Exercise Preconditioning as a Cardioprotective Phenotype

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Cardiovascular disease (CVD) is potentiated by risk factors including physical inactivity and remains a leading cause of morbidity and mortality. Although regular physical activity does not reverse atherosclerotic coronary disease, precursory exercise improves clinical outcomes in those experiencing life-threatening CVD events. *Exercise preconditioning* describes the cardioprotective phenotype whereby even a few exercise bouts confer short-term multifaceted protection against acute myocardial infarction. First described decades ago in animal investigations, cardioprotective mechanisms responsible for exercise preconditioning have been identified through reductionist preclinical studies, including the upregulation of endogenous antioxidant enzymes, improved calcium handling, and enhanced bioenergetic regulation during a supply-demand mismatch. Until recently, translation of this research was only inferred from clinically-directed animal models of exercise involving ischemia-reperfusion injury, and reinforced by the gene products of exercise preconditioning that are common to mammalian species. However, recent clinical investigations confirm that exercise preconditions the human heart. This discovery means that simply the initiation of a remedial exercise regimen in those with abnormal CVD risk factor profiles will provide *immediate* cardioprotective benefits and improved clinical outcomes following acute cardiac events. In conclusion, the prophylactic biochemical adaptations to aerobic exercise are complemented by the long-term adaptive benefits of vascular and architectural remodeling in those who adopt a physically active lifestyle. **(Am J Cardiol 2021;148:8−15)**

Sedentary behavior is one of the most preventable causative factors for cardiovascular disease (CVD), while habitual, structured physical activity (PA) is one of the most potent countermeasures in treating and preventing CVD. PA confers a cardioprotected phenotype which includes anti-atherosclerotic, anti-thrombotic, anti-ischemic, and anti-arrhythmic effects (Figure 1). Recent discoveries reveal that the immediate cardioprotective impact of short-term exercise includes transient biochemical upregulation of protective cellular mediators, a phenomenon termed *exercise preconditioning*, as a prophylactic therapy for acute coronary events. Because this subfield is based on a wealth of preclinical investigations, the clinical relevance of exercise and ischemic models from animal-based studies are reviewed. Next, emergent translational applications are detailed as confirmation that exercise cardiac preconditioning enhances clinical outcomes. Finally, we discuss the practical introduction of lifestyle PA, in addition to structured exercise, in the medical management of previously sedentary individuals at high risk for CVD.

Practical Relevance of Preclinical Investigations on Exercise Preconditioning

Exercise preconditioning is a line of scientific inquiry into the short-term biochemical mediators of cardioprotection in exercised hearts. Relative to scientific lineage, exercise preconditioning evolved from the 1986 discovery of *ischemic* preconditioning, the observation that conditioned animal hearts could be rendered resilient to acute myocardial infarction (AMI) within hours following sub-lethal bouts of coronary artery ligation.[1] The time needed to acquire a preconditioned phenotype following the adaptive stimulus (due to exercise or ischemia) is on the order of hours. This finding highlights the fundamental conclusion that cardiac preconditioning necessitates upregulation, or allosteric control, of endogenous biochemical mediators of protection.[2,3] Once evoked, the endogenous protective mediators work in concert to strategically counter the associated mechanisms of myocardial injury during AMI.

An ischemia reperfusion insult is characterized by cellular oxidative stress, cytosolic (and mitochondrial) calcium overload, and bioenergetic dysregulation. From a cellular perspective, these 3 facets of ischemic pathology are biologically intertwined, with oxidative stress and calcium dysregulation being subsequent to the bioenergetic crisis caused by cardiac ischemia. Accordingly, the mechanisms responsible for ischemic resilience in the preconditioned heart include: antioxidant enzyme fortification; prevention of calcium dyshomeostasis through bolstered calcium regulation; and, improvements in bioenergetic supply-demand ratios.[2,3] The mechanisms of exercise preconditioning have

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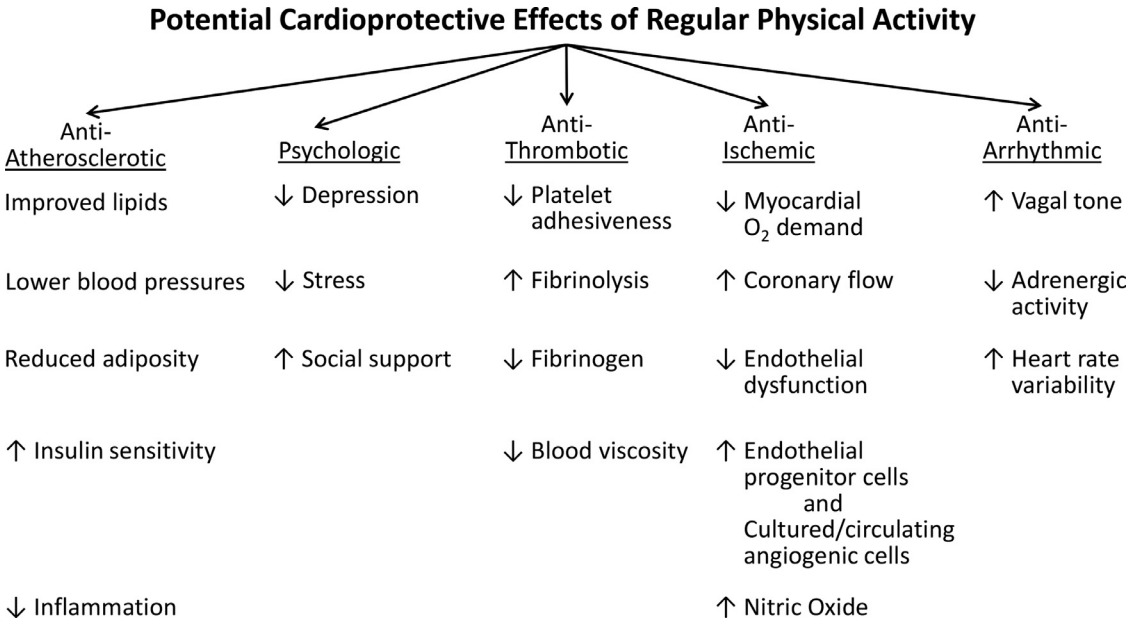

