



# Effects of Remote Ischemic Pre-Conditioning to Prevent Contrast-Induced Nephropathy after Intravenous Contrast Medium Injection: A Randomized Controlled Trial

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**Objective:** We aimed to assess the effects of remote ischemic pre-conditioning (RIPC) on the incidence of contrast-induced nephropathy (CIN) after an intravenous (IV) or intra-arterial injection of contrast medium (CM) in patient and control groups.

**Materials and Methods:** This prospective, randomized, single-blinded, controlled trial included 26 patients who were hospitalized for the evaluation of the feasibility of transcatheter aortic valve implantation and underwent investigations including contrast-enhanced computed tomography (CT), with Mehran risk scores greater than or equal to six. All the patients underwent four cycles of five minute-blood pressure cuff inflation followed by five minutes of total deflation. In the RIPC group (n = 13), the cuff was inflated to 50 mm Hg above the patient's systolic blood pressure (SBP); in the control group (n = 13), it was inflated to 10 mm Hg below the patient's SBP. The primary endpoint was the occurrence of CIN. Additionally, variation in the serum levels of cystatin C was assessed.

**Results:** One case of CIN was observed in the control group, whereas no cases were detected in the RIPC group ( $p = 0.48$ , analysis of 25 patients). Mean creatinine values at the baseline, 24 hours after injection of CM, and 48 hours after injection of CM were  $88 \pm 32 \mu\text{mol/L}$ ,  $91 \pm 28 \mu\text{mol/L}$  and  $82 \pm 29 \mu\text{mol/L}$ , respectively ( $p = 0.73$ ) in the RIPC group, whereas in the control group, they were  $100 \pm 36 \mu\text{mol/L}$ ,  $110 \pm 36 \mu\text{mol/L}$ , and  $105 \pm 34 \mu\text{mol/L}$ , respectively ( $p = 0.78$ ). Cystatin C values (median [Q1, Q3]) at the baseline, 24 hours after injection of CM, and 48 hours after injection of CM were 1.10 [1.08, 1.18] mg/L, 1.17 [0.97, 1.35] mg/L, and 1.12 [0.99, 1.24] mg/L, respectively ( $p = 0.88$ ) in the RIPC group, whereas they were 1.11 [0.97, 1.28] mg/L, 1.13 [1.08, 1.25] mg/L, and 1.16 [1.03, 1.31] mg/L, respectively ( $p = 0.93$ ), in the control group.

**Conclusion:** The risk of CIN after an IV injection of CM is very low in patients with Mehran risk score greater than or equal to six and even in the patients who are unable to receive preventive hyperhydration. Hence, the Mehran risk score may not be an appropriate method for the estimation of the risk of CIN after IV CM injection.

**Keywords:** Nephropathy; Acute kidney injury; Contrast media; Ischemic preconditioning

## INTRODUCTION

Contrast media (CM) are widely used in radiographic

imaging. However, the use of CM may expose the patients to a risk of contrast-induced nephropathy (CIN), which is a major cause of hospital-acquired renal insufficiency (1)

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and leads to considerable morbidity and mortality (2). The pathological mechanism of CIN relies on a combination of ischemia and direct cellular toxicity (3). The incidence rate of CIN varies from 0.6% to 2.3% in the general population, whereas it is likely to be much higher in the high-risk patient groups. Several risk factors have been identified, including a decline in the baseline renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m<sup>2</sup>, before intra-arterial [IA] injection; eGFR < 45 mL/min/1.73 m<sup>2</sup>, before intravenous [IV] injection), particularly in patients above the age of 70 years, diabetic nephropathy, dehydration, congestive heart failure, myocardial infarction (< 24 hours), nephrotoxic drugs, hemodynamic instability (intra-aortic balloon pump), peri-procedural hypotension, anemia, volume of the CM and IA injections (4-8). The Mehran risk score was developed to predict the risk of CIN after percutaneous coronary intervention, by means of ascertaining the cumulative risk rendered by the combination of several of the known risk factors (9).

