Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES): A Prospective, Randomized, Sham-Controlled Phase II Clinical Trial

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Background—Remote ischemic preconditioning (RIPC) has been shown to reduce infarct size in animal models. We hypothesized that RIPC before an elective vascular operation would reduce the incidence and amount of a postoperative rise of the cardiac troponin level.

Methods and Results—Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES) was a prospective, randomized, sham-controlled phase 2 trial using RIPC before elective vascular procedures. The RIPC protocol consisted of 3 cycles of 5-minute forearm ischemia followed by 5 minutes of reperfusion. The primary endpoint was the proportion of subjects with a detectable increase in cardiac troponin I (cTnI) and the distribution of such increases. From June 2011 to September 2015, 201 male patients (69±7, years) were randomized to either RIPC (n=100) or a sham procedure (n=101). Indications for vascular surgery included an expanding abdominal aortic aneurysm (n=115), occlusive peripheral arterial disease of the lower extremities (n=37), or internal carotid artery stenosis (n=49). Of the 201 patients, 47 (23.5%) had an increase in cTnI above the upper reference limit within 72 hours of the vascular operation, with no statistically significant difference between those patients assigned to RIPC (n=22; 22.2%) versus sham procedure (n=25; 24.7%; *P*=0.67). Among the cohort with increased cTnI, the median peak values (interquartile range) in the RIPC and control group were 0.048 (0.004–0.174) and 0.017 (0.003–0.105), respectively (*P*=0.54).

Conclusions—In this randomized, controlled trial of men with increased perioperative cardiac risks, elevation in cardiac troponins was common following vascular surgery, but was not reduced by a strategy of RIPC.

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Key Words: remote preconditioning • troponins • vascular surgery

Vascular surgery is considered a high-risk operation with an anticipated perioperative risk of either death or nonfatal myocardial infarction (MI) of 10% to 15%.[1,2] Myocardial injury during noncardiac surgery is associated with an increased risk of long-term mortality and can be detected with routine measurement of cardiac biomarkers, preferably cardiac troponins (cTn).[3] We have previously shown that prophylactic coronary revascularization before elective vascular surgery does not result in improved perioperative or long-term clinical outcomes, highlighting the need to test novel strategies for cardioprotection.[2,4]

Remote ischemic preconditioning (RIPC) is characterized by brief, reversible episodes of ischemia and reperfusion in 1 vascular territory that renders protection to remote tissue

during a subsequent episode of ischemia.[5,6] The mechanism by which RIPC affords cardioprotection is not well defined, but may be related to production of a humoral factor.[7–9] Although RIPC has been well validated in preclinical models, generalizing those findings to clinical situations has yielded conflicting results.[10–13] Because of the known risks associated with vascular surgery, we conducted a randomized, clinical trial to test the hypothesis that RIPC, applied noninvasively within 24 hours before a vascular operation, would reduce the proportion of patients with detectable increases in cTn, and/or the magnitude of such increases, in the immediate perioperative period.

Methods

Study Design and Patients

*C*ardiac *R*emote *I*schemic *P*reconditioning Prior to *E*lective Vascular *S*urgery (CRIPES, NCT 01558596) was a prospective, single-center, randomized, sham-controlled phase 2 trial of RIPC before elective vascular surgery. Details of the study protocol have been previously published.[14] Consenting subjects were randomized to RIPC or a sham procedure using permutated blocks of 2 or 4 subjects. Randomized treatments were placed in sealed, sequentially numbered envelopes that were opened after patient consent.

