Prospective Study Protocol

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Title: Effectiveness of Remote Ischemic Preconditioning for prevention of Contrast Induced Acute Kidney Injury in patients undergoing coronary angiograms. (RIP-CI-AKI study)

Site(s) where study will be performed: University of Texas Medical Branch (UTMB).

Funding Sponsor: Cardiology & Nephrology division of Internal Medicine Department, UTMB.

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1. Introduction and Purpose:

The use of imaging is increasing in clinical practice, either for diagnosis or intervention. In these imaging processes, contrast medium (CM) is widely used. However, CM administration can induce contrast-induced nephropathy (CI-AKI). CI-AKI is the third most common cause of renal insufficiency, and its incidence varies from 2% to 50% depending on patient risk factors; in addition, studies have shown that CI-AKI occurs in 2% to 25% of patients undergoing coronary intervention. CI-AKI is associated with significant mortality and morbidity in patients undergoing coronary angiography or other diagnostic contrast studies. We assessed the latest promising evidence on the ability of remote ischemic preconditioning (RIPC) to reduce the incidence of CI-AKI in patients undergoing Coronary Angiogram (CA) or diagnostic contrast studies such as CT angiograms, while at the same time being a non-invasive, low cost, easy, and safe method with absence of adverse effects. However, more randomized controlled trials are needed to confirm these preliminary results.

The aim of this study is to minimize the incidence of CI-AKI at the University of Texas Medical Branch (UTMB). If found to be an effective method, RIPC would help minimize the incidence of CI-AKI in all institutions across the globe, who would adopt this intervention.

The primary objective: i) reduce the rise in creatinine to < 0.5 mg/dL post-CA in moderate to high risk patients and ii) reduce the incidence of renal replacement therapy post-CA in moderate to high risk patients; iii) we also aim to establish that RIPC is safe and effective.

We hypothesize that the use of RIPC, when added to standard medical therapy (pre-and post-CA hydration), will mitigate the effects of contrast on the renal vasculature and lessen the incidence of CI-AKI in moderate to high risk patients at the University of Texas Medical Branch.

2. Background:

The use of iodinated contrast to visually enhance target vasculature is a widely used diagnostic technique that is performed daily at UTMB, and around the world, for the diagnosis and management of a variety of conditions. A common complication of this procedure is acute kidney injury (AKI), generally referred to as contrast-induced nephropathy (CI-AKI). This complication can range from an isolated rise in serum creatinine to severe renal dysfunction necessitating renal replacement therapy. The incidence of CI-AKI has been reported as approximately 2-50%, depending upon the definition and sensitivity of assay employed to assess GFR in the hospital setting[1-3]. In addition, CI-AKI is associated with significant mortality and morbidity. Rihal et al. reported that amongst hospital survivors of patients with acute kidney injury due to PCI (percutaneous coronary intervention), the 1 year and 5-year mortality rate was 12.1% and 44.6% respectively in comparison to 3.7% and 14.5% mortality rates in patients without AKI ($p<0.0001$)[3]. Also, Chertow et al. reported that an absolute increase in creatinine of more than 0.3 mg/dL was associated with a 4-fold increase in hospital mortality[4]. Lassnigg et al. found that an increase in creatinine up to 0.5 mg/dL was associated with a three-fold rise in 30-d post-operative mortality[5]. Hence, if proven to be beneficial, RIPC will bring about a reduction in incidence of CI-AKI, and thus help to reduce hospitalization and mortality from renal etiology following a given contrast procedure.

Risk factors for CI-AKI include age > 75, hypotension, CHF, anemia, diabetes, patients with a baseline serum creatinine greater than 1.5 mg /dL and the volume of contrast media used[6]. The presence of underlying renal dysfunction appears to provide particular susceptibility. Although most studies exclude patients with severe renal dysfunction, Rihal et al. report that in patients with a creatinine >3.0 (and GFR < 30) the incidence of CI-AKI was 31%[7].