Recently, the Contrast Media Safety Committee of the European Society of Urogenital Radiology proposed and recommended several methods, in order to prevent the occurrence of CIN (6, 7). The main recommendation was hyperhydration, along with the discontinuation of metformin.

Hyperhydration leads to volume expansion that can expose the patients to a risk of pulmonary edema, particularly in patients with congestive heart failure or heart valve diseases like aortic stenosis. Transcatheter aortic valve implantation is the treatment of choice for aortic stenosis in patients at a high risk of operative mortality (10). Enhanced computed tomography (CT) is required to assess the feasibility and plan the intervention (11). Elderly patients with comorbidities (11) usually require CIN prevention, but cannot be hyperhydrated. Thus, preventive measures other than hyperhydration need to be implemented.

Remote ischemic pre-conditioning (RIPC), initiated prior to the injection of CM, is a promising method for the prevention of CIN (3); based on the concept that cycles of alternating inflation and deflation of a blood pressure cuff placed on the upper limb can induce ischemia-reperfusion and thus protect other remote organs like the kidneys from prolonged ischemia (12, 13). The effect of ischemia-reperfusion on the incidence of CIN in high-risk patients undergoing coronary angiography (CA) is controversial, with several studies reporting reduced incidence of CIN (14-18),

while others contradict the same (19). However, the effect of ischemia-reperfusion after an IV CM injection, such as in contrast-enhanced CT (20), remains unknown and to the best of our knowledge, has not been studied without an adjunct hyperhydration protocol to date.

The primary aim of the present study was to compare the incidence of CIN in moderate-to-very-high-risk patients, receiving either RIPC or a sham procedure without hyperhydration and before undergoing enhanced CT, designed to evaluate the feasibility of transcatheter valve implantation (TAVI). The secondary objectives of the present study were to assess the incidence of CIN after a second administration of the CM, in order to carry out the procedure of CA, and the outcome after six months.

## MATERIALS AND METHODS

### Study Design

We conducted a prospective, randomized, controlled, single-blinded and monocentric study at the Rennes University Hospital. The study protocol was approved by the ethics committee (IRB No. 15/07-969). Prior to the initiation of any procedure, written informed consent was obtained from all the patients involved in the study. The present study, termed as the "IPC-ANGIOTRIAL study," was registered with the American National Institutes of Health database, under the reference nNCT02470247.

### Study Population

The inclusion criteria were: patients above the age of 18 years, with Mehran risk scores greater than or equal to six, who were hospitalized to evaluate the feasibility of TAVI and underwent investigations including enhanced CT. The Mehran risk score was developed to predict the occurrence of CIN after percutaneous coronary intervention (9). It involves eight variables that are independently associated with CIN (hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age above 75 years, anemia and the volume of CM). It allows the categorization of patients into four risk groups (low, intermediate, high, and very high). Scores greater than or equal to six correspond to 14% to 57.3% risk of CIN.

The exclusion criteria were: patients with superior limb conditions that restrict the use of a blood pressure cuff, patients undergoing dialysis for end-stage chronic renal failure, contraindications to CM injection (eGFR < 30 mL/min/1.73 m<sup>2</sup>; allergy to CM), pregnancy, non-affiliation with

a social protection system, patients participating in other studies, legal protection and liberty deprivation. Moreover, patients were not included if the duration of hospitalization was less than 48 hours or if another CM injection was planned within 48 hours after the procedure of enhanced CT.

During the duration of the present study, from October 2015 to August 2017, 318 patients were hospitalized for a feasibility evaluation of TAVI and underwent investigations including enhanced CT. Overall, 26 patients fulfilled the inclusion criteria and 13 patients were randomly assigned to each group.

