

# **Immediate Cardioprotective Benefits of Exercise**

## **Preconditioning: A Review**

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**ABSTRACT**

**Importance:** Long-term exercise training reduces the risk of future cardiovascular events but these cardioprotective benefits are only partly explained via gradual, but modest, improvement in cardiovascular risk factors and/or physiological remodelling of arteries.

**Observations:** Noteworthy, preclinical work shows that 1-3 episodes of exercise (with 1-3 days rest between subsequent episodes) provide strong cardioprotection which largely precludes cardiovascular risk factor modification or physiological adaptive responses as an explanation for the acute cardiovascular benefits of exercise. This review highlights the pre-clinical evidence that exercise has preconditioning effects that induce immediate protection against ischaemic myocardial injury and the severity of ischaemic cardiovascular events. The phenomenon of preconditioning refers to the ability of acute exercise to activate multiple pathways that confer immediate protection against potentially lethal ischaemic cardiac injury. To translate these pre-clinical observations to clinical benefits, we introduce the concept that exercise preconditioning represents a “first line of defense mechanism” that mitigates the impact of cardiovascular events.

**Conclusions and Relevance.** Therefore, independently from the protective benefits of chronic exercise training on risk factors and adaptation of the cardiovascular system, exercise preconditioning contributes to the immediate cardioprotective effects of exercise. Practically, this means that one episode of exercise can mediate clinically relevant cardioprotective effects.

**KEY WORDS:** cardiovascular risk; exercise training; rehabilitation; coronary artery disease

An important preventable factor for the development and progression of cardiovascular disease (CVD) is physical inactivity. A physically active lifestyle leads to a reduction in development of CVD by 42-44% (i.e. primary prevention),<sup>1,2</sup> but also reduces CVD mortality and hospital admissions in those who develop CVD (i.e. secondary prevention).<sup>3</sup> For example, 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 some of the drug interventions in several studies.<sup>5</sup>

The cardioprotective effect partly relate to the marked physiological adaptive responses of the heart and coronary arteries (**Figure 1**),<sup>6</sup> which may occur within weeks.<sup>7</sup> Training also improves CVD risk factors, although the capacity of exercise training to alter these factors is modest and takes several months to establish (**Figure 1**). It is estimated that these risk factors together explain only 27-41% 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 factors.

This review summarises evidence supporting the idea that exercise is a form of preconditioning that attenuates the detrimental impacts of ischemia. Ischaemic preconditioning refers to the observation, both observed in animals and humans, that brief periods of ischemia before prolonged occlusion reduces subsequent infarct size and/or the risk for malignant ventricular arrhythmias.<sup>9</sup> Interestingly, studies performed in animals found marked cardioprotection within 1-5 days after acute exercise,<sup>10-12</sup> a

time-course too short to induce physiological adaptation and/or improvement in traditional cardiovascular risk factors. Therefore, we explore the widely under-recognized hypothesis that exercise induces preconditioning, subsequently leading to immediate cardioprotection.<sup>13</sup>

We will first summarise evidence from population-based studies that support the impact of acute exercise preconditioning on clinical events. Subsequently, studies in animals and humans will be summarized that explore the acute impact of exercise preconditioning on the cardiovascular system and how these effects might translate to clinical relevant scenarios. Understanding the immediate cardiovascular benefits of exercise preconditioning will help to develop strategies in the primary and secondary prevention of CVD. More specifically, the concept of exercise preconditioning indicates that, after engagement in regular exercise, cardioprotective effects occur well before any changes in CVD risk factors. This suggests that clinically relevant cardioprotective effects are present after one episode of exercise.

