CHAPTER 53

Remote Ischemic Preconditioning

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OBJECTIVES

This chapter will:

1. Review the history and development of ischemic preconditioning.
2. Discuss the potential mechanisms of remote ischemic preconditioning.
3. Review preclinical and clinical studies examining the use remote ischemic preconditioning to protect against acute kidney injury.

Ischemic preconditioning refers to the protective response elicited by brief ischemia to a later, more sustained ischemic insult and the additional injury that can occur with reperfusion. The most commonly cited early experiments involving ischemic preconditioning were done by Murray et al. in 1986.[1] Their preconditioning procedure involved tying off the left circumflex coronary artery in dogs and inducing four 5-minute episodes of ischemia followed by reperfusion. The protocol of ischemia and reperfusion led to significant protection against myocardial necrosis during a subsequent prolonged period of ischemia. There was a 75% decrease in infarct size in the dogs that received the preconditioning regimen when compared with a control group of dogs.[1] In addition, around this time, investigations demonstrating the beneficial effect of ischemic preconditioning on the kidney and other organs were emerging as well. In 1985 Zager et al.[2] reported improved renal function in rats that received 15 minutes of bilateral renal artery occlusion as a preconditioning protocol followed by a second, more prolonged ischemic insult 30 minutes later when compared with a control group of rats that did not receive the preconditioning protocol.

Remote ischemic preconditioning (RIPC), whereby preconditioning by ischemia occurs at remote site, was later described in 1993 by Przyklenk et al.[3] They demonstrated that the occlusion of the circumflex artery in dogs could protect the myocardium supplied by the anterior descending coronary artery. After a 1-hour sustained episode of left anterior artery occlusion, the average infarct sizes when measured with triphenyltetrazolium staining were significantly less in the animals that had received prior episodes of circumflex artery occlusion followed by reperfusion when compared with a control group.[3] Subsequently in rabbits, ischemia to a lower limb by partially occluding the femoral artery and electrically stimulating the gastrocnemius muscle resulted in a 65% reduction in the ratio of infarct size to risk zone after 30 minutes of coronary artery blockage and four hours of reperfusion.[4]

The use of RIPC by inducing brief episodes of ischemia and reperfusion at a distant site to evoke protection to a target organ has important implications for critical care nephrology. Although the first published report of RIPC occurred more than 20 years ago, its use is not routine in nephrology or critical care medicine. This chapter reviews the most recent hypothesized mechanisms of RIPC and discusses the potential benefits of RIPC for acute kidney injury (AKI), contrast-induced AKI, and renal transplantation by summarizing the clinical studies done thus far. In addition, the potential future directions for RIPC will be discussed.

POTENTIAL MECHANISMS OF PROTECTION

The exact mechanisms of RIPC are complicated and yet to be fully determined. There are proposed processes, including a humoral trigger, a neural trigger, or possibly an overlap of both mechanisms that may explain the signal transduction that occurs from a remote tissue to a target organ. Dickson et al.[5] provides evidence of the involvement of a humoral pathway in transfer of the preconditioning stimulus. Effluent was collected during ischemia-reperfusion from donor preconditioned hearts and normal perfusion from control hearts.[5] Subsequently, the effluent was transferred to acceptor preconditioned and acceptor control hearts. All hearts then were exposed to a 40-minute period of ischemia.[5] The infarct size was found to be smaller in the acceptor and donor preconditioned hearts with an increase in adenosine and norepinephrine in the effluent of the donor preconditioned hearts.[5] Hormonal mediators that have been studied include opioids,[6] adenosine,[7] catecholamines,[8] and bradykinins.[9]

Based on observations seen in a study on patients undergoing RIPC before cardiac surgery that will be discussed later in this chapter, another possible humoral mechanism of RIPC has been proposed.[10] Specifically, renal

