Ischemic Conditioning Protects the Uremic Heart in a Rodent Model of Myocardial Infarction

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Background—Outcomes after acute myocardial infarction in patients with chronic kidney disease are extremely poor. Ischemic conditioning techniques are among the most powerful cytoprotective strategies discovered to date. However, experimental data suggest that comorbidity may attenuate the protective effects of ischemic conditioning.

Methods and Results—We conducted investigations into the effects of chronic uremia on myocardial infarct size and the protective effects of ischemic preconditioning (IPC), remote ischemic preconditioning, and ischemic postconditioning in 2 rodent models of chronic uremia. In addition, a limited investigation into the signaling mechanisms involved in cardioprotection after IPC was performed in both uremic and nonuremic animals. Myocardial infarct size was increased in uremic animals, but all 3 conditioning strategies (IPC, remote IPC, ischemic postconditioning) proved highly efficacious in reducing myocardial infarct size (relative reduction, 86%, 39%, and 65% [P<0.005, P<0.05, and P<0.05], respectively). Moreover, some protocols (IPC and ischemic postconditioning) appeared to be more effective in uremic than in sham (nonuremic) animals. Analysis of the signaling mechanisms revealed that components of both the reperfusion injury salvage kinase and survivor activating factor enhancement pathways were similarly upregulated in both uremic and nonuremic animals after an IPC stimulus.

Conclusion—Conditioning strategies may present the best opportunity to improve outcomes for patients with chronic kidney disease after an acute coronary syndrome. (Circulation. 2012;125:1256-1265.)

Key Words: ischemia ■ ischemic postconditioning ■ ischemic preconditioning ■ myocardial infarction ■ renal insufficiency

Cardiovascular disease is the leading cause of death for patients with moderate to severe chronic kidney disease (CKD; stages 3–5), and remains among the commonest causes of death for recipients of renal allografts. Although most cardiovascular deaths are due to heart failure or sudden cardiac death, the rate of acute myocardial infarction (AMI) among patients with CKD is more than twice that of patients without CKD. Patients with an eGFR ≤60 ml/min/1.73 m² make up between a quarter to nearly one third of patients presenting with an acute coronary syndrome. Despite making up a sizeable proportion of patients presenting with both ST-segment–elevation and non–ST-segment–elevation myocardial infarction, these patients are routinely excluded from clinical trials, resulting in a dearth of prospective data on which to base clinical practice guidelines. A consistent feature of observational studies has been the recognition that patients with CKD are less likely to receive reperfusion or revascularization therapies. The underuse of such treatments, so-called therapeutic nihilism, was thought to explain much of the excess mortality seen after AMI in patients with impaired renal function; indeed, this maybe a contributing factor. However, emerging data from a number of registry studies suggest that, even when they are optimally treated, outcomes for patients with CKD receiving primary percutaneous coronary intervention (PCI) for AMI remain poor. Even those patients with relatively mild CKD (stage 3;
estimated glomerular filtration rate, 30–59 mL/min) have roughly 7 times the rate of in-hospital mortality as patients without CKD.7 Furthermore, reperfusion therapy seems to have little impact on in-hospital mortality for patients with CKD, and PCI for those with the most severe degrees of renal dysfunction may actually be harmful.8,11 However, in recipients of reperfusion therapy who survive to hospital discharge, the long-term prognosis appears to be improved by primary PCI and early revascularization.4 Additionally, in patients with stable coronary artery disease, PCI does not improve outcomes for patients with mild CKD over optimal medical management.12 The factors determining outcomes for patients with CKD remain largely unstudied.