Figure 1. Multiple mechanisms by which moderate-to-vigorous physical activity may reduce the risk of initial and recurrent cardiovascular events; ↑ = increased, ↓ = decreased, O_2 = oxygen.

been previously described.[3-5] Related studies demonstrate that intracellular processes of cardioprotection appear to be activated through receptor-mediated, autocrine/paracrine pathways, due to multiple circulating factors including endogenous opioids and interleukin-6.[6,7] Importantly, the mechanisms responsible for the exercise preconditioning effects described herein are gene products common to mammalian species. Moreover, exercise preconditioning induces a phenotype which is largely unique and in contrast to the protective mediators conferred by ischemic preconditioning. Mechanistic differences between the exercise and ischemia stimuli are founded on the fact that the former is a sustainable hermetic stress,[4,5] whereas the latter is transient.[8]

The unique features, and clinical relevance, of the exercise stimulus was advanced by the observation that rats exposed to 3 days of moderate intensity treadmill running were equally protected against a surgically induced MI as compared with rats that performed several months of exercise training.[9,10] A subsequent investigation by different investigators, also using treadmill run rats, found that preconditioning against ischemia-reperfusion (IR) injury could be evoked by as little as a single bout of exercise, further highlighting the temporal nature of biochemical cardioprotection.[11] Subsequently, it was discovered that MI resistant phenotype lasted for at least 9 days following the final bout of a 3-day moderate intensity exercise regimen.[12]

With respect to clinical applicability, it was important to clarify, "*how much exercise is needed to precondition a heart?*" The encouraging answer, derived from a series of animal studies, suggests that even a minimal amount of exercise provides robust cardioprotection against an ischemic insult. To understand this finding, several aspects of the animal "exercise prescription" should be considered. First, across different animal species (albeit mostly rodents), performed by independent research groups, the exercise modalities used to precondition hearts have been experimentally designed to parallel human exercise recommendations. Thus, within these research studies, exercise frequency generally varied from 3 days/week to daily sessions. The employed cardiovascular exercise intensities ranged from ~50% to 75% of aerobic capacity (VO_{2max}) for that particular animal species. In addition, the duration of an individual exercise session ranged from 30 to 60 minutes. These research applications of animal exercise as compared with humans are illustrated in Figure 2. Finally, the exercise modalities common to cardiac preconditioning research studies include forced running on treadmills or other rodent ergometers, swimming, or ladder climbing. Although most of the previously reported investigations used aerobic exercise, researchers found that a rodent model of strength training also provided significant cardioprotection against an experimental infarction challenge.[3-5,13]

A second important aspect of clinical relevance derived from preclinical exercise preconditioning studies is that there appears to be an intensity threshold, above which the heart becomes preconditioned. Evidence for this conclusion was primarily derived from 2 different studies by independent laboratory groups working in parallel on exercise preconditioning in the early 2000s. The first observation was that regimented exercise below a moderate intensity (~50% VO_{2max}) does not protect against experimental MI in isolated perfused rodent hearts.[14,15] The second observation revealed that while moderate intensity exercise cardioprotects against AMI, higher intensity exercise does not bolster the magnitude of protection in a dose-dependent fashion. Accordingly, the biochemical mechanisms of protection are activated in a threshold-dependent fashion within exercise hearts.[15] Moreover, it cannot be inferred that higher exercise volumes (or cumulative doses of PA), performed at a low intensity relative to VO_{2max}, aren't

Frequency – whether short-duration (days/weeks) or long-duration (weeks/months), animal studies typically prescribe 3-5 exercise sessions/week.

Intensity – regimented forced exercise typically ranges from a relative intensity of 50%-75% of a known VO_2peak for various animal species

Time (duration) – exercise session duration typically ranges from 30 minutes - 60 minutes.

Type (modality) – exercise modalities include treadmill running, swimming, ladder climbing, and rodent exercise ergometers (e.g., rodent rotarods).

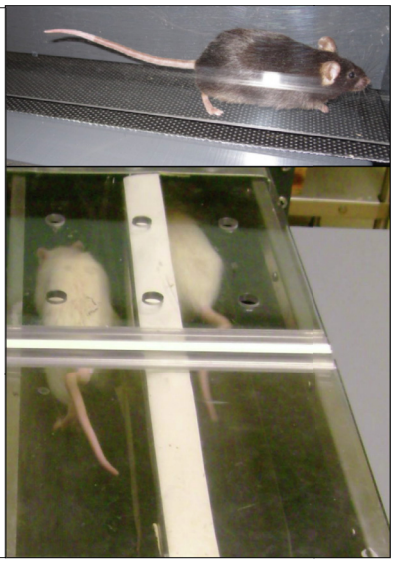

Figure 2. Clinical applicability of exercise and physical activity models used in exercise preconditioning studies. **Left** Exercise is typically prescribed for preclinical animal studies using the principle of Frequency, Intensity, Time, and Type (F.I.T.T.). The F.I.T.T. principle approach to cardioprotective exercise in animal models reflects a conscious scientific effort to parallel the elements of a human exercise prescription. **Right** Representative images of mouse (top) and rats (bottom) exercising on rodent treadmills.

cardioprotective. Although this requires additional research, cardioprotection afforded by long duration PA (<50% VO_{2max}) would also likely manifest in a threshold dependent fashion.

