

# Association of Exercise Preconditioning With Immediate Cardioprotection

## A Review

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**IMPORTANCE** Exercise reduces the risk of cardiovascular events, including through an underrecognized, clinically useful form of acute cardioprotection accessible after a single episode of exercise, which is called *cardiovascular preconditioning*.

**OBSERVATIONS** Preclinical evidence shows that 1 to 3 episodes of exercise per week will provide strong cardioprotection; gradual, modest cardiovascular risk factor modification or physiological artery remodeling cannot fully explain these benefits. This review highlights preclinical evidence that acute exercise-induced cardiac preconditioning has the ability to activate multiple pathways to confer immediate protection against ischemic events, reduce the severity of potentially lethal ischemic myocardial injury, and act as a physiological first line of defense.

**CONCLUSIONS AND RELEVANCE** Independent of the protective benefits of long-term exercise training on risk factors and adaptation of the cardiovascular system, cardiovascular preconditioning may contribute to the immediate cardioprotection of exercise. In practical terms, this means that 1 episode of exercise can create clinically relevant cardioprotection.

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An important preventable factor for the development and progression of cardiovascular disease (CVD) is physical inactivity. A physically active lifestyle leads to a 42% to 44% reduction in the development of CVD (ie, it provides primary prevention),<sup>1,2</sup> and it also reduces CVD mortality and hospital admissions in those who develop CVD (ie, it provides secondary prevention).<sup>3</sup> Among other benefits, greater physical activity is associated with improved 30-day prognosis in patients with acute coronary syndromes.<sup>4</sup> These positive effects of a physically active lifestyle have exceeded those associated with drug interventions in several studies.<sup>5</sup>

Cardioprotection is partly associated with the marked physiological adaptive responses of the heart and coronary arteries (Figure 1),<sup>6</sup> which might occur within weeks.<sup>7</sup> Exercise training also improves CVD risk factors, although the capacity of exercise to alter these factors is modest and takes several months (Figure 2). It is estimated that these risk factors together explain only 27% to 41% of the cardioprotective benefits of exercise training.<sup>7,8</sup> Therefore, the benefits of exercise training cannot be explained by simply combining physiological cardiovascular adaptations and CVD risk factor modifications.

This review summarizes the evidence supporting the idea that exercise is a form of preconditioning that attenuates the detrimental effects of ischemia. *Ischemic preconditioning* refers to the observation in both animals and humans that brief periods of ischemia before prolonged occlusion reduce subsequent infarct size and/or the risk for harmful ventricular arrhythmias.<sup>9</sup> Interestingly, studies performed in

animals found marked cardioprotection within 1 to 5 days after acute exercise,<sup>10-12</sup> a time course too short to induce physiological adaptation or improvements in traditional cardiovascular risk factors. Therefore, we explore the widely underrecognized hypothesis that exercise induces preconditioning, which leads to immediate cardioprotection.<sup>13</sup>