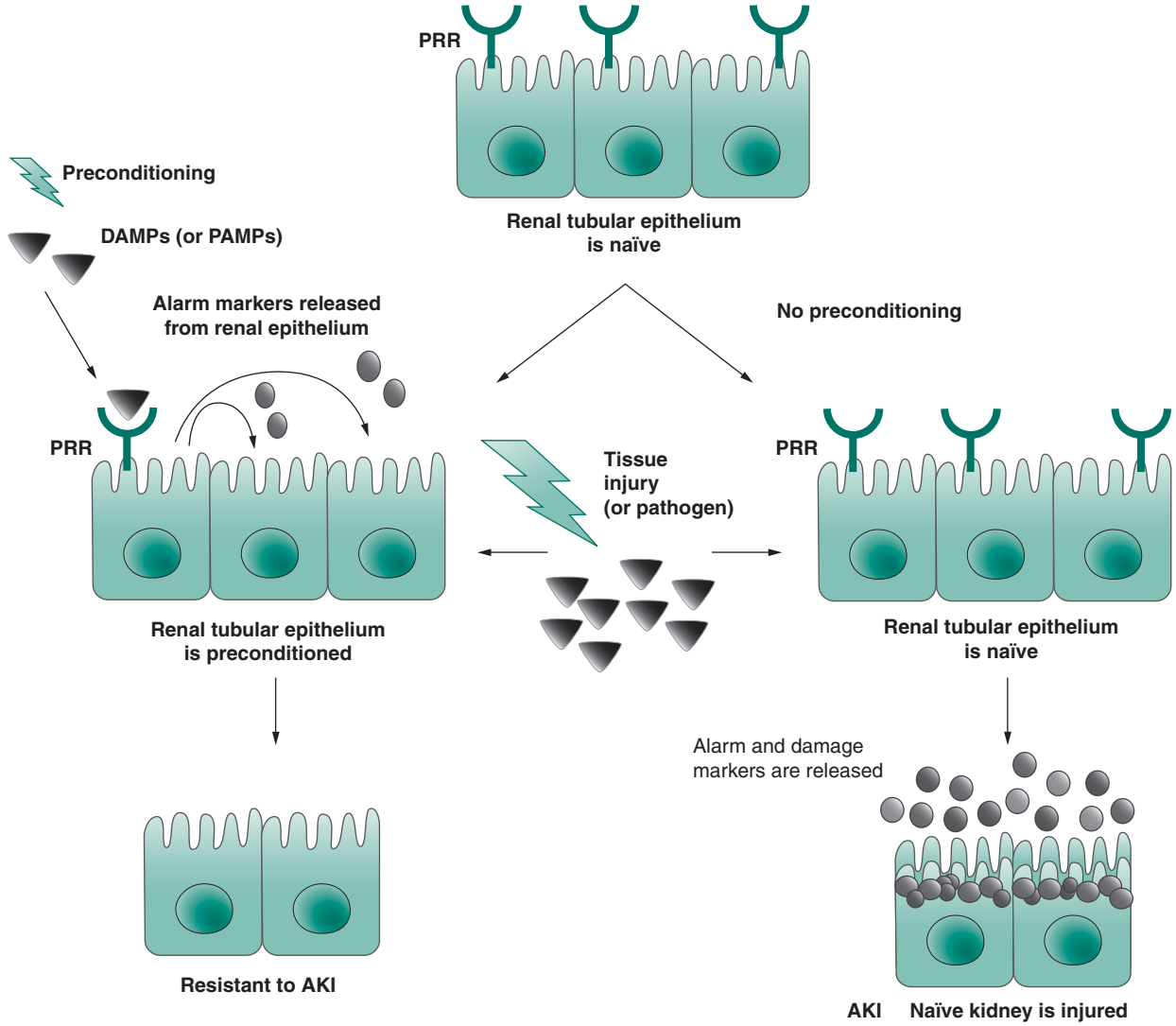

FIGURE 53.1 A potential mechanism by which remote ischemic preconditioning (RIPC) confers protection against acute kidney injury (AKI). In response to RIPC, damage-associated molecular patterns (DAMPs) or pathogen-associated molecular pattern molecules (PAMPs) bind to pattern recognition receptors (PRRs). Alarm markers such as insulin-like growth factor-binding protein 7 and metalloproteinase-2 are released and the renal tubular epithelium is preconditioned. There is resulting resistance to AKI from a later exposure to tissue injury or a pathogen in the preconditioned renal tubular epithelium. (From Zarbock A, Kellum JA. Remote ischemic preconditioning and protection of the kidney—a novel therapeutic option. *Crit Care Med*. 2015; used with permission.)

protection by RIPC may be mediated through the release of damage-associated molecular patterns (DAMPs) that are released from a remote tissue (Fig. 53.1).[11] High-mobility group box protein-1 (HMGB1), a prototypical DAMP, was measured in the urine at baseline and after RIPC in patients at very high risk for AKI before cardiac surgery.[10] A lower risk of AKI was associated with higher levels of HMGB1 in the urine immediately after RIPC (OR 0.75, CI 0.35–0.94, $p = .03$).[10] This suggests that DAMPs, after release from a remote tissue, are filtered by the kidney and subsequently bind to pattern recognition receptors (PRRs) on the surface of renal epithelial cells, potentially initiating protective mechanisms such as cell cycle arrest.[11]

The involvement of a neural pathway in signal transduction from a remote tissue to a target organ has been investigated as well. In support of this mechanism, Gho et al.[12] observed that pretreatment with the ganglion blocker hexamethonium abolished remote cardioprotection in rats receiving 15 minutes of mesenteric artery occlusion. More recently, in rabbits, vagal nerve ligation and atropine administration negated RIPC-induced reduction in myocardial infarct size.[13]