Unfortunately, robust strategies to prevent CI-AKI are minimal. Research has examined the use of sodium bicarbonate, adding N-acetylcysteine or holding RAAS (Renin-angiotensin-aldosterone system) blockers but found all these three strategies ineffective[9,10]. At this time the only validated strategy to prevent CI-AKI is the use of fluid administration to ensure adequate renal perfusion. Pre- and post-procedure intravenous fluid administration is currently considered standard of care. In one study involving 408 patients with intact renal function receiving isotonic saline (NS) (1cc/kg/h before percutaneous angiography and 24 hours after) the incidence of CI-AKI within the following 3 days was 21% in the group without NS and 11% in the NS+ group ($p=0.016$)[11]. Further, CI-AKI was associated with increased risk of death (15.2% vs 2.8%; $p<0.0001$) and need for renal replacement therapy (13.4% vs 0%; $p<0.0001$)[11]. In another trial involving 216 patients, pre- and post-procedure hydration reduced the incidence of CI-AKI in the hydrated group versus the non-hydrated control group 20.4% versus 35.2%, $p< 0.05$)[12]. These results were confirmed in the POSEIDON trial which also showed that a LVEDP (left ventricular end-diastolic pressure) guided hydration strategy for the prevention of CI-AKI results in an even greater relative and absolute risk reduction in contrast nephropathy in comparison to the standard hydration strategy[13].

A major limitation however, is that many patients requiring coronary angiography present with excess fluid, mitigating the usefulness of this strategy. Patients with an acute coronary syndrome and reduced systolic function or patients with compromised renal function are particularly sensitive to fluid administration. Specifically in POSEIDON, three patients in each group stopped intravenous fluids early because of the development of pulmonary edema[13]. Recently, research has examined the possibility of a safe, inexpensive and non-pharmacological prevention strategy termed remote ischemic preconditioning (RIPC) which may reduce the prevalence of CI-AKI.

The pathophysiology of CI-AKI is thought to involve renal artery vasoconstriction and the development of reactive oxygen species which leads to direct renal oxidative stress and ischemic injury[1]. The table below outlines the pathophysiology of CI-AKI:

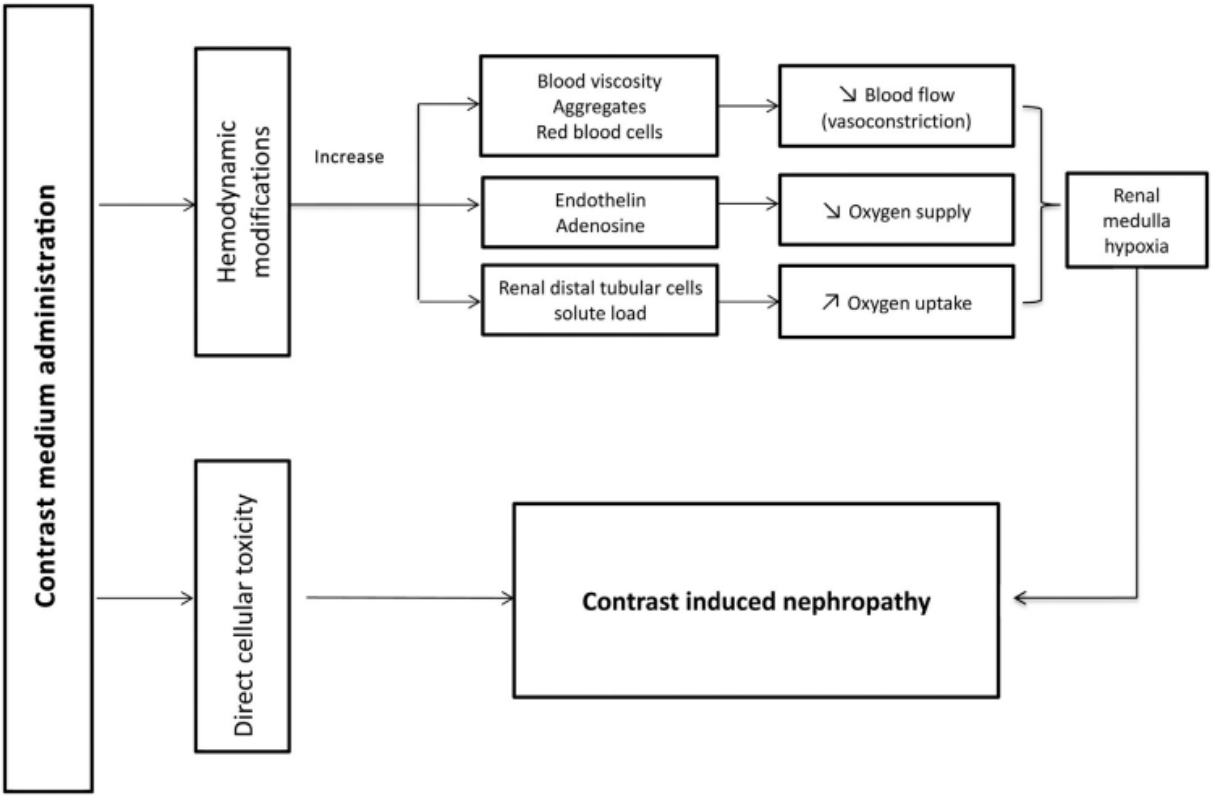

Fig. 1. Pathophysiologic mechanisms involved in contrast induced nephropathy.

Experimental research has shown that the transient induction of periods of ischemia followed by reperfusion of a tissue can potentially trigger the body's natural protective physiology against ischemic injury. This technique has been demonstrated to reduce the cardiac ischemic injury during heart surgery[14] and to reduce the incidence of cardiac and renal ischemic injury during abdominal aortic aneurysm repair[15,16]. This has created interest in utilizing RIPC to reduce the incidence of post contrast- procedural CI-AKI by priming the body, in a manner similar to exercise, to withstand ischemic injury. Although the exact pathophysiology is not completely understood, it is thought to involve modulation of inflammatory, humoral and neural pathways[17]. One of the postulated mechanisms for the nephroprotective effect of RIPC was through an ischemia-protecting effect on renal medulla by reducing the reperfusion injury. Various neuro-humoral

substances such as opioids, micro-RNA-144, bradykinin, erythropoietin, prostaglandins, nitric oxide, O-linked β-N-acetylglucosamine, and adenosine has been shown to be involved. Remote ischemic preconditioning also activates reperfusion injury salvage kinase pathway, endogenous antioxidant system, hypoxia-inducible factor system, suppressing induction of renal inflammation, and preventing renal tubular cell apoptosis. Multiple randomized controlled trials have employed the technique and the results are promising.

Er at al. conducted ischemic preconditioning in patients with chronic kidney disease (eGFR < 60 ml/min/m2. Patients were randomized into a control and experimental group (IPC) which received 4 cycles of alternating upper arm 5-minute inflation and 5-minute deflation to patient's systolic blood pressure (plus 50 mmHg) prior to coronary angiography. The authors report that the incidence of CI-AKI in the IPC group was 12% vs 40% in the control group[1]. Further, secondary end points such as the incidence of death, hospitalization or the need for hemodialysis were also significantly reduced[1]. Shokoufeh et al. randomized 96 diabetic patients who were undergoing coronary angiography to 3 cycles of 5-minute ischemia versus no ischemia and measured serum creatinine before and 24 hours post procedure. They reported that serum creatinine levels were significantly lower in the treatment group reflecting a protective effect of RIPC for the development of CI-AKI[18]. Zagiullin et al. enrolled 51 patients who were randomized to RIPC involving 3-5 minute cycle cuff pumped on the upper arm + 50 mmHg above systolic blood pressure and report a significant reduction in CI-AKI – 3.8 % in the experimental group versus 28% in the control/sham group[19]. Finally, Bafna and Shah conducted a double-blinded randomized control trial with patients at moderate to high risk of CI-AKI and reported that RIPC prior to CA reduced post-procedure elevations in creatinine compared to the control group 0.023 +/- 0.2 micromol/L versus 0.064 +/- 0.1 micromol/L ($p<0.001$) respectively[20].

A meta-analysis published in 'Kidney & Blood Pressure Research' journal in 2020, which covered 16 trials and 2,048 patients were identified. Results showed that the application of RIPC decreased the incidence of CI-AKI (relative risk, RR, 0.50, 95% confidence interval, CI, 0.39–0.65; $p < 0.001$). Subgroup analyses showed that RIPC decreased the incidence of CI-AKI in patients with eGFR <60 mL/min/1.73 m2 (RR 0.53, 95% CI 0.38–0.75; $p < 0.001$) but not in patients with eGRF ≥60 mL/min/1.73 m2 (RR 0.82, 95% CI 0.35–1.94; $p = 0.66$) at baseline. Furthermore, the increase in serum creatinine was significantly lower in patients with RIPC compared to control patients (standardized mean difference –1.41, 95% CI –2.46 to –0.35; $p = 0.009$). Conclusions: Based on 16 RCTs, this meta-analysis shows that RIPC can reduce the risk of CI-AKI in patients with moderate renal impairment undergoing PCI/CA. However, this needed to be confirmed by further high-quality evidence.

