

Ischemic Conditioning: Implications for Emergency Medicine



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Ischemic conditioning refers to the ability of brief episodes of controlled hypoperfusion around the time of an acute ischemic event to protect the target organ from reperfusion injury. A considerable body of literature suggests that interventions as simple and safe as repetitively inflating a blood pressure cuff could reduce the size and long-term morbidity of myocardial and cerebral infarction. This review introduces and summarizes the body of evidence contributing to these impressions. [Ann Emerg Med. 2016;68:268-274.]

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INTRODUCTION

Ischemic preconditioning was first described in dogs by Murry et al¹ in 1986. Brief (5-minute) repeated ischemic occlusions of the circumflex coronary artery before sustained occlusion (“preconditioning”) resulted in a 75% reduction in the size of the infarct created. We use “ischemic conditioning” inclusively to describe protection conferred to an ischemic organ by brief periods of sublethal (to cells) ischemia. Ischemic conditioning has been studied widely since 1986, from the biochemical and cellular levels to controlled clinical trials. In the study most relevant to emergency medicine, ambulance personnel randomly applied ischemic conditioning (4 inflations of a blood pressure cuff) to patients with acute myocardial infarction who were being transported for coronary intervention. Compared with usual care, ischemic conditioning subjects had greater myocardial salvage at 30 days, with no increase in adverse outcomes.^{2,3} At a median follow-up of 3.8 years, the ischemic conditioning group had 35% fewer major adverse coronary events and a 52% reduction in all-cause mortality.⁴

Thousands of studies and reviews of ischemic conditioning are in journals and textbooks worldwide. A 2014 systematic review of the MEDLINE and EMBASE electronic databases returned more than 9,500 citations for this topic.⁵ Yet the emergency medicine literature is largely devoid of references to ischemic conditioning. In January 2016, applying similar PubMed search terms to a list of 18 US and international journals related to emergency medicine identified just 42 citations. Only 4 were in journals with the word *emergency* in their title.

This extensive literature chronicles the evolution of ischemic conditioning during 3 decades. Investigators extended “preconditioning” (protection by antecedent

ischemic episodes) to variations on both the order of the “conditioning” stimulus (“pre,” “post,” “per”) and the location at which the conditioning stimulus is applied (directly to the organ of interest versus remote). The temporal relationships that define the 5 studied ischemic conditioning paradigms are depicted in the [Figure](#). Multiple recent comprehensive reviews exist.⁶⁻¹⁴

The purpose of this article is to engage emergency physicians who may never have heard of ischemic conditioning. Increased familiarity with this body of work may stimulate clinical and experimental investigations of the potential benefits of this phenomenon for emergency patients.

The goal of ischemic conditioning is to ameliorate ischemia-reperfusion injury. Prompt reperfusion (“time is brain”; “time is muscle”) is the cornerstone of therapy for the major ischemic threats to survival that challenge emergency physicians. Paradoxically, with reperfusion comes ischemia-reperfusion injury. Restoring blood flow leads to further destruction of potentially viable tissue. Reperfusion injury contributes significantly to stroke outcomes¹⁵ and is estimated to account for up to 50% of the final size of an acute myocardial infarction.⁸ It is the potential of ischemic conditioning for ischemia-reperfusion injury mitigation in the emergency department (ED) that prompted this review.

Cardiothoracic surgeons and cardiologists use ischemic conditioning in patients undergoing revascularization and reperfusion. Ischemia-reperfusion injury is common in these settings. Elective percutaneous coronary intervention for stable coronary disease produces reperfusion injury in 20% to 30% of patients.^{16,17} Coronary artery bypass graft surgery generates postoperative cardiac enzyme elevations in up to 62% of cases.¹⁸