Several signaling pathways merge at protein kinases, which have generated considerable interest as key mediators in the protection from kidney injury.[14] Armstrong et al. were the first to identify protein kinase C as a possible mediator of protection in RIPC.[15] The authors demonstrated that calphostin, a selective protein kinase C blocker, negated the protective effect of preconditioning on rabbit cardiac myocytes.[15] Additional protein kinases that also are thought to be key molecular mediators in ischemia-induced protection include protein kinase G and protein kinase A.[14] Numerous proposed signaling pathways ultimately are thought to act on the mitochondria, leading to a closure of the mitochondrial transition pore.[16] By limiting the opening of the mitochondrial transition pore, these signaling pathways prevent the influx of ions, leading to an increase in cell survival in the target organ.[16]

CLINICAL TRIALS

Numerous studies have been done examining the protective effect of RIPC on the kidneys (Table 53.1). For the RIPC procedure, the typical protocol involves the inflation of a blood pressure cuff on the upper arm for 5 minutes followed by 5 minutes of cuff deflation repeated for three to five cycles. The cuff typically is inflated to 200 mm Hg or to 50 mm Hg higher than the systolic atrial pressure. There have been no reports thus far of safety concerns or difficulty tolerating the RIPC procedure by patients.

Acute Kidney Injury

Despite the introduction of a uniform classification system for AKI and increased attention in the literature, there has been little improvement in outcomes for AKI.[42,43] The results of some clinical trials suggest that RIPC may reduce kidney damage, whereas others show no effect of RIPC on AKI. The majority of studies have investigated the effects of RIPC on the kidney in the setting of adult cardiac and vascular surgery. One of the first randomized trials, published in 2007, to evaluate the potential beneficial effect of RIPC on renal injury involved 82 patients before

