Role of β-Adrenergic Receptors and Nitric Oxide Signaling in Exercise-Mediated Cardioprotection

Exercise promotes cardioprotection in both humans and animals not only by reducing risk factors associated with cardiovascular disease but by reducing myocardial infarction and improving survival following ischemia. This article will define the role that nitric oxide and β-adrenergic receptors play in mediating the cardioprotective effects of exercise in the setting of ischemia-reperfusion injury.

Cardiovascular disease (CVD) refers to any disease that affects the cardiovascular system, including cardiac disease, vascular diseases of the brain and kidney, and peripheral artery disease. CVD continues to be a leading cause of mortality and morbidity in the world despite advances in health care practices. In the U.S. alone, it is estimated that one in three adults (roughly 82,600,000) have one or more types of CVD. Economically, it is estimated that about $500 billion is spent each year for the costs associated with treating patients suffering from CVD (58). As such, the development and implementation of therapeutic strategies to combat CVD remains an unmet need.

Age, gender, and genetics are certainly important risk factors associated with the development of CVD. However, the modern lifestyle has become an apparent risk factor. This sedentary lifestyle includes a high incidence of smoking and consists of a diet comprised mainly of saturated fats and sugar and devoid of fruits and vegetables. As a result, hypertension, hyperlipidemia, insulin resistance, obesity, and diabetes are major risk factors for the development of CVD. The good news is that, for the most part, with the exception of age, gender, and genetics, the other major risk factors for developing CVD can be targeted with preventive measures. For instance, numerous studies have linked a reduction in the rate of initial coronary artery disease events in physically active individuals (61). Coupling this with the experimental and clinical evidence demonstrating the cardioprotective effects of regular activity (9) provides a strong body of evidence that exercise reduces the risk of CVD events (39). This has resulted in an increasing awareness among physicians and the community as a whole that regular exercise results in a healthier lifestyle and leads to a reduction in the incidence of stroke and heart attack. Therefore, a better understanding of the molecular and cellular mechanisms by which exercise promotes cardiovascular health (prevention and cardioprotection) are required to develop therapeutic strategies to reduce CVD risk and to treat individuals who experience a major CVD event (12). This article will highlight recent findings regarding the role that endogenous nitric oxide (NO) and β-adrenergic receptors (β-ARs) play in mediating the cardioprotective effects of exercise in the setting of myocardial ischemia-reperfusion (I/R) injury.

Cardioprotective Effects of Exercise

Studies have reported that regular, physical exercise promotes cardiovascular health and reduces the risk of mortality associated with cardiovascular disease (21, 56). Currently, the precise mechanisms by which exercise promotes cardioprotection are not completely known. However, there is evidence to suggest that exercise reduces risk factors associated with CVD, such as obesity and elevated blood pressure, among others (7). Importantly, the protective effects of exercise are not always associated with risk reduction (21, 61). This is exemplified in animal models, which are devoid of confounding risk factors for cardiovascular disease, where exercise has consistently been shown to improve coronary vascular reactivity, decrease myocardial stunning, and reduce arrhythmias in hearts subjected to I/R injury (26). Moreover, exercise confers sustainable protection against myocardial infarction following both long-term and short-term training regimens (9) and improves survival after an ischemic event in humans (37, 50). A review of the literature indicates that reductions in cell death following exercise range from 4 to 75% depending on the ischemic model studied (permanent ischemia or I/R) and the training strategy employed (1, 6–8, 13, 16, 27, 35, 47, 71, 72, 74, 75, 77) (Table 1). Combining the results from these studies reveals that, on average, exercise training reduces injury by 34% compared with non-trained groups.
Putative Cardioprotective Mechanisms of Exercise

In a recent review article, Frasier et al. (26) posed a simple question: “Is exercise the same as preconditioning?” Based on the existing evidence in the literature, the answer to this question is not all that surprising: Yes, exercise is a form of preconditioning. Murry and colleagues (51) were the first to demonstrate the preconditioning phenomenon, which typically refers to the observation that short, discontinuous episodes (i.e., one or more) of ischemia protects tissue against a subsequent prolonged period of ischemia. Importantly, ischemia is not the only stimulus that can precondition tissue, since there is now evidence to suggest that pharmacological agents (15, 67) and interventions such as caloric restriction (62) and exercise (17, 44) also mimic the protective effects of brief ischemic insults.