The cause of the excess mortality seen in patients with CKD after AMI is likely to be multifactorial. Individuals with CKD are at increased risk of bleeding, and several studies have highlighted the risk of increased hemorrhagic complications after PCI associated with CKD.13 However, even when bleeding episodes are corrected for, the outcome for patients with CKD remains significantly worse,14 suggesting that additional factors specific to patients with impaired renal function may be of importance. Patients with CKD are significantly more likely to experience postinfarction heart failure and cardiac arrest.15

Discovered by Murry and colleagues16 in 1986, ischemic preconditioning (IPC) describes the phenomenon whereby a brief episode or episodes of “sublethal” ischemia (ie, of insufficient duration to result in tissue damage) followed by reperfusion confer resistance to a subsequent, more prolonged or lethal episode of ischemia/reperfusion. Subsequently, Przyklenk et al17 reported that vascular beds adjacent to the preconditioned territory were also rendered resistant to ischemia reperfusion injury. It was later determined that this cytoprotective effect was also seen between organs, and the term remote IPC (RIPC) was coined to describe this phenomenon. In 2003, Zhao et al18 extended the scope of conditioning when they discovered ischemic postconditioning (iPost). By interrupting reperfusion with three 30-second episodes of ischemia, they were able to achieve a substantial reduction in myocardial infarct size.

IPC, RIPC, and iPost, which we refer to together as conditioning strategies, are arguably the most powerful cardioprotective therapies yet discovered and may be considered benchmarks against which to determine the relative efficacy of potential drug therapies. Data from both animal models and small-scale human studies suggest that the effect of conditioning may be attenuated by diabetes mellitus18–20 and senescence21,22 as result of perturbations in the signal transduction mechanism.23 However, the effect of uremia on the response to conditioning stimuli is unknown.

We conducted a series of experiments to investigate the effects of chronic renal failure on the efficacy of a variety of conditioning protocols.

Models of Chronic Uremia

Subtotal Nephrectomy

Animals first underwent a 2-stage subtotal nephrectomy (SNx) or a sham procedure in a manner similar to that previously described.24–26 In brief, animals were anesthetized with isoflurane (Animalcare, York, UK) and nitrous oxide (BOC, UK) with analgesia (buprenorphine, Reckitt Benckiser Healthcare UK Ltd, Hull, UK; 0.04 mg/kg). Via a flank incision, the left kidney was decapsulated and approximately two thirds resected. Hemostasis was achieved with direct compression, after which the kidney was returned to the retroperitoneal space. Before closure, 0.5 mL saline was instilled into the peritoneal cavity. The incision was closed in layers with 4–0 vicryl for the muscle layers and surgical clips (Precise Vista 3M, Bracknell, UK) for the skin. The animals were allowed 14 days to recover before undergoing the second stage of the procedure, right total nephrectomy, which was performed via a flank incision as above. Sham animals had the appropriate kidney decapsulated only. Creation of SNx animals was carried out by a single operator to reduce variability in serum creatinine.

The animals were allowed 4 weeks after the second stage (right total nephrectomy) to recover and to develop the uremic phenotype before undergoing myocardial ischemia/reperfusion.

Adenine Diet

After a week of acclimatization, a diet containing 0.75% (by weight) adenine (AD; Special Diet Services, Essex, UK) was fed to 6-week-old male Wistar rats for 4 weeks, as described previously by Yokozawa et al.27 At the end of the 4 weeks, the animals had developed a marked degree of uremia and were used for left anterior descending artery ligation experiments. A control group was fed normal chow for 4 weeks.

Myocardial Ischemia/Reperfusion

Myocardial ischemia/reperfusion was carried out in a manner similar to that described previously.28 Animals were anesthetized with an intraperitoneal injection of sodium thiopental (73 mg/kg for SNx animals, 88 mg/kg for sham animals; LINK Pharmaceuticals, Har- sham, UK); a tracheostomy was performed; and an arterial line to monitor pulse and blood pressure was inserted into the right carotid artery. Another line was inserted into the right jugular vein to administer maintenance anesthesia and fluids.

The animals were ventilated with small-animal ventilator (Harvard Apparatus, Kent, UK). Ventilatory parameters were adjusted in response to arterial blood gas analysis (ABL77, Radiometer Ltd, Crawley, UK). A left parasternal incision was performed with electrocautery (PromhoVet, Barcelona, Spain); the ribs and thymus were retracted; and the pericardium was resected. A 6-0 silk suture was placed through the myocardium at the approximate level of the left anterior descending artery. A piece of polythene tubing (Portex, Smiths Medical, Watford, UK), flared at 1 end, was placed over the free ends of the suture to form a snare.