TABLE 53.1

Clinical Trials on the Use of Remote Ischemic Conditioning for Kidney Protection

	YEAR	N	RIPC PROCEDURE	INTERVENTION AFTER RIPC	OUTCOMES IN THE RIPC GROUP COMPARED WITH THE CONTROL GROUP	REF
AKI	2007	82	Cross-clamping of the common iliac artery	AAA repair	Reduction in renal impairment defined by a serum creatinine >2 mg/dL	17
	2010	162	Blood pressure cuff	CPB	No difference in serum creatinine levels 4 days after surgery	18
	2010	78	Blood pressure cuff	CPB	Reduction in the incidence of AKI defined by the AKIN criteria[19]	20
	2010	40	Blood pressure cuff	AAA repair	No difference in urinary retinol binding protein and albumin to creatinine ratio	21
	2011	120	Blood pressure cuff	CPB	Reduction in the relative risk of AKI defined by the AKIN criteria[19]	22
	2011	76	Blood pressure cuff	CPB	No difference in percent change in serum creatinine from baseline	23
	2012	113	Blood pressure cuff	CPB	No difference in AKI incidence defined by the RIFLE criteria[24]	25
	2012	96	Blood pressure cuff	CPB	No difference in AKI incidence defined by the RIFLE criteria[24]	26
	2013	225	Balloon Inflations	PCI	Reduction in the incidence of AKI defined by an absolute increase in serum creatinine of ≥ 0.5 mg/dL or a relative increase of ≥ 25% within 96 hours after PCI	27
	2014	62	Blood pressure cuff	AAA repair	No difference in median serum creatinine 3 days after surgery	28
	2015	240	Blood pressure cuff	CPB	Reduction in AKI defined by the KDIGO criteria[29] within 72 hours after surgery	10
	2015	86	Blood pressure cuff	CPB	No difference in the rate of AKI defined by the AKIN criteria[19] within 48 hours of surgery	30
	2015	1612	Blood pressure cuff	CPB	No difference in AKI incidence defined by the KDIGO criteria[29]	31
	2015	180	Blood pressure cuff	CPB	Reduction in the incidence of AKI defined by the RIFLE criteria[24]	32
	2015	1385	Blood pressure cuff	CPB	No difference in AKI incidence defined by the RIFLE criteria[24]	33
Contrast-induced AKI	2012	100	Blood pressure cuff	Contrast Angiography	Reduction in contrast-induced AKI	34
	2013	60	Blood pressure cuff	PCI	Reduction in the mean percent change in urinary liver-type fatty acid-binding protein	35
	2014	96	Blood pressure cuff	Coronary angiography	Less increase in serum creatinine	36
	2015	125	Blood pressure cuff	Emergency PCI	Reduction in contrast-induced AKI	37
	2015	76	Blood pressure cuff	Contrast administration	No difference in mean change in serum creatinine after contrast administration	38
Transplantation	2013	60	Blood pressure cuff	Kidney transplant	No difference in urine output and serum creatinine	39
	2014	48	Clamping of the external iliac artery	Kidney transplant	Reduction in serum creatinine	40
	2015	406	Blood pressure cuff	Kidney transplant	No difference in GFR determined with iohexol	41

AAA, Abdominal aortic aneurysm repair; *AKI,* acute kidney injury; *AKIN,* Acute Kidney Injury Network; *CPB,* cardiopulmonary bypass; *GFR,* glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes; *PCI,* percutaneous coronary intervention; *Ref,* reference; *RIFLE,* risk, injury, failure, loss of kidney function, and end-stage kidney disease; *RIPC,* remote ischemic preconditioning.

