

## Original Article

# *Efficacy of Remote Ischemic Preconditioning in the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography /Angioplasty*

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### ABSTRACT

**Background:** Contrast-induced nephropathy (CIN) is a significant common complication in patients undergoing coronary angiography. This study was carried out to determine the efficacy of remote ischemic preconditioning in the prevention of CIN in patients undergoing coronary angiography/angioplasty.

**Methods:** This randomized controlled trial assessed 171 eligible patients undergoing coronary angiography/angioplasty in Shariati Hospital between May 2018 and June 2019. The patients were randomly assigned to either the remote ischemic preconditioning group or the control group. The glomerular filtration rate (GFR), CIN, and creatinine levels were compared between the groups.

**Results:** The incidence rate of CIN was 1.2% in the intervention group and 9.4% in the control group ( $P = 0.018$ ), with a risk ratio of 0.125. There were significant improvements in creatinine and GFR in the intervention group ( $P = 0.007$  and  $P = 0.001$ , respectively), while there were no meaningful improvements in creatinine and GFR in the control group. The intervention group featured 11 patients in Stage IV chronic kidney disease, none of whom was CIN-positive, whereas the control group had 2 patients in Stage IV, both of whom were CIN-positive ( $P < 0.001$ ).

**Conclusions:** The results showed the efficacy of remote ischemic preconditioning in the prevention of CIN, the reduction of creatinine reduction, and the elevation of GFR in patients undergoing coronary angiography/angioplasty. (*Iranian Heart Journal 2021; 22(1): 100-105*)

**KEYWORDS:** Remote ischemic preconditioning, Contrast-induced nephropathy, Coronary angiography

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Contrast-induced nephropathy (CIN) is one of the significant common complications in patients undergoing coronary angiography.<sup>1,2</sup> CIN in 0.5 to 2% of

cases might necessitate dialysis, and it could cause a 36% increase in the in-hospital mortality rate and a 2-year reduction in the survival rate. Despite an increase in

adherence to the hydration protocol before and after contrast administration and the use of low-osmolality contrasts, the incidence of CIN is still significant.<sup>3</sup>

CIN is strongly associated with mortality and morbidity rates.<sup>4, 5</sup> Evidence suggests that the contrast substance exerts a direct effect on tubular cells, impairing mitochondrial function and leading to apoptosis.<sup>6, 7</sup> Remote ischemic preconditioning (RIPC) engenders resistance to ischemia in a distant organ by inducing temporary periods of nonlethal ischemia and reperfusion in the organ.<sup>8</sup> The idea was first proposed by Przyklenk et al<sup>10</sup> (1993), who were seeking to lessen the damage caused by acute myocardial infarction. Subsequent studies confirmed the efficaciousness of RIPC through the inflation of the lower limb blood pressure cuff in reducing complications following coronary artery bypass grafting and abdominal aortic aneurysm surgery. Nonetheless, the pathophysiology of the effectiveness of RIPC in decreasing the incidence of CIN has yet to be elucidated.<sup>11</sup> With respect to CIN etiology, research has thus far indicated the toxic effects of iodine on nephrons, microemboli, vasoconstriction, and ischemia due to contrast administration or microemboli.<sup>12</sup> RIPC may be effective in preventing CIN by reducing ischemia.<sup>19-13</sup> Accordingly, we designed the present study to determine the efficacy of RIPC in the prevention of CIN in patients undergoing coronary angiography/angioplasty.

## METHODS

This randomized controlled trial assessed 171 eligible patients undergoing coronary angiography/angioplasty in Shariati Hospital between May 2018 and June 2019. Patients were included if they had a creatinine level of more than 1.4 mg/dL or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min.

The patients were given standard hydration, including normal saline, 6 hours before angiography or angioplasty until 12 hours after the procedure to minimize the risk of CIN. Nephrotoxic drugs such as metformin, NSAIDs, and diuretics were discontinued 24 hours before and 48 hours after the procedure. The study population was randomly assigned either to the RIPC group or to the control group by 1:1 ratio and randomization computer codes. The RIPC group was comprised of 86 patients, in whom ischemia was induced with the aid of a blood pressure cuff in the elbow area. The cuff was inflated to 50 mm Hg above systolic pressure in 4 cycles of 5 minutes, each followed by the rapid release of the cuff for reperfusion. The control group consisted of 85 patients, in whom mock ischemia was induced by inflating the blood pressure cuff to 10 mm Hg above systolic pressure. Both groups received standard treatment. The interval between the last cuff-inflating cycle and the start of angiography or angioplasty was 45 minutes. The creatinine level was checked 48 hours after the procedure. CIN was defined as a 0.5 mg/dL increase in creatinine or a 25% decrease in eGFR. All the patients received at least 100 mL of similar low-osmotic non-ionic contrast agents for angiography/angioplasty. The study was done as double-blind research. The patients and angiography/angioplasty operators were not aware of the coding of the patients and their grouping. Informed consent was obtained from all the patients, and the study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