Another tested hypothesis in animal exercise models is that forced, regimented exercise is not required to precondition the heart. A series of studies examined whether rodents provided free access to running wheels would self-select PA the extent that their hearts would be preconditioned against IR injury. Findings indicated ventricular ectopy was attenuated during experimental MI, and myocardial bioenergetic status was preserved in the animals with running wheel access.[16,17] However, these findings cannot necessarily be generalized to clinical applications in that rodent behavior on running wheels does not replicate spontaneous PA in most humans. That is, rodents typically sprint on the running wheels for dozens of 30-60 second bouts spread throughout a 24-hour period. Other evidence, however, suggests that PA performed by rodents on running wheels may equate to humans in that the 24-hour cumulative distance run by rodents with access to a running wheel is comparable to the assigned distance run during forced exercise (i.e., equal to the distance covered for 30 to 60 minutes at 50% of VO_2 max).[4,18] Although lacking confirmation, it is tempting to speculate that biological signals prompt animals to self-select a volume of PA that elicits a cardioprotected phenotype. Nonetheless, scientific verification indicates that accumulating discontinuous bouts of daily PA will precondition the heart if the intensity of movement is sufficient. In this regard, we recently employed ethnographic models (counts of typical species behaviors) of quantifying daily PA in rodents, ranging from activities of daily living to high intensity running and jumping.[19,20] As applied to humans, these approaches to prescribing and implementing cardioprotective levels of PA in preclinical animal studies have relevance for mobilizing sedentary populations at risk for CVD.

Lastly, animal studies of preclinical exercise preconditioning are reinforced by investigations which employ quantification metrics of CVD that parallel clinical applications. IR injury is an evolutionary pathology, characterized by the appearance of electrocardiographic (ECG) abnormalities within moments of significant coronary artery occlusion. Prolonged ischemia then causes deficits in ventricular pump function, while ECG profiles worsen. Finally, unremitting ischemia results in cardiomyocyte death due to either necrotic or apoptotic processes.[2,4,5,13]

Induction of an experimental MI is most commonly performed via ligation of the left anterior descending coronary. The heart is accessed through a left thoracotomy in anesthetized and mechanically ventilated animals. Another common approach is to perform either regional or global ischemia using isolated perfused hearts from animals assigned to sedentary or exercise groups. Advantages to the former *in vivo* technique is that the animal is fully "intact," and subject to the pathological influences of the circulating factors and immune system responses. Advantages to the latter, that is, isolated perfused heart technique, is that preload and afterload can be precisely controlled, providing essential insights into ventricular function during MI.[3,4,13] Regardless of the methodology, exercise preconditioning remains one of the most scientifically reproducible observations in animal models, independent of age, sex, strain, or species.[13,21,22]

Preclinical approaches to quantify myocardial injury and tissue death due to IR are similar to those used in humans. ECG tracings are obtained from limb electrodes provide identical lead options to humans, typically defaulting to a lead II configuration. Assessments typically involve arrhythmia scoring rubrics, including ventricular ectopy.[23]