Determination of Infarct Size

As previously described,28 at the end of reperfusion, the left anterior descending artery was reoccluded, and Evans blue dye was injected via the right jugular vein to delineate the area at risk. The heart was excised and immersed in ice-cold 0.9% saline to achieve cardioplegia and then sliced in transverse sections to the level of the suture. The right ventricle was dissected from the left, and then the blue perfused portion of the left ventricle was separated from the undyed area at risk. The 2 portions of tissue were weighed, the ratio indicating the proportion of the left ventricle that was at risk. The tissue from the ischemic zone was then diced into small pieces (~1 mm3) and incubated in nitro blue tetrazolium (0.5 mg/mL) for 30 minutes. Nitro blue tetrazolium is reduced to a dark blue/purple azole in the presence of reducing compounds, enabling the necrotic tissue to be distinguished from viable tissue. The tissue was divided into 2 aliquots based on the presence of purple staining. Infarct size was given by the ratio of the weights of these 2 quantities of myocardium.

Methods

All experiments were approved by our institutional ethics committee and performed under license granted by The Home Office (United Kingdom) in accordance with the Animals (Scientific Procedures) Act 1986. Male Wistar rats were used for all experiments (Charles River Laboratories UK, Margate, UK).
Cardiac Troponin I Assay

A cardiac-specific rat troponin I ELISA (Life Diagnositics, West Chester, PA) was used. Blood was drawn into a heparinized syringe after 2 hours of reperfusion. The blood was immediately separated in a centrifuge; the plasma was aspirated and snap-frozen in liquid nitrogen before being stored at \(-80^\circ\)C until assayed. The assay was performed in accordance with the manufacturer’s instructions with the only modification being a 1:8 dilution of the plasma samples performed with the standard diluent contained in the kit. A further 1:4 dilution was performed with plasma diluent, as specified in the manufacturer’s instructions, giving a final dilution of 1:32. This was done to maintain the optical density within the range of the standard curve.

Conditioning Protocols

Ischemic Preconditioning

One or 3 cycles of 5 minutes of left anterior descending artery occlusion (ischemia) were followed by 5 minutes of reperfusion before either 25 minutes (standard) or 35 minutes of sustained ischemia (threshold experiment; see Figure 1).

Remote Preconditioning

The left femoral artery was carefully dissected out and separated from the femoral vein and nerve. A ligature was placed around the artery to assist in mobilization. A microvessel clip was used to...
occlude the artery. Pallor and a reduction in the temperature of the paw confirmed occlusion. Reperfusion was confirmed by hyperemia followed by restoration of normal color and temperature. Three cycles of 5 minutes of ischemia followed by 5 minutes of reperfusion were used.

**Postconditioning**

Left anterior descending artery occlusion (ischemia) for 25 minutes with 5 cycles of 10 seconds of reperfusion/10 seconds of ischemia on reperfusion was followed by an 1 hour 58 minutes 20 seconds of reperfusion (ie, 2 hours of reperfusion in total). At the end of the final reperfusion period, the animals were euthanized, and their hearts were harvested for determination of infarct size.

**Immunoblotting and Protein Extraction**

Hearts from sham-operated or uremic animals subjected to the IPC protocol detailed above were excised, washed once in ice-cold PBS, snap-frozen in liquid N\textsubscript{2}, and stored at \(-80^\circ\)C until further use. A total of 20 rats (10 SNx, 10 sham-operated controls) split into 4 groups of 5 were used to study the response to a preconditioning stimulus in the subtotal nephrectomy model. Another 15 rats were used to investigate signal transduction in the AD model (8 control animals split into 2 groups of 4 and 7 AD animals, 3 of which were preconditioned).

