Clinical 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 high-risk 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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Received April 30, 2013; Accepted June 12, 2013; Published June 14, 2013

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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 permuted 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 reperfusion. Masking of control subjects will occur by inflation of a blood pressure cuff to lower pressure (40-50 mmHg) that will not reperfusion.

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 μg/L. For the first part, we will compare the proportion of patients in each treatment arm that have an increase in cTnI post-surgery, 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 ≥ 99th 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 downsloping ST-depression, new 2 mm deep T wave inversion, ≥ 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...

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Table 1: Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria: All must be present</th>
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<tbody>
<tr>
<td>1. Patients scheduled to have major vascular surgery at the Minneapolis VA Healthcare system for one of the following:</td>
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<tr>
<td>• Occlusive carotid disease</td>
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<tr>
<td>• Expanding abdominal aortic aneurysm</td>
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<tr>
<td>• Occlusive lower extremity disease</td>
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<tr>
<td>• Critical limb ischemia</td>
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<tr>
<td>2. Age ≥18 years</td>
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<tr>
<td>3. Willing to participate and provide informed consent</td>
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<table>
<thead>
<tr>
<th>Exclusion Criteria: None may be present</th>
</tr>
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<tbody>
<tr>
<td>1. Acute coronary syndrome in the preceding 6 weeks</td>
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<td>2. Severe valvular disease evidenced by one of the following</td>
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<tr>
<td>• severe aortic stenosis with a valve area &lt;1.0 cm²</td>
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<tr>
<td>• ≥ 3+ aortic or mitral valve insufficiency</td>
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<td>3. Peripheral arterial disease of the upper extremities manifested by a systolic blood pressure difference of greater than 20 mmHg</td>
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<tr>
<td>4. Hypertensive crisis</td>
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<td>5. Hemodialysis with a fistula in the upper extremity</td>
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<td>6. Pregnant women</td>
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<tr>
<td>7. Patients unable to consent or inability to adhere to the study protocol</td>
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<td>8. Limited life expectancy (&lt;6 months)</td>
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<td>9. Participation in another study within the previous 30 days</td>
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</table>
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 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.

Discussion

The CRIPES trial is funded by the Office of Clinical Research and Development, Service of the Veterans Health Administration, Department of Veterans Affairs (CLIN-014-11F). Dr. Garcia is a recipient of a Career Development Award from the Office of Research and Development, Department of Veterans Affairs.

Table 2: Sample size estimates for two-part test of perioperative increases in cardiac troponin I (cTnI) under different assumptions.
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 aeurismal repair. Ali et al. showed in 82 patients undergoing open abdominal aortic aneurism 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+ ATP channel [25].

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.

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

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.

**Acknowledgements**
Dr. Garcia is a recipient of a career development award (1K2CRCX000699-01) from the VA Office of Research and Development.

**Funding**
Veterans Affairs Office of Research and Development.

**References**