UTMB, like other major academic centers, with a robust interventional cardiology program, experience multiple episodes of CI-AKI. We propose to implement a CI-AKI-preventative protocol involving RIPC to reduce the incidence of CI-AKI and improve patient outcome.

Of note, all of the trials involving RIPC have taken place outside of the US, mostly in Europe. If approved, this study would be the first study to be done in the US that closely looks at RIPC as a significant strategy in preventing CI-AKI in patients undergoing CA/Diagnostic contrast studies.

In addition, it is important to note that RIPC (with 4 cycles of BP cuff inflation identical to the one we are proposing) was performed in a case control study in University of California Los Angeles and University of Miami in 2013, to observe the effect of RIPC on coagulation profile of patients with aneurysmal subarachnoid hemorrhage. It did prove the safety of RIPC use in clinical practice.[21]

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3. Concise Summary of Project:

Kidney Disease Improving Global Outcome (KDIGO) defines CI-AKI as an increase in serum creatinine level ≥0.5 mg/dl or >25% compared with the baseline value within a period of 48-72 hours after contrast media (CM) administration.

The definition of Remote Ischemic Preconditioning is not as simple. According to a pathophysiologic concept, repeated short duration ischemia in an organ induces a ‘‘resistance’’ to a later prolonged ischemia. That is, a brief period of ischemia induces endogenous protective mechanisms that increase tissue tolerance to subsequent lethal ischemia. This is a physiological adaptive mechanism of protection of tissues faced to hypoperfusion, which has therapeutic potential when ischemia-reperfusion is induced in a targeted way. In 1982, this mechanism called ischemic preconditioning (IPC) was highlighted for the first time on canine models in myocardial infarction. In experiments, cycles of alternating ischemia and reperfusion were applied to dogs by using a balloon to occlude a coronary artery. This allowed the prevention of necrotic myocardial territories. These results have opened prospects on a possible use of this method of preconditioning for myocardial protection as well as preconditioning for renal protection in humans.

Our remote ischemic preconditioning protocol would comprise four (4) cycles of 5 min of ischemia followed by 5 min of reperfusion for the experimental group. The BP cuff would be

placed around the upper non-dominant arm (e.g upper left arm in a right-handed patient) and inflated to a pressure set at 50 mmHg higher than baseline systolic BP to induce transient ischemia followed by subsequent deflation to ensure 5 minutes of reperfusion in the RIPC group. The absence of distal pulse would be confirmed with Doppler evaluation or palpation of the radial and ulnar artery.

In the control group, sham preconditioning would be performed by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff to 10 mm Hg below diastolic pressure for 5 minutes to maintain nonischemic upper-arm compression for blinding purposes with regard to the patients; this will be followed by complete deflation of cuff for 5 minutes. Again a total of four cycles would be ensured. In individuals presenting with BMI > 30 kg/m2 , a dedicated blood pressure cuff for obese patients will be used. Time from RIPC to the procedure (either CA or diagnostic contrast study) will be within <120 min in all studies.

The patients will be randomly assigned in a 1:1 ratio to either the control group or RIPC group. Randomization will be performed by data analysis software, which would determine whether the patient would fall under the RIPC arm vs Sham-procedure arm.

Patients would be blinded to arm assignment. Moreover, both care providers (interventional cardiologist performing coronary angiography and PCI) and physicians assessing outcomes would be blinded to the original arm assignment.

All patients will receive standard care for patients with impaired renal function undergoing CA:

Recommended hydration will consist of saline 0.9% solution infusion at a rate of 1 mL/Kg/h for 12 hours prior to contrast medium injection and up to 12 hours thereafter, unless there is evidence of fluid overload thus contraindicating further fluid administration. Metformin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs will be discontinued at least 24hours before the angiography. Blood samples for basic metabolic panel (BMP) would be drawn prior to coronary intervention/diagnostic contrast study and repeated 48-72 hrs following contrast medium administration. A final BMP would be checked at 6 weeks after contrast procedure, only if the

initial BMP (at 48-72 hrs) showed evidence of CI-AKI; if the initial BMP did not show elevated creatinine levels >0.5 mg/dl, the final BMP (at 6 weeks) would not be required.