We enrolled adult patients (aged ≥18 year) referred to the Minneapolis Veterans Affairs Healthcare System for elective vascular surgery. Patients were screened for participation by trained study personnel during outpatient vascular clinic visits and deemed eligible for the study if scheduled to undergo either an open or endovascular aneurismal repair (EVAR) of an enlarged (>5.5 cm) or expanding abdominal aortic aneurysm (AAA), peripheral bypass surgery for arterial-occlusive disease of the lower extremities, or carotid artery endarterectomy. All procedures were performed under general anesthesia and required at least a planned 24-hour admission to the hospital postprocedure. All EVAR procedures were performed with surgical cut down. Exclusion criteria included an acute coronary syndrome in the preceding 6 weeks, severe uncorrected valvular heart disease (ie, aortic stenosis with mean gradient ≥40 mm Hg or aortic valve area <1 cm^2 and/or grade 3 or 4 mitral regurgitation), peripheral arterial disease of the upper extremities manifested by a systolic blood pressure difference of ≥20 mm Hg, hemodialysis, pregnancy, and inability or unwillingness to provide informed consent.[14]

The RIPC protocol consisted of 3 cycles of forearm ischemia of 5-minute duration followed by 5 minutes of reperfusion and was administered 12 to 24 hours before surgery by trained personnel. This time window of RIPC was chosen to assess delayed preconditioning ("second window of protection"), a phenomenon well characterized in animals whereby delayed adaptive cytoprotection is observed again ≈12 hours after the initial insult has been removed that can last 24 to 48 hours.[15,16] This should be distinguished from the protection observed immediately after RIPC, or "first wave or preconditioning", which is as powerful as the second wave but more transient, disappearing between 1 and 2 hours. Transient forearm ischemia was triggered by inflating a blood pressure cuff to 200 mm Hg over the brachial artery while confirming absence of a radial and ulnar pulse. Reperfusion was achieved by deflating the cuff. The total duration of the RIPC protocol was 30 minutes, equally divided between ischemia and reperfusion. Masking of controls occurred by inflation of a blood pressure cuff to a lower pressure (≈40–50 mm Hg) that resulted in no impairment of antegrade flow.

Study Endpoints and Follow-up

The primary 2-part efficacy endpoint was the proportion of subjects with a detectable increase in cardiac troponin I (cTnI) within 72 hours of vascular surgery and the distribution of such increases. A detectable increase was defined as having 1 postoperative cTnI measurement above the preoperative cTnI with at least 1 of the postoperative values above the 99th percentile for the assay. We also evaluated the proportion of patients meeting the Third Universal Definition of MI.[17] According to this definition a MI is present when there is evidence of myocardial necrosis (ie, rise and fall of cardiac biomarker) *and* one of the following (s): symptoms of myocardial ischemia, developing of pathological Q waves or new ischemic changes (1-mm horizontal or downsloping ST-depression, new 2-mm-deep T-wave inversion, ≥1 mm ST-segment elevation in 2 contiguous leads, or new left bundle branch block) in the electrocardiogram (ECG), imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and/or identification of an intra-coronary thrombus by angiography or autopsy. The diagnosis of MI was independently assessed by a board-certified cardiologist blinded to treatment assignments according to the Third Universal Definition of MI.

Secondary outcome measures included changes in N-terminal probrain natriuretic peptide (NTpro-BNP) levels in the perioperative period and incidence of renal dysfunction, defined as ≥0.5 mg/dL increase in serum creatinine within 72 hours after surgery relative to preoperative values.[18]

Biomarkers

cTnI measurements were obtained before surgery and daily for the first 72 hours or until discharge, whichever occurred first. During the study period, serial perioperative cTn measurements were obtained using 2 contemporary cTnI assays. From July 25, 2011 through March 3, 2012, the

Abbott ARCHITECT cTnI assay was utilized. This assay has a concentration of 0.009 µg/L at the limit of detection (LoD) and a 10% coefficient of variation (CV) concentration of 0.032 µg/L. The 99th percentile upper reference limit corresponds to 0.028 µg/L with a CV of 14% at this concentration.[19,20] From March 3, 2012 until study completion, the Siemens Dimension Vista cTnI assay was utilized. This assay has a concentration of 0.015 µg/L at the LoD and a 10% CV concentration of 0.04 µg/L. The 99th percentile for this assay has been reported to be 0.021 µg/L.[19,20]

Clinical and demographic variables were prospectively collected and defined according to the American College of Cardiology Foundation/American Heart Association 2011 Key data Elements and Definitions of a Base Cardiovascular Vocabulary for Electronic Health Records.[21] All patients were prospectively followed for 6 months postsurgery for assessment of vital status, readmission, and adverse events.

