The impact of a single episode of remote ischemic preconditioning on myocardial injury after elective percutaneous coronary intervention

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Abstract

Introduction: Myocardial injury after percutaneous coronary intervention (PCI) occurs in approximately 30% of procedures, and is related to worse prognosis. Effects of remote ischemic preconditioning (RIPC) on reperfusion injury have been investigated before, yielding conflicting results.

Aim: To assess the impact of a single episode of RIPC on myocardial injury after elective PCI.

Material and methods: One hundred and four patients undergoing elective PCI, with normal baseline cardiac troponin-I (cTn-I) values, were randomized to two groups. Two patients were excluded due to data loss, and 102 patients were analyzed. Five minutes of ischemic preconditioning was delivered just before the intervention to the preconditioning group, by inflating the blood pressure cuff up to 200 mm Hg on the non-dominant arm. Postprocedural 16th hour cTn-I, ΔcTn-I (difference between the 16th h and baseline cTn-I values) and the prevalence of type 4a myocardial infarction were compared between the two groups.

Results: Median cTn-I values after the procedure were compared. 16th hour cTn-I was insignificantly lower in the preconditioning arm (0.026 µg/l vs. 0.045 µg/l, p = 0.186). The incidence of cTn-I elevation 5-fold above the upper reference limit (URL) (> 0.115 µg/l) was lower in the preconditioning group, but it was also not significant (21.6% vs. 11.8%, p = 0.184).

Conclusions: A single episode of RIPC before elective PCI demonstrated less troponin elevation but failed to show a significant effect.

Key words: percutaneous coronary intervention, remote ischemic preconditioning, myocardial injury.

Introduction

Percutaneous coronary intervention (PCI) associated with myocardial enzyme elevation occurs in about 30% of interventions [1, 2]. Although its clinical significance is controversial, it has been shown that even minor troponin elevations might be related to irreversible myocardial necrosis [3, 4]. Myocardial injury after PCI can occur due to side branch occlusion, distal embolization, and ischemia/reperfusion injury [2, 5]. Remote ischemic preconditioning (RIPC) has been demonstrated to prevent PCI-associated myocardial injury in ST segment elevation myocardial infarction (STEMI) and elective PCI cases [6]. Three cycles of ischemia (each lasting 5 min) preceding reperfusion were demonstrated to be beneficial in elective PCI, and this effect was still observed after 6 years, with lower major cardiovascular and cerebral events (MACCE) in the preconditioning arm [7, 8]. However, since 3 cycles of ischemia and reperfusion are somewhat time-consuming, it is not practical to apply this technique, especially in ad-hoc PCI cases or in every patient before diagnostic angiography. There are limited data about the effects of a single episode of ischemic preconditioning. Ischemic preconditioning has been shown to be an all-or-nothing phenomenon [9, 10], but it has also been shown that additional cycles of preconditioning could be more effective [11]. A recent study investigated the effect of one cycle of RIPC before elective PCI, and demonstrated its beneficial effects [12].

Aim

In this single-center, randomized, prospective study we planned to investigate the effect of a single episode of RIPC on troponin elevation after elective PCI.

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Material and methods

Patients aged between 18 and 80 years of age, with a diagnosis of stable atherosclerotic heart disease primarily admitted to undergo elective coronary angiography between April 2015 and February 2016, were assessed for eligibility. The exclusion criteria were presence of 1) acute coronary syndrome, 2) left main disease, 3) baseline cardiac troponin-I (cTn-I) elevation (> 0.023 µg/l), 4) hemodynamic instability, 5) renal failure (a glomerular filtration rate (GFR) below or equal to a threshold value of 60 ml/min/1.73 m^2), 6) glibenclamide or nicorandil use, 7) contraindication to cuff inflation in upper extremities (lymphoedema, fistula), 8) suspicion of pregnancy. Patients who did not give written informed consent were not enrolled in the study.

The study was approved by the Local Ethics Committee and was registered in the clinicaltrials.gov database. The study was conducted in accordance with the Declaration of Helsinki.

