

# Exercise Can Protect against a Broken Heart

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## Introduction

Coronary artery disease remains a dominant cause of death around the world. The major pathology associated with coronary artery disease is ischemia reperfusion (IR)-induced cardiac injury (*i.e.*, heart attack). Given the high incidence of heart attacks, developing a practical countermeasure to protect against IR-induced cardiac damage is important. Fortunately, a simple intervention exists — regular exercise. Indeed it is well established that regular endurance exercise training (*e.g.*, running, cycling, swimming, etc.) can protect against IR-induced cardiac injury; this commonly is called exercise-induced “cardioprotection.”

This report summarizes our current understanding of how and why regular exercise provides protection against IR-induced myocardial injury. We begin with a brief summary of the evidence demonstrating that exercise is cardioprotective; this will be followed by a discussion of the mechanisms responsible for this protection. The remainder of this report focuses on how primary care physicians can translate this basic research into recommendations to encourage their patients to engage in a regular exercise program that results in cardioprotection.

## Evidence That Exercise is Cardioprotective

While it is clear that regular exercise reduces the risk of experiencing a heart attack, it also is established that exercise training protects the heart against damage resulting from an IR insult. Indeed human epidemiological studies reveal that regular exercise training reduces the risk of death during a myocardial IR insult (5). However, because of the invasive nature in studying cardioprotection, most of our basic understanding about exercise-induced cardioprotection comes from animal studies. In this regard, numerous investigations provide robust evidence that exercise training protects a rat's heart against IR-induced injury (12). Importantly, endurance exercise training can protect against all levels of IR-induced cardiac injury including arrhythmias (3), myocardial stunning (10), and myo-

cardial infarction (2) in both young and old animals (13). Interestingly, as few as three to five consecutive days of endurance exercise training is required to achieve cardioprotection in rodents (1,2,4). Although exercise-induced cardioprotection can be achieved rapidly, similar to other health benefits derived from exercise, animal studies reveal that exercise-induced cardioprotection is lost rapidly (*i.e.*, within 9 to 18 d) following the cessation of exercise training (7).

Details of the dose-response impact of exercise intensity on cardioprotection in humans remain unknown. Nonetheless, animal studies suggest that both moderate-intensity (*i.e.*, 50%  $\dot{V}O_{2max}$ ) and high-intensity (*i.e.*, 70%  $\dot{V}O_{2max}$ ) endurance exercise are protective against IR-induced cardiac injury (8). While it is clear that continuous aerobic exercise (*e.g.*, 30 to 60 min per session) produces a cardioprotective phenotype, evidence also indicates that high-intensity interval training (*i.e.*, 60-s exercise  $\geq \dot{V}O_{2max}$ ) also produces cardioprotection in rodents (9).

In contrast to the many studies using endurance exercise training as an exercise modality to produce cardioprotection, few studies have investigated the impact of resistance training. Nonetheless, a recent study suggests that 12 wk of resistance exercise training protects against IR-induced myocardial infarction in rats (14). Clearly, additional studies are required to determine the types of resistance training programs (*i.e.*, number of repetitions, sets, and exercises) that are optimal to produce cardioprotection.

## Can Exercise-Induced Cardioprotection Studies in Animals Translate Directly to Humans?

As discussed in the previous section, because of the invasive nature of investigating protection against IR injury, most of our knowledge about exercise-induced cardioprotection is derived from studies using laboratory animals. The key question becomes “Do these studies have relevance to humans?” The likely answer to this question is yes. Indeed, the structure and function of the mammalian heart is very similar across species and, therefore, exercise experiments using laboratory animal models are predicted to be relevant to humans. The fact that both laboratory animal studies and human epidemiological studies agree that endurance exercise promotes cardioprotection provides further support for the reality that animal studies are often relevant to human biology and medicine.

## How Does Exercise Training Promote Cardioprotection?

The mechanism(s) responsible for exercise-induced myocardial protection against IR injury remains an active area of

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research. In theory, exercise-induced cardioprotection could be achieved by any physiological adaptation that attenuates one or more of the damaging events that occur in the heart during the IR insult. For example, exercise-induced cardioprotection could be achieved by changes in the coronary arteries (*i.e.*, increased collateral circulation) and/or intrinsic changes in the cardiac myocyte that resist the cellular insults that occur during an IR event.

Endurance exercise-induced changes in the coronary circulation include increased conduit artery diameters, increased arteriolar densities, and diameters of arteriolar vessels (6). Furthermore regular aerobic exercise promotes functional adaptations in the coronary circulation including enhanced endothelium-dependent vasodilation (6). Although all of these training-induced adaptations in the coronary circulation can protect the heart during an IR insult, the short duration of training (*e.g.*, 3 to 5 d) needed to provide cardioprotection in animal studies suggests that changes in the coronary circulation is not the dominant factor responsible for exercise-induced cardioprotection. By elimination, it appears that exercise-induced cardioprotection is largely due to changes in the cardiac myocyte to a phenotype that resists IR-induced injury. In this regard, the cause of IR-induced damage in cardiac myocytes is complex and includes an array of damaging events including IR-induced radical production, cellular calcium overload, activation of proteases, and mitochondrial damage (11). It follows that any exercise-induced adaptation to the cardiac myocyte that protects against one or more of these damaging insults could contribute to cardioprotection.