Statistical Analysis

Baseline characteristics of the 2 study groups were described by means and SDs, medians and interquartile ranges (IQRs), or percentages, as appropriate, for the level of measurement and distributions of the data. Continuous variables were compared between groups using the nonpaired Student *t* test for normally distributed data or the Mann–Whitney *U* test for skewed data distributions.

We used a 2-part statistical test to jointly test a 2-sided null hypothesis that a reduction in 1 or both measures of increases in cTnI would indicate potential benefit of RIPC.[22] For the first part, a normal approximation chi-square test was used to compare the proportion of patients in each treatment arm that had an increase in cTnI postsurgery, as determined by systematic measurement of cTnI. The second part compared the distributions of the increases in cTnI among subjects with a detectable cTnI using the normal approximation z-test statistic of the Wilcoxon rank-sum test. The 2-part chi-square test statistic with 2 *df* is simply the sum of the chi-square test statistic from the first-part comparison and the square of standard normal z-statistic Wilcoxon statistic from the second part.

Sample size calculation

Based on previous data on the effect of RIPC before coronary angioplasty,[23] we estimated that RIPC will decrease the proportion of subjects with detectable increase in cTnI from 35% to 15% and lower the median of the distribution of detectable increases by ≈60%. The number of subjects needed in each randomly assigned treatment group to have 80% or 90% power to detect these effects was estimated to be 67 and 88, respectively, with a 2-sided alpha error of 0.05.[14,22] Therefore, we planned to enroll 180 to 200 patients over 4 years.

All statistical tests are 2-sided and a *P* value of <0.05 was considered statistically significant. All analyses were performed using STATA software (version 12.1; College Station, TX). The local institutional review board approved the study protocol. CRIPES was funded by the VA Office of Research and Development (1IK2CX000699-01).

Results

From June 2011 to September 2015, a total of 221 patients were enrolled in the study. Twenty subjects were excluded from the study before surgery for several reasons stated in the protocol (Figure 1). Therefore, the remaining 201 subjects
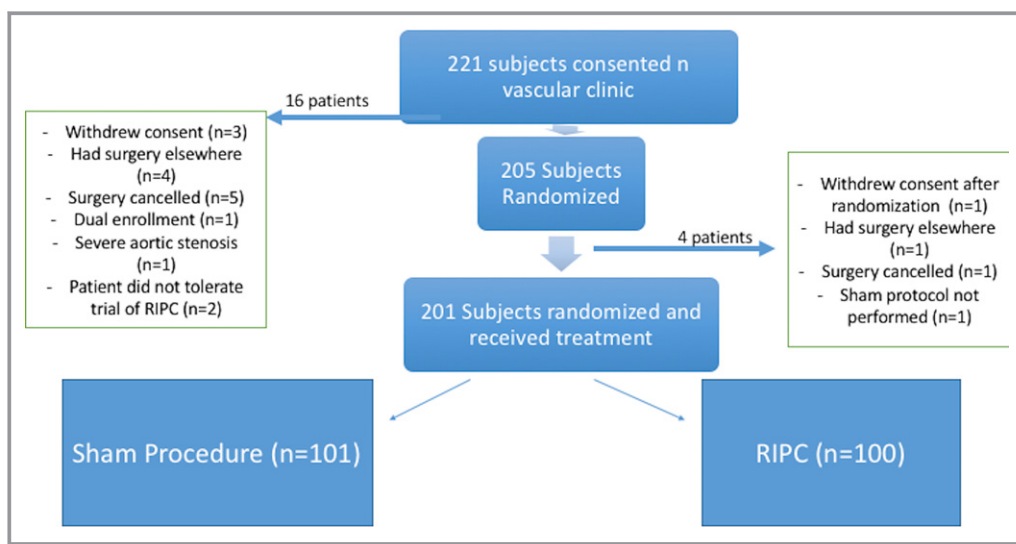

Figure 1. Flow diagram of study patients. RIPC indicates remote ischemic preconditioning.

were randomized to either RIPC (n=100) or a sham-control procedure (n=101) before vascular surgery.