Three hundred and twenty-six patients undergoing coronary angiography were assessed for eligibility. Eighty-four patients were excluded because of high baseline cTn-I values or renal failure or for refusing to participate, and 138 patients were excluded after coronary angiography (did not receive PCI). Eligible patients were randomly allocated to groups. To prevent selection bias the randomization was performed by a third person who was blinded to the clinical information of the patients. A total of 104 patients were randomized. Two patients (one in each group) were excluded from the analysis, since post-PCI troponin values were missing. Data of 51 patients in the preconditioning group and 51 in the control group (total 102) were analyzed.

All patients were already using acetylsalicylic acid before coronary angiography. 600 mg of clopidogrel was given before PCI unless the patient was already using a P2Y12 inhibitor. A 70 IU/kg intravenous bolus of unfractionated heparin (UFH) was given to all patients after femoral sheath insertion and additional UFH was administered to maintain the activated clotting time > 250 s, if needed. All patients had blood pressure cuffs around their arm, but it was inflated to 200 mm Hg for 5 min in the preconditioning group only. The guiding catheter was advanced one minute after cuff deflation. Coronary intervention was performed according to the operator's discretion.

Systolic and diastolic blood pressure and heart rate during stent implantation, presence of chest pain and ST deviation on ECG monitor, lesion characteristics on angiography, predilatations, postdilatations, stent sizes, final angiographic results, and complications were all recorded. Target vessel lesions were classified according to the American Heart Association/American College of Cardiology lesion classification [13]. Pre- and post-procedural thrombolysis in myocardial infarction (TIMI) flow [14] was assessed by two independent operators, blinded to the troponin results and assigned study group of the patient.

To estimate the magnitude of the myocardium at risk, the Alberta Provincial Project for Outcome Assessment in Coronary Heart Diseases (APPROACH) [15] lesion score was used.

Sample size was determined according to the previous studies that showed a reduction in the prevalence of cTn-I elevation achieved by RIPC. While Zografos *et al.* [12] showed about 23% reduction, Hoole *et al.* [7] demonstrated 18% reduction. We assumed that a 20% percent reduction by RIPC would be clinically meaningful, and thus 88 patients would be enough to allow such a reduction to be significant ($\alpha = 0.05$; $\beta = 0.2$; statistical power = 80%).

Laboratory measurement

Following a 12-hour fasting period, blood samples were collected before the procedure. cTn-I was measured before and at the 16th h after the intervention. cTn-I was analyzed from lithium-heparinised plasma with the AQT90 FLEX TnI immunoassay (Radiometer Medical ApS, Denmark). The limit of detection has been determined to be 0.0095 µg/l. The reportable range of the assay is 0.010–50 µg/l. The upper 99th percentile upper reference limit (URL) has been determined to be ≤ 0.023 µg/l. Values below 0.01 µg/l were accepted as 0.

Statistical analysis

Statistical analysis was performed using IBM SPSS (IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY, IBM Corp). Continuous variables (heart rate, systolic and diastolic blood pressure, etc.) were summarized as mean, standard deviation, minimum, maximum, and median, and compared using Student's *t* test or the Mann-Whitney *U* test when appropriate. Categorical data (target vessel, lesion type etc.) were expressed as numbers and percentages and compared using the χ^2 test. A value of $p < 0.05$ was accepted as significant.

Results

One hundred four patients were randomized. Two patients (one from each group) were excluded from the analysis because of missing post-PCI blood samples. The PCI was successfully performed in all randomized patients. With the exception of 2 patients in the preconditioning group all patients underwent stent implantation; in-stent balloon angioplasty was preferred in these 2 patients.

Baseline demographic and clinical characteristics

There were no significant differences between the two groups with regards to sex, age and risk factors of atherosclerosis, renal functions, and medications used.

Six patients in the control group and 4 patients in the preconditioning group had exercise-induced angina in the last 24 h but none of the patients had angina in the last 12 h (p = 0.505) (Table I).

Procedural characteristics

There were no procedural differences between the two groups. The procedural blood pressure values (systolic and diastolic) and heart rates were similar in the two groups. The two groups also did not differ significantly with regards to predilatation times and numbers, postdilatation times and numbers, total dilatation time and number, or stent size and stent numbers. Lesion type, bifurcation procedure, and APPROACH score were also similar between the two groups (Table II).

