Title: Randomized feasibility trial of remote ischemic conditioning to enhance resuscitation (RICE)

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SPECIFIC AIMS

RATIONALE FOR FEASIBILITY STUDY OF RIC IN OHCA

Out-of-hospital cardiac arrest (OHCA) is a loss of mechanical activity of the heart in the field. Quick restoration of blood flow (reperfusion) is essential to reduce the chance of death after cardiac arrest. This reperfusion causes release of circulating inflammatory molecules that cause cellular injury similar to that observed in patients with ST-elevation myocardial infarction (STEMI). The extent of this reperfusion injury (RI) is associated with the duration of ischemia and adequacy of resuscitation.

Remote ischemic conditioning (RIC) consists of application of brief episodes of ischemia then reperfusion to an organ or limb distal to the heart by inflating a blood pressure (BP) cuff around a limb. Randomized trials in animal models of cardiac arrest as well as in humans with acute myocardial infarction suggest that RIC before or after restoration of blood flow to the heart reduces RI and improves outcomes. More than two inflations of 2 to 5 minutes duration are required to optimize cardioprotection; there is no advantage to simultaneous application of RIC to multiple limbs.

Ultimately, delivering RIC at first medical contact should result in the best chance to show effectiveness of RIC treatment, as long as the application of the therapy does not result in reduced delivery of standard care to the patient. We have previous experience showing that translation of some hospital-based interventions such as induced hypothermia (IH) to the field setting may be associated with increased risk. Our pilot study showed that IH by iced intravenous saline in patients with OHCA was feasible either in hospital or in the field.[1, 2] Our subsequent large trial showed that IH in the field was associated with increased rearrest.[3] We believe that RIC as a therapy is safe when applied manually with a BP cuff, as evidenced by more than 12,000 patients having completed trials of RIC with no reported serious adverse events. But since implementation of RIC in the field may delay other important elements of care, we should demonstrate the feasibility and safety of randomization in the emergency department (ED) setting before proceeding to assess its effectiveness in the field setting.

A standard non-invasive blood pressure cuff (e.g., American Diagnostics Corporation, Hauppauge, NY but any one can be used off the shelf) and disposable plastic clamp (e.g., Medline Industries Incorporated, Mundelein, IL) can be used to apply RIC in patients resuscitated from OHCA via three cycles of 5-mins. inflation to 200 mmHg followed by 5-mins. deflation of a blood pressure cuff on a thigh. The cuff occludes the artery; the clamp maintains pressure in the air bladder of the cuff during the inflation periods. No additional benefit is associated with more than three inflations, or with treatment of more than one limb. Note that no device is approved by the Food and Drug Administration to provide RIC in the United States.

This ED-based study will identify human and other factors that may decrease the ability to implement the autoRIC device in patients with OHCA. The study will also confirm the safety of the device for use in the field. This study will use exception from informed consent for emergency research.

PRIMARY AIM FOR PILOT STUDY

Our primary aim is to evaluate the feasibility of random allocation to active RIC (intervention) versus (vs.) sham RIC (control) quickly upon ED arrival following resuscitation from OHCA. Feasibility will be assessed as attrition, defined as the proportion of randomized subjects who do not remain on allocated therapy for the intended study duration. In the intervention group, this will be defined as lack of completion of three cycles of inflation-deflation; In the control group, this will be defined as crossover to the intervention group. Included will be subjects with spontaneous circulation upon ED arrival after receiving chest compressions by emergency medical services (EMS) providers or defibrillation by laypersons or EMS providers. Excluded will be: ST elevation on first electrocardiogram; written do not attempt resuscitation; pregnant; prisoners; trauma, drowning, or hypothermia etiology of arrest; known dialysis fistula; or limb amputation. Enrolled will be 30 patients. All outcomes will be summarized descriptively. The design of a future trial will be modified based on the results of this study.

PRIMARY HYPOTHESIS FOR PILOT STUDY

The null hypothesis is that the attrition rate will be not more than 25%. We assume 59 patients annually are treated by EMS providers for OHCA (21 due to ventricular fibrillation) and have spontaneous circulation upon arrival at the participating receiving hospital. Enrollment of 30 patients (15 per group) will allow estimation of attrition with precision (as measured by half-width of 95% CI) of at least 16.8% overall (and 23.7% within each group).

BACKGROUND AND SIGNIFICANCE

BURDEN

Out-of-hospital cardiac arrest (OHCA) is common, lethal and debilitating. Cardiac arrest has multiple etiologies,

and presumptions about the etiology of arrest influence treatment decisions. Sometimes an identifiable precipitating cause is evident (e.g. traumatic injury, drowning, strangulation, or overdose). In these cases, treatment is directed not only to restoration of circulation, but also to addressing the underlying medical conditions. The majority of OHCA without obvious physical cause is secondary to acute coronary occlusion. In all cases, treatment is directed toward timely restoration of blood flow to the heart and brain.

Extrapolation from observational data reported to the Resuscitation Outcomes Consortium (ROC), suggests that about 424,000 calls to 911 are made annually for individuals who are presumed to have had a non-traumatic OHCA in the United States.[4] Many of these patients are in such serious condition upon EMS arrival that no attempts at resuscitation are made. Outcome is generally poor among all patients with OHCA treated by EMS; only about 55% of treated cardiac arrest patients having a perfusing rhythm upon transport to an ED, with only 10% of those treated surviving to discharge.

Underlying mechanisms for non-traumatic cardiac arrest are crudely categorized as a) conductive abnormalities of the myocardium leading to arrhythmias, b) chronically weakened myocardium leading to end-stage pump failure, and c) acute occlusion of a coronary artery leading to myocardial infarction. These are not necessarily mutually exclusive, especially after any delay between the cardiac arrest and arrival of EMS. Of these mechanisms of OHCA, successful resuscitation is generally most successful for isolated conductive abnormalities or for acute coronary thrombosis that is treated rapidly. Acute occlusion is most common among patients with a first recorded rhythm of VF, which hereafter includes pulseless ventricular tachycardia as well as rhythms interpreted as shockable by an automated external defibrillator (AED). Thus, OHCA is commonly categorized by the first recorded cardiac rhythm: VF, pulseless electrical activity (PEA), or asystole.

