

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

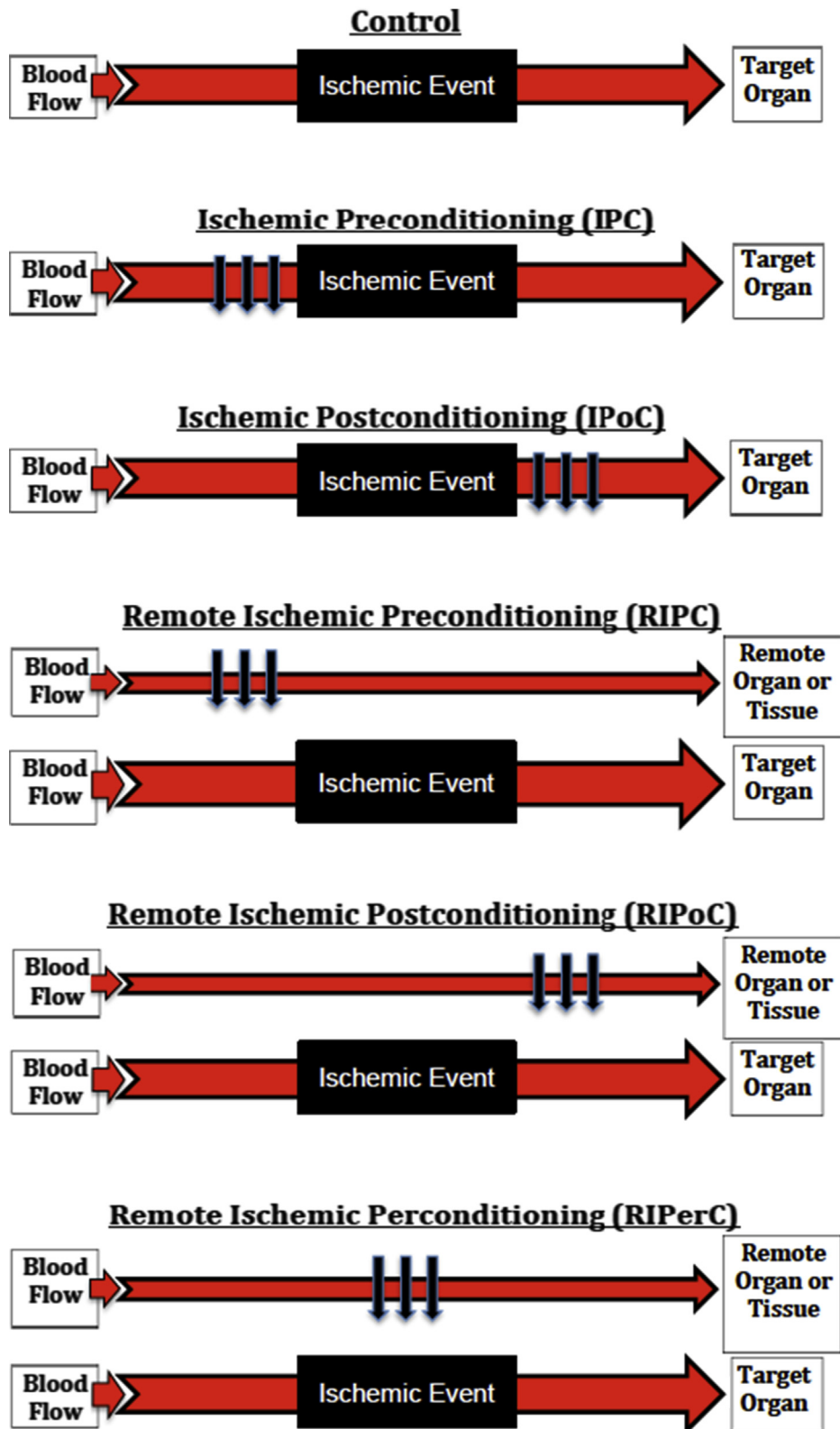


Figure. Ischemic conditioning paradigms illustrating the various temporal relationships between the conditioning stimulus (brief interruptions of flow, followed by restoration of flow=downward arrows) and the event producing ischemia and ischemia-reperfusion injury in the target organ (black box).

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