Baseline and post-PCI 16th h cTn-I values are shown in Figure 1. 16th h cTn-I values were lower in the preconditioning group, but the difference was not significant (0.032 µg/l vs. 0.057 µg/l, p = 0.186). ΔcTn-I (difference between the 16th h and baseline cTn-I values) was also compared. ΔcTn-I was lower in the preconditioning group, but the difference was not significant (0.045 µg/l (interquartile range: 0.013–0.099) vs. 0.026 µg/l (interquartile range: 0.011–0.057), p < 0.096).

The prevalence of patients with cTn-I above the upper reference limit (URL) (> 0.023 µg/l) and cTn-I elevation 5-fold above the URL (> 0.115 µg/l) was lower in the preconditioning group, but the differences were also not significant (cTn-I > URL; 64.7% vs. 72.5%, p = 0.160, cTn-I > 5 × URL; 21.6% vs. 11.8%, p = 0.184) (Figure 2).

Discussion

The present study demonstrated that single cycle RIPC just before elective PCI may have favorable effects on reducing post-PCI troponin elevation, but failed to show a statistically significant difference.

The rate of PCI related myocardial injury varies according to the biomarker and cut-off value chosen. In

Table I. Demographic and clinical data of patients

Variable	Controls (n = 51)	Preconditioning (n = 51)	P-value
Demographics:			
Age [years]	60.9 ±10.8	57.7 ±8.9	0.1
Female/male, n/n	13/38	13/38	1
Risk factors:			
Hypertension, n (%)	42 (82.4)	47 (92.2)	0.138
Hyperlipidemia, n (%)	44 (86.3)	44 (86.3)	1
Family history, n (%)	7 (13.7)	15 (29.4)	0.054
Smokers, n (%)	35 (68.6)	33 (64.7)	0.674
Diabetes mellitus, n (%)	15 (29.4)	16 (31.4)	0.830
BMI [kg/m^2]	28.55 ±4.82	29.07 ±4.24	0.563
Clinical features:			
LVEF (%)	58.68 ±8.94	58.11 ±7.54	0.729
GFR [ml/min/1.73 m^2]	91.3 ±19.1	89.5 ±16.7	0.613
CCS 2/3, n/n	18/33	30/21	0.017
Previous MI, n (%)	10 (19.6)	11 (21.6)	0.807
Previous CABG-O, n (%)	3 (5.9)	3 (5.9)	1
Last 24-hour angina, n (%)	6 (11.8)	4 (7.8)	0.505
Medications, n (%):			
β-blockers	48 (94.1)	48 (94.1)	1
ACEI/ARB	39 (76.5)	40 (78.4)	0.813
Ca-channel blocker	9 (17.6)	10 (19.6)	0.799
Statins	37 (72.5)	36 (70.6)	0.826

ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blocker, BMI – body mass index, CCS – Canadian Cardiology Society, CABG-O – coronary artery bypass graft operation, GFR – glomerular filtration rate, LVEF – left ventricular ejection fraction, MI – myocardial infarction.

Table II. Angiographic and procedural data of patients

Variable	Controls (*n* = 51)	Preconditioning (*n* = 51)	*P*-value
Angiographic parameters:			
Target vessel, *n* (%)			0.400
LAD	17	19	
LCx	5	9	
RCA	19	18	
Combined/other	10	5	
Lesion AHA/ACC, *n* (%)			0.746
Type A	8 (15.7)	11 (21.6)	
Type B	25 (49)	23 (45.1)	
Type C	18 (35.3)	17 (33.3)	
APPROACH score (%)	28.15 ±13.26	25.65 ±11.99	0.321
Stenosis severity (%)	81.7 ±9.6	81.5 ±91.3	0.891
≥ 2 mm side branch, *n* (%)	13 (25.5)	8 (15.7)	0.221
TIMI flow 0-2, *n* (%)	7 (13.7)	3 (5.8)	0.183
Procedural data:			
Heart rate [beats/min]	77.45 ±10.89	74.19 ±9.43	0.110
Systolic blood pressure [mm Hg]	138.37 ±15.03	140.7 ±18.85	0.491
Diastolic blood pressure [mm Hg]	77.54 ±7.41	75.96 ±8.11	0.305
Procedural angina, *n* (%)	26 (51)	24 (47.1)	0.692
Procedural ST deviation, *n* (%)	16 (31.4)	13 (25.5)	0.510
Bifurcation procedure, *n* (%)	3 (5.8)	4 (7.8)	0.603
DES/BMS/Balloon, *n*/*n*/*n*	46/5/0	48/1/2	0.095
Stent length [mm]	27.17 ±13.79	26.12 ±11.88	0.684
Stent number	1.31 ±0.55	1.17 ±0.52	0.196
Stent diameter [mm]	2.85 ±0.4	2.83 ±0.39	0.841
Total dilatation time [s]	74.25 ±55.5	81.4 ±44.6	0.476
Predilatation, *n* (%)	20 (39.2)	22 (43.1)	0.687
Postdilatation, *n* (%)	31 (60.8)	33 (64.7)	0.682
Predilatation time [s]	33.57 ±34.17	25.35 ±19.76	0.355
Postdilatation time [s]	43.61 ±27.78	48.47 ±25.52	0.458
Total dilatation number	3.6 ±2.8	3.7 ±2.3	0.845
Cuff deflation to stent implantation time [s]	–	432.9 ±221.1	
Post-PCI results:			
TIMI flow 2/3, *n*/*n*	0/51	2/49	0.153
Dissection	0	0	1
Death	0	0	1
TIMI flow 0-2 at side branch	0	0	1