abdominal aortic aneurysm repair.[17] Patients randomized to RIPC received clamping of the common iliac artery for 10 minutes followed by 10 minutes of reperfusion.[17] The incidence of renal impairment (defined by a peak serum creatinine greater than 2.0 mg/dL) was reduced by 23% in those who received RIPC when compared with a control group of patients.[17] Subsequently, it was shown that patients that were randomized to receive RIPC with a blood pressure cuff to the arm before cardiopulmonary bypass exposure had reduced peak serum creatinine values postoperatively when compared with controls.[22] Zimmerman et al.[22] found a 27% absolute risk reduction in AKI (defined by the AKI Network [AKIN] criteria[19] within 48 hours after cardiopulmonary bypass exposure) when comparing a randomized group of patients who received RIPC with a blood pressure cuff with those who received no intervention before surgery. Venugopal et al.[20] completed a secondary analysis of two randomized trials in which AKI was defined using the AKIN criteria.[19] They reported a decreased incidence of AKI postoperatively in those that received RIPC with a blood pressure cuff to the arm before coronary artery bypass surgery.[20] In a large multicenter, randomized double-blind clinical trial, Zarbock et al.[10] recently found that RIPC in high-risk patients before cardiac surgery was effective for reducing the occurrence of AKI (37.5% compared with 52.5% with sham; absolute risk reduction [ARR] 15%; 95% CI, 2.56–27.44; $p = .02$). Furthermore, fewer patients receiving RIPC received renal replacement therapy (RRT) (5.8% vs. 15.8%; ARR, 10%; 95% CI, 2.25–17.75; $p = .01$).

Other investigations have demonstrated no improvement in renal outcomes for patients who receive RIPC. For example, 162 patients who were randomized to receive RIPC before coronary artery bypass surgery had no improvement in serum creatinine levels between 0 to 4 days postoperatively.[18] Young et al.[26] found no difference in the severity of AKI based on the RIFLE criteria[24] in patients randomized to RIPC before cardiopulmonary bypass when compared with a control group. In a more recent study in which the primary end point was defined as AKI with an increase in serum creatinine over 0.3 mg/dL within 48 hours of surgery, there was no difference in the primary end point when comparing patients who received RIPC to those who did not before cardiopulmonary bypass exposure.[30] Candilio et al.[32] questioned if increasing the intensity of the RIPC stimulus would result in improved protection against AKI. When they randomized patients undergoing coronary artery bypass surgery and/or valve surgery, the incidence of AKI (defined by the RIFLE criteria[24]) decreased in the group that received the intensified RIPC procedure by 48%; however, this did not reach statistical significance.[32]

Two recent large multicenter trials investigating more than 3000 patients demonstrated that RIPC did not affect either composite end points or mortality.[31,33] These controversial results can be explained by the different study designs. Applying RIPC in high-risk patients improved organ function,[10] whereas the use of this intervention in low-risk patients had no effect on myocardial infarction, occurrence of AKI, and mortality.[31,33] Another very important difference between the studies that can explain the different results is the anesthetic regime during surgery, given that it has been shown that propofol can influence the effects of RIPC.[44,45] In these two recently published multicenter trials, most of the patients received propofol for anesthesia, which could have diminished or abrogated the effect of RIPC.

Investigators have quantified renal injury by using measures other than serum creatinine. For example, Walsh et al.[21] randomized patients before elective open infrarenal abdominal aortic aneurysm repair to RIPC with sequential common iliac clamping. Using urine levels of retinol binding protein and albumin as the primary measures of renal outcome, there were no statistically significant differences between groups.[21] Choi et al.[23] found no difference in AKI incidence (defined by the AKIN criteria[19]) as well as changes in plasma cystatin C and plasma neutrophil gelatinase-associated lipocalin (NGAL) after valvular surgery when comparing patients randomized to received RIPC with a blood pressure cuff or no intervention before surgery.[23] There was no difference in the incidence of AKI (defined by the RIFLE criteria[24]), initiation of dialysis, estimated glomerular filtration rate, plasma cystatin C, urine NGAL, or urine output when comparing children randomized to RIPC versus a sham procedure before the repair of complex congenital heart lesions in children.[25] Huang et al.[46] demonstrated an improved glomerular filtration rate (GFR) at 1 month (when measured with renal scintigraphy) as well as less of an increase in urine retinol binding protein 24 hours after laparoscopic partial nephrectomy in patients who were randomized to receive RIPC preoperatively.