### Study Protocol

Before the procedure of enhanced CT (on the same day), the serum creatinine, cystatin C, electrolytes and hemogram were assessed. These values were referred to as the baseline values. The patients were then randomly assigned into two groups in a 1:1 ratio without any stratification criteria via electronic processing defined by our biometrics department. Patients in group 1 underwent the RIPC procedure, whereas the patients in group 2 underwent a sham procedure (control group). A sham procedure is a fake procedure performed on the control group, with the ultimate aim of blinding the patients to the group or procedure they are randomly assigned to. In the current study, the procedure was single-blinded, with the patients being blinded to their inclusion group. The procedure was performed within 45 minutes prior to the initiation of enhanced CT. The RIPC consisted of four cycles of alternating five-minute inflation of a blood pressure cuff positioned on the arm; the cuff was inflated to 50 mm Hg above the patients' systolic blood pressure (SBP), followed by five minutes of total deflation. The sham-RIPC consisted of four cycles of five-minute inflation of a blood pressure cuff positioned on the arm; the cuff was inflated to 10 mm Hg below the patients' SBP, followed by five minutes of total deflation. Tolerance (pain) was evaluated before and after the procedure using DN4, which is a neuropathic pain standardized questionnaire, along with a numerical pain rating scale (0–10).

Patients with aortic valve stenosis did not undergo hyperhydration before enhanced CT, owing to the increased risk of heart failure. Considering the risk of heart failure associated with hyperhydration and the relevance of undergoing CT, there was no ethical concern regarding the performance of CT on these patients. Furthermore, all potentially nephrotoxic treatments (e.g., metformin, aminoglycosides, nonsteroidal anti-inflammatory drugs,

calcineurin inhibitors) were discontinued before the procedure of enhanced CT and resumed after an assessment of the renal function, 48 hours after the procedure of enhanced CT.

The contrast-enhanced CT was performed using iobitridol 300 or 350 mgI/mL (Xenetix®, Guerbet), iohexol 300 mgI/mL (Omnipaque®, GE Healthcare SAS), or iodixanol 320 mgI/mL (Visipaque®, GE Healthcare SAS).

The serum creatinine and cystatin C levels were evaluated 24 and 48 hours after the procedure of enhanced CT. In case of the patients undergoing diagnostic CA, 48 hours after the procedure of enhanced CT, the serum creatinine and cystatin C levels were re-evaluated 72 hours after the procedure of enhanced CT (i.e., 24 hours after CA). The same CMs were applied in these patients.

Six months after the procedure of enhanced CT, an evaluation was performed, in order to collect data regarding dialysis, hospitalization or death.

### Data Collection

We collected data pertaining to the patients' demographics (age, sex), comorbidities (diabetes, hypertension, coronary artery disease, or congestive heart failure), Mehran risk score, treatments, laboratory results and the outcome after six months.

### Criteria of Evaluation

The principal evaluation criterion was the incidence of CIN, defined as an increase in the serum creatinine levels higher than or equal to the value of 0.5 mg/dL or a relative increase of 25%, 48 hours after the CM injection, as stated in similar previous publications (14, 15, 21–24).

The secondary evaluation criteria were: serum cystatin C levels, estimated 24 hours after the procedure of enhanced CT; serum creatinine and cystatin C levels, estimated 24 hours after the procedure of CA (i.e., 72 hours after the procedure of enhanced CT) in patients undergoing CA; serum creatinine and cystatin C levels estimated 48 hours after the procedure of enhanced CT; tolerance of the procedure; six-month mortality; re-hospitalization and dialysis.

### Sample Size Calculations

Based on previous studies, the incidence of CIN was estimated as 15% in the RIPC group and 40% in the control group (14); with a statistical power of 80% and  $\alpha$  risk of 0.05, the calculated sample size in each group was 48. The inclusion objective was set at 100 patients.

### Statistical Analysis

The continuous variables were expressed as mean  $\pm$  standard deviation or median and interquartile range (IQR) values (Q1: first quartile, Q3: third quartile) and the categorical variables were expressed as numbers (percentages). Baseline characteristics of the two groups were compared using the *t* test or Mann-Whitney U test for quantitative variables and the chi-squared test or Fisher's exact test for qualitative variables. The main criterion was compared using the Fisher's exact test. A mixed model was applied to evaluate the creatinine and cystatin C level progression. A Wilcoxon signed-rank test was used to analyze matched data. The significance threshold was set at 0.05 for all the statistical tests. The statistical analyses

were performed using the SAS® 9.4 software (SAS Institute). Analyses were conducted on the intent-to-treat population.

