REVIEW

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The Limits of Cardiac Performance: Can Too Much Exercise Damage the Heart?

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ABSTRACT

Routine moderate-intensity physical activity confers numerous cardiovascular benefits and reduces all-cause mortality. However, the health impact of exercise doses that exceed contemporary physical activity guidelines remains incompletely understood, and an emerging body of literature suggests that high levels of exercise may have the capacity to damage the cardiovascular system. This review focuses on the contemporary controversies regarding high-dose exercise and cardiovascular morbidity and mortality. We discuss the limitations of available studies, explore potential mechanisms that may mediate exercise-related cardiac injury, and highlight the gaps in knowledge for future research.
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KEYWORDS: Athlete's heart; Cardiomyopathy; Exercise

INTRODUCTION

> 'Run Pheidippides, one race more! . . . Joy in his blood bursting his heart, he died . . .'
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> (Pheidippides from *Dramatic Idyls*, 1879)[1]

The past few decades have witnessed an increase in participation rates in organized sporting events including marathons, long-distance cycling, and triathlons.[2] This increase is largely accounted for by people without any background in competitive sport, including those >40 years old, with risk profiles different from traditional competitive athletes. Achieving competitive race times requires several hours of intense training per day, often >10-15 times the daily recommended dose of physical activity.[3] Even outside of these formal endurance events, fitness trends focusing on short periods of high-intensity exercise such as CrossFit (Washington, DC) and high-intensity interval training have gained prominence among the general population. This recent surge in enthusiasm, coupled with controversial data highlighting the potential harm of too much exercise, has put this question once again on top of the agenda—can one exercise too hard, or too much?

THE U-SHAPED CURVE BETWEEN PHYSICAL ACTIVITY AND MORTALITY

It is well established that regular low- and moderate-intensity exercise improves all-cause mortality in a dose-response fashion.[4] However, at the upper levels of the exercise dose-response curve, the relationship between exercise and mortality remains incompletely understood. Early studies using professional athletes consistently showed improved survival compared with nonathletic counterparts.[5–7] Conversely, recent data derived from the general population suggest that high doses of exercise may reduce or eliminate the mortality benefit gained from lower levels of exercise exposure. A prospective analysis of more than 1000 ostensibly healthy joggers revealed mortality risk reduction among low and moderate levels of jogging (as defined by jogging pace, duration, and frequency) but no statistical difference in mortality rates comparing "strenuous" joggers to sedentary counterparts.[8] Although this finding implies a U-shaped relationship between all-cause mortality and running dose, the "strenuous" jogger subgroup was comprised of only 36 individuals with only 2

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recorded deaths. As such, this study was underpowered to assess mortality risk among people who live in the upper end of the exercise dose-response curve. Rather than an uptick in mortality, larger epidemiologic studies have reported a mortality reduction plateau or a trend toward a relative decline in mortality benefit with high levels of exercise.[9,10]

These observational data, however, carry inherent limitations. First, cross-sectional datasets are incapable of establishing a direct cause-and-effect relationship between the amount of exercise and mortality. Second, confounding variables not fully considered in these studies, including traditional cardiovascular risk factors, dietary intake, and the principal components of exercise dose: volume and intensity, lead to questions about the mechanistic relationship between exercise and mortality. It is probable that such unmeasured or incompletely measured confounders explain much of the discrepancy in outcomes between professional athletes and those who engage in high levels of exercise in the general population. Future work relying on carefully collected prospective data and detailed phenotypic characterization will be required to delineate the true relationship between longevity and exercise exposure.

CLINICAL SIGNIFICANCE

- High levels of exercise may have the capacity to damage the heart.
- The most convincing example of an overuse pathologic cardiac phenotype is atrial fibrillation.
- Other possible manifestations of an exercise-related cardiac injury include myocardial fibrosis and coronary artery calcification.
- In the absence of prospective outcomes data, the cause-and-effect relationship between high levels of exercise and cardiac morbidity and mortality remains uncertain.

CARDIAC TROPONIN ELEVATION: A MARKER FOR ADAPTATION OR A WARNING SIGN?