The baseline characteristics of the 2 groups are presented in Table 1. Overall, nearly half of the cohort had a history of ischemic heart disease and more than one third had undergone coronary revascularization in the past. The mean (±SD) age of the study patients was 67±7 years, with a high prevalence of additional risks, including hyperlipidemia (RIPC 78% vs sham 72%; *P*=0.34), current tobacco use (RIPC 37% vs sham 31%; *P*=0.40), previous MI (RIPC 24% vs sham 23%; *P*=0.83), previous coronary artery bypass graft (CABG) surgery (RIPC 19% vs sham 16%; *P*=0.55), and a previous cerebrovascular accident (RIPC 17% vs sham 21%, *P*=0.49). Utilization of medical therapies at baseline was high in both groups (Table 1), with the majority of patients receiving antiplatelet agents such as aspirin (RIPC 87% vs sham 89%; *P*=0.64) and/or clopidogrel (RIPC 18% vs sham 13%; *P*=0.31), statins (RIPC 77% vs sham 73%; *P*=0.54), beta-blockers (RIPC 71% vs sham 61%; *P*=0.15), and/or calcium antagonists (RIPC 19% vs sham 21%; *P*=0.15) before surgery. There were no significant intergroup differences (Table 1).

Preoperative Evaluation and Surgical Characteristics

At least 1 cardiac risk factor, as enumerated by the revised cardiac risk index, was present in the majority of patients (RIPC 61% vs sham 69%; *P*=0.57; Table 2). Pharmacological stress test was frequently performed before vascular surgery and was deemed abnormal in 23% and 29% of patients randomized to RIPC or a sham procedure, respectively (*P*=0.41). Perfusion defects were moderate to large in 12% (RIPC) and 17% (sham) (*P*=0.72) of subjects.

The most common indication for vascular surgery was an expanding AAA (n=115; RIPC 52% vs sham 62%; *P*=0.12), followed by obstructive disease of the carotid arteries (n=49; RIPC 30% vs sham 19%; *P*=0.06) and of the lower extremities (n=37; RIPC 14% vs sham 18%; *P*=0.37). The most common form of AAA repair was endovascular (90% of all AAAs). General anesthesia was used in 92% of cases, with a mean (±SD) duration of 247±86 minutes in the RIPC group and 251±105 in the sham group (Table 2). Opiates were widely utilized during anesthesia (RIPC 91% vs sham 97%; *P*=0.18).

Study Endpoints

A detectable cTnI increase was present in 22 patients randomized to RIPC and 25 randomized to the sham procedure (22.2% vs 24.7%; *P*=0.67; Figure 2). The median changes in cTnI were 0.048 (IQR=0.004–0.174) and 0.017 µg/L (IQR=0.003–0.105) in the RIPC and sham groups, respectively (*P*=0.54; Figure 3). The 2-part test chi-square with 2 *df* was 0.55 (*P*=0.76). The proportion of patients with detectable cTnI increases was similar among different types of vascular procedures (AAA repair=25%; peripheral bypass=22%; carotid endarterectomy=21%; *P*=not significant).

Electrocardiographic changes consistent with myocardial ischemia were present in 7% of patients assigned to RIPC and in 11% assigned to a sham procedure (*P*=0.49). Ischemic symptoms, such as angina or dyspnea, were rare (2% vs 1%, respectively; *P*=0.55). A postoperative MI was diagnosed in 4% of patients assigned to RIPC and in 5% assigned to sham (*P*=0.74; Table 3). Pre- and postoperative levels of NTpro-BNP were similar between groups (Table 3). The median (IQR) increase in NTpro-BNP in the perioperative period was 390 (±58–871) and 287 (±81–690) in the RIPC and sham groups, respectively (*P*=0.52). Acute kidney injury developed in 1 patient randomized to RIPC and 3 randomized to a sham procedure (RIPC=1% v sham 3%; *P*=0.15).