## **WHAT IS THE EVIDENCE FOR EXERCISE PRECONDITIONING?**

### **Can the heart be preconditioned?**

In 1986, Murry *et al.* introduced the concept of ischaemic preconditioning, which involves 3-4 brief periods of ischemia, typically induced by 5-minute occlusion of an artery through surgical ligation or limb occlusion (>50 mmHg above systolic pressure), which is interspersed by 5-minutes of tissue reperfusion. To examine the impact of preconditioning in animals, studies typically perform post-mortem histologic analysis to examine the infarct size relative to the area-at-risk (i.e. the area perfused by the artery

that was occluded). Murry found that ischaemic preconditioning resulted in a ~75% smaller infarct size than in the control condition.<sup>14</sup> 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 that resulted in the clinical application of ischaemic preconditioning of a limb to protect *remote* tissues, such as the heart, against ischaemic events.<sup>16</sup> The reduction of myocardial damage by remote preconditioning, including improvement in clinical outcomes, has 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 coronary artery disease.

### **Can acute exercise precondition the heart?**

An acute episode of exercise is characterized by intermittent exposure to local effects on exercising muscles or systematic effects on myocardial ischemia. This similarity in stimuli with ischaemic preconditioning supports the idea that acute exercise represents a form of preconditioning with the potential of mediating similar cardioprotective effects.<sup>9,19</sup> Another important similarity is the temporal nature in cardioprotection observed with an acute episode of exercise and ischaemic preconditioning. Classic ischaemic preconditioning shows potent early protection (i.e. disappearing ~2-4 hr after the stimulus) and a somewhat lesser degree of late protection which reappears after ~24 hr and can last for several days.<sup>20,21</sup> Interestingly, exercise also elicits this characteristic biphasic response in protection. A study in rats found that 30-min of running exercise evoked immediate reduction in infarct size, which was subsequently

lost and reappeared 36-60 h after exercise.<sup>22</sup> Others have also reported the characteristic biphasic protection in 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 patients?**

The ability of exercise to precondition the heart was first suggested over 200 years ago, when it was observed that exercise-induced ischemia (i.e. clinical complaints like angina) was significantly reduced or even abolished on the second effort.<sup>24</sup> Several subsequent studies have confirmed this observation; so-called 'warm-up' angina. In addition to clinical symptoms, exercise-induced ischemia can also be quantified using electrocardiographic ST-segment depression. A meta-analysis, based on 34 studies and 1,053 patients, reported a significantly later onset of ST depression (91 s) and a decrease in peak ST depression (-0.38 mm) on the second exercise stress test during sequential testing.<sup>25</sup> This supports the ability of exercise to induce immediate attenuation of cardiac ischemia. Pre-clinical work 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 ischaemic preconditioning, 'warm-up' angina shows biphasic protection. The reductions in ST segment depression and onset of angina during the second episode of exercise were evident in the first 6-h, and subsequently returned 24-h after exercise.<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.* was one of the first to examine if an acute episode of exercise can reduce ischaemic myocardial injury.<sup>22</sup> A single episode of exercise prior to ischaemic myocardial injury reduced damage to the heart in a biphasic manner, indicating early and late protection. In a follow-up study, they confirmed that exercise protects the myocardium from ischemia-reperfusion injury 24-h after cessation of the episode of exercise.<sup>29</sup> In a series of studies, Domenech and co-workers explored if intermittent exercise resulted in early and late cardiac precondition.<sup>30</sup> They found that exercise prior to coronary occlusion induces early and late precondition, leading to a reduction in infarct size of 46-52<sup>30,31</sup> and 56-78%,<sup>30-32</sup> respectively.

The underlying mechanisms of exercise preconditioning were examined in a novel human-to-animal crossover study. Michelsen and colleagues examined healthy individuals who underwent exercise (intermittent running, 4 episodes of 2-min running exercise) and ischaemic preconditioning (4x5-min arterial occlusion using blood pressure cuffs).<sup>33</sup> Blood was taken after preconditioning and dialysate was used to perfuse a rabbit heart Langendorff-model of myocardial infarction, subsequently followed by 40-min occlusion of a coronary artery and assessment of the infarct size relative to the area-at-risk. Exercise and ischaemic preconditioning both reduced infarct size by ~50%. To understand the underlying mechanisms, analyses were repeated with co-administration of an opioid receptor antagonist, which abrogated the protective effects of exercise and ischaemic 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 recently confirmed by others.<sup>34</sup> This latter study found that protection of exercise-induced cardiac ischemia-reperfusion injury was abolished during infusion of ( $\delta$ )opioid-receptor blockers.