BMS – bare metal stent, DES – drug-eluting stent, LAD – left anterior descending artery, LCx – left circumflex artery, RCA – right coronary artery, PCI – percutaneous coronary intervention, TIMI – thrombolysis in myocardial infarction.

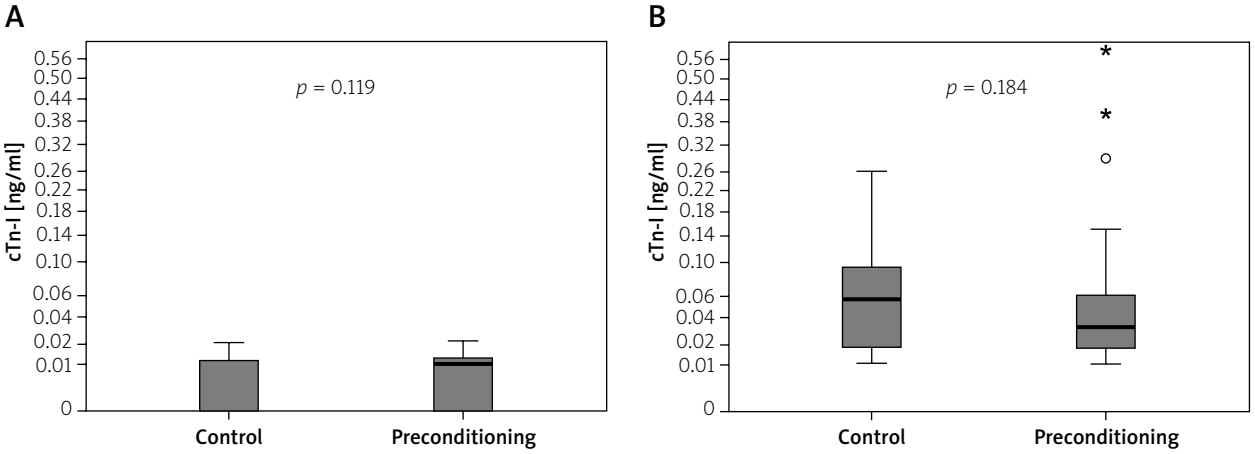

Figure 1. Median (interquartile range) cardiac troponin-I (cTn-I) values at baseline (**A**) and 16 h after PCI (**B**). The 25th and 75th percentiles are indicated by the shaded box. The line within the box represents the median value

a recently published article mild to moderate periprocedural myocardial injury was detected in 49.8% of the patients and severe myocardial injury was detected in 12.2% of the patients [16]. Some authors argue that high-sensitivity troponin measurement after PCI can be over-diagnostic; however, it has also been shown that patients with higher troponin levels have worse prognosis [4, 17]. Although there is controversy about the cut-off values for troponin and creatinine kinase (CK)-MB in the determination of PCI-related myocardial infarction [18], the third Universal Definition of Myocardial Infarction Guideline [19] recommended troponin measurement after PCI and defined myocardial infarction after PCI (type 4a MI) as a 5-fold increase of troponin with clinical or electrocardiographic evidence. Solely troponin elevation above the URL, or values 5-fold above the URL without clinical or ECG findings, is defined as myocardial injury. Myocardial injury after PCI is due to microembolization of small debris, side branch occlusion, or ischemia/reperfusion injury.