Tissues for western blot were triturated with a mortar and pestle under liquid N\textsubscript{2} and subsequently polytron homogenized (30-second bursts with 1-minute intervals on ice 3 times) in a mammalian protein extraction buffer (GE Healthcare; 10:1 vol/wt) supplemented with the following inhibitors: 1 mmol/L EDTA, 0.5 mmol/L DTT, 1% vol/vol protease inhibitor cocktail (Sigma), 1 mmol/L NaF, 5 μmol/L leupeptin (Calbiochem), 1 mmol/L Na\textsubscript{3}VO\textsubscript{4}, and 1% vol/vol phosphatase inhibitor cocktails I and III (Sigma). The tissue homogenate was incubated for 10 minutes on ice and then centrifuged at 5000 g for 10 minutes at 4°C. The supernatant was divided into aliquots and stored at \(-80^\circ\)C until further use. Protein concentrations were determined with the bicinchoninic acid assay (Pierce) with BSA (Sigma) as the protein standard.

**Statistical Analysis**

Data were analyzed with GraphPad Prism software (San Diego, CA). Given the relatively small sample size in some of the experiments, nonparametric statistical analysis was used when possible, and the data are presented as median with interquartile range (IQR). Two-way ANOVA with Bonferroni posttest comparison was used to analyze the results of experiments with a 2×2 factorial design (immunoblot studies, RIPC, and iPost); a 2-tailed Mann-Whitney U test was used to test for significance in all other experiments.

**Results**

**Determination of Myocardial Infarct Size in Uremic Animals: Reduced Ischemia Tolerance?**

In our first series of experiments, we sought to replicate previously published data suggesting that uremic animals sustain larger myocardial infarctions than nonuremic sham-operated controls.\textsuperscript{31} We were able to demonstrate a modest but statistically significant increase in myocardial infarct size in uremic rats compared with sham animals (sham, 47.2% [IQR, 39.8%–63.7%] versus SNx, 62.3% [IQR, 53.5%–69.5%]; relative increase, 32%; \(P=0.03\); Figure 2). The increase in infarct size was remarkably similar to that
reported by Dikow and colleagues (33% relative increase in infarct size). The area at risk was similar for both groups (sham, 50.9% [IQR, 43.5%–56.2%] versus SNx, 44.8% [IQR, 42.2%–51.4%]; P = 0.24).

Uremic (SNx) animals had a median serum creatinine that was roughly 3 times that of the sham animals (91 μmol/L [IQR, 83.7–116 μmol/L] versus 34.4 μmol/L [IQR, 33.4–35.7 μmol/L]) and were significantly more anemic (SNx hematocrit, 27% [IQR, 24% to 31%] versus sham, 39% [IQR, 36.3% to 41%]; P = 0.0003).

**IPC of Uremic Animals**

Using a preconditioning protocol consisting of 3 cycles of 5 minutes of ischemia and 5 minutes of reperfusion, we were able to achieve significant myocardial protection with an absolute reduction in infarct size of 50% (control, 61.2% [IQR, 54.2%–70.5%] versus IPC, 7.7% [IQR, 6% to 10%]; relative reduction [RR], 86%; P = 0.002; Figure 3A); the area at risk was similar between the 2 groups (control, 44.4% [IQR, 41.3%–49.5%] versus IPC, 42.2% [IQR, 37.5%–47.3%]; P = 0.447), as was serum creatinine (control, 3.7 μmol/L [IQR, 3.4–4.0 μmol/L] versus IPC, 3.6 μmol/L [IQR, 3.4–3.8 μmol/L]; P = 0.211).

Using the same protocol, we performed an additional experiment (Figure 3B) with an alternative model of chronic uremia (AD). These animals have significantly greater renal dysfunction (median serum creatinine 8 fold higher than in controls and 3-fold greater in SNx than sham animals). However, we still observed an RR in median infarct size of 50% (median infarct size, 50.6% [IQR, 34.9%–75.8%] in control animals versus 29.4% [IQR, 7.7%–32.1%] in the IPC group; P = 0.014).

**Threshold for IPC in Uremic Animals**

Having established convincingly that uremic animals could be preconditioned, we sought to determine whether there was an increase in the threshold for eliciting cytoprotection with IPC in uremic animals. Because nearly maximal protection was seen with 1 cycle of IPC and 25 minutes of sustained ischemia, we increased the period of sustained ischemia to 35 minutes for this series of experiments.