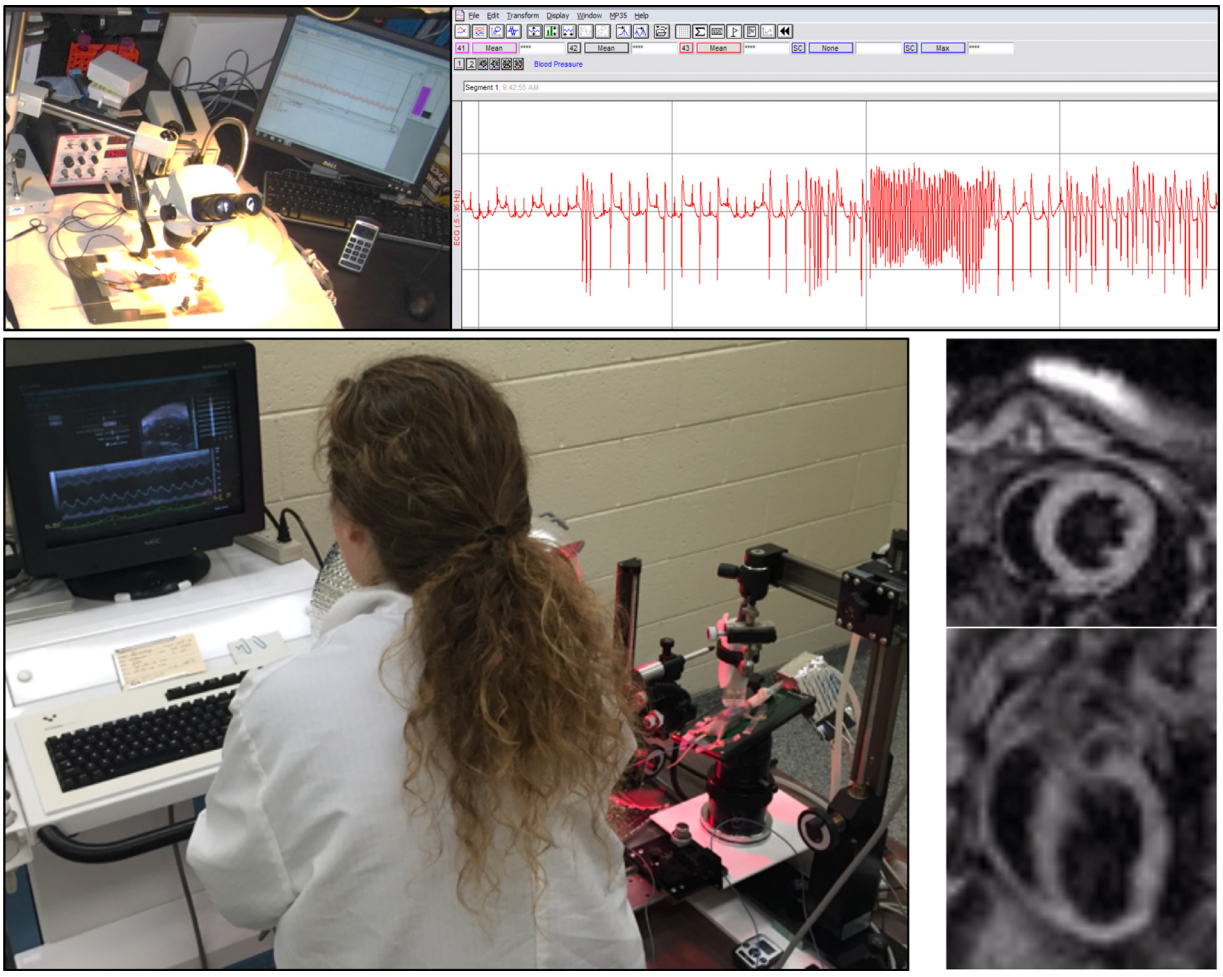

Figure 3. Clinical applicability of experimental models of myocardial ischemia reperfusion injury and cardiac imaging. Surgical induction of myocardial ischemia reperfusion injury, *in vivo* is a common experimental means of replicating MI as experienced in humans. **Upper left image** - an anesthetized mouse receives mechanical ventilation prior to a left thoracotomy and subsequent ligation of the left anterior descending coronary artery. Blood pressure and ECG tracings are recorded in real time from indwelling catheters and limb electrodes. **Upper right image** - A representative screen shot of ventricular ectopy during surgical MI reveals normal sinus rhythm (at high basal rodent heart rates) followed by bigeminal PVCs, ventricular fibrillation, and ventricular tachycardia. **Lower left image** - Short axis and long axis views of (anesthetized) rodent hearts visualized using high strength magnetic resonance imaging techniques. **Lower right image** – a technician performs transthoracic cardiac echocardiography in an anesthetized mouse.

Ventricular performance can be quantified using clinical imaging techniques (e.g., transthoracic echocardiography, magnetic resonance imaging) or implanted arterial catheters. Figure 3 illustrates several common experimental approaches in our preconditioned animal studies which parallel clinical outcomes.

Finally, use of animal models has proven essential for uncovering the mechanisms of tissue death due to AMI. While the clinical standards for circulating biomarkers of cardiac injury (e.g., cardiac specific troponin, cTnT) are also common to animal-based exercise preconditioning studies, it is the post mortem analyses from the harvesting of heart tissues that can be most revealing. Indeed, the cellular processes of necrosis, apoptosis, and even the contribution of autophagy, have been partially resolved from post mortem histological, biochemical, and molecular examination of hearts generated from exercise preconditioning studies.[4,5,13]

In summary, exercise preconditioning is founded on clinically relevant metrics of ECG abnormalities, ventricular pump function, and biological quantification of cardiac tissue death. Interestingly, the mechanisms of exercise preconditioning are not common to all forms of IR injury. For example, the upregulation of endogenous antioxidant enzymes prevent ventricular arrhythmias and tissue death during MI, but do not protect against ventricular pump dysfunction.[3,13] The cellular mechanisms essential for exercise preconditioning against cardiac dysrhythmias, ventricular contractility losses, and tissue death caused by IR injury have been previously described.[5,13] Conclusions from preclinical animal studies that underpin current scientific consensus on exercise preconditioning of the heart are summarized in Figure 4. These findings reinforce numerous lines of evidence which confirm that the mechanisms responsible for exercise-induced cardioprotection observed in animal studies are generalizable to humans.

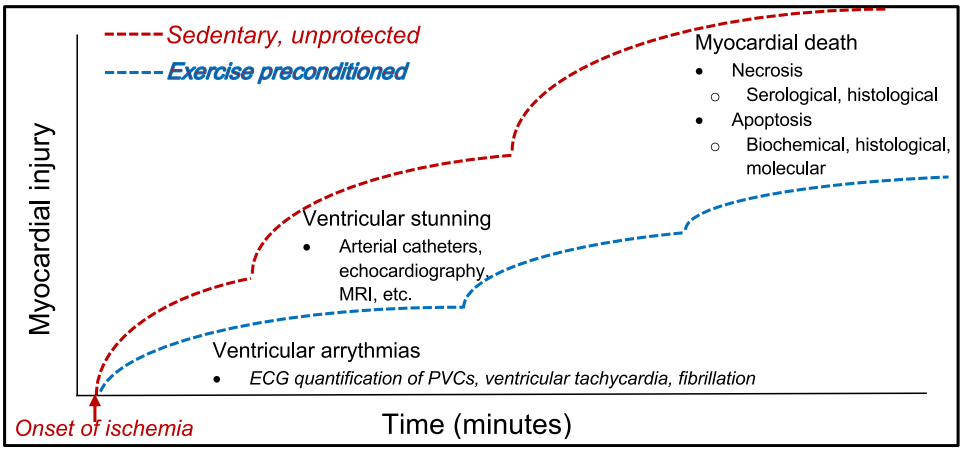

Figure 4. Exercise preconditioning prevents myocardial ischemia-reperfusion injury and death. Ischemia reperfusion injury is a time-dependent pathology, as shown conceptually above by the appearance of ventricular ectopy on the ECG, and later by declines in ventricular pump function. Unremitting ischemia is invariably marked by cardiomyocyte death due to necrotic and apoptotic processes. Exercise preconditioning lessens the magnitude of all facets of ischemia reperfusion injury (dashed line). Protection afforded by exercise is due to the upregulation multiple cellular mechanisms. Importantly, the mechanisms of biochemical cardioprotection against MI are unique to each phase of injury, for example, the factors preventing ventricular ectopy can be different than factor which prevent ventricular pump dysfunction. MRI = magnetic resonance imaging; ECG = electrocardiogram; PVCs = premature ventricular contractions.