The primary outcome would be the incidence of CI-AKI, which is defined as an increment of serum creatinine **≥** 0.5 mg/dL or a relative increase of **≥** 25% over the baseline value within a period of 48-72 hours after contrast medium administration. The secondary outcomes would be occurrence of re-hospitalization, the need for a session of hemodialysis, and mortality within 6 weeks of contrast administration/ major adverse events at 6 weeks, which would comprise death from all causes, cardiovascular death, non-fatal infarction, hemofiltration or hemodialysis, and congestive heart failure leading to hospital admission.

4. Study Procedures:

Following IRB approval, studies will begin with a target of including 400 patients in the study, with a tentative timeline of three (3) years. We will obtain BMPs on the day of the procedure (to document baseline creatinine), and then repeat 48-72 hrs after CA/diagnostic contrast studies. No additional visits would be required apart from a visit to the phlebotomist for getting the BMP checked within 48-72 hrs and potentially a repeat BMP at 6 weeks (only if the initial BMP at 48-72 hrs showed evidence of CI-AKI). . If the initial BMP did not show elevated creatinine levels >0.5 mg/dl, the final BMP (at 6 weeks) would not be required. Almost all of our patients who undergo CA will have a follow-up appointment with their PCP in the next 3-7 days, but no extra visits are required for the study purpose. No extra costs on the part of the patient would be necessary.

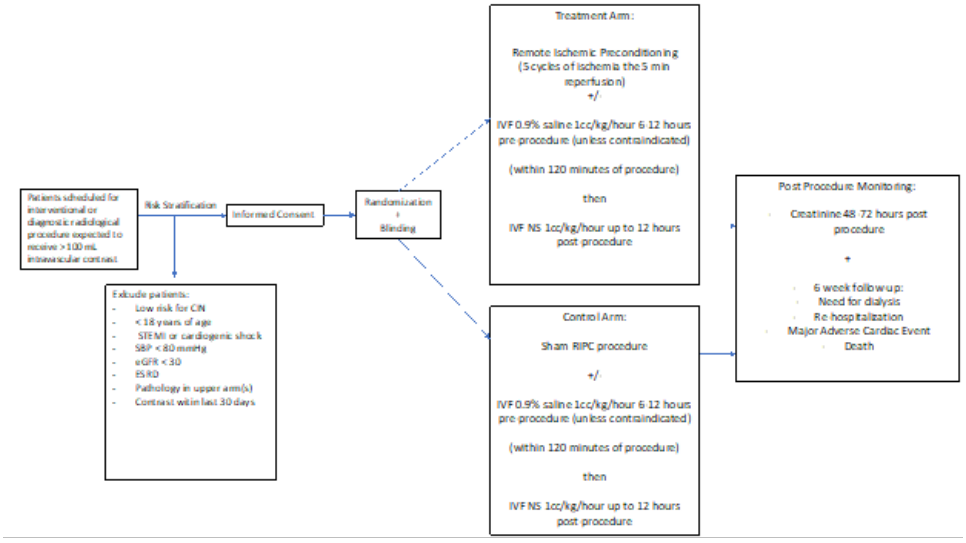
Our intervention group- remote ischemic preconditioning group- would be subject to four (4) cycles of 5 min of ischemia followed by 5 min of reperfusion for the experimental group. The BP cuff would be placed around the upper non-dominant arm (e.g upper left arm in a right-handed patient) and inflated to a pressure set at 50 mmHg higher than baseline systolic BP to induce transient ischemia followed by subsequent deflation to ensure 5 minutes of reperfusion in the RIPC group. The absence of distal pulse would be confirmed with Doppler evaluation or palpation of the radial and ulnar artery.

In the control group, sham preconditioning would be performed by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff to 10 mm Hg below diastolic pressure for 5 minutes to maintain nonischemic upper-arm compression for blinding purposes with regard to the patients; this will be followed by complete deflation of cuff for 5 minutes. Again a total of four cycles would be ensured. In individuals presenting with BMI > 30 kg/m2 , a dedicated blood pressure cuff for obese patients will be used. Time from RIPC to the procedure (either CA or diagnostic contrast study) will be within <120 min in all studies.

