

Ischemic Preconditioning for Prevention of Contrast Medium–Induced Nephropathy

Randomized Pilot RenPro Trial (Renal Protection Trial)

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Background—Contrast medium–induced acute kidney injury is associated with substantial morbidity and mortality. The underlying mechanism has been attributed in part to ischemic kidney injury. The aim of this randomized, double-blind, sham-controlled trial was to assess the impact of remote ischemic preconditioning on contrast medium–induced acute kidney injury.

Methods and Results—Patients with impaired renal function (serum creatinine >1.4 mg/dL or estimated glomerular filtration rate <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$) undergoing elective coronary angiography were randomized in a 1:1 ratio to standard care with (n=50) or without ischemic preconditioning (n=50; intermittent arm ischemia through 4 cycles of 5-minute inflation and 5-minute deflation of a blood pressure cuff). Overall, both study groups were at high risk of developing contrast medium–induced acute kidney injury according to the Mehran risk score. The primary end point was the incidence of contrast medium–induced kidney injury, defined as an increase in serum creatinine $\geq 25\%$ or ≥ 0.5 mg/dL above baseline at 48 hours after contrast medium exposure. Contrast medium–induced acute kidney injury occurred in 26 patients (26%), 20 (40%) in the control group and 6 (12%) in the remote ischemic preconditioning group (odds ratio, 0.21; 95% confidence interval, 0.07–0.57; $P=0.002$). No major adverse events were related to remote ischemic preconditioning.

Conclusions—Remote ischemic preconditioning before contrast medium use prevents contrast medium–induced acute kidney injury in high-risk patients. Our findings merit a larger trial to establish the effect of remote ischemic preconditioning on clinical outcomes.

Clinical Trial Registration—URL: <http://www.germanctr.de>. Unique identifier: U1111-1118-8098. (*Circulation*. 2012;126:296-303.)

Key Words: chronic kidney disease ■ contrast-induced nephropathy ■ coronary angiography ■ prevention

Contrast medium–induced acute kidney injury (CI-AKI) is a serious complication of coronary angiography (CA). CI-AKI is one of the leading causes of hospital-acquired acute renal failure, accounting for 12% of all cases, and is associated with considerable morbidity and mortality.^{1,2} With increasing use of contrast medium in diagnostic and interventional procedures, the prevalence of CI-AKI is expected to rise in the next few decades.

Clinical Perspective on p 303

Preexisting renal dysfunction with estimated glomerular filtration rate (eGFR) <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$ is the main predictor of CI-AKI, and its severity correlates directly with the incidence of CI-AKI.^{3–5} Other risk factors for CI-AKI

include diabetes mellitus, major cardiovascular comorbidities, hypovolemia, administration of high doses of contrast medium, and concomitant use of drugs that interfere with the regulation of renal perfusion.⁵

Patients undergoing CA are generally at high risk of developing CI-AKI because of existing comorbidities. Unfortunately, resoundingly successful prevention options are lacking. Novel prevention and treatment strategies are required to decrease the incidence of CI-AKI and to preserve kidney function in patients undergoing CA.

In this respect, remote ischemic preconditioning (IPC) may offer a novel, nonpharmacological prevention strategy for decreasing CI-AKI incidence in patients undergoing CA. It is assumed that IPC confers protective effects on tissue or organ

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Received January 27, 2012; accepted May 17, 2012.

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DOI: 10.1161/CIRCULATIONAHA.112.096370

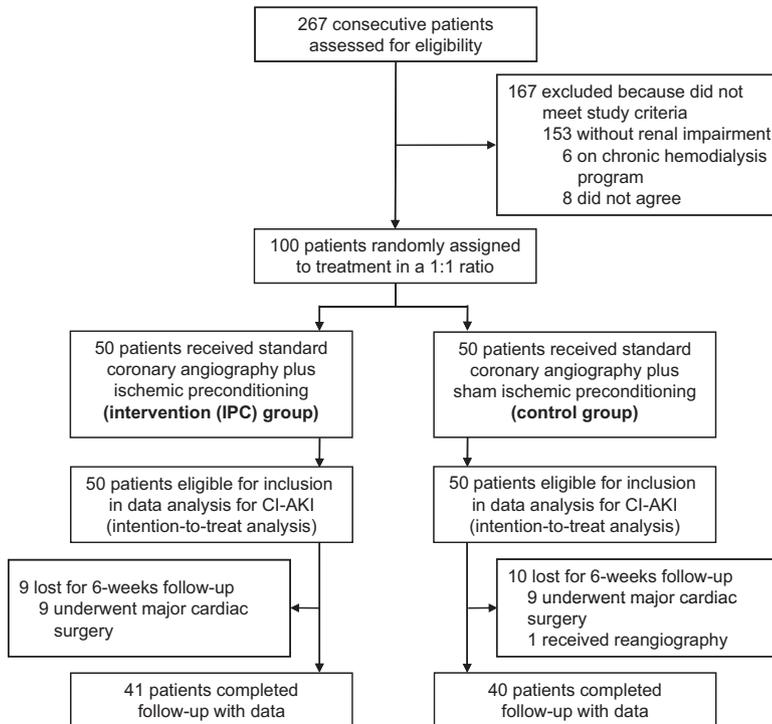


Figure 1. Study flow chart. IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury.

by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ. This simple technique can be used in all medical centers worldwide.

The role of IPC in reducing the incidence of CI-AKI is unknown. In this prospective, randomized, sham-controlled pilot study, we hypothesized that IPC applied before CA may be beneficial in the prevention of CI-AKI in patients at high risk.

Methods

Study Population

Eligible patients were ≥ 18 years of age, presented with stable angina pectoris, and were admitted to the Cardiology Department of the University Hospital of Cologne for elective CA. The renal function test revealed impaired renal function with elevated serum creatinine of >1.4 mg/dL or reduced eGFR <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$, calculated by the Modification of Diet in Renal Disease formula: $186 \times (\text{serum creatinine [mg/L]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if of African descent})$.⁶ No patient had end-stage renal failure with the need for hemodialysis.

This prospective, randomized, blinded, sham-controlled, single-center pilot trial was conducted from January 2011 until June 2011 at the University Hospital of Cologne, Germany. All patients gave their written informed consent.

Study Protocol

Sealed envelopes were used to randomly assign consecutive patients in a 1:1 ratio to receive 1 of the 2 treatments: Standard CA with sham preconditioning before CA (control group) or remote IPC before standard CA through intermittent upper-arm ischemia. In accordance with internal departmental guidelines, all patients received standard care for patients with impaired renal function undergoing CA: Oral *N*-acetylcysteine (NAC) 600 mg twice orally, the day before and on the day of CA, and continuous intravenous saline infusion (0.9%) 12 hours before to 12 hours after CA (1 mL per kilogram of body weight per hour); withdrawal of nephrotoxic drugs (eg, aminoglycosides, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, met-

formin, and others); and limitation of contrast medium application to $<5 \times \text{body weight [kg]} \times (\text{serum creatinine [mg/dL]})^{-1.7}$.

The primary outcome was the incidence of CI-AKI, which was defined as an increment of serum creatinine ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$ over the baseline value within a period of 48 hours after contrast medium administration. Secondary outcomes were the maximum elevation of serum creatinine, cystatin C, and urinary neutrophil gelatinase-associated lipocalin (NGAL) in a 48-hour period after contrast medium exposure. The composite cardiovascular end point included death, rehospitalization, or hemodialysis during 6-week follow-up.

Procedures

IPC was accomplished by performing 4 cycles of alternating 5-minute inflation and 5-minute deflation of a standard upper-arm blood pressure cuff to the individual's systolic blood pressure plus 50 mm Hg to induce transient and repetitive arm ischemia and reperfusion. IPC was started immediately before CA. The time between the last inflation cycle and the start of CA was <45 minutes.

Sham preconditioning was performed in the same way as IPC, by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff for 10 mm Hg to maintain nonischemic upper-arm compression for blinding purposes with regard to the patients. To blind the physicians, investigators performing the preconditioning procedure (A.M.N., H.D., and K.M.D.) were not involved in any other data acquisition or statistical analysis.

CA was performed according to standard clinical practice. Percutaneous intervention was performed at the physician's discretion. In all patients, Accupaque 300 (iohexol; osmolality 0.64 Osm/kg H₂O at 37°C), a nonionic low-osmolar contrast medium, was used. The postprocedural period was divided into the acute phase during hospitalization (≥ 48 hours) and follow-up (6 weeks after CA). Samples in the acute phase were obtained from all subjects during hospitalization. Data for the 6-week follow-up time point were acquired during patient visits in our outpatient clinic.