Preconditioning consists of two distinct phases: the initial window of protection and the second window of protection. The first window of protection is transient and lasts for only a few hours. The second window of protection usually appears 24 h after the preconditioning stimulus and can last for up to 72 h. Each of these phases is distinct in terms of molecular signaling cascades that are induced (76). Exercise also elicits two windows of protection. This is best exemplified in the study by Yamashita et al. (75) in which rats were subjected to treadmill running for 30 min, after which different groups were subjected to myocardial ischemia from 30 min to 72 h after the end of the training. The authors found that exercise reduced the degree of myocardial infarction in a biphasic manner. Specifically, protection was seen 30 min after the end of the training session but was lost at 24 h only to return again at 36 to 60 h after the cessation of running. Importantly, as mentioned above, the protective effects of exercise even extend to 9 days after the ending of an 8-day training period.

The cardioprotective actions of exercise training have been ascribed to its ability to increase a number of proteins associated with preconditioning. For example, studies have reported an increase in the expression of superoxide dismutase (7), catalase (44), and heat-shock proteins (HSPs) (44, 48) after exercise. Others reported that exercise increases the expression and activity of endothelial NO synthase (eNOS), resulting in an increase in NO levels (1). Still others report that exercise activates ATP-sensitive potassium channels (sarcolemmal and mitochondrial) in cardiovascular tissues (6, 57). Moreover, the type of exercise also influences the cytoprotective signaling cascades that are activated. Both treadmill running and voluntary wheel running increase the phosphorylation of AMP-activated protein kinase (17); however, voluntary wheel running does not alter the expression of HSP72, whereas treadmill running has been shown to increase its expression (44). At present, the precise molecular signaling mechanisms that mediate the cardioprotective effects of exercise remain unresolved. Moreover, additional research efforts are required to define the best strategy to elicit these mechanisms.

NO Metabolites Mediate the Cardioprotective Effects of Exercise

An intriguing finding regarding the cardioprotective effects of exercise relates to the sustainability of the protective effects. Specifically, studies have shown that the cardioprotective effects of exercise are not restricted to the training phase. In other

Table 1. Studies reporting a reduction in myocardial infarct size following exercise training

<table>
<thead>
<tr>
<th>Species</th>
<th>Exercise Duration</th>
<th>Exercise Type</th>
<th>Infarct Size Reduction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>7 days</td>
<td>Treadmill</td>
<td>34%</td>
<td>1</td>
</tr>
<tr>
<td>Mouse</td>
<td>4 wk</td>
<td>Voluntary wheel running</td>
<td>22%</td>
<td>13</td>
</tr>
<tr>
<td>Rat</td>
<td>30 min</td>
<td>Treadmill</td>
<td>64%</td>
<td>74</td>
</tr>
<tr>
<td>Rat</td>
<td>30 min</td>
<td>Treadmill</td>
<td>60%</td>
<td>75</td>
</tr>
<tr>
<td>Rat</td>
<td>60 min</td>
<td>Treadmill</td>
<td>27%</td>
<td>8</td>
</tr>
<tr>
<td>Rat</td>
<td>5 days</td>
<td>Treadmill</td>
<td>19%</td>
<td>8</td>
</tr>
<tr>
<td>Rat</td>
<td>5 days</td>
<td>Treadmill</td>
<td>24%</td>
<td>16</td>
</tr>
<tr>
<td>Rat</td>
<td>5 days</td>
<td>Treadmill</td>
<td>75%</td>
<td>35</td>
</tr>
<tr>
<td>Rat</td>
<td>5 wk</td>
<td>Swimming</td>
<td>30%</td>
<td>47</td>
</tr>
<tr>
<td>Rat</td>
<td>7 wk</td>
<td>Swimming</td>
<td>39%</td>
<td>27</td>
</tr>
<tr>
<td>Rat</td>
<td>8 wk</td>
<td>Swimming</td>
<td>24%</td>
<td>77</td>
</tr>
<tr>
<td>Rat</td>
<td>12 wk</td>
<td>Treadmill</td>
<td>21%</td>
<td>6</td>
</tr>
<tr>
<td>Rat</td>
<td>20 wk</td>
<td>Treadmill</td>
<td>25%</td>
<td>7</td>
</tr>
<tr>
<td>Dog</td>
<td>5 periods of 5 min; 10 min before ischemia</td>
<td>Treadmill</td>
<td>78%</td>
<td>22</td>
</tr>
<tr>
<td>Dog</td>
<td>5 periods of 5 min; 24 min before ischemia</td>
<td>Treadmill</td>
<td>56%</td>
<td>55</td>
</tr>
</tbody>
</table>