In addition to our above mentioned intervention (RIPC), all patients will receive standard of care for patients with impaired renal function undergoing CA as mentioned below (No.1 and No.2) :-

No.1: Recommended hydration will consist of saline 0.9% solution infusion at a rate of 1 mL/Kg/h for 12 hours prior to contrast medium injection and up to 12 hours thereafter, unless there is evidence of fluid overload thus contraindicating further fluid administration.

No.2: Metformin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs will be discontinued at least 24hours before the angiography.



6. Criteria for Inclusion of Subjects:

Inclusion criteria will be: (1) patients undergoing an interventional or diagnostic radiological procedure in which they receive intravascular contrast, including patients undergoing coronary angiogram +/- percutaneous coronary intervention (PCI) for all clinical indications except those indicated for primary PCI due to STEMI, (2) patients presenting with a renal clearance in the range of less than 60 ml/min/1.73 m2 but not declared ESRD; and (3) Patients who are not yet recruited for other pharmacological or medical device clinical trials.

7. Criteria for Exclusion of Subjects:

Exclusion criteria will be: (1) Age <18 years; (2) Patient on hemodialysis or peritoneal dialysis; (3) Simultaneous participation in another interventional study; (4) Percutaneous coiling/embolization procedures of the kidney; (5) Impossibility to perform RIPC, caused by pathology in both arms (e.g. dystrophy, recent trauma, chronic wounds), (6) No written informed consent, (7) Urgent angiography in STEMI, (8) Cardiogenic shock requiring catecholamine infusion, (9) Systolic blood pressure <80 mmHg, (10) Intra-aortic balloon counter-pulsation, (11) Contrast medium injection within the previous 30 days, (12) Expected impossibility to obtain follow-up data at 6-week follow-up, (13) Patients with Raynaud's disease

Of note, subjects would be removed from the study if they are non-compliant in there follow up BMP checks at the lab as well as if they withdraw their consent.

8. Sources of Research Material:

1. Data will be sourced through the electronic medical record (EPIC). The records will be accessed from UTMB firewall protected workstations. Study would be a Prospective clinical study. As new clinical data are generated, these will also be captured from the medical record. Charts will be accessed by the primary investigator and IRB-approved personnel only.

The following data points will be collected from EPIC: Serum creatinine before and after Coronary angiogram. In addition certain patient characteristics will be obtained from EPIC: age, gender, race, BMI (body mass index), eGFR (glomerular filtration rate), type & volume of contrast used, type of intervention performed during angiogram, presence of heart failure,

presence of DM, presence of anemia and presence of CKD on admission; we would also observe the patient's chart for any rehospitalization due to any cause (mostly due to cardiac or renal cause) within 6 weeks of the procedure.

2. Data collection will begin after subject signs the consent form and end at the end of the study period, which may be up to three (3) years after initiation of study in order to have a large enough sample size to prove our hypothesis.

9. Recruitment Methods and Consenting Process:

Subjects would only be contacted by a member of the research team, only if they had expressed interest in our study to their primary team medical provider. Once the patient communicates their interest to the primary team provider regarding participation in our study, which in most cases would be to the inpatient providers of the primary Cardiology teams (Red and White team) but could be other primary inpatient services as well, we would reach out to the patient directly when he has been hospitalized in anticipation of the coronary angiogram, to further discuss our intervention and initiate the consenting process.

Potential subjects will be patients of UTMB who are admitted for CA +/- PCI as well as patients who undergo diagnostic contrast studies. Patients would be approached in the inpatient setting by a member of the research team and will be given the option to participate in the study, where they may receive the intervention currently being studied (namely RIPC), which has been hypothesized to reduce the incidence of CI-AKI.

Potential subjects would also be recruited in the out-patient setting from the Cardiology clinic (in all campuses of UTMB). Patients who meet the inclusion criteria would be directly contacted by a member of the research team (either in person or over the phone) and would be given the choice to be in the study.

