The incidence of CI-AKI varies substantially among studies due to the lack of a uniform definition of CI-AKI.38,39 Indeed, the CI-AKI rate may be as high as >50%, depending on the presence of risk factors.34,39–41

CI-AKI is very much dependent on the patient’s risk profile. The main predictor of CI-AKI is preexisting renal dysfunction with an estimated GFR (eGFR) <60 ml/min per 1.73 m², and its severity directly correlates with the incidence of CI-AKI.34,42 Other risk factors for CI-AKI include diabetes mellitus, major cardiovascular comorbidities, hypovolemia, and administration of high doses of contrast medium and nephrotoxic drugs such as aminoglycosides or nonsteroidal anti-inflammatory drugs.43

The mechanisms of contrast-induced renal impairment are not fully understood. There is solid experimental evidence that renal ischemia, resulting from an imbalance of various vasodilator and vasoconstrictor factors, is a key factor in the pathogenesis of CI-AKI.38–40,46 This mechanism causes subsequent ischemia and hypoxia in the renal medulla, a region with extreme susceptibility to ischemic injury. In addition, oxygen free radicals contribute at least in part to the renal tubular cellular injury.47

Various treatment strategies have been investigated in an effort to decrease CI-AKI incidence in patients undergoing cardiac catheterization. Dopamine, fenoldopam, furosemide, mannitol, amionophylline, atrial natriuretic peptide, captopril, calcium channel blockers, alprostadil, and N-acetylcysteine were not effective in preventing contrast-induced nephropathy.48–53 To date, periprocedural hydration remains the most effective prophylactic measure to prevent CI-AKI. Although clinical studies have not uniformly shown that dehydration is a definite risk factor, iodinated contrast agents increase urine volume and osmolar clearance, and their effect on the kidney is prolonged by the decrease in both renal blood flow and GFR, as seen in dehydrated states.54 Therefore, by increasing the renal perfusion and subsequently diminishing the tubular fluid viscosity, adequate hydration may counteract some of the putative hemodynamic effects that may lead to CI-AKI. The positive effect of hydration has consistently been reported in several studies.52,55,56

rIPC-INDUCED RENOPROTECTION

Animal Studies

Although the majority of studies to date have demonstrated protection by rIPC against ischemia/reperfusion injury to the myocardium of animals and humans, a small number of studies have investigated the potential of rIPC to protect the kidney. In animal models, the rIPC application was associated with the striking renoprotection.

Earlier investigations demonstrated improved kidney resistance to ischemia by preceding ischemic events,57,58 suggesting potential beneficial effects of rIPC on renal function. Ateş et al. assessed the beneficial effect of brief liver ischemia and reperfusion on rat kidney function as a remote organ.59 Biochemical determination, TNF-α, and tissue thioarbituric acid–reactive substance levels and histopathologic findings were evaluated. A 10-minute hepatic ischemia with 10-minute reperfusion afforded functional and morphologic protection in rat kidney that underwent a subsequent 45-minute ischemic insult before rIPC, as confirmed by biochemical, histopathologic, and ultrastructural findings at 24 hours of reperfusion.

The corroborative evidence that application of brief small intestinal IPC can reduce renal ischemia and subsequent reperfusion injury was provided by Song et al., who investigated the effect of small intestinal IPC on renal function in rats.60 Renal ischemic injury was induced by a 45-minute renal artery occlusion and reperfusion for 2 or 24 hours in rats with a previous contralateral nephrectomy, and rIPC was induced by three cycles of 8-minute ischemia and 5-minute reperfusion of the small intestine. Indeed, pretreatment with intestinal IPC significantly alleviated renal ischemic impairment.

Renoprotective effects of brief hind limb occlusion were reported in rats.61 Rats underwent either unilateral or bilateral rIPC. After 24 hours of reperfusion, renal function was improved in both the bilateral rIPC group and in the fractionated unilateral group, albeit bilateral rIPC was more effective than unilateral rIPC. Treatment with the adenosine receptor blocker 8-(p-sulphophenyl)theophylline had no effect on fractionated or continuous rIPC.

A recently published meta-analysis of experimental data obtained in animal models evaluated three outcome measures: serum creatinine, BUN, and histologic renal damage in renal ischemic/reperfusion injury.62 IPC-associated protective effects were reported for all three parameters. Interestingly, renoprotection was not evident in the female subgroup, stressing the need for future studies in female subjects.