Reduction in infarct size is based on the difference between the size of the infarction calculated as a percentage of the area-at-risk or the entire left ventricle between the sedentary control group and the exercise group.
words, exercise training protects the heart against ischemic injury long after the training period has ended. In most cases, studies designed to test the protective effects of exercise involve training for 3 days, 7 days, or up to 12 wk, and then within 24 h of the last exercise session the animals were subjected to myocardial ischemia. Yamashita et al. (75) noticed that delaying the time between a single treadmill training session (30 min) and the onset of ischemia to 36, 48, or even 60 h resulted in similar degrees of infarct size reduction compared with animals subjected to ischemia right after the training session. This was further confirmed by a study by Lennon et al. (44). In this study, male rats were subjected treadmill running for 8 days. Different groups were then rested for 1, 3, 9, and 18 days after the last exercise session. At these time points, global myocardial ischemia was induced using the Langendorff-perfused hanging heart model. The authors found similar reductions in I/R injury in the hearts from the rats that were rested for 1, 3, and 9 days. However, protection was lost in the hearts from the rats rested for 18 days. In terms of the mechanism responsible for the protection, exercise was found to induce an increase in both catalase activity and HSP72 levels in the rats that rested for 1 and 3 days. However, by 9 days of rest, both catalase and HSP72 levels had returned to sedentary levels, suggesting that an additional mechanism contributed to the observed protection (44).

Recently, we reported that the sustainable cardioprotective effects of exercise were also evident after voluntary wheel running (13). In our study, mice were housed in cages with a running wheel and allowed to exercise voluntarily (VE) for 4 wk. Mice in the VE group and the sedentary control group were then subjected to myocardial I/R injury 24 h or 1 wk after the cessation of training. We determined that both groups of VE mice (i.e., 1 day or 1 wk posttraining) displayed a similar reduction in myocardial infarct size compared with sedentary control mice, which supported the previous findings regarding the sustainability of the cardioprotective effects of exercise. Initially, we evaluated the expression of several proteins suggested to mediate exercise-induced cardioprotection, AMPK and SOD. Both were increased in the heart immediately after the end of the exercise-training period but returned to baseline levels by 1 wk after training. This suggests that AMPK and SOD may play a role in mediating the cardioprotective effects of exercise in the acute period but do not play a role in maintaining the sustainable cardioprotective effects of exercise.

The endothelium is critically involved in exercise-induced cardioprotection. For instance, exercise increases vascular shear stress throughout the body, which in turn increases the expression and activity of eNOS, resulting in an increase in NO in both animal models and humans (18, 33, 34, 60). An important role for eNOS/NO in exercise physiology was established in studies where mice deficient in eNOS were reported to have run to a lesser degree (roughly 65% less) than age-matched, wild-type mice (49, 53). Additionally, studies employing mice deficient in eNOS have confirmed a role for eNOS/NO in mediating the cytoprotective effects of exercise (19, 29). Specifically, in the heart, it has been shown that eNOS is essential for exercise to protect against the development of heart failure, as evidenced by the findings that exercise does not attenuate left ventricular remodeling, hypertrophy, fibrosis, or apoptosis after myocardial infarction in eNOS-deficient mice (19). We, therefore, turned our attention to eNOS and NO to determine whether they played a role in mediating the sustainable cardioprotective effects of exercise. Similar to previous studies (1, 38, 60), we found that exercise training altered the expression and activity of eNOS, resulting in an increase in NO. Specifically, we found that VE did not alter the expression of total eNOS in the heart. It did, however, increase the phosphorylation of eNOS at serine residue 1177 (activation site) and decrease the phosphorylation of eNOS at threonine residue 495 (inhibition site). Importantly, these changes were evident immediately after the end of the training period and were still present 1 wk after the end of training. We also evaluated the expression and phosphorylation status of eNOS in the skeletal muscle because it is an organ that experiences blood flow changes during exercise. In the skeletal muscle, VE increased the expression of total eNOS and decreased the phosphorylation of eNOS at threonine residue 495. There was an overall increase in the expression of phosphorylated eNOS at 1177 in the skeletal muscle, but this increase was attributed to the increase in total eNOS. In contrast to the heart, the alterations in eNOS expression and phosphorylation status returned to baseline levels by 1 wk after the end of the training. These findings are interesting for several reasons. First, they suggest that exercise alters the expression and phosphorylation status of eNOS in a tissue-specific manner. Second, the degree to which exercise training mediates the changes in eNOS is also tissue-specific. Finally, these findings suggest that the alterations in eNOS play an important role in not only mediating the acute but also the sustained cardioprotective effects of exercise.