Finally, we would reach out to patients who are scheduled to undergo out-patient diagnostic contrast study (such as CT angiogram), and discuss the potential benefits of our intervention, namely RIPC. They will be given a chance to participate in our study as well. To be specific, the patients who could possibly be recruited in the out-patient setting will have to be patients of the study team members only. Hence, if a patient expresses his/her wish to participate in the study to our study team member because they are a direct patient of our study team member, then we will consider that patient to be recruited to our study. However, the research team will not recruit any patients in the out-patient setting who are not direct patients of our study team members. That is, any patient who are not direct patients of our study team members will not be eligible for recruitment into the study in the out-patient setting.

We would like to unequivocally state that if potential subjects are not patients of the investigator or patients of the study team members, they will not be contacted by study staff unless they have been informed of the study by their medical provider and express an interest in receiving more information on the study or wish to enroll in the study. Potential subjects would only be contacted by a member of the research team, after they had expressed interest in our study to their primary team medical provider, which in a vast majority of cases will be team members of inpatient cardiology teams (Red team and White team).

After recruitment, the signed consent forms will be kept within a locked file cabinet in a locked room (office of PI) that has restricted access.

During the informed consent process, undue influence or coercion will be minimized by making clear that no financial or non-financial incentive will be offered in exchange for participation. It will be made clear that no aspect of their clinical care will be influenced based on study participation.

Vulnerable populations will be not included, including prisoners, pregnant women, children and individuals under the age of 18 years.

10. Potential Risks:

1. Loss of confidentiality

2. Loss of privacy

As with all research studies, there is always the risk of accidental release of confidential information. Every effort will be made to keep the information confidential.

To minimize risk of confidentiality breach, we would ensure limited access to patient records; the deidentified data would only be available to the PI, sub-I and IRB approved study personnel.

11. Subject Safety and Data Monitoring:

The Principal Investigator (PI) will be responsible for ensuring that data is secure and accessible only to approved study staff.

Data will be stored on password-protected computer with the data stored behind the UTMB firewall.

The record will be electronic, and will be deleted upon completion of the study, on the desktop on which it was created within the UTMB firewall. Access will be limited to individuals listed on the UTMB IRB key personnel list. Files will not be shared with non-study personnel. Patients' identities will not be identifiable in publications resulting from this investigation. Data will not be disclosed to outside individuals or entities.

12. Procedures to Maintain Confidentiality:

Only PI, sub-I and IRB approved study personnel would have access to the data. After accessing subject charts and collecting the necessary data, only de-identified data would be tabulated for further analysis. Data would be collected on password-protected computer with the data stored behind the UTMB firewall /encrypted personal laptops of study personnel, which would not be accessible to other health care providers; no public computers to be used for data analysis. High standards would be maintained throughout the entire duration of this research to ensure that HIPAA would not be violated.

13. Potential Benefits:

Increasing use of diagnostic and therapeutic contrast studies corresponds to increasing incidence of CI-AKI, currently the third cause of renal insufficiency. CI-AKI is associated with significant mortality and morbidity in patients undergoing coronary angiography (CA) or other diagnostic contrast studies. Remote ischemic preconditioning is an effective procedure to reduce the risk of CI-AKI and can be considered in patients with moderate-high risk at developing CI-AKI. In addition, this intervention is a non-invasive, low cost, easy, and safe method with absence of adverse effects. However, all of the studies involving RIPC have taken place outside of the US and more high quality studies are needed to confirm the preliminary results.

Patients may or may not directly get benefit from the study. However, if our hypothesis is proven to be true, the merit of this study is the potential benefit to the patient & society of eventual prevention of CI-AKI.

14. Biostatistics: (omit this section for peer-reviewed research such as cooperative group, or NIH- sponsored studies, and for industry-sponsored research which has been submitted to FDA)

1. ***Statistical methods.*** Data will be analyzed by the primary investigator and IRB-approved key personnel. Additional assistance will be employed through the Office of Biostatistics when needed. These analyses will be conducted on UTMB firewall protected workstations. Data will be analyzed by appropriate statistical software.
2. ***Target sample size.*** Based on prior studies, in order to reach statistical power of 80%, and significance level of 0.05, we estimated the required sample size to be approximately 400 patients. Studies of this type where a model is developed in the first period and tested in the next period benefit from a large sample size. As this is a low risk study in which no additional procedures are done to patients, it is not of great value to subjects or society to do a minimal sample size approach. In fact, the larger the sample size, the better the final product, in this case the model algorithm, in terms of precision of the model estimates.