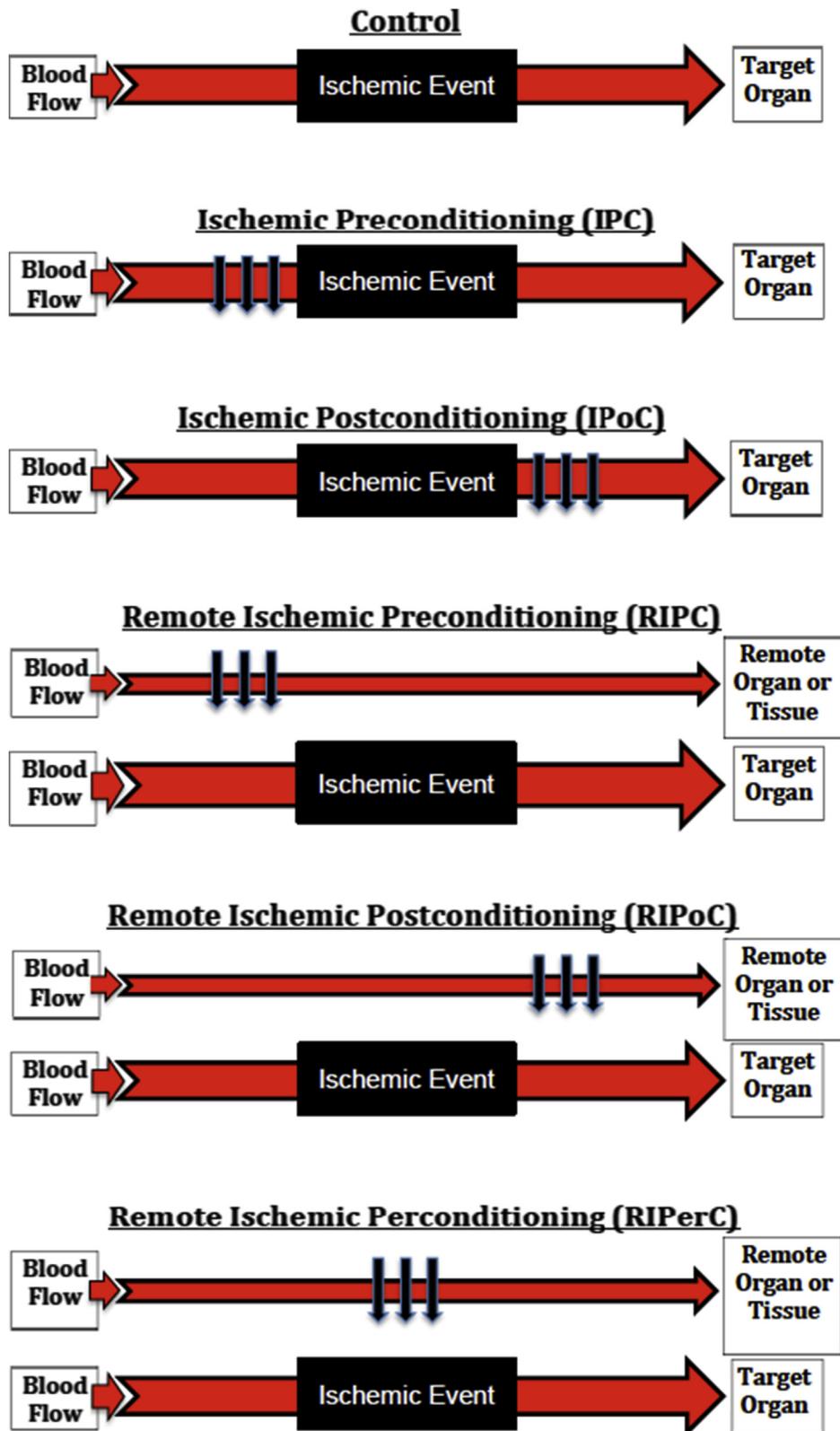


Figure. Ischemic conditioning paradigms illustrating the various temporal relationships between the conditioning stimulus (brief interruptions of flow, followed by restoration of flow=downward arrows) and the event producing ischemia and ischemia-reperfusion injury in the target organ (black box).

Ischemic preconditioning and ischemic postconditioning refer to induction of brief episodes of ischemia before or after percutaneous coronary intervention or coronary artery bypass graft surgery. The ischemic stimulus is applied in the same circulatory bed as the therapeutic intervention. An example is brief balloon inflations in a targeted coronary artery before or after angioplasty. Preconditioning reduced enzymatic infarct size in experimental models by as much as 90%¹⁹ and improved clinical outcomes in patients undergoing both elective percutaneous coronary intervention²⁰ and cardiac surgery.²¹ After percutaneous coronary intervention, postconditioning significantly reduced infarct size and other measures of reperfusion injury in patients with ST-segment elevation myocardial infarction (STEMI).²²⁻²⁵

Any interruptions of flow within an already compromised circulatory bed can add injury to the target organ (eg, from thrombotic debris or injury to the vessel wall).²⁶ Remote conditioning (inducing ischemia in an unrelated vascular bed) eliminates this risk. Dickson et al^{27,28} elegantly demonstrated remote conditioning by transferring ischemia-reperfusion injury protection from one isolated rabbit heart to another by transfusion of the preconditioned “donor” heart’s coronary perfusate. As represented schematically by the downward arrows in the [Figure](#), the remote conditioning stimulus used in human beings has commonly been peripheral limb ischemia from intermittent inflation of a standard blood pressure cuff to 200 mm Hg. Three to four 5-minute inflations are separated by 5-minute reperfusion periods.¹⁰