Importantly, survival to discharge after EMS-treated arrest varies five-fold across regions[5] and has a three-fold variation for survival after hospital admission.[6] This variation with respect to survival is beyond that which can be explained solely by sampling error. Instead, there are systematic differences between sites related to EMS practices in treating and transporting patients to the ED, and the success of hospital treatments. To the extent that treatment factors contribute to this variation, opportunities abound to reduce premature death due to OHCA by improving care during the initial post-resuscitation period.

Reperfusion Injury

Cardiac arrest involves sudden, global ischemia. Quick restoration of blood flow is essential to reduce the chance of death after cardiac arrest. Patients who have restoration of blood flow post cardiac arrest have about a 50% chance of surviving to discharge from hospital. While restoration of blood flow (reperfusion) is necessary to prevent immediate death, it triggers the release of circulating inflammatory molecules including cytokines (e.g. IL-1ra, IL-6, IL-8, IL-10), activated complement and polymorphonuclear leukocytes.[7-10] These fluxes are associated with upregulation of DNA, endothelial dysfunction, release of reactive oxygen species (ROS) and opening of mitochondrial permeability transition pores (MPTP).[7, 11-13] The latter plays a critical role in myocardial necrosis.[14, 15] After cardiac arrest, non-survivors have plasma IL-6 concentrations that are about 20-fold greater than survivors,[7] which in turn are about 50-fold greater than normal human baseline values.[16] These changes contribute to poor capillary perfusion, tissue ischemia, multi-organ dysfunction and death.[17-20] Similar cellular changes are observed after restoration of flow in patients with acute myocardial infarction or coronary artery bypass grafting (CABG). The extent of this reperfusion injury (RI) correlates with the duration of blood flow cessation and impacts how well the patient responds to treatments, as well as the likelihood of death. However, many patients with early hemodynamic dysfunction that is reduced or treated do survive to have a good neurological outcome[7, 21] and treatments that decrease early mortality related to inflammation and intractable shock could increase the number of survivors with good neurological outcomes.

Attenuation of Reperfusion Injury by Induced Hypothermia

Induction of hypothermia (IH, also known as targeted temperature management or TTM) consists of cooling the body in order to reduce neurologic injury and multi-organ dysfunction in patients with RI. It has pluripotent effects that reduce the injury associated RI in the brain[22] and heart.[23] Among these are reduced opening of the MPTP in animal models of ischemia-reperfusion.[24-27] Two trials that enrolled patients in the pre-propofol era demonstrated that rapid application of IH to comatose patients resuscitated from cardiac arrest and transported to hospital improved survival and neurologic outcomes as compared with standard care.[28, 29] Another trial in which few patients received propofol demonstrated that induction of hypothermia with endovascular methods tended to improve survival to 28 days without major neurologic damage (odds ratio 1.41, 95% confidence interval 0.93 to 2.16, p=0.107) vs. surface methods in patients resuscitated from OHCA of any rhythm.[30] A recent trial that enrolled patients in the propofol era failed to detect a difference in survival or favorable neurologic status between

patients who underwent TTM to 33°C vs. those who underwent targeted temperature management to 36°C.[31] Though the primary report of this trial did not describe the prevalence of propofol use, a sub-study at one site that enrolled 18% of the overall sample size, showed that the 33°C group received significantly more propofol than the 36°C (421±177 vs. 339±175 mg/h; p=0.005).[32] If this pattern of use of propofol was similar across sites, it may have attenuated the protective effects of TTM at the mitochondrial level and reduced the magnitude of differences in clinical outcomes between treatment groups.

In summary, evaluations of interventions to reduce RI after cardiac arrest should do so while accounting for use of IH and propofol.

Conditioning to Reduce Reperfusion Injury

Organs can be conditioned to reduce RI associated with restoration of blood flow after ischemia. Strategies designed to reduce RI by conditioning can be applied at several time periods. ***Preconditioning*** is applied ***before*** the ischemic event. ***Perconditioning*** is applied ***during*** the event. ***Postconditioning*** is applied coincident with or ***after the onset of reperfusion***. Note that preconditioning likely has limited applicability in patients with cardiac arrest since arrest is often the first manifestation of cardiovascular disease and a minority of patients have symptoms before its onset.[33] Delays in restoration of circulation can occur in all phases of treatment for cardiac arrest. These may include the initiation of bystander CPR, notification of EMS providers, arrival of EMS providers on scene, application of a monitor/defibrillator, rhythm analysis and defibrillation as indicated, transportation to hospital, and initiation of post-resuscitation care. Perconditioning seems likely to distract from other elements of resuscitation including timely initiation of EMS CPR, as well as defibrillation, since the number of EMS providers likely to be on scene of OHCA is small. Thus, postconditioning is a promising method of cardioprotection in patients with ischemia including OHCA.[34]