In contrast to diabetic and senescent animals, far from seeing a blunting of the effect of a single cycle of preconditioning in uremic animals, we demonstrated a significant reduction in the infarct size of uremic (SNx) animals receiving 1 cycle of IPC compared with nonuremic (sham) animals receiving a single cycle of IPC (median, 18.1% [IQR, 14.8%–21.5%] versus 32.1% [IQR, 22.9–46.6%], respectively; P = 0.02; Figure 3C).

**Remote Preconditioning**

RIPC markedly attenuated myocardial ischemia/reperfusion injury (P < 0.0001, 2-way ANOVA). The absolute reduction in infarct size achieved with RIPC was comparable between
the 2 groups (sham, 32.3% [P<0.001] versus SNx, 30.9% [P<0.0001], Bonferroni multiple comparison). However, the RR in infarct size was substantially but not significantly greater in nonuremic sham-operated rats (59.3% RR in sham versus 48.3% RR in SNx; P=0.328, Mann-Whitney; see Figure 4). There was a trend toward an increased infarct size in uremic animals that was of borderline statistical significance (P=0.062). No interaction between uremia and RIPC was demonstrated (P=0.572, 2-way ANOVA).

Ischemic Postconditioning
A postconditioning protocol consisting of 5 cycles of 10 seconds of reperfusion and 10 seconds of ischemia begun after a 25-minute episode of sustained ischemia was used (see Figure 5). As with all other conditioning protocols, a substantial and statistically significant reduction in myocardial infarct size was observed (47% RR for nonuremic animals, 65% RR for SNx animals; P=0.0014, 2-way ANOVA). No evidence of an interaction was seen between renal function and response to iPost; ie, iPost had an equivalent effect on infarct size reduction regardless of the presence of uremia. Although uremic animals had a greater RR in infarct size, this was not statistically significant (Mann-Whitney). The area at risk was similar for all groups.

These results were mirrored by a reduction in the levels of cardiac troponin I in postconditioned animals (P=0.0043, 2-way ANOVA; see Figure 5D). No interaction was observed (P=0.7312).

Western Blots
In light of previous reports of altered signal transduction associated with comorbidity and senescence, a limited study of signaling mechanisms was undertaken in both the SNx and AD models. A marked increase in both phosphorylated STAT3 (SNx, P=0.001; AD, P=0.02) and ERK1/2 (SNx) was consistently demonstrated after 3 cycles (5 minutes of ischemia, 5 minutes of reperfusion) of IPC (see Figures 6 and 7). The increase in phospho-STAT3 and phospho-ERK1/2 was similar in uremic and nonuremic animals (SNx, P=0.034; AD, P=0.002). However, we were unable to demonstrate a consistent result with respect to the phosphorylation of Akt in response to the preconditioning protocol.

Discussion
These data represent a comprehensive assessment of the effects of chronic uremia on ischemic conditioning and demonstrate that, unlike in diabetic, dyslipidemic, and senescent animals, chronic uremia does not appear to attenuate the effect of IPC, RIPC, or iPost. Indeed uremic animals appear to derive greater protection than nonuremic animals from protocols that involve manipulating the blood supply of the target organ directly (ie, IPC and iPost). In the context of chronic uremia, the IPC signal appears to be conducted through the same pathways.

Furthermore, we confirm the previously published observation of increased myocardial infarct size in uremic an-
Larger myocardial infarctions may in part explain the greater mortality, particularly the increased incidence of heart failure, seen in patients with CKD after AMI. Left ventricular hypertrophy is a key feature of the uremic cardiac phenotype and is extremely common in individuals with end-stage renal disease and experimental models of uremia. However, in contrast to patients with left ventricular hypertrophy with normal renal function, left ventricular hypertrophy occurring in the context of uremia appears to result in a greater degree of intermyocyte fibrosis and capillary rarefaction. Thus, there is the potential for a simultaneous increase in oxygen demand (as a result of myocyte hypertrophy) and reduction in oxygen delivery consequent to reduced capillary density and increased oxygen diffusion distance. The cardiomyocyte in the uremic heart is thus closer to the brink of ischemia.