### RESULTS

The patients' demographic and clinical characteristics are presented in Table 1. The global mean Mehran risk score was  $11.9 \pm 3.2$ . The present study did not observe any significant difference between the two groups, except in the number of chronic bronchopathy cases (eight in the RIPC group as opposed to zero in the control group,  $p = 0.002$ ).

Amongst the patients involved in the current study, one from the control group developed CIN after contrast-enhanced CT (1/25, 4%). The present study observed no

**Table 1. Patient Characteristics of Whole Population, RIPC Group and Control Group**

Parameters	Total (n = 26)	RIPC Group (n = 13)	Control Group (n = 13)	P
Age, years	83.5 $\pm$ 5.3	85.1 $\pm$ 4.2	81.9 $\pm$ 5.9	0.120
Men	13 (50.0)	5 (38.5)	8 (61.5)	0.240
Body mass index, kg/m <sup>2</sup>	25.8 $\pm$ 4.1	25.3 $\pm$ 5.0	26.2 $\pm$ 4.2	0.580
Hypertension	21 (80.8)	9 (69.2)	12 (92.3)	0.320
Smokers	8 (30.8)	4 (30.8)	4 (30.8)	1.000
Dyslipidemia	19 (73.1)	8 (61.5)	11 (84.6)	0.380
Diabetes mellitus	7 (26.9)	2 (15.4)	5 (38.5)	0.380
Peripheral artery disease	2 (7.7)	0 (0)	3 (23.1)	0.480
Angina pectoris	3 (11.5)	0 (0)	3 (23.1)	0.220
History of myocardial infarction	2 (7.7)	0 (0)	2 (15.4)	0.480
Heart failure	24 (92.3)	13 (100.0)	11 (84.6)	NA
NYHA functional class II	11 (45.8)	5 (38.5)	6 (54.5)	NA
NYHA functional class III	12 (50.0)	7 (53.8)	5 (45.5)	NA
NYHA functional class IV	1 (4.2)	1 (7.7)	0 (0)	NA
Left ventricular ejection fraction*	60.6 $\pm$ 14.2 65 (51, 70)	64.1 $\pm$ 11.4 67 (64, 70)	57.0 $\pm$ 16.2 65 (45, 67)	0.230
History of cardiac surgery	4 (15.4)	2 (15.4)	2 (15.4)	1.000
Coronary bypass	3 (75.0)	1 (50.0)	2 (100.0)	NA
Other	1 (25.0)	1 (50.0)	0 (0)	NA
Chronic obstructive pulmonary disease	8 (30.8)	8 (61.5)	0 (0)	0.002
Baseline serum creatinine, $\mu$ mol/L	94.0 $\pm$ 34.0	87.6 $\pm$ 32.2	100.4 $\pm$ 35.8	0.350
Baseline eGFR, mL/min/1.73 m <sup>2</sup>				
> 60	19 (73.1)	10 (76.9)	9 (69.2)	NA
41–60	6 (23.1)	2 (15.4)	4 (30.8)	NA
30–40	1 (3.8)	1 (7.7)	0 (0)	NA
Baseline hematocrit, %	36.3 $\pm$ 5.4	36.8 $\pm$ 4.7	35.7 $\pm$ 6.2	0.740
ProBNP, pg/mL	2382.9 $\pm$ 2763.1	2382.8 $\pm$ 2657.5	2382.9 $\pm$ 3050.3	0.760
Volume of contrast medium injected for CT, mL	140.8 $\pm$ 14.4	144.6 $\pm$ 16.6	136.9 $\pm$ 11.1	
Mehran risk score	11.9 $\pm$ 3.2	12.4 $\pm$ 2.8	11.4 $\pm$ 3.6	0.440