## Statistical Analysis

The data were analyzed using SPSS software, version 26. The statistical analyses were conducted using the  $\chi^2$  test, the Fisher exact test, the independent *t*-test, the paired *t*-test, and the Wilcoxon test based on the normality

or non-normality of the data. The significance level for the tests was considered to be 0.05.

## RESULTS

The average age of the intervention and control groups was  $66.9 \pm 5.12$  and  $67.9 \pm 4.54$  years, respectively. Men accounted for 67.4% of the RIPC group and 68.2% of the control group. The mean weight of the patients in the intervention and control groups was  $75.2 \pm 10.21$  and  $73.6 \pm 15.32$  kg, correspondingly. There were no differences between the 2 groups regarding age, gender, and weight ( $P = 0.50$ ,  $P = 0.91$ , and  $P = 0.38$ , respectively) (Table 1).

**Table 1:** Patients' characteristics regarding gender, age, weight, diabetes, creatinine, GFR, EF, and CIN

Items	Intervention	Control	P value
Gender, N, M/F	58/28	58/27	0.912
Age, y mean±SD	66.87±10.57	67.94±10.28	0.504
Weight, kg, mean±SD	75.20±12.36	73.59±11.93	0.388
Diabetes, N, Y/N	35/51	67/104	0.683
Initial creatinine, mean±SD	1.62±0.30	1.47±0.21	0.21
Final creatinine, mean±SD	1.54±0.34	1.49±0.45	0.32
Initial GFR	47.13±15.94	48.38±10.32	0.47
Final GFR	49.92±17.14	50.31±14.82	0.12
EF	45.93±10.72	46.53±10.62	0.714
CIN, N, P/N	1/85	8/77	0.018
Stage, CIN, N, P/N			
I	0/2	---	
II	0/10	2/10	0.23
III	1/62	4/67	0.11
IV	0/11	2/0	0.001
Diabetes, CIN, N, P/N			
Positive	0/35	4/28	0.47
Negative	1/50	4/49	0.74

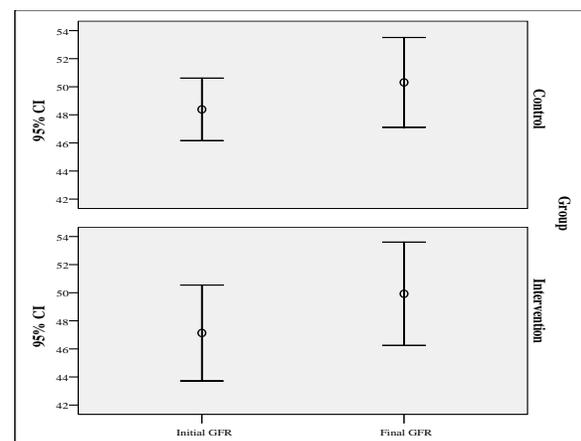
GFR, Glomerular filtration rate; CIN, Contrast-induced nephropathy; EF, Ejection fraction

The rate of diabetes was 40.7% in the intervention group and 37.6% in the control

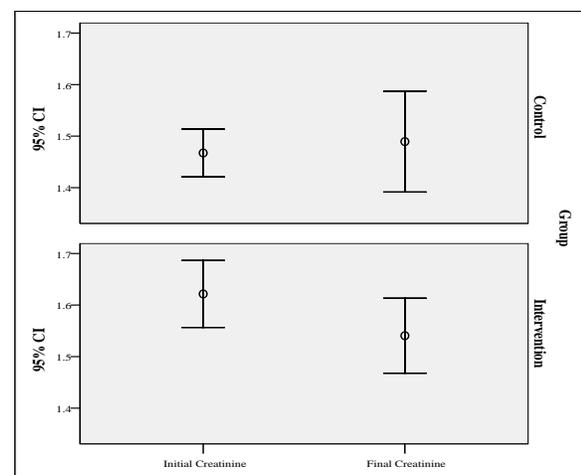
group, with the difference failing to constitute statistical significance ( $P = 0.683$ ) (Table 1).