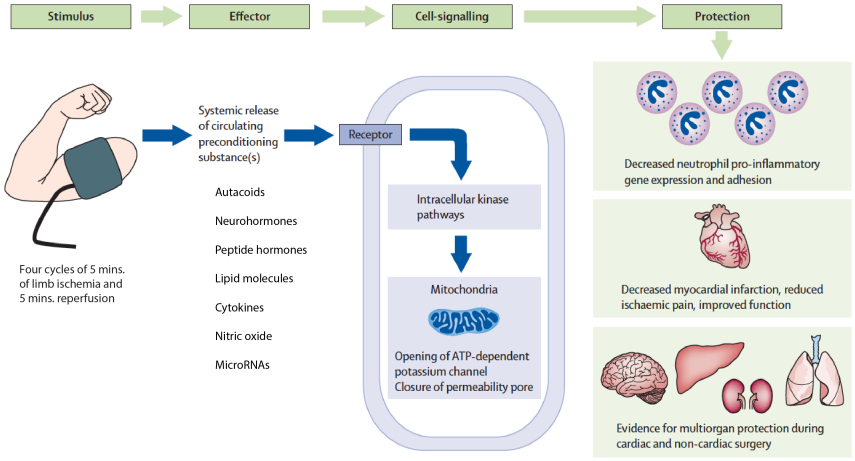
Techniques for Conditioning

Conditioning with pharmacologic (e.g. adenosine,[35, 36] erythopoetin,[37] cyclosporine,[38] or isoflurane[39]) or mechanical methods (i.e. RIC) [40] have been used in a variety of clinical conditions that are associated with RI. Pharmacological conditioning is unlikely to be adopted: adenosine is associated with a risk of sinus pause and therefore unlikely to be used in patients recently resuscitated from cardiac arrest,[41, 42] neither erythropoietin[43, 44] nor adenosine[35, 36, 45, 46] reduce infarct size in patients with STEMI, cyclosporine is also unlikely to be adopted, as it interacts with multiple medications that are commonly prescribed to patients with cardiovascular disease (e.g. angiotensin converting enzyme inhibitors and potassium-sparing diuretics), and verification of use or nonuse of contraindicated medications before initiation of conditioning with cyclosporine is unlikely to be feasible in the chaotic milieu of attempted resuscitation in the field or during the early post resuscitation period in hospital. Finally, isoflurane is a volatile anesthetic that is not readily deployable in the field and not in the current scope of practice of emergency physicians who initially treat patients resuscitated from cardiac arrest and transported to hospital. In contrast, RIC has shown reduction of infarct size across eight randomized trials encompassing more than 2,300 patients with STEMI. Thus, we believe that mechanical, rather than pharmacologic, conditioning holds the greatest promise for early application to patients resuscitated from cardiac arrest. We describe below the experience to date with mechanical methods of conditioning during each phase of an ischemic event.

Mechanism of Attenuation of Reperfusion Injury By Remote Ischemic Conditioning

Remote ischemic conditioning (RIC) is a method of mechanical conditioning that consists of application of brief episodes of ischemia followed by reperfusion to an organ (by cross-clamping arteries) or limb (by inflating a blood pressure cuff) distal to the heart. RIC initiates production of beneficial circulating molecules including autacoids such as adenosine, opioids, and bradykinin, as well as neurohormones, peptide hormones, lipid molecules, cytokines, nitric oxide and microRNAs (miR). These trigger multiple cytosolic and mitochondrial mediators which activate protein kinases, the reperfusion injury salvage kinase (RISK) and survivor activating factor enhancement (SAFE) pathways, hypoxia-inducible factor-1α, and protein expression.[47] This results in attenuation of inflammation,[48-50] reduces generation of deleterious ROS,[51, 52] closure of K-ATP channels and opening of the MPTP (Figure 1).

FIGURE 1: MECHANISM OF REMOTE CONDITIONING
Adapted from Kharbanda Lancet 2009 and Heusch Circ Research 2015



The mechanism of RIC has been further elucidated.[53] Studies with microarrays show that RIC increases, and RI decreases, levels of miR 144 in mouse myocardium. IV administration of miR 144 induced both early and delayed cardioprotection, reduced infarct size and improved functional recovery similar to that associated with RIC. As well, IV administration of a specific antisense oligonucleotide reduced levels of miR 144 in myocardium as well as abrogating the cardioprotection associated with RIC. Finally, RIC was shown to increase serum levels of miR 144 in mice and humans. Thus, increased circulating levels of miR appear to be a key component of the mechanism by which RIC reduces RI.

EFFECT OF REMOTE ISCHEMIC CONDITIONING IN ANIMAL MODELS OF CARDIAC ARREST

In a rodent model of induced VF, conditioning by electrical refibrillation (n=5) did not improve myocardial function or survival vs. the control group (n=5).[54] In another rodent model of induced VF, four cycles of 5 minutes of remote limb ischemia followed by 5 minutes of reperfusion begun 40 minutes before induction of VF (n=7) as well as that begun 5 minutes after resuscitation (n=7) showed equally improved myocardial and neurologic function vs. the control group (n=7).[55] In another rodent study by the same group, remote limb ischemia during CPR (n=7) had improved myocardial and neurologic function as well as survival vs. the control group (n=7).[56] In a swine model of cardiac arrest, limb ischemia after resuscitation (n=7) significantly decreased myocardial and neurologic deficit vs. the control group (n=6).[57]

In a pig model of induced VF followed by CPR and defibrillation, animals were randomly allocated 10 minutes after restoration of circulation to four cycles of five minutes of femoral artery occlusion followed by five minutes of reperfusion (n=11) vs. control (n-11).[58] The RIC group versus the control group had significantly less troponin leak at 4 h, as well as significantly lower serum CK at 24 h. Importantly, the RIC group had median [interquartile range, IQR] neurologic deficit score values 0 [0–15] out of 100 and 10 [7.5–22.5] out of 400 vs. 20 [5, 25] out of 100 and 40 [7.5, 75] out of 400 points in the control group ($p = 0.12$ and $p = 0.11$, respectively.) Note that a lower score on these scales indicates less disability.

EFFECT OF REMOTE ISCHEMIC CONDITIONING IN ANIMAL MODELS OF REPERFUSION INJURY

Although animal models may be poor mimics of clinical disorders,[59] RIC clearly protects multiple organs from RI, including the heart,[34, 60, 61] lungs,[62] skeletal muscle and brain,[63, 64] spinal cord,[65, 66] liver and intestines[67] as well as kidney.[68-70] Also RIC reduces myocardial infarct size by 25 to 70% in multiple species.[61, 71-73] Taken together, these studies suggest that ischemic conditioning has broad benefits against RI and that RIC may be applied before, during, or after reperfusion of the heart by using at least three cycles of remote ischemia and reperfusion.

In summary, preclinical data suggest that RIC is a) cardioprotective and neuroprotective during or after sustained global ischemia such as in cardiac arrest, and b) cardioprotective before or after sustained local ischemia such as infarction.