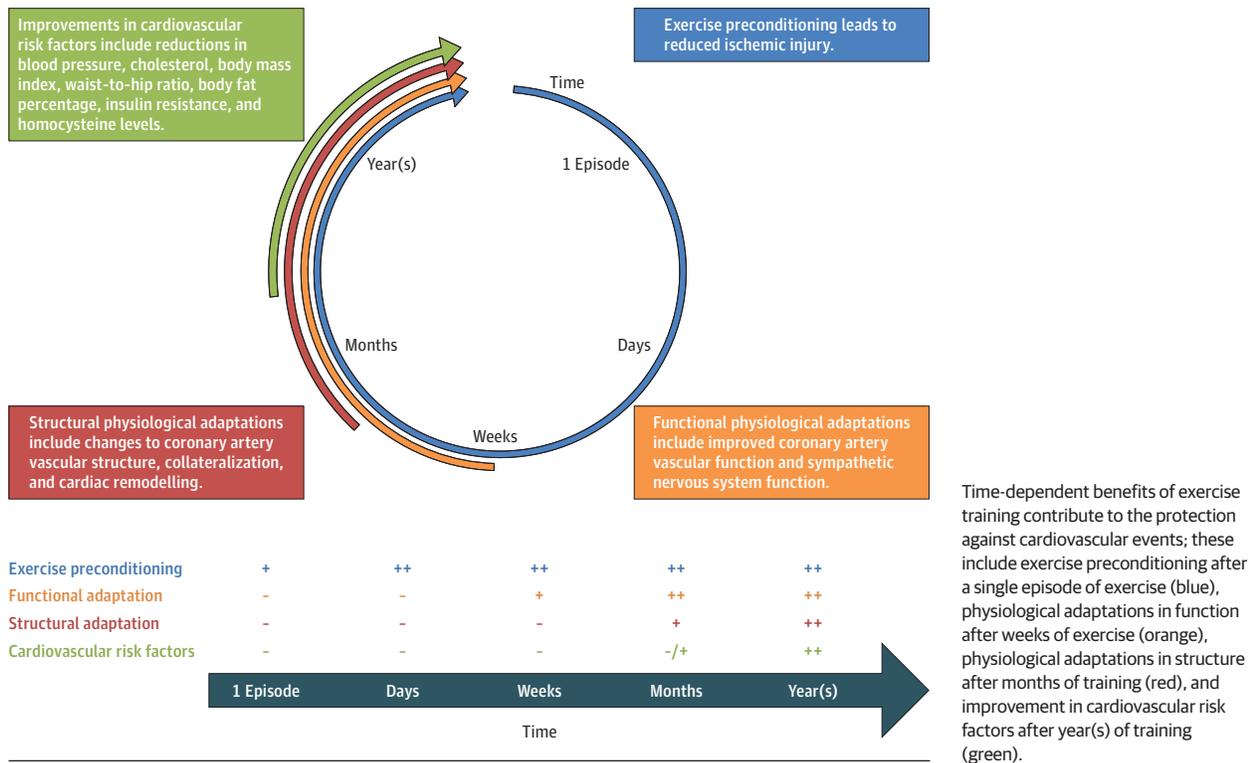
We will first summarize evidence from population-based studies that describe the association of acute exercise preconditioning with clinical events. Subsequently, we summarize studies in animals and humans that explore the association of acute exercise preconditioning with the cardiovascular system with the possible translation of these associations to relevant clinical scenarios. Understanding the immediate cardiovascular benefits of exercise preconditioning will support the development of strategies in the primary and secondary prevention of CVD. More specifically, the concept of exercise preconditioning indicates that, after engagement in regular exercise, cardioprotection occurs well before any changes in CVD risk factors. This suggests that clinically relevant cardioprotection is present after 1 episode of exercise.

## What Is the Evidence for Exercise Preconditioning?

### Can the Heart Be Preconditioned?

In 1986, Murry et al<sup>14</sup> introduced the concept of ischemic preconditioning, which involves 3 to 4 brief repetitions of ischemia, typi-

Figure 1. Benefits of Exercise Training



cally induced by 5 minutes of occlusion of an artery through surgical ligation or limb occlusion (with an increase of >50 mm Hg above baseline systolic pressure), interspersed with 5 minutes of tissue reperfusion. As has been typical in subsequent studies, this research examined the effect of preconditioning in animals by performing post-mortem tissue analysis to examine the infarct size relative to the area at risk (ie, the area perfused by the artery that was occluded); Murry et al<sup>14</sup> found that ischemic preconditioning resulted in an approximately 75% smaller infarct size than in the control population. In a follow-up study,<sup>15</sup> cycles of coronary ischemia and reperfusion were shown to also protect remote cardiac tissue not directly exposed to the preconditioning stimulus. This stimulated research resulted in the clinical application of ischemic preconditioning of a limb to protect remote tissues, such as the heart, against ischemic events.<sup>16</sup> The reduction of myocardial damage by remote preconditioning, including improvement in clinical outcomes, has since been observed in patients undergoing cardiac surgery<sup>17</sup> and in those with evolving myocardial infarction undergoing emergency coronary artery stenting.<sup>18</sup> While the field awaits definitive evidence of clinical benefit from large-scale clinical trials, the use of preconditioning is gaining significant traction in the field of coronary artery disease.