Therapeutic Confirmation of Exercise Preconditioning in Clinical Populations

Considerable indirect evidence for PA -induced myocardial preconditioning is available. In the early 1970's, Paffenbarger et al[24] reported an 18-year follow-up investigation of 3,263 longshoremen. Participants were separated based on job-associated energy expenditure, comparing sedentary workers to those performing heavy physical work. Those with physically demanding jobs had lower death rates due to ischemic heart disease as compared with sedentary counterparts. Interestingly, the beneficial cardiovascular effects attributed to the more physically demanding jobs did not extend to a lower stroke mortality – suggesting a cardioprotective link to the heightened myocardial demands in the most active workers, as summarized below:

> "The association between work activity and coronary mortality, when considered with the lack of such association with stroke mortality, suggests that physical activity influences the myocardium or its function more than the atherosclerotic process."[24]

More recently, a clinical investigation of 2,172 patients hospitalized for acute coronary syndromes evaluated the effect of preadmission PA status on in-hospital mortality and cardiovascular health outcomes 1 month after discharge.[25] After adjusting for potential confounders, high PA patients had 0.56 lower odds of in-hospital mortality and 0.80 lower odds of recurrent CVD events within the first 30 days of discharge.

In many respects, science has come full circle from early epidemiologic evidence of exercise preconditioning, to preclinical phenotyping of the exercised heart, to therapeutic confirmation that exercise preconditioning occurs in humans. In a seminal review, 4 facets of exercise-induced cardioprotection were elucidated according their serial acquisition: (1) exercise preconditioning (days-weeks); (2) functional adaptations (weeks-years); (3) structural adaptations (weeks/months-years); and, (4) risk factor modification (months-years).[26]

Despite this collective understanding, some aspects of exercise preconditioning require additional clinical verification. An example is a phenomenon termed "warm-up angina," where patients with stable angina are briefly exercised to intensities that evoke significant (≥1 mm) ST-segment depression. The combined stimulus of exercise and myocardial ischemia presumably provokes a preconditioning response that improves the symptomatic threshold at which angina is triggered. Thus, in subsequent exercise tests performed within hours to days after the initial trial, patients experience improvements in symptom limiting angina. Outcome measures observed in warm-up angina studies include a reduction in the magnitude of ST-segment depression, a prolongation of symptom limiting exercise bouts, and increases in the rate-pressure product or exercise workload at the ischemic ECG threshold.[27] Investigations using warm-up angina to stimulate preconditioning have further demonstrated improved left ventricular function,[28] although evidence of infarct sparing is anecdotal and requires confirmation.[29]

An essential question that surrounds the topic of warm-up angina is whether the salutary effects are specific to the exercise, the ischemic preconditioning stimulus, or both. From a mechanistic perspective, use of the insulin sensitizing agent Glibenclamide during and following warm-up angina tests, indicates that activated cardiac K_{ATP} channels are among the biochemical factors that mediate the cardioprotective effects.[30] Nevertheless, these clinical findings are complicated by numerous preclinical investigations which indicate that cardiac K_{ATP} channels (located at the cardiomyocyte sarcolemma or inner membrane of mitochondria) are among the few protective mechanisms

common to both ischemic and exercise forms of preconditioning.[2,4,5] Despite these uncertainties, there is inferential evidence that both exercise preconditioning and ischemia confer a cardioprotective stimulus following a bout of warm-up angina.[28] Nonetheless, the exercise preconditioning effect of warm-up angina in cardiac patients has implications for lessening the potential for a myocardial supply:demand imbalance during training.

To summarize the translative potential of exercise preconditioning in clinically stable patients for whom exercise is safe, multiple mechanisms of biochemical cardioprotection act to mitigate IR injury during a subsequent cardiac event. Preclinical studies indicate that just 3 consecutive days of moderate intensity exercise provide a cardioprotective return on investment which lasts for ≥9 days.[12] A contrived interpretation of this finding, given the fluid evolution of CVD, is how could someone reasonably coordinate the initiation of an exercise program to preempt an unexpected life-threatening cardiovascular event? Alternatively, the more pragmatic conclusion given the transformative potential of a physically active lifestyle is, why would anyone at significant risk for CVD not engage in multiple weekly bouts of exercise in order to ensure that the heart is robustly preconditioned? Superimposed on this benefit are the salutary effects of perpetual exercise, including risk factor modification, improved cardiac and autonomic function, and protective structural adaptations to the coronary vasculature and myocardium.[26]

Physical Activity and Exercise Applications of Cardiac Preconditioning

Application of exercise preconditioning research to clinical populations transcends its importance as a line of scientific inquiry. As previously described, animal exercise modalities were designed to parallel human cardiovascular exercise prescriptions, to generalize the findings to clinical populations.[4,5] The critical question is *which patients are, or could be, cardioprotected via exercise preconditioning?* The simple answer is nearly all individuals could be exercise preconditioned, although current rates of physical inactivity suggest that too many are not.[26,31]

From a public health perspective, it is essential to mobilize highly sedentary individuals, with the minimum goal of achieving the recommended levels of daily PA. While maintaining a physically active lifestyle provides remarkable cardiovascular health advantages, being aerobically fit provides additional cardioprotective benefits. Thus, delineating physically active individuals from those who are unfit, could be useful in identifying individuals who are not exercise preconditioned. Specifically, increasing a patient's PA level and improving their CRF have independent relationships to CVD risk. When examining the lowest subset of the population based on CRF, there is a precipitous 64% drop in CVD risk when compared with the 100th percentile. Moreover, there is a pronounced drop in risk when comparing the lowest to the next-lowest category for CRF. In contrast, there is only a 30% overall decline in CVD risk when comparing the same metrics for PA,[32] indicating the risk reduction is twice as great for CRF. While improving PA levels in sedentary persons will unquestionably improve