MECHANICAL CONDITIONING IN CLINICAL DISORDERS ASSOCIATED WITH REPERFUSION INJURY

The concept of RIC was first demonstrated in healthy human volunteers who were randomly allocated to RIC or control then underwent non-lethal ischemia of a forearm.[61] The intervention group (n=7) received RIC before the ischemic insult via three cycles of nonlethal ischemia (5 minutes of cuff inflation to 200 mmHg then 5 minutes of

deflation) of the contralateral arm. The control group (n=7) received no intervention. Endothelial function was assessed as forearm blood flow response to acetylcholine.[74] Before ischemia was induced, acetylcholine caused a dose-dependent increase in blood flow. This response was blunted at 15 minutes after reperfusion in the control group (p=0.03) but not in the intervention group (p=0.66). The authors concluded that RIC reduced post-ischemic endothelial dysfunction in humans.

REMOTE ISCHEMIC CONDITIONING IN HUMANS WITH ACUTE MYOCARDIAL INFARCTION

To date, acute myocardial infarction is the clinical disorder in which RIC has been evaluated that most closely resembles cardiac arrest. In randomized assessments of RIC in humans with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI)[40, 75, 76] or thrombolysis,[77] RIC applied to an upper extremity significantly reduced myocardial injury and infarct size vs. standard care. RIC also significantly increased ST-resolution vs. standard care.[78] Two small trials of RIC applied to a lower extremity of patients with STEMI failed to demonstrate a significant reduction of MRI-based infarct size vs. standard care.[79, 80] Neither of these latter trials reported whether flow in the thigh was successfully occluded. The reduction in infarct size observed with RIC and PPCI translated into improved long-term outcome.[81] No adverse events were reported in any of these trials.

Although the early mortality rate was low among all patient groups enrolled in these trials of RIC in patients with acute infarction, the observed reduced infarct size is likely to have sustained clinical benefit since ejection fraction is a strong correlate of long-term mortality post infarction.[82] Note that lower extremity conditioning may be less efficacious than upper extremity conditioning.[83] Long-term follow up in the largest of the trials that enrolled patients with STEMI demonstrated a significant and important mortality benefit.[81]

REMOTE ISCHEMIC CONDITIONING IN HUMANS WITH DIVERSE CLINICAL DISORDERS

A meta-analysis summarized the prior randomized experience with RIC in patients with RI associated with a variety of clinical disorders.[84] Eligible trials included patients with, or at risk of, ischemia who were randomly allocated to receive RIC regardless of the timing or method used vs. no conditioning. The primary outcome was mortality. Data were pooled by using random-effect models. 23 studies enrolled a total of 1,878 patients. 16 of these studies reported mortality data. Ten studies evaluated RIC in patients undergoing CABG; five in other cardiac surgery; four in patients undergoing percutaneous coronary intervention (PCI) [two elective; two acute]; and four in patients undergoing vascular surgery. Note that two of the trials of RIC in patients with acute infarction were not included. RIC was applied in most studies shortly before ischemia. One trial compared preconditioning vs. postconditioning vs. control.[85] Overall, 1.3% of the RIC group died vs. 1% of the control group (odds ratio 1.22, 95% confidence interval (CI) 0.48, 3.07). The RIC group had a significantly reduced incidence of myocardial infarction (odds ratio 0.50, 95% CI 0.31, 0.82) vs. the control group.

In humans undergoing CABG, two recent trials suggested that RIC did not reduce myocardial injury, clinical events, or mortality.[86, 87] In the first trial, all enrolled patients received propofol anesthesia while in the second trial, more than 90% of patients received propofol anesthesia. In animal models, propofol has dose-dependent effects in mitochondria: at low doses (<100 microM), it reduces harmful ROS;[88] however at high doses ($\geq$200 microM), it reduces adenosine tri-phosphate (ATP) synthesis.[88-91] These deleterious effects at the mitochondrial level are associated with dose-dependent mitochondrial damage as well as myocardial depression.[92] Previous randomized trials in humans demonstrated that propofol attenuates cardioprotection by RIC in patients undergoing CABG.[39, 93]

Collectively, the prior trials demonstrate the efficacy of RIC on an upper extremity for reducing myocardial infarction. The RIC stimulus varied with respect to the number of cycles used, as well as the remote location used. Concurrent medications including intravenous propofol[39] may have attenuated the cardioprotective effect of RIC. Although a mortality benefit was not observed, a minority of patients included in the meta-analysis had a large risk for RI as only 429 (23% of enrolled) patients had acute infarction, and the low risk of mortality in patients undergoing elective CABG, elective PCI or other surgical procedures in the meta-analysis limited detection of a mortality benefit with RIC. No patients with cardiac arrest were enrolled.

SAFETY

Application of medical devices (e.g. BP cuff) to the skin may be associated with adverse local effects such as pain or thrombophlebitis. Importantly, RIC is posited to modify the innate immune system, and so could contribute to infection or mask its diagnosis although no signal has been detected in the clinical trials of RIC. The safety of concurrent use of the autoRIC device in humans who may require defibrillation has not been evaluated.

RATIONALE FOR CURRENT PILOT STUDY

Both OHCA and STEMI share elements of RI with inflammatory changes that contribute to myocardial dysfunction and death,[94] and RIC may be beneficial in both indications: controlled studies in animal models as well as randomized trials in humans suggest that RIC attenuates RI and reduces infarct size in acute myocardial infarction, and controlled studies in animals suggest that RIC may be beneficial in cardiac arrest.

An automated device has been developed and can easily be applied to patients with OHCA to initiate RIC in the post-resuscitation period. However, the Food and Drug Administration (FDA) has not approved any device for RIC due to the absence of any controlled data demonstrating the benefit of RIC in humans with cardiac arrest. Our Institutional Review Board (IRB) has advised us that demonstration of the feasibility of randomization in the emergency department (ED) setting is necessary before proceeding to an assessment of its effectiveness in the out-of-hospital setting.