**Can Acute Exercise Precondition the Heart?**

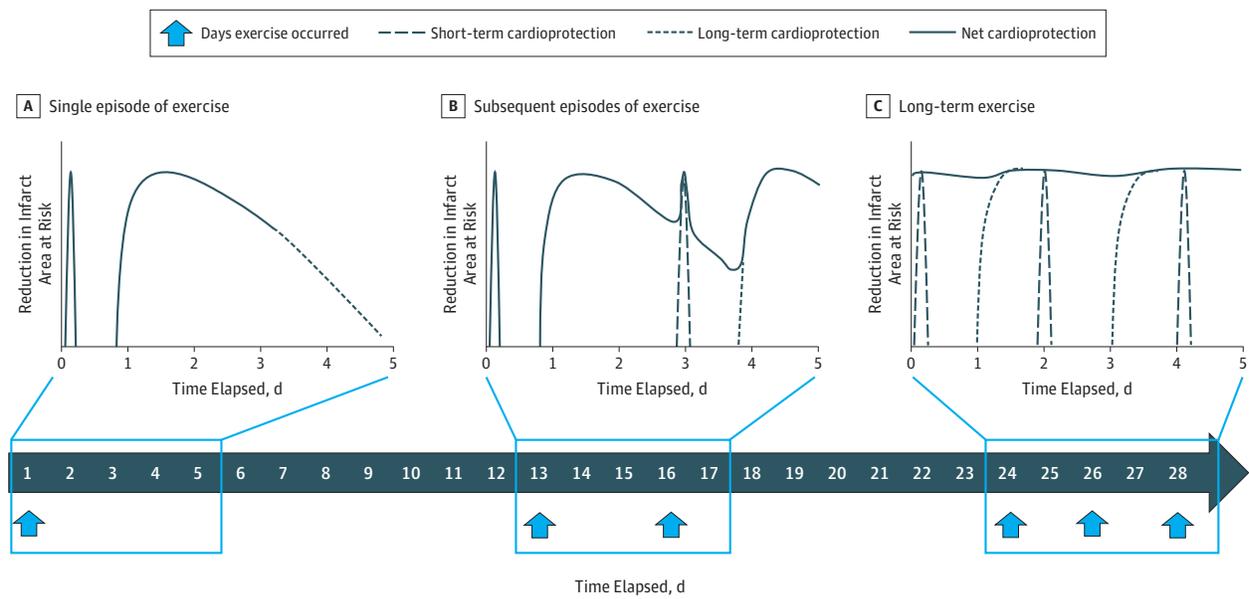
An acute episode of exercise is characterized by intermittent exposure to local effects (by exercising specific muscle groups) or systematic effects (by inducing myocardial ischemia). The similarity of this stimuli with ischemic preconditioning supports the idea that acute exercise is a form of preconditioning with the potential to mediate similar cardioprotective effects.<sup>9,19</sup>

Another important similarity is that the temporal nature in cardioprotection observed in an acute episode of exercise resembles that of ischemic preconditioning. Classic ischemic preconditioning shows potent early protection and disappears approximately 2 to 4 hours after the stimulus; it shows a somewhat slighter degree of late protection, which reappears after approximately 24 hours and can last for several days.<sup>20,21</sup> Exercise also elicits this characteristic biphasic protection response. A study of rats<sup>22</sup> found that 30 minutes of running evoked an immediate reduction in infarct size, which was subsequently lost but then reappeared 36 to 60 hours after exercise. Others have also reported the characteristic biphasic response to acute exercise, with protection evident in the second phase for up to 9 days after a single episode of exercise.<sup>23</sup> Accordingly, it is tempting to speculate that acute exercise can precondition the heart.