At 1-month follow-up, there were a total of 26 all-cause rehospitalizations (RIPC=10%; sham=16%; *P*=0.21), including 3 strokes (RIPC=2; sham=1; *P*=0.55) and 3 MIs (RIPC=1; sham=2; *P*=0.56). There were no deaths. A list of all adverse events is presented in Table S1.

At 6-month follow-up, clinical events remained low: death (RIPC=0; sham=1; *P*=0.33); MI (RIPC=1; sham=0; *P*=0.29); and stroke (RIPC=0; sham=1; *P*=0.33). There was no inter-group difference in the number of adverse events (RIPC=31; sham=28; *P*=0.46).

Discussion

The main findings of this phase II, randomized, clinical trial of remote ischemic preconditioning before vascular surgery are: (1) The proportion of patients with an elevated cTnI following vascular surgery approaches 25%; (2) RIPC did not significantly reduce the proportion of patients with cTnI elevations postsurgery; (3) among patients with a detectable increase in cTnI, RIPC did not reduce the distribution of increased cTnI levels; (4) RIPC did not have a significant effect on biomarkers of left ventricular end-diastolic filling pressure, such as NTpro-BNP; and (5) RIPC did not reduce the proportion of patients meeting a clinical definition of MI.

A seminal observation by Przyklenk et al was that infarct size after 1-hour occlusion of the left anterior descending artery was significantly smaller if animals had previously received 4 episodes of ischemia and reperfusion in the circumflex artery, each of 5-minute duration.[5] Since this landmark animal study, numerous advances have occurred in

Table 1. Baseline Characteristics of Patients Randomized to RIPC or Sham Procedure

	RIPC (n=100)	Sham (n=101)	P Value
Age, y (±SD)	69 (±7)	69 (±7)	0.48
Male sex, %	100	100	0.78
Caucasian (%)	97 (97)	98 (97)	0.99
Height, cm (±SD)	176 (±9)	175 (±8)	0.84
Weight, kg (±SD)	95 (±22)	94 (±23)	0.70
Body mass index (±SD)	31 (±11)	30 (±10)	0.54
Systolic BP, mm Hg (±SD)	134 (±17)	131 (±18)	0.88
Diastolic BP, mm Hg (±SD)	75 (±10)	76 (±9)	0.45
Heart rate, bpm (±SD)	67 (±11)	68 (±11)	0.44
Past medical history (%)			
Hyperlipidemia	78 (78)	73 (72)	0.34
Current smoker	37 (37)	31 (31)	0.40
Past MI	24 (24)	23 (23)	0.83
Past PCI	21 (21)	23 (23)	0.58
Past CABG	19 (19)	16 (16)	0.55
Congestive heart failure	7 (7)	7 (6)	0.98
Atrial fibrillation	8 (8)	11 (11)	0.48
Ischemic heart disease	45 (45)	42 (41.5)	0.62
Insulin-dependent diabetes mellitus	16 (16)	11 (11)	0.28
Cerebrovascular accident	17 (17)	21 (21)	0.49
Creatinine >2 mg/dL	3 (3)	2 (2)	0.89
Ejection fraction (±SD)	54 (±12)	56 (±9)	0.10
Laboratories			
Sodium mEq/L (±SD)	138±4	138±2	0.09
Potassium mEq/L (±SD)	4±0.4	4±0.35	0.96
Creatinine md/dL	1±0.4	1±0.3	0.70
Hemoglobin mg/dL	13±1.6	13±1.6	0.55
Baseline N-terminal probrain natriuretic peptide (pg/mL), median (IQR)	109 (65–268)	170 (81–365)	0.12
Medical therapies (%)			
Aspirin	87 (87)	90 (89)	0.64
Statins	77 (77)	74 (73)	0.54