Contrast-Induced Acute Kidney Injury

Evidence regarding the use of RIPC for the prevention of contrast-induced AKI has been encouraging. In general, regarding contrast nephropathy, there have been various treatment strategies that have been proposed and studied, yet there has been no intervention that has been shown to reduce consistently the incidence of contrast-induced AKI. As it currently stands, the most widely recommended intervention is hydration before known contrast exposure. Er et al.[34] randomized 100 adult patients with impaired renal function to either RIPC with a blood pressure cuff and standard of care or standard of care only. Contrast-induced AKI (defined as an increase in serum creatinine ≥25% or ≥0.5 mg/dL above baseline 48 hours after contrast administration) occurred in 40% of the control group and 12% of the RIPC group ($p = .002$).[34] A reduced incidence of AKI was found independent of patient comorbidities and dose of contrast medium given.[34] Deftereos et al.[27] randomized patients at the time of percutaneous coronary intervention to receive RIPC by cycles of inflation and deflation of the stent balloon or a sham procedure. The rate of AKI (defined by an increase of ≥0.5 mg/dL or ≥25% in serum creatinine within 96 hours from the intervention) was significantly less in the group that received RIPC (12.4% vs. 29.5%).[27] A study investigating the "effect of remote ischaemic conditioning on contrast-induced nephropathy (ERICCIN)" is a single-center randomized control trial aiming to recruit 362 patients at risk for contrast nephropathy undergoing coronary angiographic procedures with the primary end point being the development of contrast-induced AKI is currently underway.[47] It will be determined if RIPC affects renal impairment over a 3-month follow-up period.[47]

Transplantation Medicine

Given the ischemia and reperfusion injury that occur with kidney transplantation, there stands to be great potential benefit in the use of RIPC around the time of transplant. Acute tubular necrosis and delayed graft function are not uncommon after kidney transplantation. Over the last 10 years there has been an increase in cases of donation after circulatory death with the associated warm ischemic injury from circulatory arrest.[48] Using RIPC in donors before

transplantation, after organ procurement, or in recipients at the time of transplantation has been proposed as potential protective strategies for delayed graft function.[49]

The results of studies exploring the use of RIPC around the time of transplantation have shown conflicting results. The first report of using RIPC in renal transplantation was published by Chen et al. in 2013.[39] Carrying out the RIPC procedure with blood pressure cuff inflations and deflations, they randomized 60 pairs of adult patients undergoing renal transplantation to either RIPC in the donor, RIPC in the recipient, or no RIPC. No statistically significant differences were found between the groups regarding the measured outcomes of urine output volumes, serum creatinine, urine NGAL, urine retinal binding protein, urine N-acetyl-D-glucosaminidase, plasma superoxide dismutase, and plasma malondialdehyde at time points measured from 1 hour to 24 hours after the operation.[39] The Remote Preconditioning for Protection Against Ischemic-Reperfusion (REPAIR) study randomized 406 pairs of kidney donors and recipients to four groups of combinations of early (immediately before transplant), late (24 hours before transplant), and sham RIPC.[41] Early RIPC did not have a statistically significant effect on GFR when measured with iohexol 12 months after kidney transplant, which was thought to be due to a greater than expected variability in their iohexol measurements. When estimated GFR values were used alternatively, however, a beneficial treatment effect was seen 12 months after transplant (adjusted difference 4.98, 95% CI 1.12–8.29, $p = .001$).[41] Wu et al.[40] did demonstrate a potential benefit for RIPC in renal outcomes for kidney transplantation involving donation after cardiac death. In the study paired recipients each receiving a kidney from the same donor (n = 48) were randomized to receive RIPC by way of three 5-minute cycles of clamping and unclamping of the external iliac artery.[40] The serum creatinine and urine NGAL were lower in the group that received the RIPC procedure when compared with the control participants postoperatively.[40]