Clinical research resources are limited. The effectiveness of interventions must be demonstrated definitively if claims of their health benefit are to have scientific credibility.[95] Since some experts endorse RIC,[40, 96] while others question its merits,[97] we believe that a large trial of RIC after OHCA will inform future public policy. Planning a multi-center trial to evaluate the effectiveness of the intervention in this population is premature without preliminary evidence of its efficacy. The present study will assess the feasibility of applying the intervention early after restoration of circulation to justify the investment of limited resources in a large trial. To date, no trial has evaluated RIC in patients with cardiac arrest.

OTHER DESIGNS CONSIDERED

Note that RIC can be applied in the field or in the ED. But also note that electrocardiograms, defibrillators and fibrinolytic therapy were studied and used in the coronary care unit or ED before diffusing to the out-of-hospital setting. We believe that the feasibility of RIC needs to be demonstrated in the ED setting before this therapy diffuses to the out-of-hospital setting.

We previously conducted pilot studies that showed that IH by iced intravenous saline in patients resuscitated from OHCA was feasible either in hospital or in the field,[1, 2] but the subsequent large trial showed that IH in the field was associated with an increased incidence of rearrest as well as pulmonary edema.[3] Since implementation of RIC in the field may delay other important elements of care, and the benefit of RIC is unclear, we believe that demonstration of the feasibility of randomization in the emergency department (ED) setting is necessary before proceeding to an assessment of its effectiveness in the out-of-hospital setting.

PRELIMINARY EXPERIENCE WITH RIC IN PATIENTS WITH ACUTE CARDIOVASCULAR ILLNESS

We applied RIC to six patients resuscitated from OHCA or with presumed STEMI in our ED, using a manual cuff to inflate to 200 mg for five minutes then deflate for five minutes, clamp to reduce air leak during cuff inflation, and stopwatch to time each cycle. All patients underwent three cycles of cuff inflation-deflation. Two (33%) had air leak > 20 mmHg from the cuff, requiring manual reinflation during treatment. We have modified the use of the clamp to reduce air leak.

RESEARCH DESIGN AND METHODS

DESIGN

Individual randomized trial with stratification by rhythm and permuted blocks of concealed size (Figure 2). To reduce potential bias due to using quasi-random methods or envelopes,[98, 99] we will place sequentially numbered identically appearing active and sham RIC packages, which will be stored ready for use in a central location in the ED. When an eligible patient arrives in the ED, the medical assistant involved in their care will retrieve the next package and open it at the patient's bedside.

SETTING

Patients will be enrolled after transportation to Harborview Medical Center, Seattle, WA
which annually receives a high-volume ($\geq$ 50) of patients resuscitated from OHCA, is capable of performing PPCI 24 hours per day, seven days per week, and is staffed by investigators with a special interest in cardiac resuscitation.

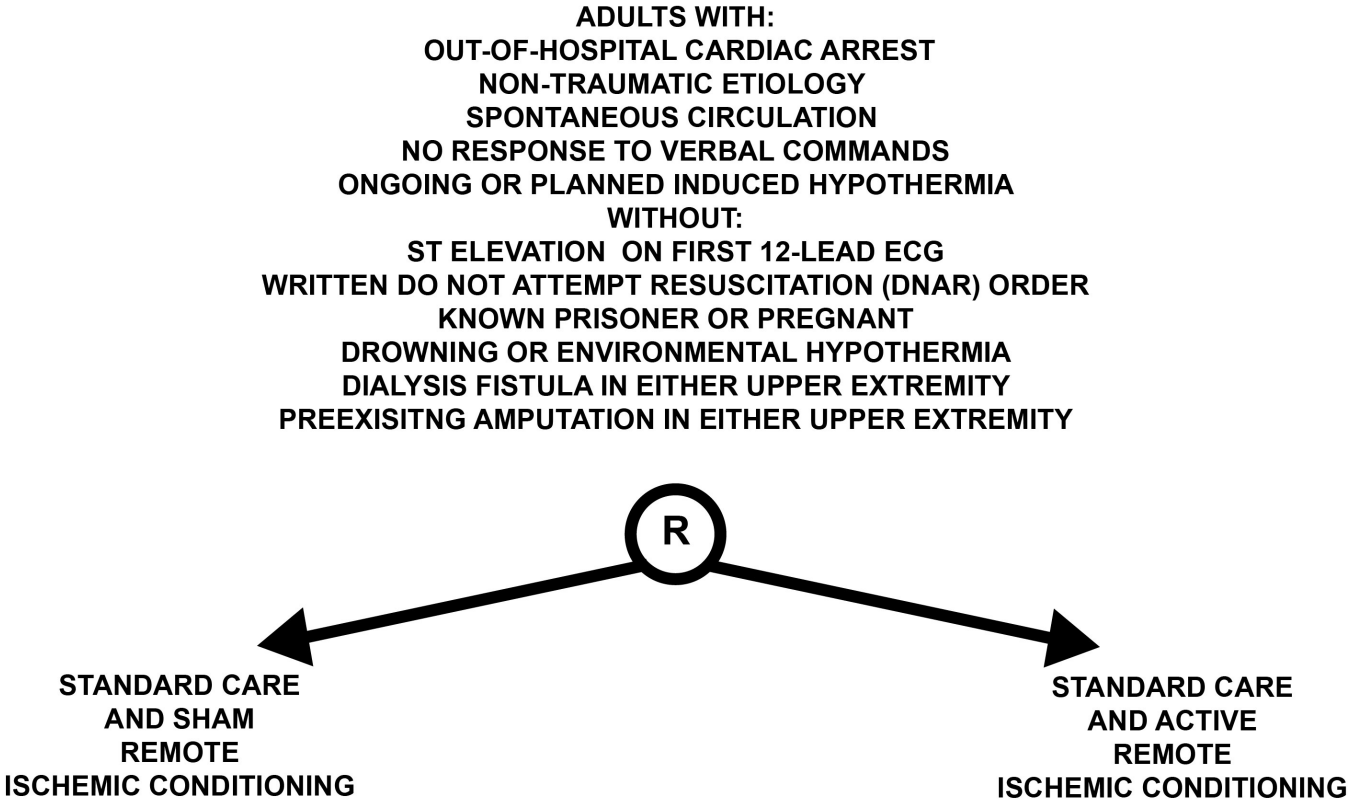
POPULATION

Included will be those with:

a) Age 18 years or more;
b) Defibrillation by laypersons or defibrillation and/or chest compressions by EMS providers dispatched to the scene;
c) Non-traumatic etiology of arrest, defined as without concomitant blunt, penetrating, or burn-related injury, or uncontrolled bleeding or exsanguination;

d) Spontaneous circulation upon emergency department arrival;
e) No response to verbal commands; and
f) Ongoing or planned induced hypothermia.