Study Oversight

The study protocol was approved by the local ethics committee and was designed in accordance with the Helsinki II declaration. The trial was conducted in accordance with the trial protocol. The Renal

Table 1. Demographical, Clinical, and Angiographic Characteristics of the Patients*

	Control Group (n=50)	IPC Group (n=50)
Age, y	72.7±11.4	73.2±9.1
Men	37 (74)	34 (68)
Body mass index, kg/m ²	27.6±5.2	27.3±3.8
Hypertension	45 (90)	46 (92)
Smokers	5 (10)	7 (14)
Dyslipidemia	36 (72)	39 (78)
Diabetes mellitus		
Insulin therapy	18 (36)	15 (30)
Diet and oral antidiabetic drugs	14 (28)	17 (34)
Peripheral artery disease	12 (24)	14 (28)
NYHA functional class		
I–II	11 (22)	9 (18)
III	31 (62)	33 (66)
Prior coronary artery disease	35 (70)	31 (62)
Prior myocardial infarction	22 (44)	19 (38)
Percutaneous intervention		
Prior	28 (56)	30 (60)
Current	11 (22)	17 (34)
Prior coronary artery bypass surgery	12 (24)	10 (20)
Left ventricular ejection fraction		
Mean	60.4±20.3	58.7±20.3
>60%	17 (34)	15 (30)
45%–59%	18 (36)	18 (36)
30%–44%	10 (20)	11 (22)
<30%	5 (10)	6 (12)
Volume of contrast medium, mL	103±41	124±44
Baseline eGFR (MDRD), mL · min ⁻¹ · 1.73 m ⁻²	41.3±11.9	40.6±8.7
Baseline eGFR (CKD-EPI), mL · min ⁻¹ · 1.73 m ⁻²	38.6±12.2	37.9±8.7
Baseline serum creatinine, mg/dL†	1.62 (1.39–1.93)	1.63 (1.47–1.81)
Baseline serum osmolarity, mOsm/L	297.8±10.4	296.6±8
Baseline hemoglobin, g/dL	12.4±2.1	12.8±1.9
Integer CI-AKI risk score (score points)		
Mean (Q1–Q3)	13 (10–16)	13 (10–17)
≤5	1 (2)	2 (4)
6–10	21 (42)	17 (34)
11–15	17 (34)	19 (38)
≥16	11 (22)	12 (24)

IPC indicates ischemic preconditioning; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI-AKI, contrast medium–induced acute kidney injury; and Q1–Q3, quartiles 1 and 3.

*Normally distributed data are presented as mean±SD and nonnormally distributed data as median (Q1–Q3); other data are shown as n (%).

†To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.

Table 2. Baseline Cardiovascular Medication Taken by the Patients

	Control Group (n=50)	IPC Group (n=50)
β-blocker	40 (80)	42 (84)
Angiotensin-converting enzyme inhibitor	25 (50)	26 (52)
Angiotensin II receptor antagonist	12 (24)	18 (36)
Calcium channel blocker	17 (34)	14 (28)
Thiazide diuretics	23 (46)	22 (44)
Loop diuretics	29 (58)	28 (56)
Loop diuretics (periprocedural)	19 (38)	21 (42)
Spirolactone	13 (26)	7 (14)

IPC indicates ischemic preconditioning.

Values are n (%).

Protection I Trial (RenPro I Trial) was initially planned as a 2-step trial. The present first step was designed as proof of concept that IPC might be beneficial in patients at high risk for CI-AKI. On the basis of the results of the present study, a second extended trial (the RenPro II Trial) was designed to test the effects of IPC on cardiovascular mortality and morbidity. The advisory board recommended reporting the present preliminary results because of the observed clearly beneficial effects of IPC.

Statistical Analysis

We calculated the sample size on the basis of a power analysis that assumed a minimum clinically important difference of 10% difference between groups in the rate of the primary end point. We assumed a contrast medium–induced nephropathy incidence between 35% and 45% in the control group.⁸ All variables were tested for normal distribution with the Kolmogorov–Smirnov test. Variables that conformed to normal distribution were summarized as means (SD) and otherwise as median and the first and third quartiles (Q1–Q3). We used Mann–Whitney *U* test and Fisher exact test to compare categorical variables.

The effect of IPC on trial outcome was evaluated with univariable and multivariable logistic regression. The latter also included 2 of 5 prespecified risk factors (ie, age, diabetes mellitus, left ventricular ejection fraction, contrast medium volume, and volume of saline infusion) that showed the strongest “univariable” association with CI-AKI. A mixed model for repeated-measures analysis was performed to compare changes between groups of serum creatinine, urine NGAL, and cystatin C at different time points.

Statistical analyses were performed with SPSS 20.0. A 2-sided probability value of <0.05 was considered to indicate statistical significance; a Bonferroni correction was applied to probability values for 7 pairwise comparisons of groups at specific time points.

Results

Figure 1 shows the trial profile. A total of 267 patients were assessed for eligibility, but 153 did not fulfill the entry criteria of impaired renal function, 6 were undergoing a chronic hemodialysis program, and 8 did not agree to the protocol. A total of 100 patients (mean age 73.2±9.1 years; 71 men, 29 women) were included. Of these patients, 50 were randomly allocated to receive standard therapy (control group) and 50 to receive standard therapy plus IPC (IPC group). None of the patients were excluded after randomization.

Table 1 shows demographic, angiographic, and clinical characteristics of the different treatment arms. The calculated risk score suggested an equal probability of developing CI-AKI in both groups.⁸ On admission, the baseline serum creatinine concentration was >1.4 mg/dL (>124 μmol/L) in

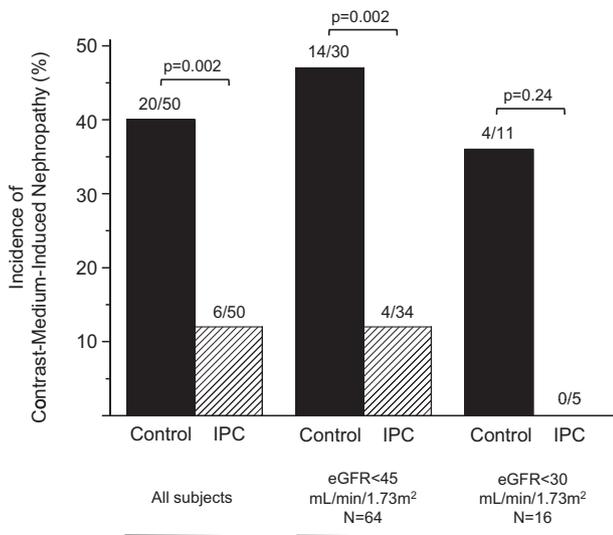


Figure 2. Incidence of contrast medium–induced nephropathy in patients with ischemic preconditioning (IPC) and control patients. eGFR indicates estimated glomerular filtration rate.

86 patients (47 in the IPC group and 39 in the control group), and eGFR was $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ in all 100 patients. Patients with IPC received larger amounts of contrast medium because of a higher rate of percutaneous interventions in this group (control group $103 \pm 41 \text{ mL}$ versus IPC group $124 \pm 44 \text{ mL}$). Cardiovascular medication use was similar in the 2 groups (Table 2). Loop diuretics were withdrawn periprocedurally and started again the day after CA. In 40 subjects (40%), 19 (38%) in the control group and 21 (42%) in the IPC group, loop diuretics were given because of heart failure symptoms.

Overall, the primary study end point, contrast medium–induced nephropathy, occurred in 26 patients: 6 (12%) in the IPC group and 20 (40%) in the control group (odds ratio in univariable analysis, 0.21; 95% confidence interval, 0.07–0.57; $P=0.002$; Figure 2; Table 3). Multivariable analysis with adjustment for contrast medium amount and diabetes mellitus status revealed that IPC was a strong independent

correlate for prevention of CI-AKI (odds ratio, 0.12; 95% confidence interval, 0.04–0.40; $P=0.001$).

Surrogate measures for acute kidney injury were acquired before and after contrast medium administration. Serum creatinine was similar in both groups at baseline (control group 1.62 mg/dL, Q1–Q3 1.39–1.91 mg/dL; IPC group 1.63 mg/dL, Q1–Q3 1.47–1.81 mg/dL) and after 24 hours (control group 1.58 mg/dL, Q1–Q3 1.39–2.00 mg/dL; IPC group 1.62 mg/dL, Q1–Q3 1.40–1.85 mg/dL; $P=0.13$) but increased significantly more after 48 hours in control patients (2.03 mg/dL, Q1–Q3 1.62–2.34 mg/dL) compared with patients with IPC (1.79 mg/dL, Q1–Q3 1.53–2.03 mg/dL; $P=0.003$; Figure 3A). Serum cystatin C increment 24 and 48 hours after CA also reflected major renal injury in the control group compared with patients with IPC (24 hours: control group 121.43%, Q1–Q3 113.33%–132.14%, and IPC group 106.70%, Q1–Q3 103.70%–111.76%; $P<0.001$; 48 hours: control group 114.64%, Q1–Q3 107.69%–127.27%, and IPC group 100.96%, Q1–Q3 97.87%–109.38%; $P<0.001$; Figure 3B). Urinary NGAL, an early marker for kidney injury, increased 6 hours after contrast medium use by 244.48% (Q1–Q3 191.61%–328.59%) in the control group and 178.28% (Q1–Q3 149.08%–212.54%) in the IPC group ($P<0.001$). This difference remained after 24 hours (control group 544.94%, Q1–Q3 363.74%–785.89%; IPC group 152.15%, Q1–Q3 125.03%–194.71%; $P<0.001$) and 48 hours (control group 316.62%, Q1–Q3 245.23%–504.76%; IPC group 119.61%, Q1–Q3 103.31%–138.95%; $P<0.001$; Figure 3C).