Table 1. Continued

	RIPC (n=100)	Sham (n=101)	P Value
Beta-blockers	71 (71)	62 (61)	0.15
Calcium-channel blockers	19 (19)	21 (21)	0.15
ACEI	44 (44)	49 (48)	0.52
Warfarin	8 (8)	7 (7)	0.77
Clopidogrel	18 (18)	13 (13)	0.31
Opiates	23 (23)	19 (19)	0.64

ACEI indicates angiotensin-converting enzyme inhibitor; BP, blood pressure; CABG, coronary artery bypass surgery; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIPC, remote ischemic preconditioning.

the field of myocardial conditioning in the last 2 decades.[24–27] These include: (1) confirmation of intracardiac, interorgan, and interspecies effects of RIPC[24]; (2) discovery of alternative (ie, nonischemic triggers) that can initiate remote conditioning, such as chemical nociception[25]; (3) better understanding of signal transfer to the heart and other tissues through neuronal and humoral pathways[7–9]; and (4) early application and validation of RIPC in human studies before coronary angio-plasty, CABG surgery, and MI.[10,11,23,26,27] To the best of our knowledge, CRIPES is the first randomized, clinical trial to assess the effects of a noninvasive protocol of RIPC before elective vascular surgery. The rationale for testing RIPC in this setting is that perioperative MI remains the leading cause of death in the perioperative period,[3] and most vascular surgeries are considered high-risk operations.

Previous feasibility studies, using different approaches to induce RIPC, showed conflicting results before vascular surgery.[28–31] Ali et al used an invasive intraoperative proce-dure to induce RIPC by intermittently cross-clamping the common iliac artery in 82 patients undergoing open aneurys-mal repair.[28] With this approach, RIPC reduced the incidence of myocardial injury, as defined by cTn, by 27% (RIPC=39% v control 12%; *P*=0.005). In contrast, Walsh et al assessed the role of various RIPC protocols before vascular surgery: (1) Lower-limb ischemia-reperfusion was applied to 40 patients undergoing EVAR and (2) 70 patients undergoing carotid endarterectomy.[29,30] In both studies, RIPC failed to improve cardiac adverse events. A third study using an invasive intraoperative cross-clamping of the iliac artery failed to improve markers of renal injury during open AAA repair.[31] CRIPES, having enrolled as many patients as all these pilot studies combined, provides additional evidence in support of the notion that RIPC lacks efficacy in the perioperative period of common peripheral vascular surgeries.

Two large, prospective, multicenter, randomized, clinical trials have recently reported similar results in patients undergoing open heart surgery, a setting where myocardial

Table 2. Preoperative Evaluation and Surgical Characteristics

	RIPC (n=100)	Sham (n=101)	P Value
Revised cardiac risk index (%)			
0	39 (39)	32 (31)	0.40
1	32 (32)	44 (43.5)	0.08
2	19 (19)	16 (16)	0.86
≥3	10 (10)	9 (9)	0.62
Stress test prior to vascular surgery	87 (87)	88 (87)	0.97
Abnormal stress test	23 (23)	29 (29)	0.41
Perfusion defect ≥moderate/large	12 (12)	17 (17)	0.76
Presenting vascular problem, %			
Expanding AAA	52	62	0.12
Obstructive lower extremity disease	14	18	0.37
Critical limb ischemia	4	1	0.16
Carotid disease	30	19	0.06
Type of vascular intervention			
Carotid endarterectomy	30	19	0.14
Open or endovascular AAA repair	52	64	0.30
Infrainguinal peripheral bypass	19	17	0.80
High-risk surgery* (%)	18 (18)	22 (22)	0.58
Anesthesia			
General anesthesia, %	92	92	0.78
Estimated blood loss	150 (±250)	214 (±402)	0.08
Duration of anesthesia-minutes, mean±SD	247±86	251±105	0.39
Opiates administered during anesthesia	91%	97%	0.18
Days in intensive care unit (ICU)	2.5±1	2.2±1	0.66