Furthermore, analysis of the gene expression profile in murine heart at 24 hours after brief cycles of occlusion of the superior mesenteric artery revealed that rIPC significantly induced the expression of many genes, including anti-inflammatory and DNA repair genes.63

Clinical Evidence

In addition to experimental evidence obtained in animal models, substantial progress has been made in translating the concept of rIPC from experimental models into clinical practice. Several clinical studies have been performed thus far that predominantly (but, importantly, not all) support the concept that rIPC can be used to reduce renal damage in humans (Table 1). Concerning the safety and tolerability of the
<table>
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<th>Reference</th>
<th>Clinical Setting</th>
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<th>Renal Outcomes</th>
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<tr>
<td>Ali et al. (2007)</td>
<td>Elective open abdominal aortic aneurysm repair.</td>
<td>64</td>
<td>Two cycles of intermittent cross-clamping of the common iliac artery with 10-min ischemia and 10-min reperfusion.</td>
<td>rIPC reduced the incidence of renal impairment, defined as peak serum creatinine level &gt;2.0 mg/dl (30% versus 7%; P=0.01).</td>
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<tr>
<td>Walsh et al. (2009)</td>
<td>Endovascular aneurysm repair.</td>
<td>40</td>
<td>Lower limb ischemia was used as the rIPC stimulus. After 10 min, the cuff was deflated, and the procedure was repeated on the other leg.</td>
<td>Reduction in urinary albumin/creatinine ratio and urinary retinol binding protein. No differences in the rates of renal impairment.</td>
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<tr>
<td>Walsh et al. (2010)</td>
<td>Elective open abdominal aortic aneurysm repair.</td>
<td>51</td>
<td>Right common iliac clamping for 10 min. After 10 min, the right iliac territory was reperfused and the clamp applied to the left common iliac artery for 10 min.</td>
<td>No statistically significant differences in renal outcome indices (median urinary retinol binding protein, albumin/creatinine ratios, serum creatinine, or GFR values).</td>
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<td>Rahman et al. (2010)</td>
<td>Elective cardiac surgery (CABG).</td>
<td>162</td>
<td>3×5-min cycles of upper-limb cuff inflation to 200 mmHg separated by 5-min periods of cuff deflation.</td>
<td>No significant differences in renal outcome indices (rates of dialysis, peak creatinine, and urinary albumin/creatinine ratio).</td>
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<td>Venugopal et al. (2010)</td>
<td>Elective cardiac surgery (CABG) in nondiabetic patients.</td>
<td>78</td>
<td>3×5-min cycles of right forearm ischemia, induced by inflating a BP cuff to 200 mmHg, after 5 min of reperfusion.</td>
<td>rIPC decreased the incidence of AKI (AKI stages 1, 2, and 3 in rIPC group were 3%, 8%, and 0% compared with 25%, 0%, and 0% in control group, respectively; P=0.01).</td>
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<tr>
<td>Zimmermann et al. (2011)</td>
<td>Elective cardiac surgery (CABG).</td>
<td>120</td>
<td>Thigh tourniquet consisting of 3×5-min intervals of ischemia separated by 5-min intervals of reperfusion.</td>
<td>rIPC decreased the rate of AKI compared with the control group (20% versus 47%; P=0.004).</td>
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<td>Choi et al. (2011)</td>
<td>Elective complex valvular heart surgery.</td>
<td>76</td>
<td>3×10-min cycles of lower limb ischemia and reperfusion with an automated cuff inflator.</td>
<td>No significant differences in serum levels of renal injury biomarkers or incidence of AKI.</td>
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<td>Pedersen et al. (2012)</td>
<td>Children undergoing surgery for complex congenital heart disease.</td>
<td>113</td>
<td>Intermittent leg ischemia through four cycles of 5-min BP cuff inflation to 40 mmHg above the systolic pressure and 5-min deflation.</td>
<td>No statistically significant differences in AKI incidence and levels of the renal biomarkers.</td>
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<tr>
<td>Er et al. (2012)</td>
<td>Elective coronary angiography in patients with impaired renal function.</td>
<td>100</td>
<td>Intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a BP cuff.</td>
<td>Decrease in CI-AKI by rIPC (40% control group versus 12% rIPC group; P=0.002) and the incidence of composite cardiovascular endpoint (death, hospitalization, or hemodialysis) (38% versus 16%; P=0.02).</td>
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<td>Deftereos et al. (2013)</td>
<td>Patients with NSTEMI undergoing PCI.</td>
<td>225</td>
<td>Remote ischemic postconditioning by cycles of inflation and deflation of the stent balloon during PCI.</td>
<td>rIPC decreased the rate of AKI (12.4% versus 29.5%; P=0.002) and reduced the 30-d mortality or rehospitalization for any cause (12.4% versus 22.3%; P=0.05) compared with the control group.</td>
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methodology, no relevant adverse events related to the rIPC application were described in the clinical studies performed to date. The inflation of the BP cuff may cause pain or a tingling sensation of the arm or leg, but this has never been so severe as to warrant abandoning the preconditioning protocol.