FIGURE 2: DESIGN



Excluded will be those with:
a) STEMI indicated on first 12-lead ECG obtained after restoration of circulation, defined as ST-elevation of ≥2 mm in two or more contiguous ECG leads;
b) Written do not attempt resuscitation (DNAR) reported to providers before randomization;
c) Drowning or hypothermia as cause of arrest;
d) Known prisoner or pregnant; or
e) Dialysis fistula in either upper extremity; or
f) Pre-existing amputation of upper extremity.

STUDY TREATMENTS

Experimental Device

A standard non-invasive blood pressure cuff (e.g., American Diagnostics Corporation, Hauppauge, NY but any one can be used off the shelf) and disposable plastic clamp (e.g.,Medline Industries Incorporated, Mundelein, IL) can be used to apply RIC in patients resuscitated from OHCA via three cycles of 5-mins. inflation to 200 mmHg followed by 5-mins. deflation of a blood pressure cuff on a thigh. The cuff occludes the artery; the clamp maintains pressure in the air bladder of the cuff during the inflation periods.

Control Group

The control group will have a sham package opened at the bedside as soon as feasible after ED arrival. This will be identical in size, weight and appearance as that in the intervention group, but will contain a sham device. Upon identification that the patient has been randomized to the control group, the care team will proceed with all other resuscitative measures as in the the intervention group.

Initial critical care management of the post-cardiac arrest patient has a large influence on neurological recovery and survival.[100-104] Combinations of hospital-based treatments improve outcomes in patients resuscitated from cardiac arrest compared to historical controls.[105-110] Moreover, patients transported to a receiving hospital with a coronary catheterization laboratory tended to have better outcomes versus transportation elsewhere.[111]

Differences in initial care may explain some of the differences in survival rates for subjects admitted to different hospitals after resuscitation from cardiac arrest.[6] Collectively, these studies demonstrate that hospital-based care of those resuscitated from OHCA impacts patient outcomes and potentially modifies the effect of interventions for cardiac arrest. Thus, experts have recommended a standardized approach to try to achieve optimal outcomes after resuscitation from cardiac arrest.[112] According to this method, protocols for hypothermia-related care and other post-resuscitation care will be mandated via investigator agreements, as well as encouraged through periodic continuing education of hospital staff throughout the study period.

Standard post-resuscitation care will include early application and maintenance of IH followed by controlled rewarming, as is current practice at our institution. We will monitor adherence with IH in hospital, and require remediation if adherence does not meet *a priori* performance standards. Two trials that monitored treatment adherence observed improved outcomes with IH vs. no hypothermia after OHCA.[29, 113] Earlier initiation of IH after hospital arrival is associated with significantly better survival.[114] In contrast, IH without documented achievement of a therapeutic temperature range was not associated with benefit among patients resuscitated from in-hospital arrest.[115] There is ongoing equipoise related to the duration and targeted temperature range of IH. In practice, most of our patients receive 24 h of IH targeted to 33°C.

The effectiveness of other components of post-resuscitation care remains unclear because observational studies may overestimate the effects of treatment vs. randomized designs.[116, 117] Importantly, we will mandate those components of post-resuscitation care likely to be associated with survival benefit and monitor others. Mandated components will include: emergent coronary angiography in patients with VF; timing of prognosis assessment and withdrawal of care; and implantable defibrillator insertion as indicated. Prohibited will be sedation with propofol. Monitored components will include: hemodynamic monitoring and support; seizure prevention and control; insulin therapy and oxygenation.

Intervention Group

The intervention group will have an RIC package opened at the bedside as soon as feasible after ED arrival. This package will be identical in size, weight and appearance as that in the control group, but will contain a manual blood pressure cuff and a clamp. The medical assistant will place the cuff around the left upper arm in the usual manner midway between the shoulder and elbow, inflate the cuff by pumping air from a bulb held in her hand through a tube into the cuff's bladder, then place a clamp on the tube to prevent air from leaking out of the bladder. The left arm is the preferred limb so as to leave the right thigh and wrists available for emergency coronary angiography. The left thigh is an alternative site but application of RIC to the upper extremity may be superior than application to the lower extremity.[83] The cuff will be kept inflated for 5 minutes then deflated for 5 minutes by the medical assistant intermittently inflating the cuff and applying the clamp or reversing the procedure. This will be repeated for three cycles (i.e. 35 minutes total—last 5 minutes is deflation). All other resuscitative measures will be the same as the control group.

All medical assistants who work in the ED of the participating hospital have been trained in how to apply RIC. These individuals completed a minimum of 720 clock hours of training in medical assisting skills to be certified as medical assistants by Washington State before the start of their employment in the ED. As such, their training most closely resembles that of entry level firefighter/emergency medical technicians. Each medical assistant will be required to demonstrate proficiency in application of the active and sham autoRIC device before study enrollment begins. Anyone who is not proficient will receive corrective training then be required to demonstrate proficiency.

Standard post-resuscitation care will be mandated and monitored as in the control group.