**Does Exercise Acutely Attenuate Cardiac Ischemia in Humans?**

The ability of exercise to precondition the heart was first suggested more than 200 years ago when it was observed that exercise-induced ischemia (eg, clinical symptoms such as angina) was significantly reduced or even abolished on a second exercise effort.<sup>24</sup> Several subsequent studies<sup>25</sup> have confirmed observations of so-called warm-up angina. In addition to clinical symptoms, exercise-induced ischemia can also be quantified by electrocardiographic measurement of ST-segment depression. A meta-analysis of 34 studies<sup>25</sup> reported a significantly later onset of ST-segment depression (91 seconds) and a decrease in peak ST-segment depression (-0.38 mm) on the second exercise stress test during sequential test-

Figure 2. Cardioprotection Through Exercise Preconditioning



Proposed cardioprotection via exercise preconditioning from a single episode of exercise (A), 2 subsequent episodes of exercise (B), and long-term exercise training (C). With respect to most research described in this review, exercise preconditioning may provide a measure of reduction in the infarct area at risk; units of measurement are variable by study method and species studied.

ing of 1053 patients with angina. This supports the idea that exercise can induce immediate attenuation of cardiac ischemia. Preclinical evidence has found that warm-up angina requires a preceding period of ischemia,<sup>26</sup> which in turn activates pathways that protect the myocardium against ischemia.<sup>24</sup> Moreover, similar to classic ischemic preconditioning, warm-up angina shows biphasic protection. The reductions in ST-segment depression and angina onset during the second episode of exercise were evident for the first 6 hours and subsequently returned 24 hours after the exercise ended.<sup>27,28</sup> This suggests that exercise attenuates cardiac ischemia in patients with angina during the second episode of exercise, which seems at least partly the result of exercise preconditioning.

Emerging evidence suggests that exercise preconditioning is not only present in those with angina. Using a rat model, Yamashita et al<sup>22</sup> was one of the first to examine if an acute episode of exercise can reduce ischemic myocardial injury in individuals without angina. A single episode of exercise prior to ischemic myocardial injury reduced damage to the heart in a biphasic manner, involving early and late protection. In a follow-up study,<sup>29</sup> they confirmed that exercise protects the myocardium from ischemia-reperfusion injury for 24 hours after cessation of the episode of exercise. In a series of studies, Domenech et al<sup>30</sup> explored if intermittent exercise resulted in early and late cardiac preconditioning. They found that exercise prior to coronary occlusion induces early and late preconditioning, leading to reductions in infarct size of 46% to 52%<sup>30,31</sup> and 56% to 78%,<sup>30-32</sup> respectively.

The underlying mechanisms of exercise preconditioning were examined in a novel human-to-animal crossover study. Michelsen et al<sup>33</sup> examined healthy individuals who underwent exercise (4 intermittent episodes of running in 2-minute bursts) and ischemic preconditioning (4 repetitions of arterial occlusion of 5 minutes each,

using blood pressure cuffs). Blood was taken from human participants after preconditioning and used as a dialysate to perfuse a rabbit heart in a Langendorff model of myocardial infarction. This was followed by a 40-minute occlusion of a coronary artery in the rabbit heart and assessment of the infarct size relative to the area at risk. Exercise and ischemic preconditioning both reduced infarct size by approximately 50%. To understand the underlying mechanisms, analyses were repeated with coadministration of an opioid receptor antagonist to the Langendorff model heart, which abrogated the protective effects of exercise and ischemic preconditioning. These observations suggest that exercise, similar to ischemia, elicits a protective preconditioning effect on the heart through a circulating, humoral factor that is dependent on opioid receptor activation. The involvement of  $\delta$ -opioid receptors in exercise preconditioning was confirmed by others in 2015,<sup>34</sup> including a study that found that the protection of exercise-induced cardiac ischemia-reperfusion injury was abolished during the infusion of  $\delta$ -opioid receptor blockers.