In patients undergoing elective cardiac surgery or percutaneous coronary intervention, remote conditioning reduced biomarkers of postprocedure cardiac injury, as well as subsequent major adverse cardiac and cerebrovascular events.²⁹⁻³¹ Patients with acute STEMI who had 3 cycles of thigh-cuff inflation during percutaneous coronary intervention had a 20% reduction in both enzymatic infarct size and T2-weighted edema on cardiac magnetic resonance imaging (MRI), plus improved ST-segment resolution.³² However, recent multicenter sham-controlled trials of remote ischemic preconditioning in patients undergoing heart surgery failed to show improved clinical outcomes.^{33,34}

STEMI

The pre- and postconditioning models above offer benefit to patients undergoing elective procedures or who are already in the catheterization suite or operating room. The most relevant ED patients arrive during their acute event. When remote ischemic conditioning is applied during ischemia and before reperfusion, it is referred to as *remote ischemic preconditioning*.

Preconditioning has demonstrated potential for reducing reperfusion injury in patients with acute STEMI. When initiated in the cardiac catheterization laboratory, remote ischemic preconditioning reduced enzymatic infarct size by 30% in patients with acute STEMI who were undergoing percutaneous coronary intervention.³⁵ Bøtker et al² added preconditioning to existing emergency medical services protocols. They randomized consecutive ambulance patients with suspected evolving STEMI to receive standard care or preconditioning (four 5-minute cycles of blood pressure cuff inflation/deflation). Patients not matching exclusion criteria then underwent primary percutaneous coronary intervention. Myocardial salvage index at 30 days (measured by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment) was improved by remote ischemic preconditioning. There were no short-term differences in major adverse coronary events² or left ventricular function.³ At a median follow-up of 3.8 years, the remote preconditioning group experienced 35% fewer major adverse cardiac and cerebrovascular events and a 52% reduction in all-cause mortality.⁴ The same investigators reported that remote ischemic preconditioning during ambulance transport for STEMI reduced negative effects of system delays in percutaneous coronary intervention on infarct size and myocardial salvage index.³⁶ White et al³⁷ also studied STEMI patients acutely undergoing percutaneous coronary intervention. Four cycles of upper limb ischemia resulted in 27% reduction in myocardial infarction size (by cardiac MRI), less myocardial edema, and improved myocardial salvage index. Pickard et al¹² cited findings presented at a recent cardiovascular workshop, showing that limb remote ischemic conditioning initiated in STEMI patients before thrombolysis reduced enzymatic myocardial infarction size by 17%.

Stroke

Rapid reperfusion is likewise the treatment of choice for acute ischemic stroke. Research was stimulated by natural experiments comparing stroke patients who had previous ischemic conditioning with those who had not. Both direct “natural” ischemic preconditioning (from transient ischemic attacks³⁸) and remote preconditioning (from untreated symptomatic peripheral vascular disease³⁹) led to less severe injury and better outcomes. Animal studies found remote ischemic preconditioning and postconditioning to be effective in reducing stroke severity.⁴⁰⁻⁴⁵

Even as efforts continue to optimize the techniques, timing, and effectiveness of cerebral reperfusion,⁴⁶ ischemic conditioning research to limit injury from reperfusion lags.^{47,48} In the first randomized controlled trial of

out-of-hospital preconditioning in stroke patients undergoing thrombolysis, Hougaard et al⁴⁹ found significant reductions in MRI measurements of infarct risk at 1 month, without measurable clinical benefit.

“Despite intensive investigation over the last 20 years, the underlying mechanisms [of remote ischemic conditioning] continue to elude researchers,”¹² a sentiment echoed by others.^{14,50,51} A recent 256-page issue of the *British Journal of Pharmacology* was devoted to the complexities of this topic.¹³ Any theory of remote conditioning will have to include the nature of the stimuli generated in the remote organ or tissue, the pathways conveying protection to the target, and the mechanisms underlying any beneficial response. Although multiple specific mechanisms are under study, an emerging consensus identifies 3 categories of “communication”: humoral, neural, and systemic.^{12,51-53} Dickson et al⁵⁴ transferred protection from one rabbit heart to another by a “humoral trigger.” Intact neural pathways seem required for local ischemia to produce remote conditioning.⁵⁵⁻⁵⁷ Systemic mediation is most commonly discussed in terms of conditioning-induced changes in the immune system^{58,59} and gene transcription⁶⁰ regulating inflammatory and other processes.^{53,61,62}