Remote ischemic preconditioning has been investigated in several studies in an effort to obviate ischemia/reperfusion injury of the myocardium. Ischemic preconditioning was first demonstrated by Murry *et al*., by applying four cycles of intermittent nonlethal ischemia and reperfusion to the left anterior descending artery of a canine heart, which resulted in a 75% reduction in infarct size in the preconditioning group [20]. Przyklenk *et al.* first reported that ischemia in a remote organ could also protect the myocardium against ischemia [21], and later in 2002 Kharbanda *et al.* showed the beneficial effects of RIPC in human subjects [22]. Further RIPC studies have been performed in STEMI, in cardiac surgery and in elective PCI cases [7, 8, 23–26].

The exact mechanism underlying the protective effect of RIPC on reperfusion injury is not fully understood yet. Although RIPC has promising effects, there are limited data about its effects in planned PCI. Different protocols,

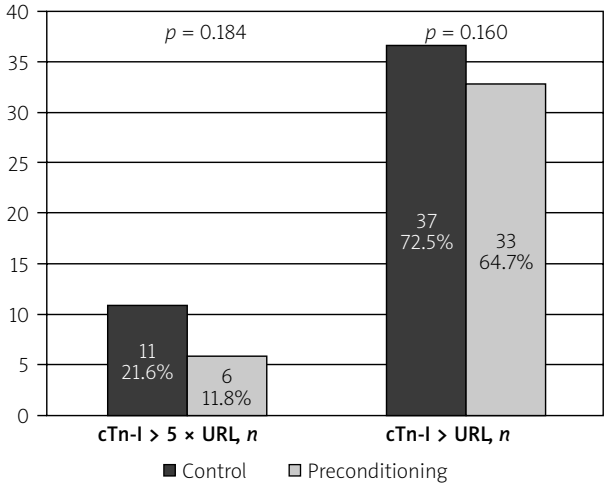

Figure 2. Prevalence of cardiac troponin-I (cTn-I) above upper reference limit (URL) and above 5 × URL

to test the possible protective effects of RIPC, were chosen in the previous studies [7, 12, 25–30]. The study by Iliodromitis *et al*. was the first to investigate the effect of RIPC in elective PCI [25]. In that study, 41 patients (20 in the RIPC group and 21 controls) were enrolled, and 3 cycles of 5-minute ischemia were administered to bilateral arms; as a result no cardioprotection was achieved. Moreover, troponin release was exacerbated in the RIPC group. Hoole *et al.* demonstrated that 3 cycles of 5-minute RIPC administered before planned PCI diminished PCI-related myocardial injury, but did not demonstrate an effect on the prevalence of type 4a MI [7]. In the study of Ahmed *et al.*, although there was less procedure-related MI in the preconditioning group, the difference did not reach statistical significance; but the authors also demonstrated attenuated troponin release [27]. In contrast to these 2 studies, Luo *et al.* were able to achieve 15% fewer type 4a MIs in the RIPC group (39% vs. 54%, $p = 0.029$) [26]. Prasad *et al.* [28] used a different protocol and delivered

3 cycles of 3-minute ischemia/reperfusion immediately before PCI, but they were not able to show cardioprotection. Unlike the studies of classical preconditioning, Liu *et al.* demonstrated that late RIPC also had beneficial effects on patients undergoing elective PCI [29]. Although there is heterogeneity in RIPC protocols, meta-analyses of the major RIPC studies in elective PCI indicated that ischemic preconditioning had beneficial effects on post-PCI myocardial injury [31–33].

The RIPC is a simple, cheap and practical technique, but the optimal protocol to achieve the most effective cardioprotection has not yet been demonstrated. There are controversies about the number of cycles, ischemia duration and the limbs used for ischemia. Different protocols have been investigated to minimize the delay of intervention and to improve practicality because 3 cycles of 5-minute RIPC are rather time-consuming and ad-hoc PCI is more commonly performed. In a study by Ghaemian *et al.* 2 cycles of 5-minute ischemia/reperfusion were administered to the lower limb, which revealed a 27.5% reduction in PCI-related myonecrosis [34]. Prasad *et al.* [28] induced 3 cycles of 3-minute RIPC, to shorten the duration of preconditioning, but, consistent with the study of Iliodromitis *et al.* [25], they failed to achieve cardioprotection. One possible reasons for this negative effect was attributed to the shorter duration of ischemia, which implies that 3 min of cuff inflation might not generate sufficient preconditioning.

