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**Research Article** 

# Cardiac Remote Ischemic Preconditioning Prior to Elective Major Vascular Surgery (CRIPES): Study Design and Rationale

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#### Abstract

**Background:** Vascular surgery is considered a high-risk operation with an anticipated perioperative risk of serious cardiac ischemic complications in excess of 10%. One potential strategy for reduction of myocardial ischemia during the perioperative period is Remote Ischemic Preconditioning (RIPC).

**Design:** The Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES, NCT: 01558596) is a prospective, randomized, sham-controlled phase 2 trial using RIPC prior to elective vascular surgery. CRIPES plans to enroll and treat 180 patients over 4 years and gather safety and efficacy data for one-month after surgery. Preliminary estimates for two potential measures of efficacy will be examined: 1) a two-part test of postsurgical increases in cardiac troponin I as a measure of myonecrosis and 2) the proportion of patients in each treatment arm meeting the universal definition of myocardial infarction.

**Discussion:** Knowledge gained from the CRIPES study will help inform further testing of RIPC prior to non-cardiac surgery.

Keywords: Vascular surgery; Clinical trials; Ischemic preconditioning

## Background

Over 300,000 surgical revascularization procedures are performed in the United States (US) annually as part of the treatment of expanding abdominal aortic aneurysms, critical limb ischemia, and severe carotid artery disease [1]. Vascular surgery is considered a highrisk operation with an anticipated perioperative risk of either death or non-fatal myocardial infarction of 10-15% [2]. The occurrence of a cardiovascular complication after surgery, related to a non-fatal Perioperative Myocardial Infarction (PMI), is associated with an increased risk of long-term mortality [3].

Angiographic studies have shown that coronary artery disease is highly prevalent among patients with Peripheral Arterial Disease (PAD) undergoing vascular surgery [4]. However, in the Coronary Artery Revascularization Prophylaxis (CARP) trial a strategy of prophylactic coronary artery revascularization did not improve clinical outcomes [5]. In the CARP trial, despite high utilization rates of statins and beta-blockers, 16% of patients suffered a PMI [5]. Moreover, among patients with multiple risk factors and evidence of myocardial ischemia detected by nuclear imaging the incidence of PMI was 25% (Figure 1) [6]. These data highlight the limitations of preventive therapies available in clinical practice and reinforce the need to develop new strategies to reduce perioperative cardiac complications.

One potential strategy for reduction of myocardial ischemia during surgery is ischemic preconditioning, which describes the cardioprotection obtained from application of one or more non-lethal episodes of myocardial ischemia and reperfusion before the index myocardial ischemic event [7,8]. Unlike spontaneous myocardial infarction the majority of PMIs are thought to result from an imbalance between oxygen supply and demand in the setting of severe, yet stable, coronary artery disease [9,10]. Therefore, remote ischemic preconditioning applied prior to vascular surgery may prepare the myocardium to better tolerate prolonged perioperative ischemia.

The Cardiac Remote Ischemic Preconditioning Prior to Elective

Vascular Surgery (CRIPES, NCT: 01558596) was designed to determine the feasibility and safety of using remote ischemic preconditioning (RIPC) prior to vascular surgery, and to obtain preliminary estimates



**Figure 1:** Impact of prophylactic coronary revascularization according to number of risks enumerated in the Revised Cardiac Risk Index (RCRI). Although the RCRI predicts the risk of death or non-fatal Myocardial Infarction (MI) 30-days post-surgery, prophylactic revascularization did not have a beneficial effect in any of the higher-risk subsets. Reproduced with permission from Garcia S, et al. [6].

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of its effects on detectable postsurgical increases in cardiac troponin I (cTnI) and PMIs.

# Methods

## **Trial design**

CRIPES is a prospective, randomized, feasibility trial with a single blind (patient), sham-controlled design.

## **Patient population**

We plan to enroll 180 patients over a 4-year period at the Minneapolis VA healthcare system. Inclusion and exclusion criteria are displayed in Table 1.

The rationale for including patients undergoing elective vascular surgery in a study of myocardial protection is supported by angiographic studies that demonstrated a high prevalence of coronary artery disease in this population [4]. Moreover, vascular surgery is accompanied by significant hemodynamic stress and postoperative ischemic events [5].