### **Does acute exercise reduce infarct size in humans?**

In a series of studies, Rengo *et al.* retrospectively assessed subjective physical activity patterns in the week before a myocardial infarction.<sup>35,36</sup> They found that greater physical activity levels in the week preceding an event was associated with lower in-hospital mortality and nonfatal cardiac events. Similarly, engaging in physical activity in the week prior to coronary artery bypass grafting was linked to better survival.<sup>37</sup> Finally, repetitive exercise with brief rest periods in patients with significant coronary artery disease attenuated the degree of myocardial stunning.<sup>38</sup> Unfortunately, these studies have not corrected for physical activity patterns, which makes it difficult to differentiate between physical activity patterns *per se* and physical activity in the days preceding an event. Until clinical studies in humans are performed with distinct physical activity patterns before ischaemic injury, it will remain difficult to truly answer this question.

## **CAN ACUTE EXERCISE PRECONDITION THE CARDIOVASCULAR SYSTEM?**

### **Can exercise training precondition arteries?**

*Animals.* The first study to describe the cardioprotective effects of exercise preconditioning was published in 1978 and demonstrated that 5-weeks of swim training in rats resulted in a smaller myocardial infarct size.<sup>39</sup> Several subsequent



studies in animals have supported these original findings. These studies adopted 2-12 weeks of regular (5-7 days/week) exercise training, involving running or swim training, and consistently reported significantly smaller infarct sizes than in their sedentary counterparts.<sup>12,40-45</sup> 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 1-week after cessation of 4-week exercise training,<sup>47</sup> supporting the sustainability of these benefits. This study also revealed that nitric oxide (NO) metabolites contribute to the sustained cardioprotective effects. More specifically, exercise upregulated cardiac endothelial NO synthase, resulting in increased storage of NO metabolites (nitrite and nitrosothiols) that may contribute to an increase in NO bioavailability during myocardial injury.

Studies in animals are importantly limited by the difficulty around extrapolation to humans with CVD. Another limitation of animal studies examining exercise preconditioning is that most studies only present infarct size. However, several investigators have explored the functional consequences. For example, surgical ligation of the left coronary artery was performed after 7 weeks of swimming exercise training. After another 4 weeks to allow for recovery, exercise-trained rats demonstrated smaller scar size and higher arteriole density, which was associated with improved cardiac function on *in vivo* echocardiography.<sup>48</sup> The ability of exercise training to prevent post-infarct cardiac dysfunction was supported by others, while these benefits further translated to improved survival.<sup>12</sup> Interestingly, improved survival was not present in

mice that were trained *after* myocardial injury.<sup>12</sup> This suggests that prior exercise can both improve cardiac function, but also survival, after ischaemic cardiac injury.

*Humans.* A model frequently used in humans to study ischemia-reperfusion injury applies prolonged ischemia to the forearm through 15-20 minutes of cuff inflation around the upper arm, followed by 15-20 minutes of reperfusion. This leads to a decrease in brachial artery endothelial function, which is prevented when preceded by ischaemic preconditioning.<sup>49</sup> Although the forearm vasculature shows good agreement with coronary vascular responses,<sup>50</sup> care is warranted to extrapolate these findings to cardiac tissue. Using this model, Seeger *et al.* explored the ability of exercise, similar to limb-ischaemic preconditioning, to prevent endothelial ischemia-reperfusion injury *in vivo*.<sup>51</sup> A single episode of interval, 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 this was evident during interval exercise.<sup>51</sup> Nevertheless, Brunt *et al.* recently reported that single exposure to warm water immersion, a stimulus not associated with ischemia, prevented endothelial ischemia-reperfusion injury.<sup>52</sup> This suggests that the potential mechanisms underlying exercise preconditioning may not simply relate to ischemia alone.