The reduction in infarct size for uremic animals subjected to IPC was significantly greater than in nonuremic animals subjected to IPC, and a substantial difference of borderline statistical significance was seen in animals that received iPost. These observations might be the result of a type 2 error. However, it should also be noted that there was a nonsignificant trend toward a smaller area at risk in the SNx animals that received a single cycle of preconditioning. Alternatively, it is possible that, as a result of a lower hematocrit, the uremic animals had less no reflow, and thus the combination of either IPC or iPost and more extensive reperfusion resulted in even smaller infarcts in these animals compared with the less anemic sham-operated (nonuremic) animals. It is interesting to compare these results with those of Gritsopoulos et al., who found that remote postconditioning was a more potent cytoprotective strategy than classic postconditioning, suggesting that further direct interference with the dependent vascular bed, which had experienced the index ischemic episode, was not entirely without consequence.

Given that aging, diabetes mellitus, and a variety of other metabolic disturbances have been acknowledged to reduce the efficacy of conditioning in both animal and human models, it is somewhat surprising that renal dysfunction does not appear to have a similar effect. We examined the effect of IPC in 2 different models of chronic uremia, the subtotal

Figure 6. Immunoblots for phosphorylated (p) ERK, total (tot) ERK, pSTAT3, and tot-STAT3. A, Representative immunoblot. B, A significant increase in pERK was seen in both uremic and nonuremic animals after 3 cycles of ischemic preconditioning (IPC; *P=0.034). C, No differences in total ERK levels were seen in either uremic or nonuremic animals. D, The ratio of pERK to tot-ERK was significantly increased after IPC but did not differ in magnitude between uremic and nonuremic animals (P=0.013) E, Levels of pSTAT3 were significantly increased by IPC (**P=0.0014). F, There was no significant difference between the 4 groups in the levels of total STAT3. G, The ratio of p-STAT3 to tot-STAT3 was significantly increased after IPC but did not differ between uremic and nonuremic animals (**P=0.0001). Bar charts show mean with SEM (n=5 for each group).
nephrectomy (SNx) model, the most commonly used model to study the pathophysiology of the uremic state, and AD-induced uremia. In our hands, SNx animals are typically hypertensive with left ventricular hypertrophy and have more significant anemia compared with those animals with renal dysfunction induced by AD. However, animals with AD may be considered more uremic in that the median serum creatinine is \( \approx 8 \) times that of controls, whereas the median serum creatinine is \( \approx 3 \)-fold greater in SNx animals. Despite this apparent disparity in the degree of renal dysfunction, the infarcts in AD animals that received preconditioning were nearly 50% smaller. We believe that this agreement in results obtained from experiments with these 2 different models is mutually supportive.

In addition, we have provided evidence that 3 cycles of IPC (5 minutes of ischemia, 5 minutes of reperfusion) are associated with a robust and reproducible increase in phospho-Stat3 and phospho-ERK1/2 representing key components of the 2 putative signal transduction mechanisms: the reperfusion injury salvage kinase (RISK) pathway and the survivor activating factor enhancement (SAFE) pathway.

IPC is thought to be triggered by a number of factors, including adenosine, bradykinin, and endogenous opioids. Two major intracellular signaling cascades have been proposed as mediators of the preconditioning stimulus, the RISK pathway and the SAFE pathway. In addition, both these pathways have been implicated in mediating the infarct size-limiting effects of iPost.