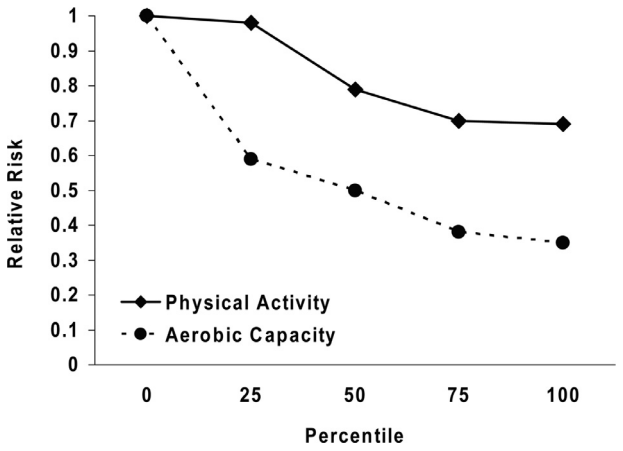

Figure 5. The risks of coronary heart disease and cardiovascular disease decrease linearly in association with increasing percentiles of physical activity. In contrast, there is a precipitous drop in risk when comparing the lowest to the next-lowest (25th %) category for aerobic capacity or cardiorespiratory fitness. Beyond this demarcation, the reductions in risk parallel those observed with increasing physical activity, but are essentially twice as great for aerobic capacity. Adapted from Williams.[32] Reprinted with permission from the American Heart Association.

cardiovascular health, achieving a given percentile of CRF is superior to a comparable level of PA (Figure 5).

Based on this understanding, it is important first address populations that are low fit. Indeed, medical professionals can expect, with high confidence, that the biochemical mediators of ischemic resistance are upregulated in the hearts of those meeting contemporary exercise guidelines.[31] This is based on the observation that the exercise dose is largely proportional to cardiovascular health and inversely related to CVD morbidity and mortality. Because exercise preconditioning is a threshold-dependent phenomenon, the long-term relation between exercise dose and improved cardiovascular health reflects the cumulative impact of cardioprotection – preconditioning, functional/structural adaptations over time, and CVD risk factor modification.[26]

For those who are physically active, but perhaps do not regularly meet current exercise guidelines, there remains reason for optimism. As presented conceptually in Figure 6, the most significant drop in relative risk for exercise-related AMI, occurs in the transition from mobilizing a habitually sedentary individual to performing vigorous PA 1-2 days/week.[33,34] In essence, the more frequently vigorous exercise is performed, the lower the relative risk of each exercise bout. Individuals completing vigorous PA 1 to 2 days/week might still attain an exercise preconditioned phenotype because of these practices. A common example of this is the classic "weekend warrior" approach to PA. Weekend warriors exhibit a lower than prescribed exercise frequency, but may experience cardiac preconditioning by extension of preclinical research findings that a few bouts of moderate-to-vigorous PA (≥50% VO_{2max}) can protect the heart against an ischemic insult for at least 9 days following the last exercise session.[12]

Exercise preconditioning effects may also apply to active-but-not-fit individuals who have a lower than average VO_{2max}. Consider that, at a minimum, moderate

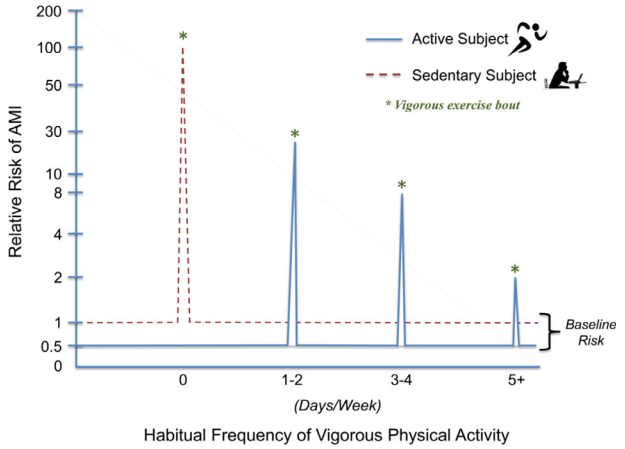

Figure 6. The relative risk for an acute myocardial infarction (AMI) is presented at rest (baseline relative risk of 1.0) and during vigorous activity. Performance of no vigorous physical activity elevates the risk of exercise-related AMI by orders of magnitude. Performing 1 to 2 days of weekly vigorous physical activity dramatically lowers AMI risk during vigorous physical exertion. More frequent performance of vigorous physical activity further lowers exercise-related AMI risk, although the relationship is not linear.[34] Reprinted with permission from the American Heart Association.

intensity exercise (≥50% of VO_{2max}) is required to upregulate the biochemical mechanisms of exercise preconditioning.[14,15] One must also delineate the relative and absolute cut points for moderate intensity PA (40% to 59% VO_{2max} or 3−5.9 METs) and vigorous PA (≥60% VO_{2max} or ≥6 METs) used in many population-based studies, where 1 MET = 3.5 ml/kg/minute. Accordingly, someone with an aerobic capacity of 10 METs (i.e., VO_{2max} ~35 ml/kg/minute) could exercise at 5 METs, corresponding to 50% of their functional capacity, and would presumably benefit from exercise preconditioning provided the workout duration was adequate (e.g., >30 total minutes).