Eighteen patients (9 in each group) underwent major cardiovascular surgery or intervention during 6 weeks of follow-up (10 coronary artery bypass surgeries, 6 surgical valve replacements, and 2 transcatheter aortic valve implantations). One patient underwent repeated CA. Data for these 19 patients were included until the date of surgical or interventional procedure and excluded thereafter. Outcome measures after surgical or percutaneous intervention are shown separately in Tables 4 and 5. Seven patients required hemodialysis after surgery or percutaneous coronary intervention (7 in the control group versus 0 in the IPC group;

Table 3. Trial Outcomes

	Control Group (n=50)	IPC Group (n=50)	P
Primary end point			
Contrast medium–induced nephropathy, n (%)	20 (40)	6 (12)	0.002
Secondary end point			
Serum creatinine at 48 h, mg/dL (Q1–Q3)	2.03 (1.62–2.34)	1.79 (1.53–2.03)	0.01
Urinary neutrophil gelatinase-associated lipocalin, peak change from baseline, % (Q1–Q3)	544.94 (363.74–785.90)	178.28 (149.08–212.54)	<0.001
Serum cystatin C, peak change from baseline, % (Q1–Q3)	121.43 (113.33–132.14)	106.70 (103.70–111.76)	<0.001
Composite cardiovascular end point, n (%)			
Death, rehospitalization or hemodialysis	19 (38)	8 (16)	0.018
Death	2 (4)	0 (0)	0.49
Rehospitalization	18 (36)	7 (14)	0.016
Hemodialysis	2 (4)	1 (2)	1.00

IPC indicates ischemic preconditioning; Q1–Q3, first and third quartiles.

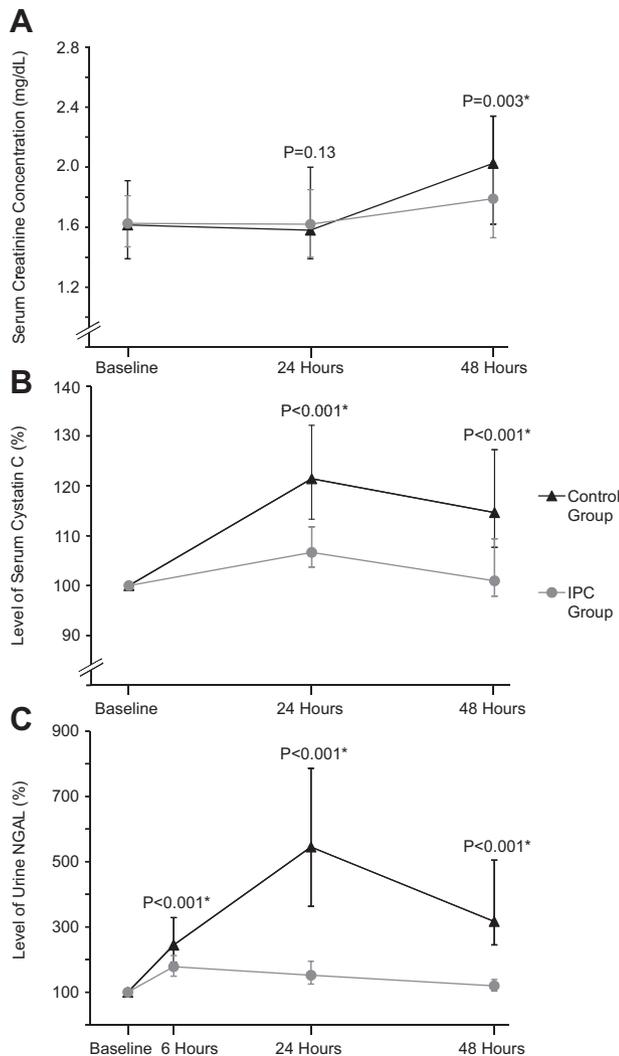


Figure 3. Surrogate measures for acute kidney injury. Changes in serum creatinine (A), serum cystatin C (B), and urine neutrophil gelatinase-associated lipocalin (NGAL; C) at different time points compared with baseline in patients with ischemic preconditioning (IPC) and control patients (median and first and third quartiles). *Bonferroni corrected.

$P=0.001$). Eight patients died after surgery or percutaneous coronary intervention (4 in each group).

The composite cardiovascular end point occurred in 27 patients, 19 (38%) in the control group and 8 (16%) in the IPC group ($P=0.018$; Table 3). Two patients in the control group died during follow-up (1 of myocardial infarction and 1 of intracerebral bleeding; $P=0.49$) versus no deaths in the IPC group. Rehospitalization was significantly less frequent in patients with IPC than in control patients (7 [14%] in the IPC group versus 18 [36%] in the control group; $P=0.016$). The most common reason for hospitalization was dyspnea caused by worsening of heart failure symptoms (Table 6). Hemodialysis was necessary in 2 patients in the control group and in 1 with IPC ($P=1.00$).

No major adverse events occurred during sham-control preconditioning and IPC. In 2 patients with IPC, 2 instead of 4 cycles of upper-arm ischemia were performed because of patient discomfort. Six additional patients with IPC devel-

oped mild reversible petechial spots distal to the blood pressure cuff.

Discussion

The present study demonstrates that remote IPC, induced by intermittent upper-arm ischemia before an invasive coronary procedure, dramatically reduces the incidence of contrast medium-induced nephropathy in patients with chronic kidney disease and high risk for CI-AKI. Additionally assessed surrogate measures support the preventive effect of IPC. This protective effect appeared to be independent of all other factors, eg, contrast medium amount and comorbidities of the patients. In addition, IPC significantly decreased the incidence of the composite cardiovascular end point, which consisted of death, hospitalization, or hemodialysis.

CI-AKI is a frequent and serious complication after CA with or without percutaneous coronary intervention. Moreover, CI-AKI has been shown to be an independent predictor of 1-year mortality in patients with coronary artery disease.⁸ The incidence of CI-AKI varies substantially among several studies because of the lack of a uniform definition of CI-AKI.^{9,10} Rates of CI-AKI may be as high as >50%, depending on the presence of risk factors such as chronic renal insufficiency and diabetes mellitus or heart failure.^{4,8,10,11}

In 2004, Mehran et al⁸ developed a risk classification system to predict risk for contrast medium-induced nephropathy in patients undergoing CA. This most comprehensive and best-validated risk stratification score includes 8 clinical and procedural variables and is divided into 4 classes of risk of developing CI-AKI: Low (risk score ≤ 5), moderate (risk score 6–10), high (risk score 11–15), and very high (risk score ≥ 16). The calculated mean integer score for both groups in the present study was 13, thus determining the present study population as a group at high risk of developing CI-AKI ($\approx 60\%$ of the subjects were at high or very high risk). Indeed, the reported incidence of 40% in the control arm of the study is within the reported range¹² and corresponds exactly to the serum creatinine-based CI-AKI incidence predicted by Mehran et al.⁸

The demonstrated CI-AKI incidence in the present study cohort is higher than in other publications with comparable baseline eGFR.¹³ This is attributed at least in part to the high incidence of comorbidities in the RenPro study population ($\approx 80\%$ had congestive heart failure, and >60% had diabetes).

Despite its broader prevalence, the precise pathophysiological mechanisms of CI-AKI have not been elucidated clearly. The pathogenesis of CI-AKI is multifactorial, because vascular, hemodynamic, and tubular factors contribute to its development. The most common pathophysiological concept of CI-AKI is the induction of renal ischemic injury, possibly caused by iodinated contrast medium-induced reduction in renal blood flow and oxygen free radical-mediated direct tubular toxicity.¹⁴ Other underlying mechanism for pathological changes in CI-AKI include contrast medium-induced natriuresis and diuresis, which activate the tubuloglomerular feedback response with subsequent vasoconstriction of the glomerular afferent arterioles, causing a decrease in glomerular filtration rate.

Table 4. List of Patients With Major Cardiac Surgery or Percutaneous Intervention

Age, y	Procedure	Timing of Procedure (Days After Inclusion)	Initial Treatment Group, IPC vs Control	CI-AKI	Hemodialysis	Death (Cause)
83	CABG	12	Control	Yes	Yes	Yes (sepsis)
68	CABG	16	IPC	No	No	No
67	CABG	10	Control	No	Yes	No
81	CABG	8	IPC	No	No	Yes (SCD)
56	CABG	5	IPC	Yes	No	Yes (ICB)
78	CABG	26	IPC	No	No	Yes
81	CABG	14	Control	Yes	Yes	No
74	CABG	7	IPC	Yes	No	Yes (MI)
69	CABG	8	Control	No	Yes	No
79	CABG	10	IPC	No	No	No
68	AVR	7	Control	Yes	Yes	No
65	AVR	7	Control	No	No	No
62	AVR	19	Control	No	No	No
60	AVR	11	IPC	No	No	No
69	MVR	9	IPC	No	No	No
71	MVR	23	IPC	No	No	No
85	TAVI	15	Control	Yes	Yes	Yes (PC)
86	TAVI	17	IPC	No	No	No
84	Re-CA	7	Control	Yes	Yes	Yes (MOF)

IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury; CABG, coronary artery bypass graft; SCD, sudden cardiac death; MI, myocardial infarction; ICB, intracranial bleeding; AVR, aortic valve replacement; MVR, mitral valve replacement; TAVI, transfemoral aortic valve implantation; PC, procedural complication; Re-CA, repeated coronary angiography and percutaneous coronary intervention; and MOF, multiorgan failure.