The RISK pathway is considered to consist of 2 arms, 1 arm involving MEK1/2 and ERK1/2 and the other involving PI3 kinase and Akt. Both arms are thought to be triggered by the binding of specific ligands with G-protein–coupled receptors and terminate on glycogen synthase kinase-3-\( \beta \) to reduce the likelihood of mitochondrial permeability transition pore opening and thus attenuate reperfusion injury.39

The SAFE pathway was first identified as the mediator of cardioprotection induced by tumor necrosis factor-\( \alpha \).40 However, JAK/Stat signaling, which is at the heart of the SAFE pathway, is now recognized to be important in the transduction of a number of other infarct size–limiting therapies and has been implicated in IPC (both the early and late phases41), iPost,42 and RIPC. As with the RISK pathway, it is thought that inhibition of the mitochondrial permeability transition pore is the end effector of this pathway.

It has been nearly a quarter of a century since Murry and colleagues16 made their seminal discovery of IPC, but despite the widespread acknowledgement that ischemic conditioning represents the most powerful cytoprotective strategy yet discovered with overwhelming animal data to attest to the benefit of conditioning, it has failed to gain acceptance within the broader medical community or to be adopted into routine clinical practice. This is possibly due to a perceived comparative lack of efficacy of conditioning in humans. Human trials conducted to date have mostly been small scale, usually from a single center, with limited follow-up and thus have been underpowered to demonstrate mortality differences. They have therefore used surrogate outcome measures such as the magnitude of rise in biomarkers of cardiac ischemia.43
Animal models that evaluate cytoprotective strategies usually use healthy, juvenile animals. This is in marked contrast to human disease, which rarely occurs in the absence of comorbidities. Such comorbid conditions may influence the efficacy of experimental treatments. Furthermore, animal studies typically compare treated with untreated animals, whereas in clinical trials, a new treatment in addition to existing therapy is compared with existing therapy alone. Renal dysfunction is a common comorbidity in those presenting with AMI and engenders an adverse prognosis. It may also modulate the risk-benefit relationship for existing therapies. The fundamental purpose of our studies was to examine the effect of impaired renal function on conditioning strategies.

It has been suggested that reperfusion therapy alone is sufficient to maximally limit infarct size for the majority of strategies. The effect was most marked for those with the largest area at risk. For a given area at risk, patients who received remote ischemic conditioning had a smaller infarct. This effect may also modulate the risk-benefit relationship for existing therapies. Therefore, we would envisage that post-AMI outcome might be improved for patients with CKD by the addition of a conditioning strategy to early reperfusion.

The higher event rate seen in patients with CKD and end-stage renal disease could in theory allow trials sufficiently powered to detect differences in mortality to be conducted with a smaller sample size. It would be desirable to corroborate our findings in human subjects with CKD and end-stage renal disease.

Conclusions

We report for the first time that conditioning strategies provide powerful cardioprotection in the setting of experimental uremia. There is an urgent and at present unmet need to improve outcomes for patients with CKD suffering from AMI. The routine exclusion of individuals with impaired renal function from clinical trials impedes the advancement of the care of these patients. Patients with CKD may derive benefit from conditioning strategies over and above that seen in patients without CKD.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Ischemic conditioning encompasses a number of established experimental techniques that provide powerful protection for an organ or vascular bed against ischemia/reperfusion injury. However, by and large, clinical trials have not delivered on the promise of preclinical studies undertaken in animals. A number of comorbid conditions such as diabetes mellitus and dyslipidemia have been demonstrated in animal models to attenuate the efficacy of ischemic conditioning. Up to one third of patients presenting with an acute coronary syndrome have chronic kidney disease. These patients have a particularly poor prognosis after acute myocardial infarction that has not been improved by enhanced reperfusion rates. Moreover, patients with chronic kidney disease are frequently excluded from clinical trials. The present study demonstrates that renal dysfunction per se is not a barrier to achieving substantial myocardial protection with ischemic preconditioning, remote ischemic preconditioning, and ischemic postconditioning. The survival pathways thought to be important in transducing the protective effect of ischemic preconditioning, remote ischemic preconditioning, and ischemic postconditioning appear to be preserved and activated to the same degree in 2 different models of experimental renal failure. This study provides the preclinical data to justify the inclusion of patients with chronic kidney disease in future clinical trials of ischemic conditioning as adjuvant therapy to reperfusion in the setting of acute myocardial infarction.
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