**Does Acute Exercise Reduce Infarct Size in Humans?**

A series of studies by Franco Rengo, MD, and colleagues<sup>35,36</sup> retrospectively assessed subjective physical activity patterns in the week before a myocardial infarction. They found that greater physical activity levels in the week preceding an event were associated with lower in-hospital mortality and more nonfatal (as opposed to fatal) cardiac events. Similarly, engaging in physical activity in the week prior to coronary artery bypass grafting was linked to higher rates of survival.<sup>37</sup> Finally, repetitive exercise with brief rest periods in patients with significant coronary artery disease attenuated the degree of exercise-induced myocardial stunning.<sup>38</sup> Unfortunately, these studies have not corrected for long-standing participant physical activity patterns, which makes it difficult to differentiate between the

effects of physical activity patterns in the experimental setting and those of physical activity in the days preceding the experiment. Until clinical studies in humans are performed with distinct physical activity patterns before ischemic injury, it will remain difficult to clearly answer this question.

### Can Acute Exercise Precondition the Cardiovascular System? Can Exercise Training Precondition Arteries?

The first study to describe the cardioprotective effects of exercise preconditioning in rats<sup>39</sup> was published in 1978 and demonstrated that 5 weeks of swimming exercise resulted in a smaller myocardial infarct size. Several subsequent studies in animals have supported these original findings.<sup>12,40-45</sup> These studies adopted 2 to 12 weeks of regular, frequent exercise (5-7 d/wk), involved running or swimming, and consistently reported significantly smaller infarct sizes than in the sedentary controls. The attenuated myocardial injury, at least in part, is related to an accelerated recovery of myocardial tissue oxygenation<sup>40</sup> and/or improved myocardial contractile performance during reperfusion.<sup>46</sup> Interestingly, the cardioprotective effects were preserved for 1 week after cessation of the 4-week exercise program,<sup>47</sup> supporting the sustainability of these benefits. This study<sup>47</sup> also revealed that nitric oxide metabolites contribute to the sustained cardioprotective effects. More specifically, exercise up-regulated cardiac endothelial nitric oxide synthase, resulting in increased storage of the nitric oxide metabolites nitrite and nitrosothiols, which might contribute to an increase in nitric oxide bioavailability during myocardial injury.

#### Limitations of Existing Evidence

An important limitation of animal studies that examine exercise preconditioning is that most studies only present infarct size. However, several investigators have also explored functional consequences. For example, 1 study<sup>48</sup> performed surgical ligation of the left coronary artery in rats after 7 weeks of swimming exercise. After allowing another 4 weeks of recovery, exercise-trained rats demonstrated smaller scar size and higher arteriole density on postmortem tissue examination than untrained rats; the changes were associated with improved cardiac function on in vivo echocardiography.<sup>48</sup> The ability of exercise training to prevent postinfarct cardiac dysfunction was supported by others,<sup>12</sup> while these benefits further translated to improved survival.<sup>12</sup> Interestingly, improved survival was not present in mice trained after myocardial injury.<sup>12</sup> This suggests that prior exercise can improve cardiac function and survival after ischemic cardiac injury.

Another important limitation to animal studies is the difficulty of extrapolating the data to humans with CVD. In addition, care is also required when extrapolating from 1 part of the human body to another. A model frequently used to study ischemia-reperfusion injury in humans involves applying prolonged ischemia to the forearm through 15 to 20 minutes of cuff inflation around the upper arm, followed by 15 to 20 minutes of reperfusion. This leads to a decrease in brachial artery endothelial function, which is prevented when preceded by ischemic preconditioning.<sup>49</sup> Although the forearm vascular response shows good correlation with coronary vascular responses,<sup>50</sup> care is warranted to extrapolate these findings to cardiac tissue. Using this model, Seeger et al<sup>51</sup> explored the ability of exercise, similar to limb-ischemic preconditioning, to prevent endothelial ischemia-reperfusion injury in vivo. A single episode of

interval exercise, but not an isocaloric endurance exercise, induced protection against endothelial ischemia-reperfusion injury. While this observation indicates the potency of exercise preconditioning, it also raises questions regarding the stimuli mediating these responses. A potential explanation is that endurance exercise was unable to induce local ischemia, while interval exercise evidently could induce it.<sup>51</sup> Nevertheless, Brunt et al<sup>52</sup> reported in 2016 that a single exposure to warm water immersion, a stimulus not associated with ischemia, prevented endothelial ischemia-reperfusion injury. This suggests that the potential mechanisms underlying exercise preconditioning might not simply relate to ischemia alone.