To date, there is no effective prophylactic regimen to prevent CI-AKI. Dopamine, fenoldopam, furosemide, mannitol, aminophylline, atrial natriuretic peptide, captopril, calcium channel blockers, and alprostadil were not effective in reducing the incidence of CI-AKI.^{15–18} Initial studies assessing the ability of NAC to prevent CI-AKI were encouraging; however, the role of NAC in prevention of CI-AKI has been questioned, because subsequent larger trials failed to demonstrate an NAC-associated benefit.^{19,20} Likewise, there are inconsistent data on the effects of NAC on serum creatinine. In healthy volunteers with normal renal function and no exposure to contrast medium, there was a small but significant decrease in mean serum creatinine and urea concentrations and a significant increase in eGFR.²¹ Levels of cystatin

C remained unchanged after NAC administration. However, no change in serum creatinine or cystatin C was observed in patients with chronic kidney disease.^{22,23}

Our hypothesis that IPC may be nephroprotective was largely based on earlier reports showing the beneficial action of IPC in several clinical settings. IPC has been reported to decrease the incidence of perioperative myocardial injury during cardiac surgery in adults^{24,25} and children²⁶ and to diminish both myocardial and renal injury incidence during surgery for endovascular²⁷ and open surgical²⁸ repair of abdominal aortic aneurysm. Very recently, IPC before hospital admission increased myocardial salvage by attenuation of reperfusion injury in patients with evolving myocardial infarction.²⁹

Although serum creatinine is the most widely used serum marker of renal function, serum cystatin C and urinary NGAL

Table 5. Outcomes in Patients With Cardiac Surgery or Percutaneous Intervention

	Control Group (n=9)	IPC Group (n=10)
CI-AKI	5	2
Hemodialysis	7	0*
Before surgery/PCI	0	...
After surgery/PCI	7	...
Death	4	4

IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury; and PCI, percutaneous coronary intervention.

*P=0.001.

Table 6. Reasons for Hospitalization During 6-Week-Follow-Up

	Control Group (n=18)	IPC Group (n=7)
Dyspnea	8	3
Angina pectoris	5	2
Syncope	1	0
Symptomatic arrhythmia	1	1
Pneumonia	2	0
Transitory neurological deficit	1	0
Other	0	1

IPC indicates ischemic preconditioning.

have been reported to be more specific and sensitive to acute and early deteriorations in renal function.^{30–33} Indeed, serum creatinine is not an adequate marker for CI-AKI.^{34,35} Thus, >50% of renal function must be lost before an elevation in serum creatinine is detected. In addition, serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require several days.³³ The serum cystatin C level and NGAL are more sensitive in identifying moderate renal insufficiency than the serum creatinine level.³⁶ Furthermore, cystatin C is not affected by renal tubular secretion or pharmacological treatments.^{23,37} In particular, NGAL has been shown to be an early, sensitive, specific, and predictive biomarker of acute kidney injury after contrast medium administration.³⁸ Therefore, both measures were also investigated in the present study and correlated well with the eGFR reduction and, subsequently, contrast medium–induced renal damage. Consistently, both early markers of the CI-AKI were raised after exposure to contrast agent. This was evident at 6 and 24 hours after contrast medium application, whereas serum creatinine was unchanged at the same time.

Given the results of the present study, a novel concept of cytoprotection by IPC before CA may be considered for the prevention of CI-AKI in numerous patients. We calculated that 4 patients at elevated risk for CI-AKI have to be treated by IPC to prevent 1 CI-AKI (number needed to treat 3.6; 95% confidence interval, 2–9). Moreover, IPC can be applied easily, and virtually no safety concerns exist if it is performed appropriately. Even if the underlying mechanisms of IPC-mediated beneficial effects remain largely unknown, the noninvasive IPC protocol is likely to have direct effects on decreasing renal ischemia/reperfusion injury incidence as part of the systemic protective effect of this phenomenon.

It has been postulated that a remote organ releases humoral factors such as adenosine or bradykinin into the systemic circulation, which subsequently protect the remote region or organ. Other underlying mechanisms may include erythropoietin, activation of the K_{ATP} channel, nitric oxide, delta 1-opioid, and free radicals.³⁹ Some studies have also suggested that the protective effect of IPC may be caused by its beneficial anti-inflammatory or antioxidant effects and decreased extracellular levels of noxious metabolites, such as protons and lactate.^{39,40} Additionally, some other studies have favored a neurogenic pathway.⁴¹

Overall, our concept suggests a humoral basis for the underlying renoprotective effects, because in the additional experimental setting, we found elevated erythropoietin plasma levels and mRNA expression in a reperfusion-ischemia mouse model (V. Burst et al, unpublished data, 2012). It is well known that reperfusion injury involves several pathways, including alterations in cellular metabolism, endothelial dysfunction, inflammation, hypercontracture, and necrosis/apoptosis.⁴² Thus, IPC-mediated counterregulatory protective pathways may eventually offer an additional clinical benefit and contribute to better clinical outcomes.

Among those patients with major cardiac surgery or percutaneous coronary intervention, more control patients than patients with initial IPC required hemodialysis. Although this difference was statistically significant, the small

number in the subgroup limits this effect, but it may merit further investigation.

However, the present study has several limitations. This pilot investigation of the beneficial effects of IPC on renal function is a single-center trial with a limited sample size. Although we sought to prevent any bias by blinding the patients and the data analysis team, the study design cannot prevent all influential effects. The a priori sample size calculation was based on inaccurate assumptions and calculations because of the pilot nature of the study. Nevertheless, it is of no question that the described hypothesis is a highly appealing and practicable method to reduce potential life-threatening complications of organs in general.

In this study, we demonstrated that the simple and well-tolerated application of IPC in high-risk patients with renal dysfunction undergoing CA reduced the incidence of procedure-related CI-AKI. In addition, the nephroprotective effect of IPC was associated with improved clinical outcomes at 6 weeks. Thus, the use of IPC may be a feasible and highly attractive therapeutic procedure and should be investigated in future trials.

Sources of Funding

The trial was undertaken under the auspices of the Department of Internal Medicine III, University Hospital of Cologne (Germany), a nonprofit public law institution. The RenPro Study Investigators, an investigator-initiated study group (by F.E.), was solely responsible for the study design, data collection, data analysis, data interpretation, and writing of the report.

Disclosures

None.

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CLINICAL PERSPECTIVE

The prevention of contrast medium–induced acute kidney injury is a major challenge for interventional cardiologists. Several patient and procedure-associated risk factors were identified in previous studies. Only a few contrast medium–induced acute kidney injury prevention strategies exist. Ischemic preconditioning has been shown in the RenPro (Renal Protection) Trial to be an effective, safe, and economic method for prevention of contrast medium–induced acute kidney injury in high-risk patients. The broad application of this method in daily clinical settings may remarkably influence the cardiovascular outcome in high-risk patients.

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허혈 전처치 요법이 조영제에 의한 콩팥장애를 예방한다

조 상 호 교수 한림대학교 성심병원 순환기내과

Summary

배경

조영제-유발 급성 신손상(contrast medium-induced acute kidney injury, CI-AKI)의 환자 이환율 및 사망률과의 연관성은 잘 알려져 왔다. 그 기전 중 하나로 허혈성 신손상이 거론되어 왔다. 본 연구는 원격 허혈성 전처치(remote ischemic preconditioning, rIPC)가 CI-AKI에 미치는 영향을 알아보기 위한 무작위 이중맹검 임상연구이다.

방법 및 결과

관상동맥조영술을 받는 환자 중 신장 기능이 저하된 [serum creatinine >1.4mg/dL 또는 eGFR(estimated glomerular filtration rate) <60mL/min/1.73m²] 환자를 대상으로 하였으며, 이들을 일반 치료군(50명)과 rIPC군(50명)으로 1:1 배정하였다. rIPC는 수은 혈압계로 5분간 상완을 조이고 5분간 푸는 방법을 1사이클로 하여 4사이클을 반복하였다.

Mehran risk score를 사용하였을 때 양군 환자들의

CI-AKI의 위험도는 전반적으로 높았다. 일차 목표점은 CI-AKI였는데, 이는 조영제에 노출된 후 기저치에 비해 serum creatinine이 $\geq 25\%$ 또는 $\geq 0.5\text{mg/dL}$ 상승으로 하였다.

CI-AKI는 전체 대상 환자 중 26명에서 발생하였는데 (26%), 20명(40%)이 대조군에서, 6명(12%)이 rIPC군에서 발생하였다(odds ratio, 0.21; 95% CI, 0.07-0.57; $P=0.002$). 주요 심혈관계 사건과 rIPC는 연관이 없었다.

결론

조영제 사용 전의 rIPC는 고위험 환자에서 CI-AKI를 예방한다. 이 연구는 추후 rIPC의 임상적 효과를 확인하기 위한 대규모 연구의 시행을 위한 이론적 배경이 될 수 있다.

Commentary

CI-AKI는 관상동맥조영술 시행의 주요 합병증으로써 전체 입원 환자의 신기능 저하 중 12%를 차지하며, 이들 원인 중 3위에 해당한다. 이러한 사실의 중요성은 CI-AKI로 인해 합병증과 사망이 증가한다는 점에 있다. 현재 고령의 죽상경화성 환자들이 증가하면서 조영제 사용 및 CI-AKI가 증가할 것이라고 여겨지고 있기 때문에 향후 더욱 중요한 의료 문제가 될 가능성이 높다.