Importantly, the changes that we observed in the expression and phosphorylation status of eNOS resulted in an increase in NO levels, as evidenced by an increase in circulating and tissue levels of both nitrite (NO\textsubscript{2}) and nitrosothiols (RXNO). Nitrite is...
produced by the oxidation of NO in aerobic conditions (68), whereas nitrosothiols are formed when cysteine thiols in proteins are modified by NO in a process known as S-nitrosylation (25). Classically, blood levels of nitrite and nitrosothiols served as biomarkers of NO bioavailability and as surrogates of endothelial function (40, 78). In recent years, this classic paradigm has shifted as accumulating evidence has come to light demonstrating a physiological role for both nitrite and nitrosothiols. Nitrite is widely considered a storage form of NO in both blood and tissues (20, 43) that is very readily converted into NO by either acid reduction or by various nitrite reductases during ischemia or hypoxia (59, 68, 79). Importantly, administration of exogenous nitrite modulates cardioprotective signaling in animal models of I/R injury when given before, during, or after ischemia (23, 32, 63, 68). Currently, the exact mechanism(s) by which nitrite elicits its cardioprotective effects are not known. However, there is consensus that nitrite-mediated tissue protection is in large part dependent on the generation of NO (23, 63).

Endogenous nitrosothiols also exert a critical physiological role as well as a pathophysiological role in a variety of human diseases (25). S-nitrosylation of myocardial target proteins associated with β-adrenergic receptor signaling and/or calcium handling influences the contraction of the heart (31, 54, 69). In regard to pathophysiology, increasing the S-nitrosylation of proteins during myocardial I/R can attenuate a number of adverse processes (10, 36, 64), such as apoptosis (46) and inflammation (14), and even stimulate protective processes (10, 36, 64). S-nitrosylation of N-ethylmaleimide-sensitive factor inhibits endothelial cell exocytosis and neutrophil infiltration following myocardial I/R (73). Additionally, S-nitrosylation of cyclophilin D prevents the opening of the mitochondrial permeability transition pore (MPTP) (52). Finally, caspase-3-like activity can be inhibited via protein S-nitrosylation (41), which will also contribute to less cell death following myocardial I/R. Interestingly, nitrite via its reduction to NO can also form nitrosothiols and thereby modify complex I of the mitochondrial transport chain, resulting in a reduction of reactive oxygen species generation during early reperfusion (63).

Circulating levels of nitrite and nitrosothiols are elevated during exercise in both rodents and humans (6, 78). However, under the traditional view regarding the physiological role of these NO metabolites, an increase was just considered evidence that NO production was increased. As such, what role if any they played in mediating the cardioprotective effects of exercise was overlooked. In our recent study (13), we provided evidence that the formation of nitrite and nitrosothiols during exercise training contributes, in part, to the acute and sustained cardioprotective effects of exercise (FIGURE 1). In regard to the acute effects, we observed an increase in plasma, skeletal muscle, and heart levels of nitrite and nitrosothiols immediately after the end of the training period. The finding that the blood and myocardial levels were significantly increased before myocardial ischemia is an important observation given that eNOS activity and NO bioavailability are attenuated during ischemia following increased production of reactive oxygen species (30, 68). Therefore, during myocardial ischemia, the nitrite stored following exercise can be converted into NO by any of the identified nitrite reductases found in the heart. Similarly, previously stored nitrosothiols prevent the irreversible oxidation of proteins by acting as a reversible protective cap during I/R and also by acting as a redox-sensitive NO donor (36). The increased NO generated in an NOS-independent manner from either nitrite or nitrosothiols