There were also no significant differences between the 2 groups concerning initial creatinine and initial GFR ( $P = 0.21$  and  $P = 0.47$ , correspondingly) (Table 1).

The incidence of CIN was 1.2% in the RIPC group and 9.4% in the control group ( $P = 0.018$ ), with a risk ratio of 0.125. There were significant improvements in creatinine and GFR in the intervention group ( $P = 0.007$  and  $P = 0.001$ , respectively) (Fig. 1 & 2), whereas there were no significant improvements in creatinine and GFR in the control group (Fig. 1 & 2).



**Figure 1:** Figure illustrates post-angiography/angioplasty creatinine and glomerular filtration rate (GFR).



**Figure 2:** Figure illustrates post-angiography/angioplasty creatinine and glomerular filtration rate (GFR).

The ejection fraction was 45.9% in the intervention group and 46.5% in the control group ( $P = 0.714$ ) (Table 1).

Apropos the stages of chronic kidney disease, Stage I was detected in 12.8% of the patients in the RIPC group and 2.4% of those in the control group; the difference between the groups was statistically significant ( $P = 0.031$ ). In the intervention group, 11 patients were in Stage IV, none of whom was CIN-positive; however, 2 patients in the control group were in Stage IV, both of whom were CIN-positive ( $P < 0.001$ ) (Table 1).

## DISCUSSION

In the current study, we aimed to assess the efficacy of RIPC in lessening the incidence of CIN. Our results revealed incidence rates of 1.2% and 9.4% for CIN in the RIPC and control groups, respectively, which showed a significant difference between the 2 groups. The risk rate of RIPC was 0.125, the absolute risk reduction rate was 8.4%, and the NNT rate was 12.3. In the intervention group, the decrease in creatinine and the increase in GFR showed a significant trend, while creatinine and GFR changes did not exhibit a significant trend in the control group.

The pathophysiology of RIPC in ameliorating CIN is still far from clear.<sup>11</sup> Several causes for CIN have thus far been cited; they include the toxic effects of iodine on nephrons, microemboli, vasoconstriction, and ischemia begotten by contrast administration or microemboli.<sup>12</sup> RIPC may be effective in preventing CIN by reducing ischemia.

In a study by Fikr et al<sup>13</sup> (2012), 50 candidates for angiography with a high risk of CIN development based on the Mehran risk score underwent distal ischemia in the arm area through the inflation of a blood pressure cuff in 4 cycles of 5 minutes. They reported that the incidence of contrast medium-induced acute kidney injury was

significantly lower in the intervention group than in the control group, comprised of 50 patients who received standard treatment. Their results are consistent with those in the current study.

Whittaker et al<sup>14</sup> (2011) evaluated 65 patients who underwent angioplasty due to acute myocardial infarction. They divided the study population into 2 groups of angioplasty with 1 to 3 balloons and angioplasty with at least 4 balloons and assessed the effects on creatinine and eGFR. With more balloons on the third day after the procedure, the decrease in renal function was significantly less, which we also observed in the case of creatinine in our case group.

Zarbock et al<sup>15</sup> (2015) performed a study on 240 patients who underwent heart surgery to assess the effects of RIPC on postoperative kidney injury by inflating a blood pressure cuff in 1 arm in three 5-minute cycles, followed by deflating and emptying rapidly. After the induction of anesthesia, they found significant reductions in acute renal injury, intensive care unit stay, urinary insulin-like growth factor binding protein-7, and tissue inhibitor of metalloproteinases-2 in the RIPC group. In our study, by comparison with the control group, in the intervention group, the increase in creatinine was low and the increase in GFR was high.

Sterenberget al<sup>16</sup> (2014) assessed the reduction in CIN after RIPC. They measured changes in creatinine levels 48 to 72 hours from baseline after contrast administration and reported that RIPC conferred a drop in the prevalence of CIN following angioplasty. Their findings chime in with those in the current investigation.

Soleimani et al<sup>17</sup> (2019) assessed 140 patients who required angiography or angioplasty and showed that there was no significant change in the incidence of acute kidney injury in the control group and the

RIPC group. The sample size in their investigation was smaller than that in our study.

Balbir et al<sup>18</sup> (2016) evaluated 102 patients with diabetes who were candidates for elective percutaneous coronary intervention. The patients in the RIPC and mock ischemia group had GFR of less than 60 or an albumin-to-creatinine ratio of greater than 300 mg/g. Their results demonstrated similar GFR, neutrophil gelatinase-associated lipocalin, and creatinine in both groups.