AAA indicates abdominal aortic aneurysm; RIPC, remote ischemic preconditioning.
*High-risk surgery: open AAA repair or peripheral bypass.

injury occurs almost universally.[32,33] The Remote Ischemic Preconditioning for Heart surgery (RIPHeart) randomized 1403 patients undergoing elective cardiac surgery to RIPC or a sham procedure. The primary endpoint was a composite of death, MI, stroke, or acute renal failure at hospital discharge and was no different between groups (RIPC=14.3% vs sham=14.6%; *P*=0.89). Likewise, the Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery (ERICCA) trial randomized 1612 patients undergoing on-pump CABG
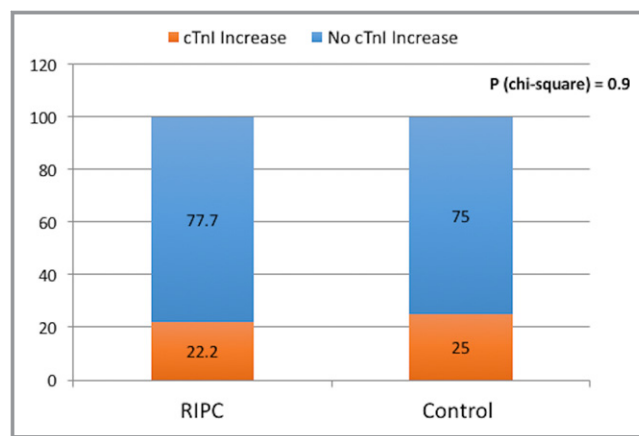

Figure 2. Primary endpoint: proportion with cardiac troponin I (cTnI) increases. RIPC indicates remote ischemic preconditioning.

with or without valve surgery to RIPC or a sham procedure. The primary endpoint was death from cardiovascular causes, MI, coronary revascularization, or stroke at 12 months. In the ERICCA trial, RIPC did not improve clinical outcomes at 1 year (26.5% vs 27.7%; *P*=0.58). Importantly, in both studies, RIPC did not attenuate perioperative myocardial injury, as demonstrated by similar area under the curves of cTn release.

In contrast, RIPC has been shown to reduce infarct size before elective percutaneous coronary intervention (PCI) and before mechanical or pharmacological reperfusion therapy for acute ST-segment elevation myocardial infarction.[26,34] Given that the positive results of RIPC before cardiac surgery in small studies[11,35] were not replicated in large clinical trials such as ERICCA and RIPHeart, confirmation of these positive early results in large, multicenter, clinical trials is warranted.
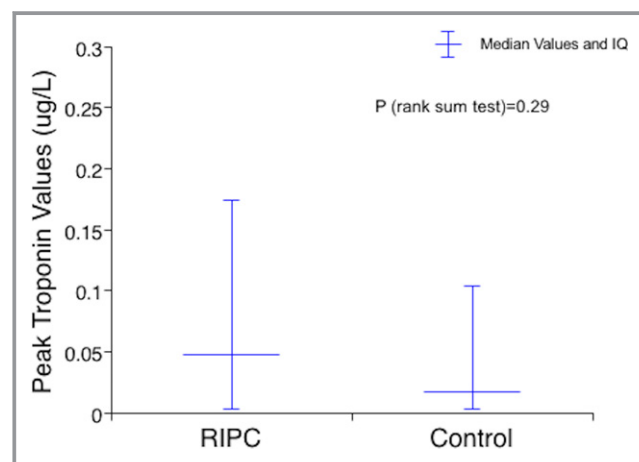

Figure 3. Distribution of cardiac troponin I according to assigned treatment. RIPC indicates remote ischemic preconditioning.