The specific adaptations in the cardiac myocyte that are essential for exercise-induced cardioprotection remain a topic of debate. Nonetheless, evidence indicates that exercise training can protect against radical-mediated damage by improvements in the antioxidant capacity in cardiac myocytes along with changes in cardiac mitochondria that result in a mitochondrial phenotype that resists IR-induced damage (12). It appears likely that these collective changes protect against radical-mediated damage to mitochondria and play a required role in the development of exercise-induced cardioprotection.

It is important to appreciate that experiments designed to understand the mechanisms responsible for exercise-induced cardioprotection achieve much more than satisfying scientific curiosity. Indeed investigating the mechanisms responsible for exercise-induced cardioprotection can lead to discovery of unique biological targets that can be ma-

nipulated pharmacologically to protect the heart during an IR insult. Specifically, basic science experiments have led to the development of mitochondria-targeted antioxidants that can be administered to patients during an acute myocardial infarction. In animal studies, these mitochondria-targeted antioxidants provide significant protection against IR-induced cardiac injury. Importantly, two of these cardioprotective drugs are now in phase II clinical trials en route to Food and Drug Administration approval. Therefore, investigating the mechanism(s) responsible for exercise-induced cardioprotection represent a classic example of how the study of exercise biology is important and can lead to drug discovery.

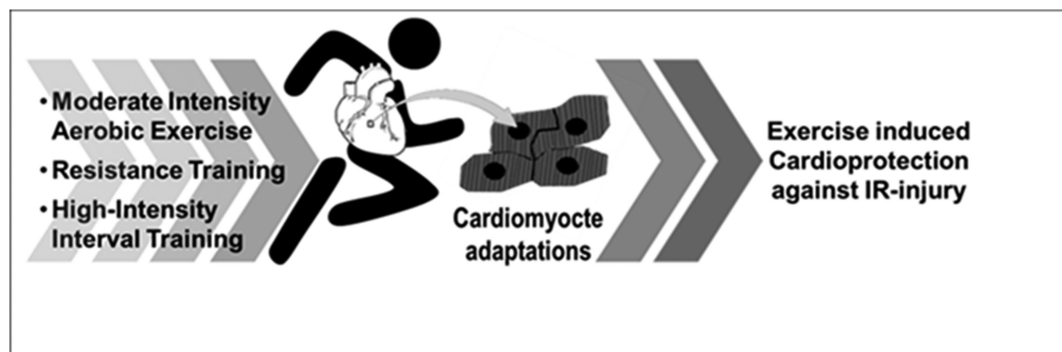
### Summary of Exercise-Induced Cardioprotection

IR-induced cardiac injury remains a dominant cause of mortality around the world and, therefore, protecting the heart against IR injury is important. Currently, the only established method of providing sustainable cardioprotection against IR-induced myocardial injury is the performance of endurance exercise training. Indeed, routine endurance exercise training protects the heart against all levels of IR-induced injury. It also is feasible that some types of resistance training programs also can promote cardioprotection. It follows that exercise training programs combining both resistance exercise and endurance exercise are likely to produce cardioprotective benefits (Figure).

How much exercise is enough to produce exercise-induced cardioprotection? If the animal studies translate directly to humans, the available evidence suggests that 30 to 60 min of continuous exercise at intensities  $\geq 50\%$   $\dot{V}O_{2\max}$  for 3 or more consecutive days is sufficient to produce cardioprotection. This likely would translate into performing endurance exercise three to five times per week. Furthermore interval training (*e.g.*, 60 s of high-intensity exercise) also is likely to produce cardioprotection in humans. Encouraging patients to engage in routine exercise is important because, similar to the other beneficial effects of regular exercise, cardioprotection is lost rapidly following the stoppage of exercise training.

### A Final Word — Primary Care Physicians and Cardioprotection

Primary care physicians can play an important role in both encouraging patients to exercise and providing patients with advice on the appropriate exercise prescription to



**Figure:** Regular bouts of endurance exercise, high-intensity interval training, and/or resistance exercise can promote changes in the heart, resulting in protection against an IR insult (*i.e.*, cardioprotection).

achieve cardioprotection. Indeed among all medical specialties, primary care doctors are well positioned to influence a large number of patients and inspire them to engage in regular exercise to reduce their risk of cardiovascular disease and to protect against IR-induced damage in the event of a heart attack.

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