A previous cross-sectional study in humans found that the magnitude of brachial artery endothelial ischemia-reperfusion injury was lower in those engaged in habitual resistance exercise.<sup>53</sup> In a follow-up study, the same researchers compared endothelial

ischemia-reperfusion injury between young and middle-aged endurance-trained versus sedentary individuals.<sup>54</sup> They reported that middle-aged individuals had greater endothelial ischemia-reperfusion injury, while habitual endurance exercise partly protected against these age-related effects. Recently, Maessen *et al.* provided further evidence that long-term exercise training can prevent ischemia-reperfusion injury.<sup>55</sup> They found that lifelong athletes had reduced endothelial ischemia-reperfusion injury and preserved local preconditioning efficacy, compared to their sedentary peers. This would suggest that, in line with animal studies, exercise training reduces ischemia-reperfusion injury in humans and, accordingly, that 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/or coronary artery responses.

### **What is the time course of training-induced myocardial preconditioning?**

Experimental studies in animals have demonstrated remarkable potency of exercise preconditioning to mediate rapid cardioprotection. In addition to the immediate cardioprotection after a single episode of exercise, 5-7 days of exercise training also evokes strong cardioprotective effects, demonstrated by a significantly smaller infarct size<sup>56,57</sup> and better post-ischaemic recovery (i.e. myocardial contractile performance).<sup>10</sup> Also 3 days of 60-min exercise per day is sufficient to induce cardioprotective effects, evidenced by smaller infarct size<sup>58,59</sup> and better post-injury recovery.<sup>10,11,60</sup> Given these effects of short-term training, one may question whether the duration of training affects the ability to reduce infarct size. To examine this question, Sun *et al.* compared effects of 3-day vs 3-week intermittent running exercise in rats.<sup>42</sup> Using isoproterenol-induced

cardiac injury, no differences in myocardial damage were observed between 3-days or 3-weeks training. These latter data further support the concept that exercise training-induced preconditioning occurs immediately, and that benefits are independent of the duration of training. Since these studies showed no structural adaptation, this further supports exercise preconditioning as an explanation for immediate cardioprotection upon (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 whether the cardioprotective effects of repeated exercise preconditioning are summative or 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-days or 4-weeks preserved cardioprotection up to 7-9 days after the last episode of exercise.<sup>23,47</sup> This is longer than 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 post-exercise.<sup>61</sup> While the duration of protection is somewhat unclear, these studies suggest that cardioprotective effect of a single episode of exercise may be prolonged when followed by continuing exercise training.

To more directly examine this topic, one study found that 2-weeks of running exercise in mice was associated with increased myocardial tolerance against ischemia-reperfusion injury.<sup>62</sup> Although these effects were lost after 1-week of inactivity, 1-3 days of exercise fully restored the cardioprotective effects. The comparable effects of 2-weeks training vs. 1-3 episodes of exercise were paralleled by changes in glycogen synthase kinase3beta and epidermal growth factor receptor, proteins related to injury and survival, respectively.<sup>62</sup> However, other proteins related to survival were upregulated after 2-weeks of training (AKT, AMP-activated protein kinase, heat shock protein-27), but remained unaltered upon 1-3 episodes of exercise. In another study, the time-course of a single and 2 subsequent episodes of exercise were explored.<sup>61</sup> The single episode of exercise showed the typical biphasic pattern of cardioprotection, whereas two episodes of exercise (separated by 48-h) resulted in protection that was consistently present across the 60-h 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 may, 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 upregulation of pro-survival signalling pathways, increase in kinase phosphorylation, decreased levels of phosphates and increased resistance of mitochondrial permeability transition pore-opening.<sup>64-66</sup> Since no impact of 4-week exercise training was found on glucose, cholesterol, insulin, fat mass or body mass,<sup>66</sup> restoration of preconditioning occur 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 ischaemic 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.* found that in trained older rats, but not in sedentary older rats, local preconditioning reduced post-ischemic myocardial injury.<sup>68</sup> This study also revealed an important role for exercise-induced release of norepinephrine, since these effects of training were abolished when blocking exercise-induced release of norepinephrine.<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 recent 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?**

*Exercise-induced ischemia.* 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. Firstly, repeated exposure to tachycardia, in the absence of ischemia, reduced myocardial infarct size in a canine model.<sup>71</sup> Secondly, exercise is associated with the release of several hormones, including well-known factors that trigger ischaemic preconditioning (e.g. adenosine, bradykinin, opioids). Although these hormones are released in a dose-dependent manner, an episode of moderate-intensity exercise (i.e. 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.