그동안 연구된 예방법으로는 항산화제, 혈관 확장제, 혈액투석 등 여러 약제와 물리적인 방법들이 시도되었으나, 단순 saline hydration 이외에는 효과가 없음이 증명되었다. 특히, 그동안 효과에 대해서 많은 논란을 불러일으켜 왔던 항산화제인 N-acetylcysteine에 대해서는 최근의 대규모 전향적 무작위 연구에서 효과가 없음이 밝혀졌기에¹ saline hydration 이외의 추가적 예방법이 필요한 실정이다.

본 연구의 이론적 배경은 장기의 허혈성 손상을 억제하고자 다른 장기(대표적으로 사지의 근육)를 일시적이고 반복적인 허혈 상태에 노출시키면 원래 장기의 손상이 감소한다는 데 있다. 주로 간이나 신장 이식 분야, 심장수술 시에 이러한 rIPC가 장기 손상을 예방할 수 있다는 데이터가 발표되어 왔고, 심장내과학 분야에서는 관상동맥 스텐트 삽입술 시에 원격 혹은 직접적인 허혈 전처치가 심근 손상을 최소화할 수 있다는 보고들이 꾸준히 있었다.

특히, ST분절상승 급성 심근경색증 환자에서의 직접 및 원격 허혈 전처치가 경색 크기를 감소시키는 데 효과적일 수 있다는 소규모 파일럿 연구 결과는 실제 임상 적용의 가능성을 열어 놓았다.

본 논문은 심근 보호뿐만 아니라, 신장 기능의 보호에도 이러한 허혈 전처치가 효과적인지에 대한 전향적 무작위 배정 연구로서 우선 그 아이디어가 돋보인다. CI-AKI의 여러 기전 중 하나인 신장 허혈을 이 방법으

로 예방하고자 하였고, 실제 CI-AKI가 80%나 감소하여 통계적인 유의성도 획득하였다. 더욱 주목할만한 것은 임상 사건인데 사망과 재입원, 혈액 투석 환자의 발생이 rIPC군에서 의미 있게 적었다. 이는 사망이나 투석이 아닌 주로 재입원 감소에 기인한 것이었다.

비록 소규모 연구이며, 과연 이러한 surrogate marker의 이득이 임상 예후의 향상으로 직결될지는 추후 연구가 더 필요하지만, 비교적 간단하고 부작용이 없으며 비용 효과적으로 안전한 예방법임을 고려한다면 실제 임상예의 적용도 큰 무리가 되지 않으리라 생각된다. 항산화제가 모두 실패한 현재 상황에서 CI-AKI의 새로운 예방법을 제시하였다는 데 큰 의미가 있는 중요 연구 성과로 생각한다.

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Ischemic Preconditioning for Prevention of Contrast Medium–Induced Nephropathy

Randomized Pilot RenPro Trial (Renal Protection Trial)

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Background—Contrast medium–induced acute kidney injury is associated with substantial morbidity and mortality. The underlying mechanism has been attributed in part to ischemic kidney injury. The aim of this randomized, double-blind, sham-controlled trial was to assess the impact of remote ischemic preconditioning on contrast medium–induced acute kidney injury.

Methods and Results—Patients with impaired renal function (serum creatinine >1.4 mg/dL or estimated glomerular filtration rate <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$) undergoing elective coronary angiography were randomized in a 1:1 ratio to standard care with (n=50) or without ischemic preconditioning (n=50; intermittent arm ischemia through 4 cycles of 5-minute inflation and 5-minute deflation of a blood pressure cuff). Overall, both study groups were at high risk of developing contrast medium–induced acute kidney injury according to the Mehran risk score. The primary end point was the incidence of contrast medium–induced kidney injury, defined as an increase in serum creatinine $\geq 25\%$ or ≥ 0.5 mg/dL above baseline at 48 hours after contrast medium exposure. Contrast medium–induced acute kidney injury occurred in 26 patients (26%), 20 (40%) in the control group and 6 (12%) in the remote ischemic preconditioning group (odds ratio, 0.21; 95% confidence interval, 0.07–0.57; $P=0.002$). No major adverse events were related to remote ischemic preconditioning.

Conclusions—Remote ischemic preconditioning before contrast medium use prevents contrast medium–induced acute kidney injury in high-risk patients. Our findings merit a larger trial to establish the effect of remote ischemic preconditioning on clinical outcomes.

Clinical Trial Registration—URL: <http://www.germanctr.de>. Unique identifier: U1111-1118-8098. (*Circulation*. 2012;126:296-303.)

Key Words: chronic kidney disease ■ contrast-induced nephropathy ■ coronary angiography ■ prevention

Contrast medium–induced acute kidney injury (CI-AKI) is a serious complication of coronary angiography (CA). CI-AKI is one of the leading causes of hospital-acquired acute renal failure, accounting for 12% of all cases, and is associated with considerable morbidity and mortality.^{1,2} With increasing use of contrast medium in diagnostic and interventional procedures, the prevalence of CI-AKI is expected to rise in the next few decades.

Clinical Perspective on p 103

Preexisting renal dysfunction with estimated glomerular filtration rate (eGFR) <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$ is the main predictor of CI-AKI, and its severity correlates directly with the incidence of CI-AKI.³⁻⁵ Other risk factors for CI-AKI

include diabetes mellitus, major cardiovascular comorbidities, hypovolemia, administration of high doses of contrast medium, and concomitant use of drugs that interfere with the regulation of renal perfusion.⁵

Patients undergoing CA are generally at high risk of developing CI-AKI because of existing comorbidities. Unfortunately, resoundingly successful prevention options are lacking. Novel prevention and treatment strategies are required to decrease the incidence of CI-AKI and to preserve kidney function in patients undergoing CA.

In this respect, remote ischemic preconditioning (IPC) may offer a novel, nonpharmacological prevention strategy for decreasing CI-AKI incidence in patients undergoing CA. It is assumed that IPC confers protective effects on tissue or organ

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Received January 27, 2012; accepted May 17, 2012.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.112.096370

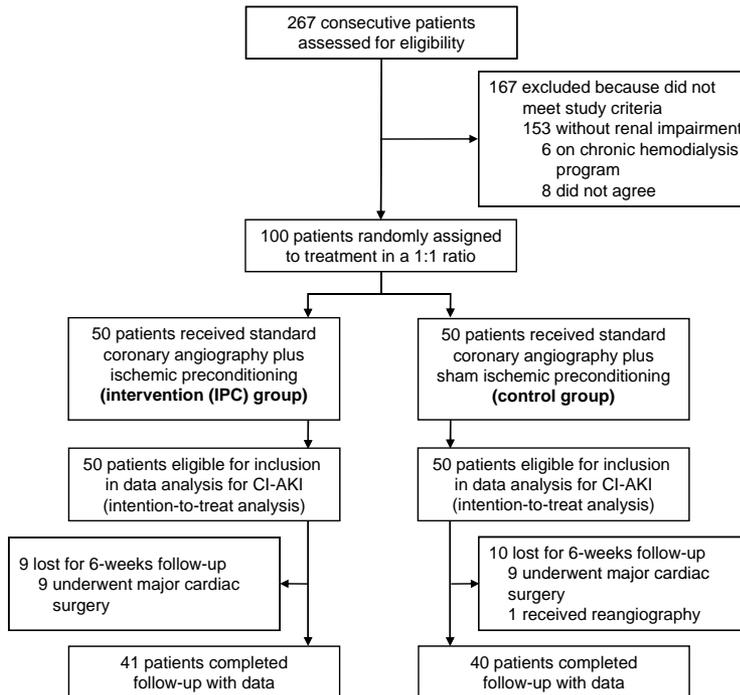


Figure 1. Study flow chart. IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury.

by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ. This simple technique can be used in all medical centers worldwide.

The role of IPC in reducing the incidence of CI-AKI is unknown. In this prospective, randomized, sham-controlled pilot study, we hypothesized that IPC applied before CA may be beneficial in the prevention of CI-AKI in patients at high risk.

Methods

Study Population

Eligible patients were ≥ 18 years of age, presented with stable angina pectoris, and were admitted to the Cardiology Department of the University Hospital of Cologne for elective CA. The renal function test revealed impaired renal function with elevated serum creatinine of >1.4 mg/dL or reduced eGFR <60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$, calculated by the Modification of Diet in Renal Disease formula: $186 \times (\text{serum creatinine [mg/L]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if of African descent})$.⁶ No patient had end-stage renal failure with the need for hemodialysis.

This prospective, randomized, blinded, sham-controlled, single-center pilot trial was conducted from January 2011 until June 2011 at the University Hospital of Cologne, Germany. All patients gave their written informed consent.

Study Protocol

Sealed envelopes were used to randomly assign consecutive patients in a 1:1 ratio to receive 1 of the 2 treatments: Standard CA with sham preconditioning before CA (control group) or remote IPC before standard CA through intermittent upper-arm ischemia. In accordance with internal departmental guidelines, all patients received standard care for patients with impaired renal function undergoing CA: Oral *N*-acetylcysteine (NAC) 600 mg twice orally, the day before and on the day of CA, and continuous intravenous saline infusion (0.9%) 12 hours before to 12 hours after CA (1 mL per kilogram of body weight per hour); withdrawal of nephrotoxic drugs (eg, aminoglycosides, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, met-

formin, and others); and limitation of contrast medium application to $<5 \times \text{body weight [kg]} \times (\text{serum creatinine [mg/dL]})^{-1.7}$.