Exercise and Nitric Oxide Homeostasis

Vascular shear stress in response to exercise leads to increases in the generation of nitric oxide (NO) from endothelial NO synthase (eNOS). The generated NO can either be used immediately to induce vasodilation in an effort to match blood flow to metabolic demands or be metabolized into nitrite and nitrosothiols. This conceivably would continue with each passing exercise period, resulting in elevated steady-state levels of the metabolites in the heart. Increasing these stores before myocardial ischemia is important because NO bioavailability is dampened during ischemia. Therefore, the stored nitrite can be reduced to NO during myocardial ischemia by either acid reduction or by any of the identified nitrite reductases. Additionally, nitrosothiols can act to protect proteins during the early oxidative burst of reperfusion and then act as a redox-sensitive NO donor later. The increased NO from either nitrite or nitrosothiols can then protect the heart against ischemic injury by any of its known cardioprotective actions.

FIGURE 1. Schematic diagram highlighting the effects of exercise on nitric oxide homeostasis
serves as a crucial cytoprotective signaling molecule that protects the heart and circulation against myocardial I/R injury. As such, these findings suggest that NO derived from both nitrite and nitrosothiols more than likely contributes to the acute cardioprotective effects of exercise. This is supported by the schematic diagram highlighting the activation of eNOS via β-adrenergic receptor stimulation.

**FIGURE 2.** Schematic diagram highlighting the activation of eNOS via β-adrenergic receptor stimulation

Activation of the β₁-adrenergic receptor (β₁-AR) results in increased heart rate, cardiac stroke work, and cardiac output to meet the demands placed on the heart during strenuous exercise. Furthermore, during exercise, sympathetic stimulation via the β₂-adrenergic receptor (β₂-AR) and perhaps the β₃-adrenergic receptor (β₃-AR) leads to the activation of eNOS, resulting in an increase in the production of NO. One of the primary mechanisms related to activation of eNOS is the concomitant increased phosphorylation of eNOS at Ser₁⁴⁷⁷ and the decreased phosphorylation of eNOS at Thr⁴⁹⁵. Together, this results in robust activation of eNOS with increased generation of NO. The increase in NO can then protect the heart against ischemic injury.
by the findings that the infarct-lowering effects of exercise were lost in eNOS-deficient mice. Our findings also suggest that skeletal muscle may serve as a source of NO to protect the heart against myocardial I/R injury. This is based on our previous findings that nitrite and nitrosothiols exert endocrine actions and NO that can be generated in one organ is transported via the circulation in the form of nitrite and/or nitrosothiols to protect another organ against I/R injury (24). We found that nitrite and nitrosothiols levels remained elevated in the hearts of trained mice for 1 wk after the end of the training period. Further evidence supporting a role for nitrite and nitrosothiols stems from our recent findings that, when mice were recovered for 4 wk after training, both nitrite and nitrosothiol levels returned to baseline levels and cardioprotection was ablated. Finally, we extended our investigation into humans and found that nitrosothiols, not nitrite, levels were elevated in the plasma of trained endurance athletes (12). This suggests that nitrosothiols may play a more prominent role in mediating protection during exercise given that both nitrite and NO can form nitrosothiols (11). However, further work investigating larger pools of human samples is needed to test this hypothesis.

Our findings and those of others clearly demonstrate that eNOS and eNOS-derived NO metabolites play a critical role in mediating both the acute and sustained cardioprotective effects of exercise. However, there are questions that remain to be answered. For instance, 1) what is the signaling mechanism by which the alterations in eNOS phosphorylation status remain for 1 wk after the cessation of training? 2) What duration and intensity of exercise is required to increase the steady-state levels of nitrite and nitrosothiols in the heart? 3) Do the increased levels of heart nitrite and nitrosothiols remain after eNOS activity returns to normal, and, if so, how long? Additionally, given that our present study provides the only data to suggest that eNOS and NO metabolites (i.e., nitrite and nitrosothiols) play a role in mediating the sustained cardioprotective effects of exercise, more work with loss-of-function and/or NO scavenging experiments is needed to definitively test this hypothesis. It is also important to determine whether other types of exercise have the same effect on eNOS and NO metabolites.