#### Randomization and study intervention

Consenting subjects will be randomly assigned to RIPC or a similar control procedure using permutated blocks of 2 or 4 subjects. Randomly assigned treatments will be placed in sealed, sequentially numbered envelopes that will be opened by the study nurse before consented subjects undergo an elective vascular surgery in time to administer the 30-minute intervention.

The RIPC protocol will consist of three cycles of the following: 5-minute inflation of a blood pressure cuff around the upper arm to 200 mmHg (or 20 above the systolic blood pressure if baseline BP > 200 mmHg) to allow for external compression of the brachial artery resulting in transient forearm ischemia, followed by a 5-minute interval of cuff deflation to allow for reperfusion. The total duration of the protocol is 30 minutes equally divided between ischemia and reperfusion. Masking of control subjects will occur by inflation of a blood pressure cuff to lower pressure (40-50 mmHg) that will not impede arterial forearm blood flow. The study intervention is to be applied in the patient room within 24 hours prior to the scheduled vascular surgery.

# Trial end points

Feasibility: The feasibility of enrolling 180 subjects (4 subjects per

month) will be determined. The proportion of patients able to safely tolerate the RIPC protocol will be recorded, as will measures of pain and discomfort during the preconditioning procedure.

Efficacy endpoints: To assess the extent of cardiac myonecrosis during surgery, perioperative increases in troponin I will be compared. Depending on the level of ischemic risk among enrolled subjects, we expect to see a number of subjects in each treatment group that do not have a detectable increase in cTnI during the first 3 days after surgery. Therefore, we will use a two-part statistical test to compare postsurgical increases in cTnI [11]. Cardiac troponin I will be measured by the Dade Behring Dimension Analyzer. The lower limit of detection of this assay is  $0.03 \mu g/L$ . For the first part, we will compare the proportion of patients in each treatment arm that have an increase in cTnI postsurgery, as determined by systematic measurement of cTnI on days 0, 1, 2, and 3 of surgery. The second part will compare the distributions of the increases in troponin among subjects with a detectable cTnI. A reduction in one or both measures of increases in cTnI would indicate potential benefit of pre-operative RIPC prior to vascular surgery.

The second endpoint of interest is the proportion of patients in each treatment arm meeting the universal definition of myocardial infarction (MI) [12]. According to this definition a postoperative myocardial infarction is considered to have occurred when a typical rise and fall in troponin, with at least one value  $\geq 99^{\text{th}}$  percentile URL, is seen in conjunction with one or more of the following: 1-electrocardiographic changes consistent with myocardial ischemia or infarction (1-mm horizontal or down sloping ST-depression, new 2 mm deep T wave inversion,  $\geq 1$  mm ST-segment elevation in 2 contiguous leads or Q waves), 2- symptoms suggestive of ischemia such as chest pain or breathlessness, 3- new loss of previously viable myocardium on cardiac imaging, 4- new coronary thrombus detected on angiography or pathology.

Electrocardiograms (EKGs) will be obtained preoperatively and on days 0, 1, 2, and 3 in all patients. Additional EKGs may be obtained at various intervals if clinically indicated. Only a fraction of the subjects that have an increase in cTnI are expected to meet these criteria for PMI.

**Safety**: Any new or worsening medical event noted from the start of the intervention to within 30 days after the operation will be recorded as a possible adverse event. A serious adverse event of interest will be defined as a myocardial infarction, death, stroke, vascular complication

Inclusion Criteria: All must be present							
1.	Patients scheduled to have major vascular surgery at the Minneapolis VA Healthcare system for one of the following:						
•	Occlusive carotid disease						
•	Expanding abdominal aortic aneurysm						
•	Occlusive lower extremity disease						
•	Critical limb ischemia						
2.	Age ≥18 years						
3.	Willing to participate and provide informed consent						
Exclusion Criteria: None may be present							
1.	Acute coronary syndrome in the preceding 6 weeks						
2.	Severe valvular disease evidenced by one of the following						
•	severe aortic stenosis with a valve area <1.0 cm <sup>2</sup>						
•	≥ 3+ aortic or mitral valve insufficiency						
3.	Peripheral arterial disease of the upper extremities manifested by a systolic blood pressure difference of greater than 20 mmHg						
4.	Hypertensive crisis						
5.	Hemodialysis with a fistula in the upper extremity						
6.	Pregnant women						
7.	Patients unable to consent or inability to adhere to the study protocol						
8.	Limited life expectancy (<6 months)						
9.	Participation in another study within the previous 30 days						

Table 1: Inclusion and exclusion criteria.

or any rehospitalization. In addition to recording all spontaneously reported events, subjects will be contacted 1, 3, and 6 months after surgery to inquire about any new or worsening medical events.

