

# Exercise: Great for Heart Health, Just as Great for Cardiac Preconditioning Research

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Ischemic heart disease remains a leading cause of morbidity and mortality in the United States and other industrialized countries [1]. Ongoing research efforts within the biomedical science community seek to discover counter therapies that will mitigate ischemic damage in those with coronary artery disease. Candidate therapies are intended to invoke cardioprotection by pharmacologic activation of endogenous mechanisms of cellular protection [2]. In concept the process of pharmacologic development is fundamentally simple: a cardioprotective pathway against ischemic injury is discovered, animal-based experiments provide proof of concept for pharmacologic induction of cardioprotection, and then clinical trials are undertaken. The reality, however, is somewhat more complicated. Within the context of discovery at different organizational levels (isolated cells, isolated organs, whole animal), numerous cellular pathways that elicit robust cardioprotection against ischemic injury are now well characterized [3]. Translation of this knowledge into clinical practice has proven far more difficult than expected. The point is famously articulated in a 2004 position paper by preeminent physicians and scientists is Circulation Research, “over the past 30 years, hundreds of experimental interventions (both pharmacologic and nonpharmacologic) have been reported to protect the ischemic myocardium in experimental animals; however, with the exception of early reperfusion, none has been translated into clinical practice” [4]. Given the collective effort to date, this is the central question: What scientific breakthrough is needed to translate our understanding of cardiac preconditioning into clinical practice? The underlying premise of this editorial is that the major limitation of cardiac preconditioning research is the nature of the stimulus, which traditionally has been derived from ischemia-induced adaptations.

Ischemic preconditioning research is historically founded on the classic 1986 Murry study, which was the first to demonstrate that brief intervals of sub-lethal ischemia conferred a subsequent window of protection against an ischemic insult of longer duration [5]. Twenty five years later, the ischemic preconditioning phenotype is well characterized as a polygenic response with redundant protective mediators including up-regulation of myocardial inducible nitric oxide synthase (iNOS), heat shock proteins (HSP) including HSP-72, cyclooxygenase-2 (COX-2), and the sarcolemmal ATP-sensitive potassium channel ( $K_{ATP}$ ) (reviewed in [6]). Activation of these and other protective mediators appear to converge upon the mitochondrial  $K_{ATP}$  channel, often heralded as the ‘holy grail’ of protective mediators [3]. Experimental evidence clearly demonstrates that pharmacologic agonists for these various mechanisms elicit transient cardioprotection (reviewed in [7]). It’s the transient nature of this protection that may best explain why an ischemic stimulus has proved so difficult to translate clinically.

The fundamental hindrances to translating ischemic preconditioning research into clinically viable solutions are evident by multiple caveats. First, heart attacks, even in high risk individuals, are currently impossible to predict accurately. Common sense might suggest that prophylactic use of cardioprotective agonists in high risk individuals is the obvious answer to the unpredictable nature of cardiac

events. However, another hurdle preventing the translation of ischemic preconditioning research is the fact that pharmacologic induction of cardioprotection is itself transient. The initially protected myocardium is rapidly adaptable and quickly habituates to the pharmacologic stimulus within a matter of days, and comparatively “sustainable” cardioprotection dissipates after a maximum of 7 days [8]. Perhaps most importantly, the canonical cellular mediators of cardioprotection are inflammatory in nature. Thus, activated by the signaling molecules NFkB and TNF $\alpha$ , hormetic up-regulation of iNOS and COX-2 is not “biologically intended” as a sustainable solution to cellular dyshomeostasis [9]. Given this rationale, we have sought to investigate the mechanisms of cardioprotection against ischemic insults using a scientific model of exercise preconditioning.

Whereas ischemic preconditioning has been invaluable in understanding the fundamental principles of ischemic injury and cardioprotection, exercise preconditioning may prove essential in discovering therapeutic translation. From a clinical perspective the differences between ischemic and exercise stimuli are obvious. Cardioprotective exercise is a long established lifestyle intervention for improved heart health, while sustained exposure to periodic ischemia promotes heart failure in clinical populations [10]. Recent animal-based research reveals important differences between ischemic and exercise models of cardiac preconditioning. One of the first key discoveries was that a few days of moderate intensity exercise elicits profound ischemic protection in rats, and longer duration (months) exercise regimens confer no additional protection [11-13].

Chronic exercise, in the longitudinal context of a lifestyle, is among the most well established interventions for improved heart health. However, a few consecutive days of moderate intensity exercise is insufficient to remodel the cardiac vasculature or architecture. The observed infarct resistance must then be attributed to short term up-regulation of protective biochemical factors in the exercised heart. Ample evidence from multiple labs now indicates that the exercise and ischemic stimuli exhibit several important differences. In contrast to ischemic preconditioning that confers a 3-4 day window of cardioprotection [3], Three days of exercise elicits an ischemic injury resistant phenotype that persists for at least nine days following exercise cessation [14]. The mechanisms responsible for exercise-induced cardioprotection have been described through a series of reductionist

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studies conducted over the last decade. Key biochemical mediators of exercise induced cardioprotection include manganese superoxide dismutase (MnSOD) [12,15-17], calcium handling proteins [15,18], endogenous opioids [19], and sarcolemmal and mitochondrial  $K_{ATP}$  channels [20-23]. It is a notable fact that the identified mechanisms of exercise preconditioning are not central to ischemic-based protection. Moreover, the aforementioned mechanisms responsible for ischemic preconditioning, including iNOS, COX-2 and HSP-72 have been ruled out as mediators of exercise-induced cardioprotection [24-27]. The clinical relevance of these animal-based studies is punctuated by the fact that both ischemic and pharmacologic approaches to cardioprotection are ineffective in aged rodents [28]. In contrast, several investigations clearly demonstrate that the aged heart is thoroughly cardioprotected against ischemic insults by a few days of moderate intensity exercise [26,29,30].

Medical advances over the last 40 years have yielded incremental improvements in treating and preventing ischemic heart disease, and yet the clinical, financial, and personal burdens of heart disease remain [1]. Exercise is cardioprotective in that regular exercise participation reduces the incidence and severity of heart disease, modifies risk factors for cardiovascular disease, and beneficially remodels the heart [10]. In contrast to these 'exercise for improved heart health' points of interest, the current editorial presents a rationale whereby exercise is employed as a novel scientific model for understanding cardioprotection within the biomedical sciences. The proposed exercise-based approach is pragmatic, sustainable, and cost effective. Given the increased competition for federal research dollars, exercise-based research studies offer a high potential return. This editorial focus on exercise-induced preconditioning against ischemia reperfusion injury serves as a prime example why additional funds from federal source should be directed to high quality investigations designed to understand protective mechanisms and translational potential of exercise.

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