Table 3. Study Outcomes According to Treatment Assignments

	RIPC (n=100)	Sham (n=101)	*P* Value
Troponin increase, %	22	24.7	0.74
Median cTnI increase, μg/L (IQR)	0.048 ± (0.004–0.174)	0.017 (0.003–0.105)	0.54
ECG ischemic changes, %	7	11	0.49
Perioperative myocardial infarction, %	4	5	0.74
Postoperative N-terminal probrain natriuretic peptide (pg/mL) median, (IQR)	556 ± (182–1118)	459 (210–922)	0.73
Delta N-terminal probrain natriuretic peptide (pg/mL), median (IQR)	390 ± (58–871)	287 (81–690)	0.52
Acute kidney injury (%)	1	3	0.15

cTnI indicates cardiac troponin I; ECG, electrocardiogram; IQR, interquartile range; RIPC, remote ischemic preconditioning.

Several potential mechanisms have been postulated to explain why the effects of RIPC, which have been clearly demonstrated in animals, may be blunted or absent in human models. First, opiates and some commonly used anesthetic agents, such as propofol, are known to attenuate the effects of RIPC during surgery.[36] Second, cardiac comorbidities, such as diabetes mellitus can also mitigate the effects of RIPC on myocardial tissue by affecting O-linked β-*N*-acetylglucosamine signaling leading to a state of inherent chronic activation that renders the diabetic myocardium resistant to RIPC.[37] Finally, it is plausible that RIPC is present during daily activities in patients affected by coronary or peripheral arterial disease (ie, claudication, angina pectoris, and silent ischemia), therefore rendering additional application of RIPC before surgery of limited value.[38]

Limitations

The study has some important limitations. First, we included surgical procedures that carried a low-to-intermediate surgical risk. For the purpose of assessing the effects of RIPC, we would have preferred to include a higher number of patients undergoing open AAA repairs instead of EVAR procedures. However, CRIPES reflects the shift that has occurred in the field of vascular surgery away from open AAA repair and toward endovascular approaches. Second, the study was conducted at a single medical center and the cohort is comprised predominantly of Caucasian males. Caution is warranted when extrapolating these results to other populations. Third, Zelis et al. showed that a blood pressure cuff inflated at 70 mm Hg in the upper arm for 3 hours to induce venous congestion can reduce arterial blood flow in the forearm by 49%.[39] Therefore, it is possible that the sham protocol might have caused transient reduction in arterial blood flow, but it is unlikely that this level of reduction, achieved with a shorter and milder protocol, would have

resulted in forearm ischemia that would trigger a preconditioning response. Fourth, of the 4 participants that left the study after randomization, 3 dropped out for reasons that preempted delivery of the randomly assigned intervention and collection of endpoint data, as stated in Figure 1. Hence, it seems unlikely that these dropouts biased the comparison. Finally, the RIPC protocol was applied 12 to 24 hours before surgery ("second window of protection") and before anesthesia. Therefore, we were unable to blind the investigators with a surgical drape as others have done.[33] Nonetheless, the primary endpoint (troponin elevation) was objective and unlikely to change with a different design.

Conclusions

Upper-limb RIPC applied 12 to 24 before a vascular operation did not reduce myocardial injury or infarct size, as assessed by serial cTnI measurements.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. List of reported adverse events at 1 month

RIPC (25%)	Sham (31.6%)
Stroke (2)	Infection at surgical site (5)
Cellulitis (2)	Ileus
Drainage from incision	Coronary artery bypass graft (CABG) surgery following an MI
Cataract surgery	Seen in ER for fever (2)
Seen in ED for fever	Pacemaker implantation
Heart failure	Abdominal pain
Back pain	Bruising
Infected toe	Atrial fibrillation
Dysphagia (2)	Critical limb ischemia
Tingly fingers since protocol	Dizziness/syncope (2)
Pneumonia (2)	Pneumonia (1)
Biliary stent removed	Dehiscence of surgical suture
Swelling at surgical site	Seen in ED for fatigue
Groin hematoma	Pruritus
Rash	Groin bleed
Headaches	Constipation
Infection at surgical site	UTI
Wound hematoma	MRSA infection
Myocardial infarction	Epistaxis
	Suicidal ideation
	Unable to void, requires bladder catheter
	Stroke
	Myocardial infarction