The primary outcome was the incidence of CI-AKI, which was defined as an increment of serum creatinine ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$ over the baseline value within a period of 48 hours after contrast medium administration. Secondary outcomes were the maximum elevation of serum creatinine, cystatin C, and urinary neutrophil gelatinase-associated lipocalin (NGAL) in a 48-hour period after contrast medium exposure. The composite cardiovascular end point included death, rehospitalization, or hemodialysis during 6-week follow-up.

Procedures

IPC was accomplished by performing 4 cycles of alternating 5-minute inflation and 5-minute deflation of a standard upper-arm blood pressure cuff to the individual's systolic blood pressure plus 50 mm Hg to induce transient and repetitive arm ischemia and reperfusion. IPC was started immediately before CA. The time between the last inflation cycle and the start of CA was <45 minutes.

Sham preconditioning was performed in the same way as IPC, by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff for 10 mm Hg to maintain nonischemic upper-arm compression for blinding purposes with regard to the patients. To blind the physicians, investigators performing the preconditioning procedure (A.M.N., H.D., and K.M.D.) were not involved in any other data acquisition or statistical analysis.

CA was performed according to standard clinical practice. Percutaneous intervention was performed at the physician's discretion. In all patients, Accupaque 300 (iohexol; osmolarity 0.64 Osm/kg H₂O at 37°C), a nonionic low-osmolar contrast medium, was used. The postprocedural period was divided into the acute phase during hospitalization (≥ 48 hours) and follow-up (6 weeks after CA). Samples in the acute phase were obtained from all subjects during hospitalization. Data for the 6-week follow-up time point were acquired during patient visits in our outpatient clinic.

Study Oversight

The study protocol was approved by the local ethics committee and was designed in accordance with the Helsinki II declaration. The trial was conducted in accordance with the trial protocol. The Renal

Table 1. Demographical, Clinical, and Angiographic Characteristics of the Patients*

	Control Group (n=50)	IPC Group (n=50)
Age, y	72.7±11.4	73.2±9.1
Men	37 (74)	34 (68)
Body mass index, kg/m ²	27.6±5.2	27.3±3.8
Hypertension	45 (90)	46 (92)
Smokers	5 (10)	7 (14)
Dyslipidemia	36 (72)	39 (78)
Diabetes mellitus		
Insulin therapy	18 (36)	15 (30)
Diet and oral antidiabetic drugs	14 (28)	17 (34)
Peripheral artery disease	12 (24)	14 (28)
NYHA functional class		
I-II	11 (22)	9 (18)
III	31 (62)	33 (66)
Prior coronary artery disease	35 (70)	31 (62)
Prior myocardial infarction	22 (44)	19 (38)
Percutaneous intervention		
Prior	28 (56)	30 (60)
Current	11 (22)	17 (34)
Prior coronary artery bypass surgery	12 (24)	10 (20)
Left ventricular ejection fraction		
Mean	60.4±20.3	58.7±20.3
>60%	17 (34)	15 (30)
45%–59%	18 (36)	18 (36)
30%–44%	10 (20)	11 (22)
<30%	5 (10)	6 (12)
Volume of contrast medium, mL	103±41	124±44
Baseline eGFR (MDRD), mL · min ⁻¹ · 1.73 m ⁻²	41.3±11.9	40.6±8.7
Baseline eGFR (CKD-EPI), mL · min ⁻¹ · 1.73 m ⁻²	38.6±12.2	37.9±8.7
Baseline serum creatinine, mg/dL†	1.62 (1.39–1.93)	1.63 (1.47–1.81)
Baseline serum osmolarity, mOsm/L	297.8±10.4	296.6±8
Baseline hemoglobin, g/dL	12.4±2.1	12.8±1.9
Integer CI-AKI risk score (score points)		
Mean (Q1–Q3)	13 (10–16)	13 (10–17)
≤5	1 (2)	2 (4)
6–10	21 (42)	17 (34)
11–15	17 (34)	19 (38)
≥16	11 (22)	12 (24)

IPC indicates ischemic preconditioning; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI-AKI, contrast medium-induced acute kidney injury; and Q1–Q3, quartiles 1 and 3.

*Normally distributed data are presented as mean±SD and nonnormally distributed data as median (Q1–Q3); other data are shown as n (%).

†To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.

Table 2. Baseline Cardiovascular Medication Taken by the Patients

	Control Group (n=50)	IPC Group (n=50)
β-blocker	40 (80)	42 (84)
Angiotensin-converting enzyme inhibitor	25 (50)	26 (52)
Angiotensin II receptor antagonist	12 (24)	18 (36)
Calcium channel blocker	17 (34)	14 (28)
Thiazide diuretics	23 (46)	22 (44)
Loop diuretics	29 (58)	28 (56)
Loop diuretics (periprocedural)	19 (38)	21 (42)
Spironolactone	13 (26)	7 (14)

IPC indicates ischemic preconditioning.

Values are n (%).

Protection I Trial (RenPro I Trial) was initially planned as a 2-step trial. The present first step was designed as proof of concept that IPC might be beneficial in patients at high risk for CI-AKI. On the basis of the results of the present study, a second extended trial (the RenPro II Trial) was designed to test the effects of IPC on cardiovascular mortality and morbidity. The advisory board recommended reporting the present preliminary results because of the observed clearly beneficial effects of IPC.

Statistical Analysis

We calculated the sample size on the basis of a power analysis that assumed a minimum clinically important difference of 10% difference between groups in the rate of the primary end point. We assumed a contrast medium-induced nephropathy incidence between 35% and 45% in the control group.⁸ All variables were tested for normal distribution with the Kolmogorov-Smirnov test. Variables that conformed to normal distribution were summarized as means (SD) and otherwise as median and the first and third quartiles (Q1–Q3). We used Mann-Whitney *U* test and Fisher exact test to compare categorical variables.

The effect of IPC on trial outcome was evaluated with univariable and multivariable logistic regression. The latter also included 2 of 5 prespecified risk factors (ie, age, diabetes mellitus, left ventricular ejection fraction, contrast medium volume, and volume of saline infusion) that showed the strongest “univariable” association with CI-AKI. A mixed model for repeated-measures analysis was performed to compare changes between groups of serum creatinine, urine NGAL, and cystatin C at different time points.

Statistical analyses were performed with SPSS 20.0. A 2-sided probability value of <0.05 was considered to indicate statistical significance; a Bonferroni correction was applied to probability values for 7 pairwise comparisons of groups at specific time points.

Results

Figure 1 shows the trial profile. A total of 267 patients were assessed for eligibility, but 153 did not fulfill the entry criteria of impaired renal function, 6 were undergoing a chronic hemodialysis program, and 8 did not agree to the protocol. A total of 100 patients (mean age 73.2±9.1 years; 71 men, 29 women) were included. Of these patients, 50 were randomly allocated to receive standard therapy (control group) and 50 to receive standard therapy plus IPC (IPC group). None of the patients were excluded after randomization.

Table 1 shows demographic, angiographic, and clinical characteristics of the different treatment arms. The calculated risk score suggested an equal probability of developing CI-AKI in both groups.⁸ On admission, the baseline serum creatinine concentration was >1.4 mg/dL (>124 μmol/L) in

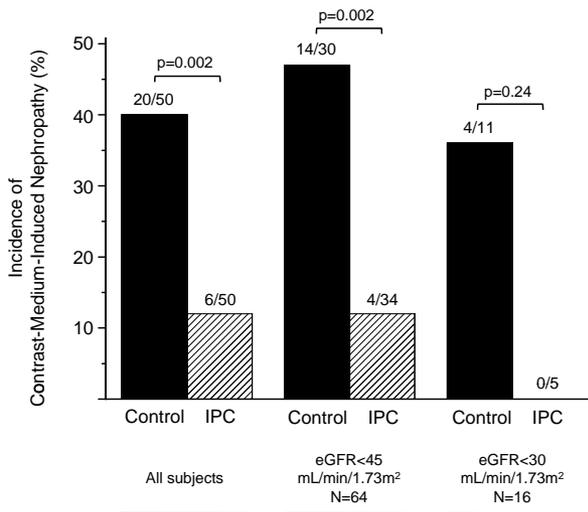


Figure 2. Incidence of contrast medium-induced nephropathy in patients with ischemic preconditioning (IPC) and control patients. eGFR indicates estimated glomerular filtration rate.

86 patients (47 in the IPC group and 39 in the control group), and eGFR was $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ in all 100 patients. Patients with IPC received larger amounts of contrast medium because of a higher rate of percutaneous interventions in this group (control group $103 \pm 41 \text{ mL}$ versus IPC group $124 \pm 44 \text{ mL}$). Cardiovascular medication use was similar in the 2 groups (Table 2). Loop diuretics were withdrawn periprocedurally and started again the day after CA. In 40 subjects (40%), 19 (38%) in the control group and 21 (42%) in the IPC group, loop diuretics were given because of heart failure symptoms.

Overall, the primary study end point, contrast medium-induced nephropathy, occurred in 26 patients: 6 (12%) in the IPC group and 20 (40%) in the control group (odds ratio in univariable analysis, 0.21; 95% confidence interval, 0.07–0.57; $P=0.002$; Figure 2; Table 3). Multivariable analysis with adjustment for contrast medium amount and diabetes mellitus status revealed that IPC was a strong independent

correlate for prevention of CI-AKI (odds ratio, 0.12; 95% confidence interval, 0.04–0.40; $P=0.001$).