FUTURE OF REMOTE ISCHEMIC PRECONDITIONING

Over the last decade there has been an increase in the understanding of the complex mechanisms of RIPC. In addition, from 2005 to 2016 there have been more than 20 randomized clinical trials published exploring the use of RIPC for renal protection. Despite the recent increase in the number of investigations exploring the use of RIPC, the results of studies have been controversial, likely contributing to its lack of widespread routine clinical use. Differences in the RIPC procedure may contribute to the heterogeneity of study results. There is presently no standard algorithm for performing RIPC with differences noted between studies regarding the timing of the RIPC procedure, the location of blood pressure cuff placement, the number of RIPC cycles, and the duration of cuff inflation. Furthermore, some investigators report the use of intraoperative artery clamping and unclamping, rather than the placement of a blood pressure cuff to the arm or leg. Future studies comparing the effect of arm versus leg cuff inflations or differing doses of RIPC cuff inflation and deflation on renal outcomes would be useful toward developing a standard RIPC procedure.

Future studies exploring the effects of different patient medication exposures on RIPC effect may explain differences in study results. There have been reported preconditioning effects of inhaled anesthetics.[8,50] Alternatively, there are medications that are thought to attenuate the effects of RIPC. For example, treatment with certain sulfonamide medications have been shown to negate the effects of RIPC.[51] In addition, as discussed above, propofol may inhibit the protective properties of RIPC, explaining the lack of beneficial effect of RIPC in two multicenter, randomized trials.[31,33,44,45]

Future investigations stratifying patients by risk factors and comorbid conditions are warranted. Those patients at higher risk for renal injury may be more likely to respond to RIPC when compared with a lower risk patient group. Stratifying patients by biomarker values before RIPC may help to identify the individuals most likely benefit from the procedure. In addition, further studies on the release of biomarkers immediately after RIPC may provide targets for the RIPC response. As discussed above, Zarbock et al.[10] found that the effectiveness of RIPC was associated strongly with the release of certain biomarkers, specifically tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protinen-7 (IGFBP7). Patients with urinary [IGFBP7]•[TIMP-2] ≥ 0.5 $(ng/mL)^2/1000$ before surgery, but immediately after receiving RIPC, had a significantly reduced rate of AKI compared with patients with lower urinary concentrations of these biomarkers (RR, 67%; 95% CI, 53% to 83%, $p < .001$).[10] Furthermore, it was only the group that achieved an increase in urine [TIMP-2]•[IGFBP7] to ≥ 0.5 (56% of patients treated with RIPC) who showed a benefit from RIPC.[10] Referred to as cell-cycle arrest biomarkers, IGFBP7 and TIMP-2 are inducers of G_1 cell-cycle arrest.[52,53] Cells can use cell-cycle arrest to avoid cell division during times of damage or stress as a protective mechanism.[54] Inducing the release of cell-cycle arrest biomarkers with RIPC before a renal insult, such as cardiopulmonary bypass exposure, may result in protection against AKI.[55]

CONCLUSION

As a renal-protective strategy RIPC shows great promise for use in critical care nephrology. Increased research attention is needed to further understand the complex molecular mechanism of RIPC. Differences in study protocols, medication exposure, and the risk categories of patients may explain the differential beneficial effect of RIPC between investigations. Before the routine clinical application of RIPC in critical care nephrology practice, further work is required to explore the use of RIPC in stratified patient risk groups, perhaps through the use of biomarkers.

Key Points

1. Experimental evidence suggests that the underlying mechanisms for RIPC include a humoral trigger, neural trigger, or possibly an overlap of both mechanisms.
2. Clinical studies suggest that RIPC may reduce the risk of AKI and contrast-induced nephropathy and serve as a protective strategy after kidney transplantation, whereas other investigations show no beneficial effect.
3. Future studies exploring the potential causes for discrepancies in study findings, such as differences

in medication exposure, the RIPC procedure, and patient risk groups, are warranted before the use of RIPC in critical care nephrology becomes routine.

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