**Institutional review approval and informed consent:** The study protocol conforms to the International Conference on Harmonization/ Good Clinical Practice standards. The protocol has received approval by a duly constituted institutional review board. Written informed consent will be obtained from all study participants.

#### Data analyses

**Feasibility:** The number of potential subjects that are screened for inclusion along with the number who consent and reasons for not participating will be tracked as will completion of the RIPC or sham procedure. The cumulative accrual of randomized subjects will be plotted.

**Group characteristics**: Baseline characteristics of the two study groups will be described by means and standard deviations, medians and interquartile ranges or percentages as appropriate for the level of measurement and distributions of the data. At baseline, continuous variables will be compared between groups using the non-paired Student t test for normally distributed data or the Mann Whitney U test for non-normally distributed data. Proportions will be compared with Pearson's chi-square or Fisher's exact test.

Efficacy: All consenting subject that are randomly assigned to a treatment group will be included in an intent-to-treat analysis. The proportions that do not have a detectable increase in troponin I and the differences thereof will be reported. The distributions of the detectable increases in troponin I will be summarized by histograms along with the median and interquartile range.

A two-part statistical test will be used to jointly test a two-sided null hypothesis that parts 1 and 2 will be equal in the two groups (control versus RIPC) [11]. A chi-square test with two degrees of freedom will be derived as the sum the square of the z-test for binomial proportions (part 1) and the square of Mann-Whitney rank sum test U statistic comparing the distributions of the detectable increases in troponin (part 2). If the distributions of the detectable troponins are normal or log normal, then a more powerful square of the Student's t-test statistic will be used in place of the rank sum test. Using our preliminary data obtained by review of cases that had vascular surgery (3) to estimate ball park values for parts 1 and 2 and the effects of RIPC seen in the Cardiac Remotes Ischemic Preconditioning in Coronary Stenting (CRISP) study [13], RIPC is expected to decrease the proportion of subjects undergoing vascular surgery that have a detectable increase in troponin from approximately 35% to 15% and lower the median of the distribution of detectable increases by approximately 60%. The number of subjects needed in each randomly assigned treatment group to have 80% or 90% power to detect these effects is estimated to be 67 and 88, respectively, with a 2-sided alpha error of 0.05 [14]. These estimates assume the distributions of the detectable increases in troponin are log normal with equal variances. Sample estimates for less robust RIPC effects are presented in Table 2.

No formal interim analyses are planned for this preliminary investigation.

A secondary analysis will make adjustments for any baseline differences that are seen in the randomly assigned treatment groups. Logistic regression (the square of z value of the adjusted treatment effect) will be used to make adjustments to part 1 and quantile (median) regression (the square of t value of the adjusted treatment effect) for part 2. No tests for interactions with treatment are planned for this modest-sized, feasibility study.

**Safety:** All new or worsening medical events will be recorded on case report forms. The number (%) of each group that has a nonserious and serious adverse event will be categorized by system organ class and tabulated overall and for each treatment group. Deaths, nonfatal myocardial infarction, non-fatal stroke, surgical complications, any rehospitalization, and pain and tingling, numbness in the arm subjected to RIPC that occurs within 30 days of randomization will be of particular interest. Proportions that experience various adverse events will be compared by Fisher's exact test without any adjustment for multiple comparisons although this study still will not have sufficient power to detect all important differences in adverse events.

## Funding

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#### Discussion

The translation of ischemic preconditioning from the experimental laboratory to the clinical arena has been disappointing and slow [15]. Kloner et al. provided a framework for conducting clinical trials using preconditioning in at-risk populations [16]. The model

% Without detectable	increase in cTnI	N each group	N each group						
Control (%)	RIPC (%)	(90% power)	(80% power)						
20% decrease in mean of non-zero increases in troponin									
0.60	0.80	117	91						
0.65	0.85	108	83						
0.70	0.90	95	73						
40% decrease in mean of non-zero increases in troponin									
0.60	0.80	103	80						
0.65	0.85	99	76						
0.70	0.90	90	69						
60% decrease in mean of non-zero increases in troponin									
0.60	0.80	89	68						
0.65	0.85	88	67						
0.70	0.90	83	64						

RIPC: Remote ischemic preconditioning

 Table 2: Sample size estimates for two-part test of perioperative increases in cardiac troponin I (cTnI) under different assumptions.