If unspecified, results were expressed as mean  $\pm$  standard deviation or in number of positive results (percentage). \*Results were expressed in mean  $\pm$  standard deviation, or median (first quartile, third quartile). CT = computed tomography, eGFR = estimated glomerular filtration rate, NYHA = New York Heart Association, ProBNP = pro brain natriuretic peptide, RIPC = remote ischemic pre-conditioning

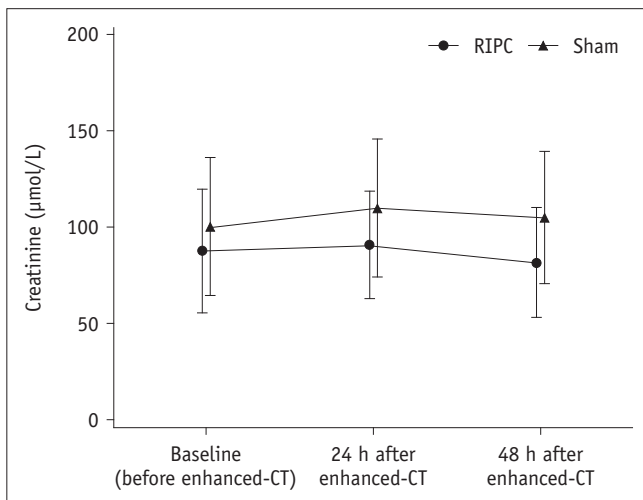
statistically significant difference in the incidence of CIN between the RIPC and control groups (no patient in the RIPC and one patient in the control groups,  $p = 0.48$ ). The patient with CIN exhibited a baseline Mehran risk score of 11 and a baseline creatinine level of 60  $\mu\text{mol/L}$ , with the latter progressing to 77  $\mu\text{mol/L}$ , 48 hours after the procedure of contrast-enhanced CT. This represents a 28.3% increase in the serum creatinine level, whereas the cystatin C level increased from 0.86 mg/L to 0.89 mg/L.

In the RIPC group, mean creatinine values at the baseline, 24 hours after injection of CM, and 48-hour after injection of CM were  $88 \pm 32 \mu\text{mol/L}$ ,  $91 \pm 28 \mu\text{mol/L}$  and  $82 \pm 29 \mu\text{mol/L}$ , respectively ( $p = 0.73$ ), whereas in control group, they were  $100 \pm 36 \mu\text{mol/L}$ ,  $110 \pm 36 \mu\text{mol/L}$ , and  $105 \pm 34 \mu\text{mol/L}$ , respectively ( $p = 0.78$ ). In the RIPC group, median cystatin C values (median [Q1, Q3]) at the baseline, 24 hours after injection of CM, and 48 hours after injection of CM were 1.10 [1.08, 1.18] mg/L, 1.17 [0.97, 1.35] mg/L, and 1.12 [0.99, 1.24] mg/L ( $p = 0.88$ ), respectively, whereas in the control group, cystatin C values at the baseline, 24 hours after CM injection and, 48 hours after CM injection were 1.11 [0.97, 1.28] mg/L, 1.13 [1.08, 1.25] mg/L, and 1.16 [1.03, 1.31] mg/L, respectively ( $p = 0.93$ ). The current study did not observe a statistically significant difference in the variations in serum creatinine and cystatin C levels between the two groups, estimated within 48 hours after the procedure of enhanced CT ( $p = 0.20$  and  $p = 0.44$ , in the