*Characteristics of exercise.* No previous studies have compared the impact of different modes of exercise (i.e. swimming, running), while some explored the importance of performing moderate-intensity endurance vs high-intensity interval exercise. A study performed in rats, found that 6-weeks of high-intensity sprint interval training, but not endurance training, was associated with improved tolerance to myocardial ischemia-reperfusion.<sup>74</sup> Nevertheless, the relatively low intensity of endurance exercise training may have confounded these effects. In a more recent study in humans, the impact 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.<sup>51</sup>

These results suggest that interval exercise may 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.

*Intensity of exercise.* To date, only 2 studies have directly compared the impact of different exercise intensities to precondition the heart. Bowles *et al.*<sup>72</sup> examined the effect of 11-16 week exercise training in rats that underwent exercise at low (60-min/day at 20 m/min), moderate (60-min/day at 30 m/min with 5% grade) and high intensity (10 episodes of 2-min at 60 m/min at 5% grade). Independent of the intensity, exercise training 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 (60-min/day at 55% maximal oxygen consumption ( $VO_{2max}$ )) or high-intensity exercise training (60-min/day at 75%  $VO_{2max}$ ).<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 AND CONCLUSIONS**

Exercise preconditioning represents an attractive explanation for immediate cardioprotective effects evoked by exercise, which are already present after a single or few episodes of exercise. The concept of exercise preconditioning is under-recognized,



while emerging evidence supports its presence in the heart, and also in other organs. For example, a recent meta-analysis including studies performed in animals that underwent cerebral ischaemic injury revealed that exercise was associated with a 25% smaller cerebral infarct size and 38% better neurobehavioural score.<sup>75</sup> This further supports the validity and (clinical) relevance of exercise preconditioning to explain the immediate protective benefits of exercise training.

*Future perspective.* 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 (e.g. guidelines, cost-effectiveness), but also regarding promotion to patients. Second, this knowledge will also manage expectations from both patient and clinician, in that strong and sustainable cardioprotection is present after episodes of exercise, effects that are found in the absence of changes in CVD risk factors. This will help to motivate patients to start and continue exercise training and provide impetus for clinicians to recommend exercise as a first line *and* life-long treatment. Finally, the immediate benefits of exercise preconditioning achieved through a few sessions of exercise can initiate novel exercise training strategies. For example, exercise in the days preceding planned cardiac interventions (“prehabilitation”) may reduce (in-hospital) mortality and morbidity.

*Conclusion.* This review discusses the concept of “exercise preconditioning”, which indicates that upon the start of regular exercise, potent cardioprotective effects are found. Exercise induces a cardioprotective ‘preconditioning’ stimulus, with early protection for 2-3 hours and a more robust and longer period of late protection after

24-h that remains for several days. Importantly, these effects are present upon the first episode of exercise, with subsequent exercise sessions reactivating protective pathways leading to ongoing beneficial effects against myocardial ischemia. Practically, this suggests that cardioprotective effects in subjects who start exercise training begin after the first training episode. Although moderating effects (e.g. obesity, age) impair the immediate preconditioning effects of exercise, regular exercise training restores 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 golden rule: Use it or lose it!