Surrogate measures for acute kidney injury were acquired before and after contrast medium administration. Serum creatinine was similar in both groups at baseline (control group 1.62 mg/dL, Q1–Q3 1.39–1.91 mg/dL; IPC group 1.63 mg/dL, Q1–Q3 1.47–1.81 mg/dL) and after 24 hours (control group 1.58 mg/dL, Q1–Q3 1.39–2.00 mg/dL; IPC group 1.62 mg/dL, Q1–Q3 1.40–1.85 mg/dL; $P=0.13$) but increased significantly more after 48 hours in control patients (2.03 mg/dL, Q1–Q3 1.62–2.34 mg/dL) compared with patients with IPC (1.79 mg/dL, Q1–Q3 1.53–2.03 mg/dL; $P=0.003$; Figure 3A). Serum cystatin C increment 24 and 48 hours after CA also reflected major renal injury in the control group compared with patients with IPC (24 hours: control group 121.43%, Q1–Q3 113.33%–132.14%, and IPC group 106.70%, Q1–Q3 103.70%–111.76%; $P<0.001$; 48 hours: control group 114.64%, Q1–Q3 107.69%–127.27%, and IPC group 100.96%, Q1–Q3 97.87%–109.38%; $P<0.001$; Figure 3B). Urinary NGAL, an early marker for kidney injury, increased 6 hours after contrast medium use by 244.48% (Q1–Q3 191.61%–328.59%) in the control group and 178.28% (Q1–Q3 149.08%–212.54%) in the IPC group ($P<0.001$). This difference remained after 24 hours (control group 544.94%, Q1–Q3 363.74%–785.89%; IPC group 152.15%, Q1–Q3 125.03%–194.71%; $P<0.001$) and 48 hours (control group 316.62%, Q1–Q3 245.23%–504.76%; IPC group 119.61%, Q1–Q3 103.31%–138.95%; $P<0.001$; Figure 3C).

Eighteen patients (9 in each group) underwent major cardiovascular surgery or intervention during 6 weeks of follow-up (10 coronary artery bypass surgeries, 6 surgical valve replacements, and 2 transcatheter aortic valve implantations). One patient underwent repeated CA. Data for these 19 patients were included until the date of surgical or interventional procedure and excluded thereafter. Outcome measures after surgical or percutaneous intervention are shown separately in Tables 4 and 5. Seven patients required hemodialysis after surgery or percutaneous coronary intervention (7 in the control group versus 0 in the IPC group;

Table 3. Trial Outcomes

	Control Group (n=50)	IPC Group (n=50)	P
Primary end point			
Contrast medium-induced nephropathy, n (%)	20 (40)	6 (12)	0.002
Secondary end point			
Serum creatinine at 48 h, mg/dL (Q1–Q3)	2.03 (1.62–2.34)	1.79 (1.53–2.03)	0.01
Urinary neutrophil gelatinase-associated lipocalin, peak change from baseline, % (Q1–Q3)	544.94 (363.74–785.90)	178.28 (149.08–212.54)	<0.001
Serum cystatin C, peak change from baseline, % (Q1–Q3)	121.43 (113.33–132.14)	106.70 (103.70–111.76)	<0.001
Composite cardiovascular end point, n (%)			
Death, rehospitalization or hemodialysis	19 (38)	8 (16)	0.018
Death	2 (4)	0 (0)	0.49
Rehospitalization	18 (36)	7 (14)	0.016
Hemodialysis	2 (4)	1 (2)	1.00

IPC indicates ischemic preconditioning; Q1–Q3, first and third quartiles.

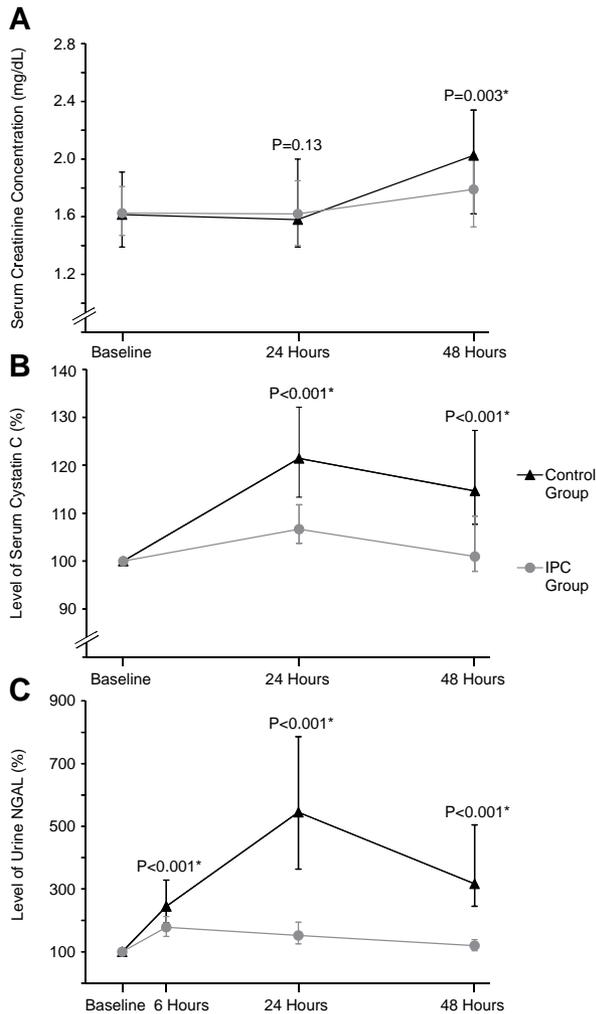


Figure 3. Surrogate measures for acute kidney injury. Changes in serum creatinine (A), serum cystatin C (B), and urine neutrophil gelatinase-associated lipocalin (NGAL; C) at different time points compared with baseline in patients with ischemic preconditioning (IPC) and control patients (median and first and third quartiles). *Bonferroni corrected.

$P=0.001$). Eight patients died after surgery or percutaneous coronary intervention (4 in each group).

The composite cardiovascular end point occurred in 27 patients, 19 (38%) in the control group and 8 (16%) in the IPC group ($P=0.018$; Table 3). Two patients in the control group died during follow-up (1 of myocardial infarction and 1 of intracerebral bleeding; $P=0.49$) versus no deaths in the IPC group. Rehospitalization was significantly less frequent in patients with IPC than in control patients (7 [14%] in the IPC group versus 18 [36%] in the control group; $P=0.016$). The most common reason for hospitalization was dyspnea caused by worsening of heart failure symptoms (Table 6). Hemodialysis was necessary in 2 patients in the control group and in 1 with IPC ($P=1.00$).

No major adverse events occurred during sham-control preconditioning and IPC. In 2 patients with IPC, 2 instead of 4 cycles of upper-arm ischemia were performed because of patient discomfort. Six additional patients with IPC devel-

oped mild reversible petechial spots distal to the blood pressure cuff.

Discussion

The present study demonstrates that remote IPC, induced by intermittent upper-arm ischemia before an invasive coronary procedure, dramatically reduces the incidence of contrast medium–induced nephropathy in patients with chronic kidney disease and high risk for CI-AKI. Additionally assessed surrogate measures support the preventive effect of IPC. This protective effect appeared to be independent of all other factors, eg, contrast medium amount and comorbidities of the patients. In addition, IPC significantly decreased the incidence of the composite cardiovascular end point, which consisted of death, hospitalization, or hemodialysis.

CI-AKI is a frequent and serious complication after CA with or without percutaneous coronary intervention. Moreover, CI-AKI has been shown to be an independent predictor of 1-year mortality in patients with coronary artery disease.⁸ The incidence of CI-AKI varies substantially among several studies because of the lack of a uniform definition of CI-AKI.^{9,10} Rates of CI-AKI may be as high as >50%, depending on the presence of risk factors such as chronic renal insufficiency and diabetes mellitus or heart failure.^{4,8,10,11}

In 2004, Mehran et al⁸ developed a risk classification system to predict risk for contrast medium–induced nephropathy in patients undergoing CA. This most comprehensive and best-validated risk stratification score includes 8 clinical and procedural variables and is divided into 4 classes of risk of developing CI-AKI: Low (risk score ≤ 5), moderate (risk score 6–10), high (risk score 11–15), and very high (risk score ≥ 16). The calculated mean integer score for both groups in the present study was 13, thus determining the present study population as a group at high risk of developing CI-AKI ($\approx 60\%$ of the subjects were at high or very high risk). Indeed, the reported incidence of 40% in the control arm of the study is within the reported range¹² and corresponds exactly to the serum creatinine–based CI-AKI incidence predicted by Mehran et al.⁸

The demonstrated CI-AKI incidence in the present study cohort is higher than in other publications with comparable baseline eGFR.¹³ This is attributed at least in part to the high incidence of comorbidities in the RenPro study population ($\approx 80\%$ had congestive heart failure, and >60% had diabetes).