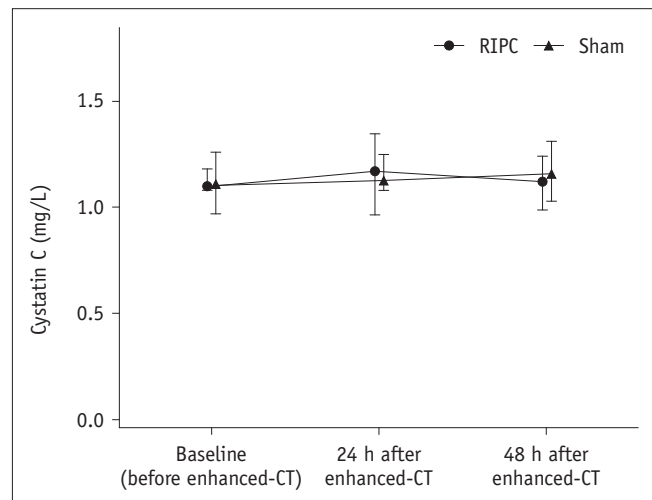
RIPC and control groups, respectively, for interaction group/time) (Figs. 1, 2).

Among the patients involved in the current study, 19 underwent CA, 48 hours after the procedure of enhanced CT; nine from the RIPC group and ten from the control group. The mean volume of injected CM was  $67.3 \pm 27.7 \text{ mL}$ , with an IQR of 48.5–73.5 mL and a median of 64 mL (RIPC group [mean,  $63.9 \pm 26.8 \text{ mL}$ ; IQR, 47–77 mL; median, 64 mL]; control group [mean,  $71.6 \pm 30.5 \text{ mL}$ ; IQR, 57–70 mL; median, 64 mL];  $p = 0.71$ ). In these patients, no significant difference was observed between the baseline serum creatinine levels and the levels estimated 24 hours after the procedure of CA (baseline serum creatinine [mean,  $94.8 \pm 31.4 \mu\text{mol/L}$ ; IQR, 69–107  $\mu\text{mol/L}$ ; median, 92  $\mu\text{mol/L}$ ] versus 24 hours after CA [mean,  $94.2 \pm 29.4 \mu\text{mol/L}$ ; IQR, 75–100  $\mu\text{mol/L}$ ; median, 86  $\mu\text{mol/L}$ ];  $p = 0.73$ ). Moreover, the current study did not observe a statistically significant difference in the variation in the serum creatinine and cystatin C levels between the two groups, estimated 72 hours after the procedure of enhanced CT (i.e., 24 hours after the procedure of CA) ( $p = 0.23$  and  $p = 0.44$ , in the RIPC and the control groups, respectively, for interaction group/time) (Figs. 3, 4).

The current study did not observe any significant difference between the two groups on comparing the pre-procedure and post-procedure values of the tolerance assessment, recorded using the DN4 and a numerical pain

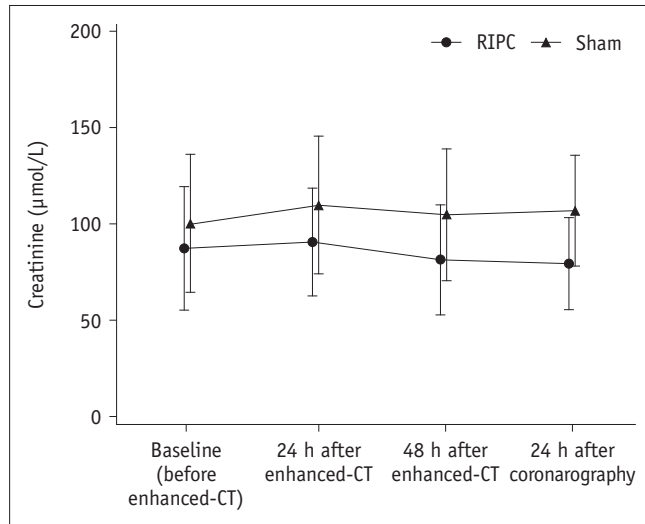


**Fig. 1. Evolution of serum creatinine before and after enhanced CT.** Variation in serum creatinine levels from baseline values (before procedure of enhanced CT) to values estimated 24 and 48 hours after procedure of enhanced CT in RIPC and control groups;  $p = 0.20$  for interaction between group and time. There was no statistical difference in evolution of serum creatinine between two groups. CT = computed tomography, RIPC = remote ischemic pre-conditioning