rIPC-mediated effects on the kidney have been extensively investigated in the setting of adult cardiac or vascular surgery. In a landmark study, rIPC-induced cardioprotection and renoprotection were evaluated in 82 adults undergoing abdominal aortic aneurysm repair.64 rIPC, induced by two cycles of intermittent cross-clamping of the common iliac artery, was associated with a 23% decrease in AKI (30% versus 7%; P=0.01). In addition, rIPC significantly reduced the incidence of myocardial infarction.

A separate study in the same clinical scenario, but with fewer patients (N=51) and a different type of rIPC stimulus (common iliac artery clamping), did not find statistically significant differences in renal outcome indices.65 In another randomized clinical trial, the same authors aimed to determine whether rIPC can reduce renal injury in a smaller number of patients (N=40) after endovascular aneurysm repair.66 rIPC was induced by sequential lower limb ischemia. Although there were no significant differences in the rates of renal impairment, rIPC reduced renal injury during procedure, as demonstrated by a reduction in postoperative urinary biomarker levels.

In a prospective randomized placebo-controlled trial (N=162), Rahman et al. tested whether rIPC improves myocardial or other end-organ protection after on-pump coronary surgery.67 Renal outcomes were among the secondary end points. The results showed that in patients undergoing multivessel coronary artery bypass graft (CABG) surgery, the incidence of AKI in those who received rIPC was similar to that of controls. However, this study was performed in anesthetized and, thus, patients were pain free. On the other hand, there is evidence from several experimental studies that pain may be a strong trigger of preconditioning,68 and rIPC is dependent on intact local neural pathways.69 In this context, cautious interpretation of these results is needed, warranting further rIPC efficacy studies in anesthetized versus nonanesthetized subgroups.

In 2010, another retrospective study of nondiabetic patients undergoing elective CABG surgery found that rIPC using transient ischemia of the forearm decreased the incidence of AKI.70 A total of 78 consented patients were randomly assigned to either rIPC (N=38) or control (N=40) groups before CABG surgery. Of 40 patients in the control group, 10 (25%) developed stage 1 AKI and none developed stage 2 or 3 AKI. In contrast, only 1 of 38 patients (3%) in the rIPC group developed stage 1 AKI, although 3 patients developed stage 2 AKI. The overall difference in AKI between the two groups was statistically significant (P=0.01). There was no difference in duration of hospital stay.

The study group was at lower risk of AKI than a standard cardiac surgery cohort, because patients with diabetes and established kidney failure were excluded from this study. Therefore, it is reasonable to hypothesize that any protective effect of rIPC on kidney function may be even more pronounced in a higher-risk cohort. Indeed, our group recently addressed the effects of rIPC in a high-risk patient populations in the RenPro trial.5

This study included 100 adults (mean age 73.2 years) with impaired renal function (serum creatinine >124 μmol/L and/or eGFR <60 ml/min per 1.73 m²; mean Mehran score 13) who underwent elective coronary angiography. Enrolled patients were randomly assigned to either control group (N=50) or to rIPC before cardiac intervention (N=50). The primary study outcome, CI-AKI (defined as a serum creatinine increase of >44 μmol/L or a relative increase of ≥25% from baseline within 48 hours after exposure to contrast medium), occurred in significantly fewer patients in the rIPC group than in the control group (12% versus 40%; P=0.002). No major adverse events related to the procedure were reported. Overall, there was a substantial decrease in the number of patients developing CI-AKI in individuals who received rIPC before coronary angiography, suggesting that rIPC was particularly renoprotective in high-risk patients.

Similar results were obtained in another study of lower limb preconditioning in patients undergoing elective CABG.71 The primary end point was AKI defined as an elevation of serum creatinine of ≥0.3 mg/dl or ≥50% within 48 hours after surgery. Sixty patients were randomized to rIPC or control groups. Significantly fewer patients in the rIPC group had AKI within 48 hours after surgery compared with the control group (20% versus 47%, P=0.004), reflecting an absolute risk reduction of 0.27 (95% confidence interval, 0.24–0.76) and a significantly reduced relative risk due to preconditioning of 0.43 (95% confidence interval, 0.10–0.42).