MONITORING OF CONCURRENT CARE

Initial critical care management of patients with EC has an influence on subsequent neurological recovery and survival.[101, 103, 104, 118, 119] Case-control studies have evaluated the effectiveness of combinations of hospital-based treatments in patients resuscitated from cardiac arrest in a variety of settings.[105-109, 120] All of these studies reported improved outcomes vs. historical controls. As well, greater survival to discharge was associated with greater adherence to recommended hospital-based post-resuscitative care guidelines.[121] Collectively, these studies demonstrate that hospital-based care of patients with OHCA impacts outcomes and may modify the effect of interventions evaluated in a trial. Failure to monitor these elements of care may attenuate the effect of the study treatment.

A summary of use of mandated, monitored and prohibited care processes, without patient outcome, will be provided to hospital providers at least quarterly. If performance deviates from expectations, we will work with hospital providers to address these concerns.

STUDY ASSESSMENTS

Screening and Pretreatment Assessments

There is limited time for screening and pretreatment assessments in this trial because of the acute life-threatening nature of OHCA. Study personnel will screen each OHCA patient transported to the recruiting hospital. Information about patient baseline characteristics and processes of care will be abstracted from the clinical record after enrollment.

The initial neurological[122] and cardiopulmonary status[123] upon hospital arrival are important determinants of outcomes after OHCA. Also, the initial degree of cardiopulmonary failure upon hospital arrival is predictive of subsequent development of multi-organ failure. Treating providers will be asked to document neurological status (assessed using the Full Outline of UnResponsiveness [FOUR] score)[124] and cardiopulmonary dysfunction (assessed using Serial Organ Failure [SOFA] score)[125-127] before randomization. These scores are important covariates and will be useful for exploratory secondary analyses.

Documentation of Treatment

This will be assessed as treatment assigned; treatment received; time points used to monitor the time-dependent nature of the intervention including call to 911, sustained restoration of spontaneous circulation (ROSC), initiation of RIC, completion of treatment cycles.

Monitoring for Outcomes

Study staff will review subject's clinical record daily to monitor for outcomes and potential adverse events as well as to monitor use of concomitant treatments.

PRIMARY OUTCOME

Attrition assessed as the proportion of randomized subjects who do not remain on allocated therapy for the intended study duration among subjects randomly allocated. In the intervention group, this will be defined as lack of completion of three cycles of inflation-deflation; In the control group, this will be defined as crossover to the intervention group. Secondary and Exploratory Outcomes

Treatment Success assessed as the proportion of intervention group patients who remain alive and on their allocated therapy for the intended study duration.

Cardiac Function assessed as left ventricular ejection fraction (LVEF) using echocardiograms ordered for clinical indications.

Cardiogenic Shock assessed as systolic BP < 80 mmHg during any 6 h period within 48 h of the index arrest not due to a correctable cause, and treated with pressors or inotropes or placement of a mechanical cardiac assist device (e.g. intra-aortic balloon pump). Cardiogenic shock correlates with survival after resuscitation from cardiac arrest.[21, 123]

STEMI assessed as the presence of electrocardiographic (ECG) and biomarker criteria for acute myocardial infarction within 48 h of the index arrest.[128] Note that ST-elevation on the first 12-lead ECG after resuscitation is a poor predictor of acute infarction in this population.[129] These patients often develop infarctions during the subsequent 48 h.

Myocardial Injury assessed as peak serum troponin in ng/mL at any time point within 24 h of index arrest.

Renal Dysfunction assessed using Risk, Injury, Failure, Loss, End Stage criteria.[130, 131]

Hospital Free Survival (HFS) assessed as number of days alive and permanently out of hospital up to 30 days post arrest. Patients who die before discharge will be assigned zero days out of hospital. Note that other randomized trials that enrolled patients with cardiac arrest have described similar outcomes such as days on a ventilator, in an intensive care unit or in hospital.[31, 132, 133] However such assessments were potentially limited because they did not account for the differential timing of mortality. Importantly, HFS has been used as an outcome in trials in patients with heart failure,[134, 135] renal failure,[136] cancer,[137] or need for intensive care.[138] As well, HFS is recommended as an outcome in trials that enroll patients with need for intensive care.[139] The description of HFS will provide additional granularity to our results.

Withdrawal of Care assessed as the reduction of support (i.e. reducing pressors, lab draws or medications) or withdrawal of support (i.e. extubation, stopping drips/meds, changing to comfort care only) during hospitalization.

Favourable Neurologic Status at Discharge assessed using modified Rankin Score (MRS) $\leq$ 3 at hospital discharge or 30 days after index arrest.

Survival to Discharge assessed as alive when discharged from hospital to home, nursing facility or rehabilitation. Patients transferred to another acute care facility (e.g. to undergo implantable defibrillator placement) will be considered still hospitalized.

Clinical Instability at Discharge assessed using the Kosecoff Index[140] measured at discharge based on the presence of nine symptoms and signs associated with increased risk of rehospitalization. Instability will be the presence of any of these.

Survival to 30 Days After Cardiac Arrest assessed as alive 30 days after the index cardiac arrest as confirmed by a brief telephone interview. Note that some experts suggested that the primary outcome of trials in patients with OHCA should be assessed 90 days after discharge.[141] However, we showed that such post-discharge scores were well correlated with assessments before discharge.[142] As well, post-discharge assessment was susceptible to informative missingness as the characteristics of those who consented for follow up were different from those who did not. Lyden and colleagues made similar observations about short vs. long-term outcomes after stroke.[143] Importantly, post discharge assessments burden patients and prolong study duration. We will confine post-discharge assessment to a brief telephone interview at 30 days.

Accrual is the proportion of eligible subjects who have the study device applied.

SAFETY OUTCOMES

Expected Adverse Events

Device Failure Malfunctions are unlikely due to the simple construction and durable materials of the devices. However, device failure will be defined as discontinuation of use of the device prior to the end of allocated treatment interval because of mechanical failure as opposed to provider preference.

Related to Device RIC is generally well-tolerated, but several side effects will be monitored. Most important are pain at the site of application, or thrombophlebitis, or infection.

Pain assessed using the Richmond Agitation-Sedation Scale at 30 and 60 minutes after randomization in control and intervention group patients.[144, 145] No gold standard exists for pain assessment in sedated and ventilated patients.[146]

Thrombophlebitis assessed as symptomatic non central nervous system venous or arterial thrombus documented radiographically or ultrasonographically.