Practitioners are cautioned against taking a dogmatic view of PA breakpoints, as the above-referenced MET thresholds for defining moderate and vigorous PA can be misleading for individuals with a low aerobic capacity. For example, someone with an aerobic capacity of 7 METs who exercised for 30 minutes at a 5 MET workload would be exercising at ~70% of VO_{2max}. In this example, the relative intensity qualifies as "vigorous PA," but the absolute MET value as "moderate PA." Using an absolute exercise intensity classification scheme, does not account for the fact that the cardiac demand of any PA is not solely determined by the specific MET level but by the metabolic demand relative to the individual's VO_{2max}. Consequently, lower MET requirements can still place considerable stress on the cardiovascular system of unfit, older individuals and those with morbid obesity or established CVD. Thus, despite the low absolute METs workload, the relative exercise intensity may induce exercise preconditioning.[14,15]

Finally, it is important to consider individuals that are neither aerobically fit nor physically active.[31] Indeed, many sedentary "at risk" individuals are initially unwilling or unable to achieve moderate-intensity PA for a minimum of 30 minutes on 5 days each week. Thus, when mobilizing individuals that have been highly sedentary (whether lifelong or in recent years), it is reasonable to expect that they will need to perform discontinuous bouts of PA, ideally accumulated toward a weekly goal that meets or approaches contemporary exercise guidelines.[31] Fortunately, cardioprotection against IR injury can be afforded by accumulated bouts of PA which do not achieve the traditional benchmarks for a structured exercise prescription. This conclusion is predicated on bouts of PA that achieve an intensity of at least 50% of VO_{2max}, a goal that may be easily attained in those with a low aerobic capacity. Thus, mobilizing completely sedentary individuals, with even brief bouts of accumulated, moderate intensity PA, may provide immediate dividends in improved cardiovascular health.

Relative to the prescription of PA for previously sedentary individuals, brief discontinuous repeated bouts of moderate intensity PA may serve as vigorous-to-high intensity interval training (HIIT) when applied to the highly deconditioned. For individuals who are medically stable, this form of training may be the only means of achieving the exercise intensity needed to precondition the heart. In support, an investigation of AMI patients treated by angioplasty found that exercise capacity was more predictive of 2- and 5-year mortality than measures of left ventricular ejection fraction. Specifically, patients with an exercise capacity ≥4 METs had improved long-term survival, while those with an exercise capacity <4 METs exhibited the highest mortality rates.[35] Moreover, our recent systematic review of cardiac rehabilitation studies which compared HIIT training to conventional moderate intensity continuous training found that with the exception of modest additional improvements in aerobic capacity (+0.5 METs with HIIT), moderate intensity was similar to HIIT relative to the restoration of cardiac function, CVD risk modification, and exercise adherence.[36]