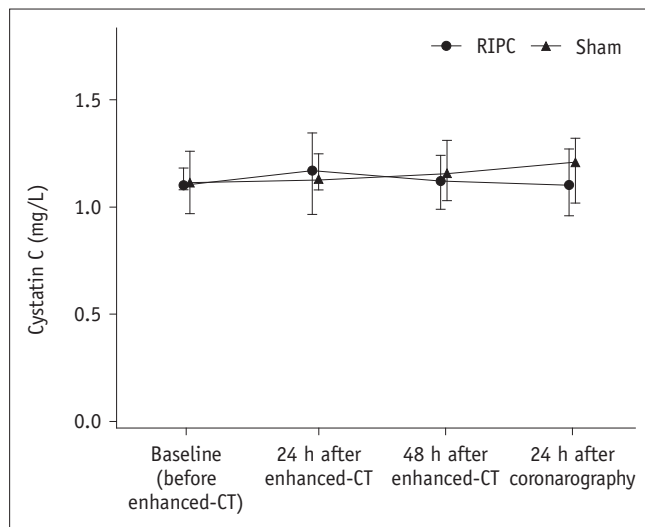


**Fig. 2. Evolution of serum cystatin C before and after enhanced CT.** Variation in cystatin C levels from baseline (before procedure of enhanced CT) values to values estimated 24 and 48 hours after procedure of enhanced CT in RIPC and control groups;  $p = 0.44$  for interaction between group and time. There was no statistical difference in evolution of cystatin C between two groups.





**Fig. 3. Evolution of serum creatinine before and after CA.** Variation in serum creatinine levels from baseline values (before procedure of enhanced CT) to values estimated 24, 48, and 72 hours after procedure of enhanced CT in patients who underwent CA, 48 hours after procedure of enhanced CT, in RIPC and control groups;  $p = 0.23$  for interaction between group and time. There was no statistical difference in evolution of serum creatinine between two groups. CA = coronary angiography



**Fig. 4. Evolution of cystatin C before and after CA.** Variation in cystatin C levels from baseline values (before procedure of enhanced CT) to values estimated 24, 48, and 72 hours after procedure of enhanced CT in patients who underwent CA, 48 hours after procedure of enhanced CT, in RIPC and control groups;  $p = 0.44$  for interaction between group and time. There was no statistical difference in evolution of cystatin C between two groups.

rating scale (Table 2).

During the six-month evaluation period post-inclusion, no patient required dialysis or expired. Overall, 16 patients were hospitalized, one each for anemia, acute limb ischemia and pacemaker implantation and 13 for TAVI.

## DISCUSSION

The prevention of CIN in the patients who cannot receive hyperhydration presents an issue (25). In these patients, RIPC may be a potential nephroprotective method. The current study included patients undergoing enhanced CT, designed to evaluate TAVI feasibility in patients with Mehran risk scores greater than or equal to six. The present study did not observe any significant difference in the incidence of CIN between the RIPC and control groups, without associated hyperhydration in either group. The RIPC was well tolerated, with a marginal increase in scores, measured using two pain scales. Only one case of CIN was observed among the 26 patients included in the study. Predictably, owing to the incidence of only one case of CIN, no hospitalization related to kidney injury or dialysis was reported within six months after the procedure of enhanced CT.

In patients with a moderate-to-high risk of CIN, who underwent IA CM injection for CA or percutaneous coronary angioplasty, the effects of RIPC are controversial, with several controlled studies demonstrating that RIPC reduces the incidence of CIN (14-17, 24), while others reported no difference in the incidence of CIN (19, 21, 22). However, several meta-analyses have concluded that RIPC is effective in reducing the risk of CIN (26-28). In the aforementioned studies, the patients were hyperhydrated prior to the injection of CM, in order to prevent CIN. Therefore, the current study involved a specific group of patients who could not be hyperhydrated, enabling a better assessment of the distinctive preventive effects of RIPC. The patients who were referred to our department, especially to assess TAVI's feasibility (i.e., with aortic valve stenosis exposing them to the risk of pulmonary edema, if hyperhydrated), were selected to be included in the present study.