Sepsis assessed within one week of index arrest as either i) the presence of microbiologically proven, clinically proven, or suspected infection; or ii) presence of Systemic Inflammatory Response Syndrome (SIRS); and iii) development of at least one organ dysfunction within the preceding 24 hours.[147]

Related to Cardiac Arrest The following are commonly observed in patients who experience cardiac arrest, and may or may not be attributable to specific resuscitation therapies. These will be monitored and reported but not classified as serious adverse events. Clinical diagnoses of pneumonia, cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, rearrest, pulmonary edema, serious rib fractures, sternal fractures, internal thoracic or abdominal injuries as noted in the hospital discharge summary.

Unexpected Adverse Events (UAE)

These will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application, or any other unexpected serious problem associated with a device that relates to the rights, safety or welfare of subjects. Death or neurological impairment will not be considered an adverse event in this study, as it is an expected part of the natural history of the illness for a large proportion of the population.

Covariates Key covariates of interest include but are not limited to:

Initial rhythm: (i) VF, vs. (ii) PEA, vs. (iii) asystole, vs. (iv) unknown.

Observational status of arrest:[148] (i) witnessed by EMS, vs. (ii) witnessed by bystanders, vs.(iii) unwitnessed;

Bystander CPR status:[149] (i) performed, vs. (ii) not performed, vs. (iii) unknown.

Response time interval from call to initiation of CPR by EMS:[150] among witnessed cardiac arrests grouped as (i) < 10 minutes, vs. (ii) ≥ 10 minutes.

Gender;[151] (i) male vs. (ii) female.

Strata of initial depth of coma:[124] based on FOUR score.

Strata of initial cardiopulmonary dysfunction:[125-127] based on SOFA score.

ANALYSES

Interim Analyses

The data will be monitored regularly by an independent data safety monitoring board (DSMB) to ensure study integrity and patient safety.

Monitoring of Study Conduct

The timeliness, completeness, and accuracy of data entry will be analyzed continuously, with reports provided monthly to the Study Executive Committee. This information will be provided in periodic reports to the DSMB.

Analyses

All outcomes will be summarized descriptively, without statistical comparison as recommended for pilot studies. No claims will be made based on the results of this trial.

ANALYSIS POPULATIONS

Safety Population

This will include all randomized patients, regardless of initial rhythm and duration of exposure to RIC. Patients will be analyzed within their assigned treatment arm, thereby using an intent-to-treat strategy. This is appropriate given that there are no controlled prior data related to RIC in patients with OHCA. Therefore, we are interested in testing the safety of RIC.

Efficacy Population

This will include all randomized patients whose initial rhythm was VF, regardless of duration of exposure to RIC. Patients will be analyzed within their assigned treatment arm, thereby using a modified intent-to-treat strategy. Note that rhythm is a pre-randomization variable.

SAMPLE SIZE

The null hypothesis is that the attrition rate will be not more than 25%. We assume 59 patients are treated by EMS providers for OHCA (21 due to VF) and have spontaneous circulation upon arrival at the participating receiving hospital annually. We will enroll 30 patients (15 per group) as recommended for pilot studies.[152] These numbers will allow estimation of accrual with precision (as measured by half-width of 95% CI) of at least 16.8% overall (and 23.7% within each group).

SAFETY AND DATA MONITORING PLAN

Clinical staff will report potential adverse events as soon as possible. The DSMB will review and approve the protocol before the study begins, evaluate rates of outcomes and adverse events throughout the study period, and determine the final monitoring plan. We will forward reports of DSMB recommendations to the FDA, Institutional Review Board (IRB), and sponsoring agencies as required by regulations for human subjects' research.

HUMAN SUBJECT ISSUES

Obtaining informed consent of patients resuscitated from OHCA, or from their legally authorized representative (LAR) is difficult. Patients are in an immediate life-threatening situation with a mortality rate before discharge of about 50%. Since study procedures must be initiated as soon as feasible after restoration of flow to ensure its efficacy,[72, 153] we will seek approval from the FDA and IRB to conduct the study under exception from informed consent (EFIC) for emergency research.(CFR 50(24)) The initiation of study procedures prior to notification and consent will only apply to the application of the study device.

EFIC requires community consultation before study initiation as well as public notification before and after study enrollment. We will conduct a random digit dialing telephone survey to meet this requirement, as we have done previously.[154, 155] This will be supplemented by multiple outreach efforts (e.g. face-to-face, social media, etc.). Patients and their LAR will be notified of enrollment as soon as feasible, and consent obtained for ongoing participation. We will notify the community of the results of the study upon completion of enrollment.

CO-ENROLLMENT

Until recently, it was unlikely that a patient with a time-sensitive condition such as cardiac arrest would be enrolled in multiple trials due to the paucity of trials of resuscitation interventions.[156] But patients that are treated in the field are transported to receiving hospitals that may participate in trials evaluating other acute interventions.[1, 157-159] Thus co-enrollment can occur as: a) existing participants in a trial (e.g. cancer) become eligible for a resuscitation trial at the onset of an acute life-threatening illness; b) simultaneous or near simultaneous recruitment to more than one trial; or c) participants in a resuscitation trial become eligible later for enrollment in other trials (e.g. in intensive care setting). The receiving hospital participated in the Resuscitation Outcomes Consortium, National Institutes of Health (NIH)'s Stroke Network, and NIH's Prevention and Early Treatment of Acute Lung Injury (PETAL) network. We are aware of at least one case where conflict over co-enrollment in NIH trials required adjudication by a Dean of Medicine.

We will apply guidelines that we previously proposed for co-enrollment to facilitate co-enrollment in trials if appropriate.[160] There is no regulatory prohibition on co-enrollment in more than one study as long as the timing of the interventions differs and one trial can not affect the outcome of the second trial. Trials of interventions for a variety of clinical conditions have allowed co-enrollment without any reported impact.

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