Despite its broader prevalence, the precise pathophysiological mechanisms of CI-AKI have not been elucidated clearly. The pathogenesis of CI-AKI is multifactorial, because vascular, hemodynamic, and tubular factors contribute to its development. The most common pathophysiological concept of CI-AKI is the induction of renal ischemic injury, possibly caused by iodinated contrast medium–induced reduction in renal blood flow and oxygen free radical–mediated direct tubular toxicity.¹⁴ Other underlying mechanism for pathological changes in CI-AKI include contrast medium–induced natriuresis and diuresis, which activate the tubuloglomerular feedback response with subsequent vasoconstriction of the glomerular afferent arterioles, causing a decrease in glomerular filtration rate.

Table 4. List of Patients With Major Cardiac Surgery or Percutaneous Intervention

Age, y	Procedure	Timing of Procedure (Days After Inclusion)	Initial Treatment Group, IPC vs Control	CI-AKI	Hemodialysis	Death (Cause)
83	CABG	12	Control	Yes	Yes	Yes (sepsis)
68	CABG	16	IPC	No	No	No
67	CABG	10	Control	No	Yes	No
81	CABG	8	IPC	No	No	Yes (SCD)
56	CABG	5	IPC	Yes	No	Yes (ICB)
78	CABG	26	IPC	No	No	Yes
81	CABG	14	Control	Yes	Yes	No
74	CABG	7	IPC	Yes	No	Yes (MI)
69	CABG	8	Control	No	Yes	No
79	CABG	10	IPC	No	No	No
68	AVR	7	Control	Yes	Yes	No
65	AVR	7	Control	No	No	No
62	AVR	19	Control	No	No	No
60	AVR	11	IPC	No	No	No
69	MVR	9	IPC	No	No	No
71	MVR	23	IPC	No	No	No
85	TAVI	15	Control	Yes	Yes	Yes (PC)
86	TAVI	17	IPC	No	No	No
84	Re-CA	7	Control	Yes	Yes	Yes (MOF)

IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury; CABG, coronary artery bypass graft; SCD, sudden cardiac death; MI, myocardial infarction; ICB, intracranial bleeding; AVR, aortic valve replacement; MVR, mitral valve replacement; TAVI, transfemoral aortic valve implantation; PC, procedural complication; Re-CA, repeated coronary angiography and percutaneous coronary intervention; and MOF, multiorgan failure.

To date, there is no effective prophylactic regimen to prevent CI-AKI. Dopamine, fenoldopam, furosemide, mannitol, aminophylline, atrial natriuretic peptide, captopril, calcium channel blockers, and alprostadil were not effective in reducing the incidence of CI-AKI.^{15–18} Initial studies assessing the ability of NAC to prevent CI-AKI has been encouraging; however, the role of NAC in prevention of CI-AKI has been questioned, because subsequent larger trials failed to demonstrate an NAC-associated benefit.^{19,20} Likewise, there are inconsistent data on the effects of NAC on serum creatinine. In healthy volunteers with normal renal function and no exposure to contrast medium, there was a small but significant decrease in mean serum creatinine and urea concentrations and a significant increase in eGFR.²¹ Levels of cystatin

C remained unchanged after NAC administration. However, no change in serum creatinine or cystatin C was observed in patients with chronic kidney disease.^{22,23}

Our hypothesis that IPC may be nephroprotective was largely based on earlier reports showing the beneficial action of IPC in several clinical settings. IPC has been reported to decrease the incidence of perioperative myocardial injury during cardiac surgery in adults^{24,25} and children²⁶ and to diminish both myocardial and renal injury incidence during surgery for endovascular²⁷ and open surgical²⁸ repair of abdominal aortic aneurysm. Very recently, IPC before hospital admission increased myocardial salvage by attenuation of reperfusion injury in patients with evolving myocardial infarction.²⁹

Although serum creatinine is the most widely used serum marker of renal function, serum cystatin C and urinary NGAL

Table 5. Outcomes in Patients With Cardiac Surgery or Percutaneous Intervention

	Control Group (n=9)	IPC Group (n=10)
CI-AKI	5	2
Hemodialysis	7	0*
Before surgery/PCI	0	...
After surgery/PCI	7	...
Death	4	4

IPC indicates ischemic preconditioning; CI-AKI, contrast medium–induced acute kidney injury; and PCI, percutaneous coronary intervention.

* $P=0.001$.

Table 6. Reasons for Hospitalization During 6-Week-Follow-Up

	Control Group (n=18)	IPC Group (n=7)
Dyspnea	8	3
Angina pectoris	5	2
Syncope	1	0
Symptomatic arrhythmia	1	1
Pneumonia	2	0
Transitory neurological deficit	1	0
Other	0	1

IPC indicates ischemic preconditioning.

have been reported to be more specific and sensitive to acute and early deteriorations in renal function.^{30–33} Indeed, serum creatinine is not an adequate marker for CI-AKI.^{34,35} Thus, >50% of renal function must be lost before an elevation in serum creatinine is detected. In addition, serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require several days.³³ The serum cystatin C level and NGAL are more sensitive in identifying moderate renal insufficiency than the serum creatinine level.³⁶ Furthermore, cystatin C is not affected by renal tubular secretion or pharmacological treatments.^{23,37} In particular, NGAL has been shown to be an early, sensitive, specific, and predictive biomarker of acute kidney injury after contrast medium administration.³⁸ Therefore, both measures were also investigated in the present study and correlated well with the eGFR reduction and, subsequently, contrast medium-induced renal damage. Consistently, both early markers of the CI-AKI were raised after exposure to contrast agent. This was evident at 6 and 24 hours after contrast medium application, whereas serum creatinine was unchanged at the same time.

Given the results of the present study, a novel concept of cytoprotection by IPC before CA may be considered for the prevention of CI-AKI in numerous patients. We calculated that 4 patients at elevated risk for CI-AKI have to be treated by IPC to prevent 1 CI-AKI (number needed to treat 3.6; 95% confidence interval, 2–9). Moreover, IPC can be applied easily, and virtually no safety concerns exist if it is performed appropriately. Even if the underlying mechanisms of IPC-mediated beneficial effects remain largely unknown, the noninvasive IPC protocol is likely to have direct effects on decreasing renal ischemia/reperfusion injury incidence as part of the systemic protective effect of this phenomenon.

It has been postulated that a remote organ releases humoral factors such as adenosine or bradykinin into the systemic circulation, which subsequently protect the remote region or organ. Other underlying mechanisms may include erythropoietin, activation of the K_{ATP} channel, nitric oxide, delta 1-opioid, and free radicals.³⁹ Some studies have also suggested that the protective effect of IPC may be caused by its beneficial anti-inflammatory or antioxidant effects and decreased extracellular levels of noxious metabolites, such as protons and lactate.^{39,40} Additionally, some other studies have favored a neurogenic pathway.⁴¹

Overall, our concept suggests a humoral basis for the underlying renoprotective effects, because in the additional experimental setting, we found elevated erythropoietin plasma levels and mRNA expression in a reperfusion-ischemia mouse model (V. Burst et al, unpublished data, 2012). It is well known that reperfusion injury involves several pathways, including alterations in cellular metabolism, endothelial dysfunction, inflammation, hypercontracture, and necrosis/apoptosis.⁴² Thus, IPC-mediated counterregulatory protective pathways may eventually offer an additional clinical benefit and contribute to better clinical outcomes.

Among those patients with major cardiac surgery or percutaneous coronary intervention, more control patients than patients with initial IPC required hemodialysis. Although this difference was statistically significant, the small

number in the subgroup limits this effect, but it may merit further investigation.

However, the present study has several limitations. This pilot investigation of the beneficial effects of IPC on renal function is a single-center trial with a limited sample size. Although we sought to prevent any bias by blinding the patients and the data analysis team, the study design cannot prevent all influential effects. The a priori sample size calculation was based on inaccurate assumptions and calculations because of the pilot nature of the study. Nevertheless, it is of no question that the described hypothesis is a highly appealing and practicable method to reduce potential life-threatening complications of organs in general.

In this study, we demonstrated that the simple and well-tolerated application of IPC in high-risk patients with renal dysfunction undergoing CA reduced the incidence of procedure-related CI-AKI. In addition, the nephroprotective effect of IPC was associated with improved clinical outcomes at 6 weeks. Thus, the use of IPC may be a feasible and highly attractive therapeutic procedure and should be investigated in future trials.

Sources of Funding

The trial was undertaken under the auspices of the Department of Internal Medicine III, University Hospital of Cologne (Germany), a nonprofit public law institution. The RenPro Study Investigators, an investigator-initiated study group (by F.E.), was solely responsible for the study design, data collection, data analysis, data interpretation, and writing of the report.

Disclosures

None.

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CLINICAL PERSPECTIVE

The prevention of contrast medium-induced acute kidney injury is a major challenge for interventional cardiologists. Several patient and procedure-associated risk factors were identified in previous studies. Only a few contrast medium-induced acute kidney injury prevention strategies exist. Ischemic preconditioning has been shown in the RenPro (Renal Protection) Trial to be an effective, safe, and economic method for prevention of contrast medium-induced acute kidney injury in high-risk patients. The broad application of this method in daily clinical settings may remarkably influence the cardiovascular outcome in high-risk patients.

Ischemic Preconditioning for Prevention of Contrast Medium–Induced Nephropathy: Randomized Pilot RenPro Trial (Renal Protection Trial)

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Circulation. 2012;126:296-303; originally published online June 26, 2012;
doi: 10.1161/CIRCULATIONAHA.112.096370

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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