Cardiac troponins (cTn), when detected in the peripheral blood, are specific for cardiomyocyte injury. However, cTn is detectable in healthy athletes without signs or symptoms of myocardial infarction after completion of acute bouts of exercise. When using the latest high-sensitivity assays, cTnT almost always transiently increases after running a marathon.[11–16] The cTn elevation also increases after other endurance events (cycling,[17] triathlon[18]), shorter running distances,[19] and high-intensity interval training sprint protocols.[20] The cTn does not, however, increase after short bouts of strength-based exercises, for example, weightlifting.[21,22]

The mechanism of cTn release during exercise remains unknown, leading to the central controversy about whether it is a physiological or pathologic phenomenon. Pathologic cTn elevation is typically attributable to 1 of 3 distinct mechanisms: 1) ischemia and necrosis resulting from a ruptured coronary arterial plaque and subsequent coronary occlusion; 2) demand/supply mismatch leading to ischemia and necrosis in the absence of plaque rupture; and 3) nonischemic injury from direct myocardial damage.[23] The cTn release during exercise in the symptom-free athlete without underlying coronary disease does not clearly fit into any of the above categories, nor does it necessarily represent a pathologic process, given the frequency of its occurrence in healthy athletic individuals. One of the strongest lines of evidence supporting a physiological mechanism of exercise-induced cTn release is derived from the kinetics of postexercise cTn elevation. Compared with acute myocardial infarction, peak cTn levels after exercise are significantly lower and normalize rapidly after exercise.[24] In acute myocardial infarction, however, a similar small transient elevation is observed within a few hours of ischemia followed by a second greater—and more sustained—increase. The initial increase is due to leakage from an intracellular pool, whereas the second peak is the result of cell necrosis with destruction of contractile apparatus. Therefore the relatively small and transient increase in cTn post exercise may also be related to mobilization of intracellular pool of cTn.

Alternatively, troponin elevation after exercise could represent apoptosis-induced cardiac myocyte death. In skeletal muscle, severe exertion causes death of skeletal myocytes, which have the ability for complete repair and regeneration, resulting in functional and structural adaptations.[25] Recent data characterizing myocardial physiology suggest that the ability for repair is far greater than once thought, with cardiomyocyte regeneration readily occurring in physiological states.[26,27] In animal studies, transient increases in preload and stretch cause troponin release related to apoptosis-mediated cell death.[28,29] A similar mechanism can also explain troponin release after endurance events and vigorous high-intensity interval training, as well as the relative absence of troponin elevation after strength-based training. If this were true, it is conceivable that exercise-induced cardiomyocyte death would carry a more favorable prognosis than cell necrosis related to coronary artery disease.

Although speculative, exercise-induced apoptotic cell death may represent a key component of the cardiac repair processes, akin to skeletal muscle, that occurs after exercise and may be the mechanistic pathway underlying the functional and structural changes that are characteristic of the "athlete's heart". However, the significance of exercise-induced cTn elevation in patients with abnormal underlying substrate (eg, underlying cardiomyopathy) may be different. Specifically, vigorous exertion in the setting of heart muscle pathology may induce aberrant or exaggerated repair processes, leading to deleterious adaptations.

ATRIAL FIBRILLATION

Atrial fibrillation not only increases the risk of thromboembolic events, heart failure, and mortality,[30] but also reduces cardiac efficiency, often leading to a noticeable decline in athletic performance. People who engage in low to moderate levels of exercise appreciate a protective effect with lower risk of incident atrial fibrillation.[31,32] However, case-control studies over the past 2 decades consistently document associations between high levels of endurance exercise and incident atrial fibrillation.[33–40]

The first case series was derived from middle-aged male orienteering competitors who experienced a higher burden of lone atrial fibrillation than more sedentary control subjects.[33] Subsequent data from *Vasaloppet*, a 90-km competitive Nordic skiing event in Sweden, demonstrated a compelling dose- and intensity-dependent association between endurance exercise and atrial fibrillation.[40] In this cohort of >50,000 skiers, the number of races completed by participants, as well as their performance, were potent predictors of atrial fibrillation. In another longitudinal cohort study of more than 300,000 middle-aged men followed up for 20 years, men self-reporting intense physical activity levels were 3 times more likely than sedentary males to be prescribed flecainide (used as a surrogate marker for a diagnosis of lone atrial fibrillation).[41] Similarly, a meta-analysis including 6 case-control studies revealed a fivefold increase in the risk of developing atrial fibrillation among older endurance athletes compared with nonathletes.[42] In aggregate, these analyses represent a persuasive body of literature linking high levels of endurance sport in middle-aged individuals to an enhanced risk of atrial fibrillation.