Moreover, previous studies on RIPC were primarily

**Table 2. Tolerance Evaluation of RIPC and Sham Procedure**

Parameters	Total (n = 26)	RIPC Group (n = 13)	Control Group (n = 13)	P
Numerical pain rating scale difference between before and after procedure	0.5 ± 1.1	0.6 ± 1.0	0.5 ± 1.1	0.72
DN4 difference between before and after procedure	0.5 ± 0.8	0.6 ± 0.9	0.4 ± 0.7	0.45

Results are expressed in mean ± standard deviation

focused on the effects following IA CM injection, with only one previous study focusing on IV CM injection (20). In the present study, the subgroup of patients with a reduced baseline eGFR ( $< 90 \text{ mL/min/1.73 m}^2$ ) displayed a significantly lower relative risk of increased serum creatinine, 48 hours after the procedure of CT, in the RIPC group, compared to the control group and the risk of CIN was observed to be reduced by 60%. In our study population involving patients who required the assessment of TAVI feasibility, enhanced CT was mandatory. Hence, including these patients enabled us to investigate the effects of RIPC without hyperhydration, in the prevention of CIN after IV CM injection.

Despite the lack of hyperhydration and the inclusion of moderate-to-very-high-risk patients (Mehran risk score  $\geq 11$  in 77% of patients), the incidence of CIN after the procedure of enhanced CT was observed to be very low (4%). This incidence was lower than that reported by other studies, which evaluated the effects of RIPC on the incidence of CIN (14-18); probably because these studies evaluated CIN following IA injection, as in a percutaneous coronary intervention setting with a higher risk of induced-CIN (29, 30). In the present study, no significant difference was observed in the serum creatinine level progression between the patients who underwent CA 48 hours after the procedure of enhanced CT and the patients' baseline values and the values estimated 24 hours after the procedure of CA.

Interestingly, this result was confirmed by measuring the serum cystatin C levels, a marker that could be superior to serum creatinine levels in reflecting the eGFR. This marker represents an earlier rise in kinetics, without being affected by non-renal variables (31-33). In the current study, the variation in cystatin C levels recorded were concurrent with those observed with respect to the creatinine levels. In brief, the two groups in the current study did not display a statistically significant difference in the progression of the cystatin C levels from the baseline values to the values estimated 48 hours after enhanced CT, as well as between the baseline values and the values estimated 24 hours after the procedure of CA; thereby confirming the absence of CIN among the patients involved in the study.

The current study has several limitations. The number of patients required at the end of the inclusion period could not be included in the study. This difficulty was chiefly due to the fact that all blood sample analyses had to be performed in our own laboratory, in order to avoid any bias. Therefore, patients had to be hospitalized, in order

to participate in the study. Nonetheless, owing to the reimbursement charges in our health care system, fewer patients were hospitalized, thereby limiting our ability to include more patients in the study. Furthermore, towards the end of the expected inclusion period, the scientific committee associated with the study decided to terminate the current study, due to the fact that the incidence of CIN cases were much lower (4%) than the expected value (55%) based on the Mehran risk score. However, the authors would like to offer a reminder that this score was established to estimate the risk of CIN, following IA CM injections. Our results regarding the incidence of CIN was consistent with those reported by previous studies, which estimated the incidence of CIN in high-risk patients to be nearly 3% (34). This low incidence limits the interpretation of the results of the current study, considering the relatively small number of patients included.

In conclusion, the risk of CIN appears to be low in the patients receiving IV CM injection with Mehran risk scores greater than or equal to six, who are unable to receive preventive hyperhydration. The present study did not reveal any beneficial effects of RIPC regarding the reduction in the incidence of CIN. Therefore, the Mehran risk score may not be an appropriate method to estimate the risk of CIN after IV CM injections.

#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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