In conclusion, exercise preconditioning provides an underappreciated independent and additive mechanism for protecting the heart against AMI. This conclusion represents the current scientific consensus and is based on a wealth of outcomes-oriented preclinical studies which indicate that even a few bouts of moderate intensity exercise elicit robust biochemical protection against the evolutionary manifestations of AMI. Clinical findings support the notion that exercised hearts exhibit transient antiarrhythmic and anti-ischemic effects against ischemic injury.[37] The benefits of exercise preconditioning are attributed to a host of endogenous biochemical factors activated within hours to days following the first bout of PA, and appears to be continuously activated in those who remain regularly engaged in exercise. Accordingly, exercise preconditioning is distinct from other established cardioprotective adaptations, such as CVD risk factor modification as well as vascular and ventricular remodeling.[4,5,13,26,37] Most importantly, the immediate benefits of exercise preconditioning can be conferred in individuals who engage in even brief bouts of PA that achieve a minimum threshold of 50% VO_{2max}.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74:1124–1136.
2. Bolli R, Becker L, Gross G, Mentzer R Jr., Balshaw D, Lathrop DA. Myocardial protection at a crossroads: the need for translation into clinical therapy. *Circ Res* 2004;95:125–134.
3. Powers SK, Quindry JC, Kavazis AN. Exercise-induced cardioprotection against myocardial ischemia-reperfusion injury. *Free Radic Biol Med* 2008;44:193–201.
4. Quindry JC. Exercise-induced cardioprotection and the therapeutic potential of RIPC. *J Cardiovasc Pharmacol Ther* 2017;22:397–403.
5. Quindry JC, Franklin BA. Cardioprotective exercise and pharmacologic interventions as complementary antidotes to cardiovascular disease. *Exerc Sport Sci Rev* 2018;46:5–17.
6. McGinnis GR, Ballmann C, Peters B, Nanayakkara G, Roberts M, Amin R, Quindry JC. Interleukin-6 mediates exercise preconditioning against myocardial ischemia reperfusion injury. *Am J Physiol Heart Circ Physiol* 2015;308:H1423–H1433.
7. Miller LE, McGinnis GR, Peters BA, Ballmann CG, Nanayakkara G, Amin R, Quindry JC. Involvement of the δ-opioid receptor in exercise-induced cardioprotection. *Exp Physiol* 2015;100:410–421.
8. Wilson EM, Diwan A, Spinale FG, Mann DL. Duality of innate stress responses in cardiac injury, repair, and remodeling. *J Mol Cell Cardiol* 2004;37:801–811.
9. Demirel HA, Powers SK, Zergeroglu MA, Shanely RA, Hamilton K, Coombes J, Naito H. Short-term exercise improves myocardial tolerance to in vivo ischemia-reperfusion in the rat. *J Appl Physiol (1985)* 2001;91:2205–2212.
10. Powers SK, Demirel HA, Vincent HK, Coombes JS, Naito H, Hamilton KL, Shanely RA, Jessup J. Exercise training improves myocardial tolerance to in vivo ischemia-reperfusion in the rat. *Am J Physiol* 1998;275:R1468–R1477.
11. Yamashita N, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M. Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. *J Exp Med* 1999;189:1699–1706.
12. Lennon SL, Quindry J, Hamilton KL, French J, Staib J, Mehta JL, Powers SK. Loss of exercise-induced cardioprotection after cessation of exercise. *J Appl Physiol (1985)* 2004;96:1299–1305.
13. Powers SK, Smuder AJ, Kavazis AN, Quindry JC. Mechanisms of exercise-induced cardioprotection. *Physiology (Bethesda)* 2014;29:27–38.
14. Starnes JW, Taylor RP, Ciccolo JT. Habitual low-intensity exercise does not protect against myocardial dysfunction after ischemia in rats. *Eur J Cardiovasc Prev Rehabil* 2005;12:169–174.
15. Lennon SL, Quindry JC, French JP, Kim S, Mehta JL, Powers SK. Exercise and myocardial tolerance to ischaemia-reperfusion. *Acta Physiol Scand* 2004;182:161–169.
16. Collins HL, Dicarlo SE. Acute exercise increases the ventricular arrhythmia threshold via the intrinsic adenosine receptor system in conscious hypertensive rats. *Am J Physiol Heart Circ Physiol* 2005;289:H1020–H1026.
17. Collins HL, Loka AM, Dicarlo SE. Daily exercise-induced cardioprotection is associated with changes in calcium regulatory proteins in hypertensive rats. *Am J Physiol Heart Circ Physiol* 2005;288:H532–H540.
18. Lightfoot JT, Leamy L, Pomp D, Turner MJ, Fodor AA, Knab A, Bowen RS, Ferguson D, Moore-Harrison T, Hamilton A. Strain screen and haplotype association mapping of wheel running in inbred mouse strains. *J Appl Physiol (1985)* 2010;109:623–634.
19. Ballmann C, Denney T, Beyers RJ, Quindry T, Romero M, Selsby JT, Quindry JC. Long-term dietary quercetin enrichment as a cardioprotective countermeasure in mdx mice. *Exp Physiol* 2017;102:635–649.
20. Ballmann C, Denney TS, Beyers RJ, Quindry T, Romero M, Amin R, Selsby JT, Quindry JC. Lifelong quercetin enrichment and cardioprotection in Mdx/Utrn+/- mice. *Am J Physiol Heart Circ Physiol* 2017;312:H128–H140.
21. Quindry J, French J, Hamilton K, Lee Y, Mehta JL, Powers S. Exercise training provides cardioprotection against ischemia-reperfusion induced apoptosis in young and old animals. *Exp Gerontol* 2005;40:416–425.
22. Chicco AJ, Johnson MS, Armstrong CJ, Lynch JM, Gardner RT, Fasen GS, Gillenwater CP, Moore RL. Sex-specific and exercise-acquired cardioprotection is abolished by sarcolemmal KATP channel blockade in the rat heart. *Am J Physiol Heart Circ Physiol* 2007;292:H2432–H2437.
23. Miller LE, Hosick PA, Wrieden J, Hoyt E, Quindry JC. Evaluation of arrhythmia scoring systems and exercise-induced cardioprotection. *Med Sci Sports Exerc* 2012;44:435–441.
24. Paffenbarger RS, Gima AS, Laughlin E, Black RA. Characteristics of longshoremen related fatal coronary heart disease and stroke. *Am J Public Health* 1971;61:1362–1370.
25. Pitsavos C, Kavouras SA, Panagiotakos DB, Arapi S, Anastasiou CA, Zombolos S, Stravopodis P, Mantas Y, Kogias Y, Antonoulas A, Stefanadis C, Investigators GS. Physical activity status and acute coronary syndromes survival The GREECS (Greek Study of Acute Coronary Syndromes) study. *J Am Coll Cardiol* 2008;51:2034–2039.
26. Thijssen DHJ, Redington A, George KP, Hopman MTE, Jones H. Association of exercise preconditioning with immediate cardioprotection: a review. *JAMA Cardiol* 2018;3:169–176.
27. Lalonde F, Poirier P, Sylvestre MP, Arvisais D, Curnier D. Exercise-induced ischemic preconditioning detected by sequential exercise stress tests: a meta-analysis. *Eur J Prev Cardiol* 2015;22:100–112.
28. Rinaldi CA, Masani ND, Linka AZ, Hall RJ. Effect of repetitive episodes of exercise induced myocardial ischaemia on left ventricular function in patients with chronic stable angina: evidence for cumulative stunning or ischaemic preconditioning? *Heart* 1999;81:404–411.
29. Marongiu E, Crisafulli A. Cardioprotection acquired through exercise: the role of ischemic preconditioning. *Curr Cardiol Rev* 2014;10:336–348.
30. Tomai F, Danesi A, Ghini AS, Crea F, Perino M, Gaspardone A, Ruggeri G, Chiariello L, Gioffre PA. Effects of K(ATP) channel blockade by glibenclamide on the warm-up phenomenon. *Eur Heart J* 1999;20:196–202.
31. U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans*. 2nd edition Washington, DC: U.S. Department of Health and Human Services; 2018.
32. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc* 2001;33:754–761.
33. Franklin BA. Preventing exercise-related cardiovascular events: is a medical examination more urgent for physical activity or inactivity? *Circulation* 2014;129:1081–1084.
34. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 1993;329:1677–1683.
35. Dutcher JR, Kahn J, Grines C, Franklin BA. Comparison of left ventricular ejection fraction and exercise capacity as predictors of two- and five-year mortality following acute myocardial infarction. *Am J Cardiol* 2007;99:436–441.
36. Quindry JC, Franklin BA, Chapman M, Humphrey R, Mathis S. Benefits and risks of high-intensity interval training in patients with coronary artery disease. *Am J Cardiol* 2019;123:1370–1377.
37. Franklin B, Quindry JC. Biochemistry of exercise training and mitigation of cardiovascular disease. In: Tidus P, MacPheroson R, Leblanc PJ, eds. Biochemistry of Exercise. New York: Routledge Publishers; 2021.