In the present study, we performed a single episode of 5-minute ischemia. The number of cycles has been investigated in various studies, and the results were conflicting. In their study of ischemic preconditioning, Li *et al.* stated that preconditioning was an all-or-nothing phenomenon and demonstrated that cardioprotection could be achieved with one cycle of ischemia [9]. In an animal study by Lu *et al.* one cycle of preconditioning did not provide protection, but 3 cycles of ischemia did [35]. Further studies also showed that supplementary cycles could achieve more protection [10, 36]. A recently published animal study compared the effects of the number of cycles of RIPC, duration of ischemia, and one or two hind-limb ischemia on ischemia/reperfusion injury [37]. Two, 4, 6 and 8 cycles of ischemia (each lasting 5 min) preceding reperfusion were compared; 2 cycles of RIPC were found ineffective. The authors concluded that the number of cycles and duration of ischemia were the major determinants of efficient preconditioning. Zografos *et al.* were the first to assess the effect of one cycle of RIPC on elective PCI [12]. Unlike our study, they were able to demonstrate significant reduction in the prevalence of type 4a MI (42.6% vs. 19.1%, $p = 0.014$) and in ΔTn-I (0.04 µg/l vs. 0.19 µg/l, $p < 0.001$). The most remarkable difference of the Zografos *et al.* study compared with the present study is the higher prevalence of type 4a MI (42.6% vs. 21.6%), which can be explained by the higher rate of complications and higher APPROACH score. With the exception that the percentage of patients with diabetes was lower in the study of Zografos *et al.*, the sample size and study population were similar in both studies (21% vs. 31%). The presence of DM could attenuate the protective effects of RIPC [30]. The diabetic group in our study constituted about one third of the study population, without a significant difference between groups. In the Hoole *et al.* and Zografos *et al.* studies the percentage of diabetic patients was about 20%, whereas about 30% of the Ahmed *et al.* and Luo *et al.* studies were diabetic; all were able to achieve positive results with RIPC. As with the previous studies, the present study was also underpowered to investigate the effect of these factors on RIPC.

The time between the cuff deflation and stent implantation can also be argued as a cause for the discrepancies between the previous studies with 3 cycles of ischemia. However, classical conditioning as we applied is described as preconditioning within 3 h of the ischemic event, and its effect starts immediately and vanishes in about 2–3 h [38]. We delivered 5 min of RIPC just before the PCI. The mean cuff deflation to stent implantation time was 432.9 ±221.1 s. Zografos *et al.* achieved positive results with a shorter time between cuff deflation and stent implantation.

One can argue that the control group might also gain benefit from pre- or post-conditioning due to predilatations or postdilatations during PCI. With this study we tried to show the effect of RIPC in real-life clinical practice. The comparison of procedural data (balloon dilatations, duration and number) between the two groups were found similar, so this could not have a significant effect.

Limitations of the study

One of the major limitations of our study is the small sample size. The results might be different with a larger sample size, and the difference between the groups might be more significant. The other major limitation is that we used cTn-I to detect myocardial injury. Although guidelines recommended cTn-I for the detection of type 4a MI, it may be over-diagnostic and not clinically important. Troponin elevation after PCI occurs between 12 and 24 h. As such serial cTn-I measurements would be more sensitive in detecting the magnitude of myocardial injury. By taking a single blood sample at the 16th h of the intervention, we might have missed the maximum concentration. Long-term follow-up and magnetic resonance imaging could have given us more objective data about post-PCI myocardial injury and its clinical relevance.

Conclusions

Remote ischemic preconditioning is a promising technique for reducing PCI-related myocardial injury. Due to the lack of homogeneity of the previous studies, the optimum protocol has not yet been standardized. Although

we were able to demonstrate less cTn-I elevation with one cycle of RIPC, we could not show a statistically significant reduction, indicating that one cycle of RIPC might not generate adequate preconditioning. Further randomized, prospective, multi-center, larger scale studies with a long follow-up are needed to determine the most effective RIPC model.

Conflict of interest

The authors declare no conflict of interest.

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