## CONFLICTS

The authors have no conflicts of interest

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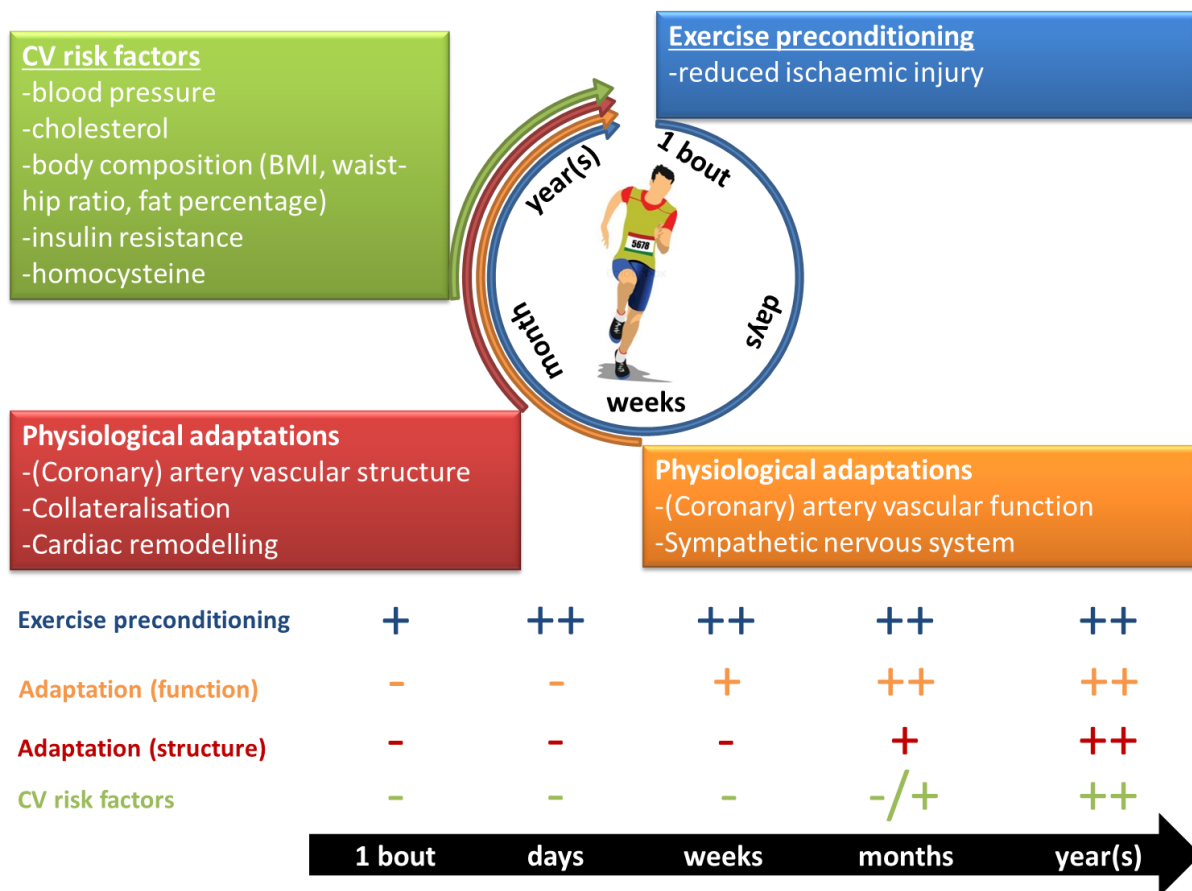
**FIGURE LEGENDS**

**FIGURE 1.** Time-dependent benefits of exercise training that contribute to the protection against cardiovascular events, which relate to immediate (blue: effect of a single episode of exercise via exercise preconditioning), short-term (orange: weeks of exercise, mediated through physiological adaptations in function), medium-term (red: months of training, which induces physiological adaptations in structure) and long-term (green: year(s) of training, leading to improvement in cardiovascular (CV) risk factors).

**FIGURE 2.** Proposed cardioprotection via exercise preconditioning from a single episode of exercise (A, blue), two subsequent episodes of exercise (B, red, protection from the 2<sup>nd</sup> episode indicated with the dashed lines), and during chronic exercise training (C, green, protection from individual episodes are indicated with the dashed lines).



Figure 1.



**Figure 2.**