**β-Adrenergic Receptors Mediate Exercise-Induced Cardioprotection via NO**

β-Adrenergic receptors (β-ARs) belong to a superfamily of G-protein-coupled receptors and regulate cardiac function in response to catecholamines (28). In the heart, there are three isoforms of β-ARs: β₁-AR, β₂-AR, and β₃-AR (66). The physiological roles of the β₁- and β₂-ARs in the myocardium have been studied extensively. For instance, it is established that stimulation of β₁-ARs leads to increases in the rate of contraction and the force of contraction, as well as an acceleration of relaxation. In regard to stimulation of the β₃-AR in the heart, the exact physiological and pathophysiological roles are not known. However, there is evidence to suggest that stimulation of the β₃-AR induces the production of NO from eNOS to elicit a negative inotropic effect (66). Along these lines, we (13) found that the activation of eNOS (i.e., phosphorylation) and generation of NO in response to exercise is mediated in part by stimulation of the β₃-AR. Specifically, we observed sustained and significant elevations in circulating catecholamines following voluntary exercise in mice coupled with increased myocardial expression of the β₃-AR in the absence of alterations in β₁- and β₂-AR expression. Interestingly, we also observed significant eNOS activation and NO generation following a single injection of physiological levels of epinephrine (13). Furthermore, we found that exercise failed to result in eNOS activation or increase plasma and heart levels of NO metabolites in mice with genetic deficiency of the β₃-AR. Similar to eNOS-deficient mice, β₁-AR-deficient mice also exercised to a lesser degree than wild-type control mice, which suggests that β₁-ARs are important mediators of the physiological response to exercise in addition to their role in exercise-mediated cardioprotection. Furthermore, β₃-AR is important for exercise-mediated cardioprotection, as evidenced by the finding that β₃-AR-deficient mice displayed exacerbated myocardial injury when subjected to I/R injury following the completion of a 4-wk exercise period. On the basis of these results, it can be suggested that increased catecholamine levels during exercise lead to increased β₃-AR stimulation, which in turn through downstream signaling activates eNOS. The resultant increase in NO bioavailability can then protect the heart against ischemic injury as described above (FIGURE 2). The exact mechanism by which β₁-ARs are linked to eNOS activation is not completely understood. However, there is evidence from in vitro experiments with endothelial cells to suggest that stimulation of the β₁-AR activates eNOS via a Rac1-PKA-Akt pathway (42). Given that Akt has been shown to regulate eNOS activation in response to exercise (3) and that Rac1 is activated in contracting skeletal muscle (65) and by shear stress (70), it is possible that this pathway regulates links of β₃-ARs to eNOS during exercise. However, this pathway has not been definitively tested in response to exercise, so further work is needed to elucidate the mechanism(s) by which the β₃-AR stimulation regulates eNOS in response to exercise. Additionally,
further work is required to determine the mechanism(s) by which deficiency in β2-ARs leads to exacerbated myocardial injury after training.

It is also possible that increased sympathetic activation and increased catecholamine release during exercise may result in activation of the β2-AR receptor on endothelium or cardiac myocyte to upregulate eNOS function and NO signaling (FIGURE 2). Recent experimental evidence demonstrates that stimulation of β2-ARs activates eNOS via a Src kinase-P53K/Akt-dependent but cAMP/PKA-, MAPK-, and AMPK-independent pathway (2). Additionally, activation of the β2-AR promotes eNOS activation, increased NO metabolites, and myocardial protection following I/R in mice (4). However, the precise role or potential mechanism by which β2-AR activation mediates exercise-induced cardioprotection has not been investigated.

Perspective and Conclusions

Despite the well documented beneficial cardiovascular effects of exercise training, our understanding of the protective mechanisms elicited by exercise (5), especially as it relates to myocardial I/R injury, remains largely unknown. As documented above and in other studies, exercise is a preconditioning modality, as evidenced by the findings that exercise induces a number of classic preconditioning signals. However, in regard to other preconditioning strategies, exercise is unique in that it can elicit sustainable protection that extends well beyond the training period. As such, exercise remains an fascinating approach to diminish the severity of myocardial infarction following ischemic injury given that it is widely accessible to almost all patient populations, is relatively inexpensive, and is safe (12). Therefore, continued investigation into the unknown cardioprotective mechanisms of exercise are extremely important given their enormous health care implications. Specifically, a better understanding of the signaling cascades induced by exercise will hopefully provide the framework for developing therapeutic strategies designed to mimic the cardioprotective effects of exercise.

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