A previous cross-sectional study<sup>53</sup> in humans found that the magnitude of brachial artery endothelial ischemia-reperfusion injury was lower in those engaged in habitual resistance exercise. In a follow-up study,<sup>54</sup> the same researchers compared endothelial ischemia-reperfusion injury between young and middle-aged endurance-trained individuals vs sedentary individuals. They reported that middle-aged individuals had greater endothelial ischemia-reperfusion injury, while habitual endurance exercise partly protected against these age-related effects. In 2017, Maessen et al<sup>55</sup> provided further evidence that long-term exercise training can prevent ischemia-reperfusion injury. They found that lifelong athletes had reduced endothelial ischemia-reperfusion injury and preserved local preconditioning efficacy, compared with their sedentary peers. This would suggest that, in line with animal studies, exercise training reduces ischemia-reperfusion injury in humans and that, accordingly, exercise may serve as a preconditioning stimulus. Future studies are needed to better understand the effects of exercise preconditioning in humans, preferably directly examining cardiac and coronary artery responses.

#### What Is the Time Course of Training-Induced Myocardial Preconditioning?

Experimental studies in animals have demonstrated the remarkable potency of exercise preconditioning to mediate rapid cardioprotection. In addition to the immediate cardioprotection after a single episode of exercise, 5 to 7 days of exercise training also evoke strong cardioprotective effects, demonstrated by a significantly smaller infarct size<sup>56,57</sup> and better postischemic recovery (ie, myocardial contractile performance).<sup>10</sup> Also, 3 days of exercise for 60 minutes per day is sufficient to induce cardioprotective effects, evidenced by smaller infarct size<sup>58,59</sup> and better postinjury recovery.<sup>10,11,60</sup> Given these effects of short-term training, one might question whether the duration of training affects the ability to reduce infarct size. To examine this question, Sun and Pan<sup>42</sup> compared effects of 3-day vs 3-week intermittent running exercise in rats. Using isoproterenol-induced cardiac injury, they observed no differences in myocardial damage between the 3-day or 3-week training groups. These data<sup>42</sup> further support the concept that exercise training-induced preconditioning occurs immediately and that benefits are independent of the duration of training. Because these studies showed no structural adaptation, this further supports exercise preconditioning as an explanation for immediate cardioprotection on short-term exercise.

#### Is Cardioprotection From Exercise Training Summative or Related to the Last Episode of Exercise?

The presence of protective effects of exercise preconditioning after a single episode of exercise raises the question of whether the

cardioprotective effects of repeated exercise preconditioning are summative, or if they simply relate to the benefits generated by the last episode(s) of exercise. When exploring the sustainability of these effects, exercise training in animals for 5-day or 4-week spans preserved cardioprotection up to 7 to 9 days after the last episode of exercise.<sup>23,47</sup> This is longer than was reported in a previous study that explored the time course of the infarct-sparing effects of a single episode of exercise, which was present up to 60 hours postexercise.<sup>61</sup> While the duration of protection is somewhat unclear, these studies suggest that the cardioprotective effect of a single episode of exercise might be prolonged when followed by repeated exercise training.