LIMITATIONS

The limitations of translation from animal experiments to clinical benefit in humans are an obvious and primary concern.⁵² Clinical trials face the complexities inherent in studying the sorts of patients who need thrombolysis, cardiac surgery, or percutaneous coronary intervention.^{5,7,8,12,52,62-70}

DISCUSSION

The failure of 2 recent large-scale controlled trials in cardiac surgery^{33,34} may temper enthusiasm for remote ischemic preconditioning in patients undergoing cardiopulmonary bypass. However, factors hypothesized as contributing to failed preconditioning in the operating room (hypothermia, cardioplegia, and anesthesia)⁶⁹ do not apply to percutaneous coronary intervention or thrombolysis.

Practically, four 5-minute cycles of cuff inflation and deflation require 40 minutes and (probably) a dedicated provider. Feasibility has been demonstrated in both ground and air ambulances,^{2,71} but ED implementation or abbreviated protocols have not been studied. Short transports and time-pressured ED implementation of acute stroke and STEMI protocols can interfere with the preconditioning paradigm.⁷¹ As an alternative to manually

operating a standard blood pressure cuff, some investigators use automated devices specifically designed to provide the required remote conditioning cycles without provider intervention.^{11,72-74} Such a device could be left in place from the identification of an acute event, reducing delays, interruptions in care, and the need for dedicated personnel.

Safety concerns are not a barrier to research or clinical implementation. Repetitive cuff inflation and deflation on an extremity has been remarkably innocuous. In an extensive review, Ndegwa¹¹ found no “safety issues or complications associated with [remote ischemic conditioning]...in any of the trials.” We found no safety issues mentioned in any of the articles we reviewed. In 2 studies of stroke prevention, elderly Chinese patients (average age 61 [±10] in 1 study,⁷² and ranging from 81-95 in the other⁷³) received 5 cycles of bilateral arm-cuff inflation and deflation twice daily for up to 300 consecutive days without consequences. Martin-Gill et al⁷¹ recently demonstrated the safety and feasibility of this procedure in STEMI patients undergoing air medical transport for percutaneous coronary intervention.

Ischemic conditioning paradigms addressing cardiac and cerebral reperfusion injury have shown benefit in measures of infarct size. Basic science, animal, and phase 2 clinical trials have largely positive results and are consistent and reproducible. There is a strong consensus that more and larger trials are needed and that the safety of inflating a blood pressure cuff a few times is not a barrier to such efforts.

Although recent work questions the value of remote conditioning in open-heart surgery,⁶⁹ acute STEMI patients undergoing urgent percutaneous coronary intervention have consistently benefited.^{12,35-37} Remote ischemic preconditioning is most relevant to the out-of-hospital and ED management of STEMI and acute ischemic stroke. Remote ischemic preconditioning trials offer evidence of benefit from myocardial salvage, persisting for years.^{2,4,31} By reducing ischemia-reperfusion injury, ischemic conditioning has demonstrated the potential to moderate the size and associated morbidity of myocardial infarction in ED patients.

Fewer studies examined reducing cerebral ischemia-reperfusion injury through ischemic conditioning. Most were conducted in animals (but see Hougaard et al⁴⁹). Yet the experimental findings reviewed hold out hope for similar benefits. One real possibility is the use of preconditioning to extend the window for successful interventions (as noted for STEMI by Pryds et al³⁶).

The science behind the various paradigms of ischemic conditioning has mushroomed into more than 9,500 articles since the first description by Murry et al¹ 30 years ago. Yet a role for the ED remains uninvestigated. A search of www.clinicaltrials.gov on January 1, 2016, for “ischemic” AND

“conditioning” found 73 registered trials (12 in the United States). Only 5 of these (none of them in the United States) appeared to include the ED, and none targeted stroke.

In cooperation with cardiologists and neurologists, emergency physicians lead in managing reperfusion for acute STEMI and stroke (the number one and two causes of death worldwide⁷⁵). In doing so, ED providers go to great lengths to optimize benefit and limit risks, balancing precise timing, ECG and computed tomography result interpretation, inclusion and exclusion criteria, consent, consultation, stroke scales, and door-to-balloon and door-to-needle times. Yet the role of emergency physicians in mitigating ischemia-reperfusion injury from interventions is unexplored. We hope that this review provides clinical and experimental evidence to provoke such study on behalf of emergency patients.

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