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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Remote Ischemic Conditioning

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ABSTRACT

In remote ischemic conditioning (RIC), brief, reversible episodes of ischemia with reperfusion in one vascular bed, tissue, or organ confer a global protective phenotype and render remote tissues and organs resistant to ischemia/reperfusion injury. The peripheral stimulus can be chemical, mechanical, or electrical and involves activation of peripheral sensory nerves. The signal transfer to the heart or other organs is through neuronal and humoral communications. Protection can be transferred, even across species, with plasma-derived dialysate and involves nitric oxide, stromal derived factor-1α, microribonucleic acid-144, but also other, not yet identified factors. Intracardiac signal transduction involves: adenosine, bradykinin, cytokines, and chemokines, which activate specific receptors; intracellular kinases; and mitochondrial function. RIC by repeated brief inflation/deflation of a blood pressure cuff protects against endothelial dysfunction and myocardial injury in percutaneous coronary interventions, coronary artery bypass grafting, and reperfused acute myocardial infarction. RIC is safe and effective, noninvasive, easily feasible, and inexpensive. (J Am Coll Cardiol 2015;65:177–95) © 2015 by the American College of Cardiology Foundation.

Remote ischemic conditioning (RIC) is the intriguing phenomenon whereby brief, reversible episodes of ischemia and reperfusion applied in one vascular bed, tissue, or organ confer global protection, rendering remote tissues and organs resistant to ischemia/reperfusion injury. Its discovery 2 decades ago in the heart (1) was not serendipitous, but evolved from a mathematical model developed by Whittaker and Przyklenk (2–4), in which brief episodes of pre-conditioning ischemia in one coronary bed were predicted to trigger activation, release, or transport of one or more unknown "protective factors" throughout the myocardium. To test this hypothesis, anesthetized dogs underwent 4 episodes of 5-min ischemia applied in the left circumflex coronary territory, followed by a 1-h sustained ischemic insult in the left anterior descending coronary artery bed. As anticipated, compared with control subjects that underwent left anterior descending occlusion alone, animals that received brief antecedent episodes of circumflex occlusion before sustained left anterior descending occlusion displayed a robust reduction of infarct size (1).

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CABG = coronary artery bypass grafting

CMR = cardiac magnetic resonance

PCI = percutaneous coronary intervention

RIC = remote ischemic conditioning

RIPC = remote ischemic pre-conditioning

RISK = reperfusion injury salvage kinase

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

HISTORICAL BACKGROUND AND CONCEPT OF RIC

EVOLUTION OF THE PARADIGM. Although this first report of "intracardiac" RIC was provocative and met with considerable skepticism (4), the concept also engendered curiosity and raised the question: can the RIC paradigm be extrapolated to other remote triggers?

Spatial evolution: from intracardiac to interorgan RIC. During the past 2 decades, multiple variations on the theme of RIC have been investigated, encompassing both in vitro and in vivo models. Cardioprotection by collection and transfer of perfusate among isolated buffer-perfused hearts is a notable example (5–8). Specifically, coronary effluent released from donor rabbit hearts throughout a standard, conventional pre-conditioning stimulus (3 cycles of 5-min global ischemia with 10-min reperfusion) or a time-matched control period was collected, reoxygenated, warmed, and used as the perfusate for 2 cohorts of naïve, acceptor hearts. All 4 groups of hearts then underwent 40 min of sustained global ischemia. Infarct sizes were significantly smaller in both, donor hearts subjected to brief pre-conditioning ischemia and naïve acceptor hearts that received the effluent from pre-conditioned donors, versus donor and acceptor control subjects. There was no difference in the magnitude of the infarct-sparing effect seen in donor- and acceptor-pre-conditioned groups, implying that the efficacy of cardioprotection triggered by RIC was comparable to that achieved by conventional ischemic pre-conditioning (5). This general strategy, involving transfer of effluent or perfusate, has been refined to include collection of serum following brief pre-conditioning ischemia applied in vivo and its administration to either isolated hearts or cultured cells subjected to a sustained ischemic or hypoxic insult (9–11). This strategy also provided evidence of cross-species protection by RIC, including treatment of isolated buffer-perfused rabbit hearts with human serum (9,11).

It could be argued that intracardiac RIC or cardioprotection achieved by transfer of perfusate between hearts is a laboratory curiosity providing mechanistic insight, but of limited translational relevance. Accordingly, the observation of interorgan RIC was a pivotal pre-clinical advance (12). Initial evidence revealed that brief episodes of ischemia/reperfusion in kidney and mesentery rendered the heart resistant to infarction (12–15). Moreover, a number of studies documented RIC-induced attenuation of ischemia/reperfusion injury in brain, lungs, liver, kidney, intestine, skin, and other tissues (reviewed in Candilio et al. [16]). However, the first reported seminal extension of interorgan RIC in a clinically-relevant, large-animal (swine) model (17), which demonstrated that brief episodes of peripheral limb ischemia, achieved by simple tourniquet occlusion of one hindlimb, was sufficient to evoke a profound reduction in myocardial infarct size, accelerated subsequent implementation of phase II trials aimed at establishing efficacy in patients (17).

Conceptual evolution: from ischemic to non-ischemic triggers. In the aforementioned studies, intercardiac and interorgan RIC were (by definition) initiated by a brief ischemic stimulus. However, accumulating evidence from a spectrum of in vivo and in vitro models (some involving perfusate transfer among models) suggests that transient ischemia or interruption of blood flow is not a requisite trigger for remote protection. Multiple alternative triggers capable of recapitulating the infarct-sparing effect of RIC have been proposed, including peripheral nociception (initiated by skin incisions made on the abdomen and termed "remote pre-conditioning of trauma"), direct peripheral nerve stimulation, and noninvasive transcutaneous nerve stimulation and electroacupuncture (18–23). Perhaps the most attractive, for its potential as a clinical cardioprotective strategy, is nontraumatic peripheral nociception instigated by chemical stimulation of sensory C-fibers in the skin (18,21). A >70% reduction in infarct size was reported in mice treated with 0.1% capsaicin cream, applied topically to a 2 cm^2 area of skin along the abdominal midline 15 min before the onset of coronary artery occlusion, compared with untreated control subjects (18). In spite of its inherent appeal, this concept has not yet been translated to clinical investigation.

Temporal variants: remote pre-, per-, and post-conditioning. In all studies discussed thus far, the remote conditioning stimulus was administered prophylactically in the ~30- to 40-min period before the onset of sustained myocardial ischemia. However, pre-treatment is not a requirement for RIC-induced cardioprotection: reduction of infarct size has also been described with concurrent application of the remote ischemic stimulus during sustained coronary occlusion (remote ischemic *per*-conditioning) or at the time of reperfusion (remote ischemic post-conditioning) (24,25).

The first documentation of infarct size reduction with remote per-conditioning utilized brief renal ischemia/reperfusion as the trigger, applied during