To more directly examine this topic, 1 study<sup>62</sup> found that 2 weeks of running exercise in mice was associated with increased myocardial tolerance against ischemia-reperfusion injury. Although these effects were lost after 1 week of inactivity, 1 to 3 days of exercise fully restored the cardioprotective effects. The comparable effects of 2 weeks of training vs 1 to 3 episodes of exercise were paralleled by changes in glycogen synthase kinase-3 $\beta$  and epidermal growth factor receptor, proteins related to injury and survival, respectively.<sup>62</sup> However, other proteins related to survival were up-regulated after 2 weeks of training (ie, AKT, adenosine monophosphate-activated protein kinase, heat shock protein 27) but remained unaltered on 1 to 3 episodes of exercise.<sup>62</sup> Another study<sup>61</sup> explored the time course of a single and 2 subsequent episodes of exercise. The single episode of exercise showed the typical biphasic pattern of cardioprotection, whereas 2 episodes of exercise (separated by 48 hours) resulted in protection that was consistently present across the 60-hour period. This suggests that subsequent episodes of exercise, with the second episode timed during late preconditioning, provide continuous protection against myocardial ischemia-induced injury. Possibly, long-term benefits of exercise preconditioning might at least partly relate to the continuous activation of late preconditioning (Figure 2).

## Moderating Factors of Exercise Preconditioning

### Do Risk Factors for CVD Impair Exercise Preconditioning?

Studies suggest that efficacy of classic preconditioning is attenuated in the presence of risk factors for CVD.<sup>63</sup> Studies have assessed if exercise training restores the attenuated efficacy of classic preconditioning associated with obesity. Regular exercise training in obese rats<sup>64</sup> or obese mice<sup>65</sup> can partly restore the attenuated efficacy of preconditioning in experimental myocardial infarction. These effects of exercise were related to the up-regulation of prosurvival signaling pathways, increase in kinase phosphorylation, decreased levels of phosphates, and increased resistance of mitochondrial permeability transition pore opening.<sup>64-66</sup> Because no effect of 4-week exercise training was found on glucose level, cholesterol level, insulin level, fat mass, or body mass,<sup>66</sup> the restoration of preconditioning occurs independent of changes in traditional CVD risk factors. Although more work is required, these preliminary studies highlight the ability of exercise training (in obese animals) to restore attenuated cardioprotection afforded by classic ischemic preconditioning.

Older age is another risk factor that is strongly associated with impaired ability of classic preconditioning to prevent ischemia-

reperfusion injury.<sup>67</sup> Emerging evidence suggests that these effects of older age are partly reversible through exercise training. Abete et al<sup>68</sup> found that in trained older rats, but not in sedentary older rats, local preconditioning reduced postischemic myocardial injury. This study also revealed an important role for exercise-induced release of norepinephrine because these effects of training were abolished when exercise-induced release of norepinephrine was blocked.<sup>68</sup> Follow-up studies provided further evidence that exercise training in older rats can restore the ability to reduce cardiac injury using preconditioning.<sup>69,70</sup> These findings are in agreement with 2017 cross-sectional findings in humans, where lifelong older athletes showed preserved ability of preconditioning to prevent endothelial ischemia-reperfusion injury.<sup>55</sup> This indicates that the age-related impaired preconditioning is at least partly related to physical inactivity and, importantly, can be restored by training.

### Which Exercise Factors Mediate Exercise Preconditioning?

Various factors might mediate exercise preconditioning. Of these, variations in exercise-induced ischemia, exercise quality or type, and exercise intensity require further exploration.

Based on our understanding of classic preconditioning, ischemia may be obligatory for exercise preconditioning. Nevertheless, studies directly examining this hypothesis provide little support for this idea. First, repeated exposure to tachycardia, in the absence of ischemia, reduced myocardial infarct size in a canine model.<sup>71</sup> Second, exercise is associated with the release of several hormones, including well-known factors that trigger ischemic preconditioning (eg, adenosine, bradykinin, and opioids). Although these hormones are released in a dose-dependent manner, an episode of moderate-intensity exercise (ie, below the lactate threshold) already releases these hormones. Finally, moderate-intensity exercise has shown to evoke infarct-sparing effects.<sup>72,73</sup> These data suggest that presence of ischemia during exercise is not obligatory for cardioprotection via exercise preconditioning.