Valappil et al<sup>19</sup> (2018) evaluated patients with Stage III chronic kidney disease candidates for coronary angioplasty and divided them into 2 groups: RIPC and control. The incidence of CIN was 22% in the RIPC group and 36% in the control group. The preliminary results of creatinine at 24 hours, 48 hours, 2 weeks, and 6 weeks after contrast administration showed a significant improvement in the RIPC group by comparison with the control group. Still, in the long-term follow-up, the need for dialysis, death, and hospitalization exhibited no change in the control and RIPC groups. In our study, we did not perform a long-term follow-up; be that as it may, there was no difference between the RIPC and control groups vis-à-vis the need for dialysis and the mortality rate.

## CONCLUSIONS

The results of the present study showed the efficacy of RIPC in the prevention of CIN, creatinine reduction, and GFR increase in patients undergoing coronary angiography/angioplasty.

## REFERENCES

1. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002, 39:930–936.
2. Morcos SK, Thomsen HS, Webb JA: Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* 1999, 9:1602–1613.
3. Mitchell AM, Jones AE, Tumlin JA, Kline JA: Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. *Clin J Am Soc Nephrol* 2010, 5:4–9.
4. From AM, Bartholmai BJ, Williams AW, Cha SS, McDonald FS: Mortality associated with nephropathy after radiographic contrast exposure. *Mayo Clin Proc* 2008, 83:1095–1100.
5. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J: A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract* 2003, 93:C29–C34.
6. Sendeski MM: Pathophysiology of renal tissue damage by iodinated contrast media. *Clin Exp Pharmacol Physiol* 2011, 38:292–299.
7. Evans RG, Ince C, Joles JA, Smith DW, May CN, O'Connor PM, Gardiner BS: Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol* 2013, 40:106–122.
8. Hausenloy, D. J. and D. M. Yellon (2008). "Remote ischemic preconditioning: underlying mechanisms and clinical application." *Cardiovascular research*.
9. Wever KE, Warle MC, Wagener FA, van der Hoorn JW, Masereeuw R, van der Vliet JA, Rongen GA: Remote ischaemic preconditioning by brief hindlimb ischaemia protects against renal ischaemia-reperfusion injury: the role of adenosine. *Nephrol Dial Transplant* 2011, 26:3108–3117.
10. Przyklenk, K., et al. (1993). "Regional ischemic preconditioning protects remote

- virgin myocardium from subsequent sustained coronary occlusion." *Circulation* 87(3): 893-899.
11. Er, F., et al. (2012). "Ischemic preconditioning for prevention of contrast-medium-induced nephropathy: randomized pilot RenPro-trial (renal protection trial)." *Circulation*: CIRCULATIONAHA.112.096370.
  12. Mann, D. L., et al. (2014). *Braunwald's heart disease: a textbook of cardiovascular medicine*, Elsevier Health Sciences.
  13. Er, F., et al. (2012). "Ischemic preconditioning for prevention of contrast-medium-induced nephropathy: randomized pilot RenPro-trial (renal protection trial)." *Circulation*: CIRCULATIONAHA.112.096370.
  14. Whittaker, P. and K. Przyklenk (2011). "Remote-conditioning ischemia provides a potential approach to mitigate contrast medium-induced reduction in kidney function: a retrospective observational cohort study." *Cardiology* 119(3): 145-150.
  15. Zarbock, A., et al. (2015). "Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial." *Jama* 313(21): 2133-2141.
  16. Thomas B Sterenberg ., et al.(2014). "Remote ischemic preconditioning to reduce contrast-induced nephropathy: study protocol for a randomized controlled trial" *Trials* 2014, 15:119
  17. SanazSoleymani., et al.(2019). "Is there a protective effect with remote ischemic preconditioning on contrast-induced acute renal injury after coronaryangiography in low-risk patients?" *J Nephrothol.* 2019;8(4):e38.
  18. Gillian Balbir Singh., et al.(2016). "Remote Ischemic Preconditioning for thePrevention of Contrast-Induced Acute Kidney Injury in Diabetics Receiving Elective Percutaneous Coronary Intervention " *PLoS ONE* 11(10): e0164256. doi:10.1371/journal.pone.0164256.
  19. SanjaiPattuValappil., et al. "Remote ischemic preconditioning for prevention of contrast induced nephropathy—Insights from an Indian study". *Indian Heart Journal* 70 (2018) 857–863.
  20. Tintinalli JE. *Tintinalli's emergency medicine: a comprehensive study guide*. 7th edition. 2011