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First author/ reference	Clinical situation	Sample size	RIPC protocol	End-point	Key findings
Hoole et al. [13]	Elective coronary angioplasty	242	Three 5-minute cycles of right upper arm ischemia	Periprocedural troponin T release	Reductions in median troponin values and increase in the proportion with no detectable troponin I from 24% to 48%
Hausenloy et al. [18]	Coronary-Artery Bypass Grafting	57	Three 5-minute cycles of right upper arm ischemia	Perioperative troponin T release	RIPC reduced area under the curve by 43%
Ali et al. [19]	Vascular Surgery	82	Two cycles of intermittent crossclamping of the common iliac artery with 10 minutes ischemia followed by 10 minutes reperfusion	Perioperative troponin I release	RIPC reduced myocardial injury by 27% and myocardial infarction by 22%

Table 3: Selected clinical trials reporting a benefit with Remote Ischemic Preconditioning (RIPC) in adult patients prior to cardiac or vascular procedures commonly associated with myocardial ischemia.

of "prophylactic" preconditioning refers to those clinical situations where myocardial ischemia is likely (i.e. coronary artery bypass surgery, percutaneous coronary interventions, vascular surgery) and/ or unavoidable (i.e. heart transplant). In these clinical situations a protocol of RIPC applied prior to the procedure has shown promising early results [13,17-19] (Table 3).

Illes et al. assigned patients to receive one-minute of aortic cross clamping during normothermic cardiopulmonary bypass or a matched control period prior to performing CABG [17]. Although no intergroup differences were seen for morbidity and mortality end-points significant improvements in functional parameters were seen in the preconditioned arm. Hausenloy et al. randomized 57 patients undergoing elective CABG to RIPC or standard of care and demonstrated that RIPC was associated with a 43% reduction in the area under the curve for troponin T when compared to standard of care [18].

The study of preconditioning in the setting of major vascular surgery is limited to one study in which an invasive protocol was applied to patients undergoing open aneurismal repair. Ali et al. showed in 82 patients undergoing open abdominal aortic aneurysm repair that a protocol of RIPC applied during the operation, 10-minute occlusion of the right common iliac artery followed by a 10-minute occlusion of the left common iliac artery, resulted in a significant reduction in troponin I release in the postoperative period (intergroup difference in area under the curve of 23 ng/ml, p < 0.001) [19]. No study has ever been conducted to test whether RIPC applied noninvasively to the brachial artery before vascular surgery can reduce cardiac necrosis.

The actual mechanism through which RIPC protects the myocardium is unclear, although studies in animals have suggested that cardioprotection may be mediated through a neuronal or humoral pathway [18]. Supporting a neuronal pathway, studies have shown that cardioprotection can be abolished by the ganglionic blocker hexamethonium [19,20] or by pretreatment sensory nerves with capsaicin [21]. It is unclear whether the humoral mediators associated with ischemic preconditioning, which include adenosine, bradykinin, and opioids, are released into the bloodstream or locally in response to neural activation [22,23]. In favor of a humoral mechanism Kostantinov et al. demonstrated using a pig model of heart transplantation that application of RIPC to recipient hearts protected the donor heart against myocardial infarction [24]. At a cellular level the currently favored model involves stimulation of G protein-coupled receptors with subsequent activation of multiple kinases, followed by phosphorylation and activation of a membrane bound target, most likely the mitochondrial K<sup>+</sup> ATP channel [25].

# Conclusion

CRIPES was designed to determine whether a protocol of Remote

Ischemic Preconditioning (RIPC) applied prior to vascular surgery is feasible, safe and leads to a reduction in detectable increases in cardiac troponin I relative to a sham control group. Results of this phase 2 investigation will help inform decisions for additional evaluation of RIPC on a larger and broader scale.

#### **Trial Status**

Currently enrolling patients. Total number of participants enrolled: 62.

#### **Competing interests**

The authors declare that they have no competing interests.

## Authors' contributions

SG, TSR, SS, and EM made substantial contributions to the study conception and design; and are co-applicants on the grant application. SG, MYZ, AM, YS, SM and RC coordinate the management and execution of the trial. All authors read and approved the final manuscript.

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