To our knowledge, no previous studies have compared the effect of different modes of exercise (eg, swimming and running), while some explored the importance of performing moderate-intensity endurance vs high-intensity interval exercise. A study performed in rats<sup>74</sup> found that 6 weeks of high-intensity sprint interval training, but not endurance training, were associated with improved tolerance to myocardial ischemia-reperfusion. Nevertheless, the relatively low intensity of the endurance exercise might have confounded these effects. In a 2015 study in humans,<sup>51</sup> the effect of acute exercise to protect against endothelial ischemia-reperfusion injury was compared between high-intensity interval exercise and (isocaloric) moderate-intensity endurance exercise. In line with observations in animals, interval exercise, but not endurance exercise, prevented endothelial ischemia-reperfusion injury of the brachial artery. These results suggest that interval exercise might yield larger benefits than endurance exercise. However, follow-up studies, including intervention studies that include both types of exercise for prolonged periods in humans, are required to better understand these effects.

To our knowledge, only 2 studies have directly compared the effects of different exercise intensities to precondition the heart. Bowles et al<sup>72</sup> examined the effect on rats of exercise training at low (60 min/d at 20 m/min on a flat surface), moderate (60 min/d at 30 m/min on a 5% grade) and high (10 episodes of 2 minutes at 60 m/min on a 5% grade) intensities for 11 to 16 weeks. Independen-

dent of the intensity, exercise successfully mediated intrinsic adaptation that allowed for greater recovery of cardiac output after myocardial ischemia. In line with these observations, another study in animals found comparable myocardial protection against ischemia-reperfusion injury after moderate-intensity exercise training (60 min/d at 55% maximal oxygen consumption) or high-intensity exercise training (60 min/d at 75% maximal oxygen consumption).<sup>73</sup> These studies suggest that the intensity of exercise does not alter the magnitude of cardioprotection. That said, we cannot exclude that other factors, such as the time course of adaptation, may have influenced these results.<sup>7</sup>

## Future Perspective

Exercise preconditioning represents an attractive explanation for the immediate cardioprotective effects evoked by exercise, which may be present after a single episode or a few episodes of exercise. The concept of exercise preconditioning is underrecognized, even while emerging evidence supports its presence in the heart and other organs. For example, a 2014 meta-analysis<sup>75</sup> including studies performed in animals that underwent cerebral ischemic injury revealed that exercise was associated with a 25% smaller cerebral infarct size and 38% better neurobehavioral score. This further supports the validity and clinical relevance of exercise preconditioning to explain the immediate protective benefits of exercise training.

An important area of future research relates to translating this knowledge to clinical scenarios. First, knowledge on exercise preconditioning will contribute to the evidence-based prescription of exercise (eg, clinical guidelines and cost-effectiveness planning), and it will also contribute to health promotion to patients. Second, this knowledge will alter expectations from both patients and clini-

cians, in that strong and sustainable cardioprotective effects are present after episodes of exercise, even in the absence of changes in CVD risk factors. This will help to motivate patients to start and continue exercise training and will provide impetus for clinicians to recommend exercise as a first-line and lifelong treatment. Finally, the immediate benefits of preconditioning achieved through a few sessions of exercise can initiate novel training strategies. For example, exercise in the days preceding planned cardiac interventions (“prehabilitation”) may reduce in-hospital mortality and morbidity.

## Conclusions

This review discusses the concept of exercise preconditioning, which indicates that on the start of regular exercise, potent cardioprotection may be found. Exercise induces a cardioprotective preconditioning stimulus with early protection of the cardiovascular system for 2 to 3 hours and a more robust and longer period of protection that emerges after 24 hours and remains for several days. Importantly, these associations are present on the first episode of exercise, with subsequent exercise sessions reactivating protective pathways and leading to ongoing beneficial effects with myocardial ischemia. In practical terms, this suggests that cardioprotection in individuals who start exercising begins after the first training episode. Although moderating factors (eg, obesity and age) impair the immediate preconditioning associations with exercise, regular training may restore these protective responses. Taken together, cardioprotection through exercise preconditioning is a facile, inexpensive, and potent therapy that deserves greater recognition and further resources to establish the optimal dose. Nonetheless, as is so often the case with the benefits of exercise, its prescription follows the cardinal rule: use it or lose it.

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