The effect of rIPC on renal impairment was also investigated in patients.
undergoing laparoscopic partial nephrectomy. The primary outcome was the absolute change in GFR of the affected kidney by renal scintigraphy from baseline to 6 months. rIPC, which consisted of three 5-minute cycles of right lower limb ischemia and 5 minutes of reperfusion during each cycle, was associated with the lower incidence of GFR reduction at 1 month after the procedure (8.8% versus 15% in the control group, \(P=0.03\)). However, no differences in the GFR change of the affected kidney or serum creatinine were observed at 6 months of follow-up.

Deftereos et al. recently provided additional evidence that remote ischemic postconditioning may also be effective in preventing acute kidney damage in intermediate-risk patients (mean Mehran risk score 10).\(^7\) The authors evaluated the renoprotective effect of remote ischemic postconditioning in patients with a non–ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention \((N=225)\).

In the intervention group, four 1-minute cycles were performed, each consisting of 30-second inflation of the stent balloon and 30-second deflation. The CI-AKI rate in the rIPC group was significantly lower than in the control group (12.4% versus 29.5%, \(P=0.002\)). Furthermore, the 30-day rate of death or rehospitalization for any cause was 22.3% in the control group versus 12.4% in rIPC patients \((P=0.05)\).

Some studies have failed to demonstrate a beneficial effect of rIPC on renal function. Thus, the trial of leg preconditioning in children undergoing surgery for complex congenital cardiac disease found no evidence that rIPC protected renal function.\(^7\) End points were AKI development, initiation of dialysis, plasma creatinine, eGFR, plasma cystatin C, plasma and urinary neutrophil gelatinase-associated lipocalin, and urinary output. Similar results were reported by another study on 76 patients undergoing complex valvular heart surgery.\(^7\) rIPC consisted of three 10-minute cycles of lower limb ischemia and reperfusion with an automated cuff inflator. Primary end points were comparisons of biomarkers of renal injury including serum creatinine, cystatin C and neutrophil gelatinase–associated lipocalin, and incidence of AKI. There were no significant differences in serum levels of renal markers or eGFR between the groups throughout the study period. The AKI incidences also did not differ between the groups, and none of the patients required hemodialysis. Despite the lack of a renal protective effect, rIPC was associated with a significantly lower creatinine kinase MB level at 24 hours after surgery and with a shorter stay in the intensive care unit compared with the control.

Strategies to attenuate ischemic-reperfusion injury are particularly important in transplantation medicine, given the high incidence of dialysis-requiring renal dysfunction in the setting of kidney transplantation and the easier applicability of the rIPC procedure in both organ donors and recipients on the other side. Despite experimental evidence demonstrating a decrease in renal allograft injury and improvement of allograft function, only one small-sized study thus far has evaluated the role of rIPC in human renal transplantation. rIPC, consisting of three 5-minute cycles of leg ischemia and 5 minutes of reperfusion in donors or recipients, failed to improve early renal function in patients receiving living-donor renal transplantation.\(^7\) One possible explanation for inefficiency of the procedure might be a unilaterally performed rIPC stimulus in donors or recipients. Conversely, simultaneously applying rIPC in both donors and recipients may yield different results and should be addressed in future trials in solid organ transplantation.

Overall, particularly in view of the latest published reports, it seems that rIPC is beneficial in patients at intermediate or high risk, whereas no significant renoprotective effect is detectable in patients at low risk or patients with absent renal impairment. However, further studies are necessary to establish the therapeutic value of rIPC in the clinical setting.

**FUTURE DIRECTIONS**

Since the first evidence of rIPC was reported almost 20 years ago, this simple procedure has been the focus of extensive experimental and clinical research. However, the exact mode of communication between the site of the ischemia application and the target tissue remains unknown. Several cellular, neurogenic, and humoral pathways have been proposed to be the candidate mechanisms involved as a complex cascade in transduction of the preconditioning stimulus with overlap between various signaling pathways.

Nevertheless, substantial work has been done that expanded the paradigm of rIPC beyond the initial observation of intracardiac protection and yielded novel insights into both the spatial and temporal characteristics of this phenomenon. With regard to the kidney, several recently published proof-of-concept clinical studies have reported encouraging results. The results of some other clinical studies, however, have been disappointing for a number of reasons. Thus, different stimuli protocols in terms of the number, duration, and timing of cycles as well as the heterogenous patient population (high versus low risk) may explain discrepant results obtained in clinical studies. Furthermore, additional studies are needed to elucidate the optimal choice of application site (e.g., arm versus leg versus internal organs such as the intestine or kidney). Large multicenter randomized clinical trials are now underway to investigate the effect of rIPC on clinical outcomes in patients with renal impairment, and to prove that rIPC, a type of “distant healing,” may indeed be a new renoprotective strategy.

**DISCLOSURES**

None.

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