Although atrial fibrillation represents the most convincing example of an overuse pathologic cardiac phenotype, data defining causal mechanisms and optimal treatment strategies for atrial fibrillation in the athletic population are lacking. In the absence of data dictating a clinical standard of care for athletes with atrial fibrillation, extrapolation from treatment studies conducted on sedentary individuals and anecdotal experience with athletes are appropriate fallback options in the clinical setting. Future work will be required to advance this field and to address key unanswered questions about issues including anticoagulation and sinus rhythm maintenance in this unique population.

LEFT VENTRICULAR FUNCTION

The association between high levels of endurance exercise and myocardial dysfunction is complex, and its clinical significance remains uncertain. Immediately on completion of a triathlon, left ventricular ejection fraction decreases compared with prerace measurements, with 75% of athletes showing new wall motion abnormalities.[43] Even at rest, data from strain mapping in elite college rowers after a period of training intensification reveals subtle regional decrements in left ventricular systolic mechanics.[44] After 90 days of intense physical training, although there was an adaptive gain in function in the longitudinal and radial vectors, there was a decrease in circumferential strain in regions adjacent to the right ventricle. Interestingly, this decrement in function was inversely proportional to training-induced right ventricular dilation. Similar observations were seen among professional cyclists when followed up between 1995 and 1998.[45] In this cohort of Tour de France cyclists, there was progressive chamber enlargement and a decrease in resting left ventricular ejection fraction. Moreover, left ventricular ejection fraction was lower in cyclists with left ventricular dilatation compared with those without dilation. If these observations are to be taken in isolation, this pattern of left ventricular morphology and dysfunction is concerning for the development of an exercise-related dilated cardiomyopathy. It is important to note, however, that assessment of left ventricular systolic function using ejection fraction is misleading because left ventricular geometry changes as a result of endurance training. Specifically, left ventricular end-systolic volume increases to a greater degree than end-diastolic volume,[44,45] leading to a reduction in calculated ejection fraction, despite preservation of resting stroke volume. It is important to note that it is not ejection fraction but rather stroke volume that is precisely regulated by the cardiovascular system.

In aggregate, there are no convincing data suggesting that exercise in isolation, no matter how high the dose, can cause clinically relevant myocardial systolic dysfunction. However, there is a clear signal toward cardiac fatigue in the period immediately after high levels of endurance exercise. Although this is likely a transient phenomenon, it is possible that repeated bouts of strain and fatigue may predispose to fibrosis and scar formation, especially in the setting of inadequate recovery.

MYOCARDIAL FIBROSIS

Myocardial fibrosis has the potential to act as an arrhythmogenic substrate.[46] Myocardial fibrosis is categorized into 2 distinct forms: replacement and interstitial fibrosis.[47] Replacement fibrosis is characterized by myocyte cell necrosis leading to focal areas of scar tissue. Interstitial fibrosis represents an expansion of the interstitium with collagen accumulation, in the absence of cell necrosis.[48] Late gadolinium enhancement (LGE) on cardiac magnetic resonance reflects focal scar formation attributable to replacement fibrosis, whereas newer T_1 mapping magnetic resonance imaging techniques permit quantification of interstitial fibrosis.

Over the past decade, several studies have documented the presence of LGE in both younger competitive endurance athletes[49] and veteran endurance athletes,[50] with prevalence reported as high as 50% in the latter. However, careful inspection into the distribution of LGE in endurance athletes reveals both subendocardial and epicardial LGE, suggestive of prior myocardial infarction and subclinical myocarditis, respectively. In the absence of a more detailed assessment of underlying atherosclerotic risk factors and

other confounding variables, it therefore remains difficult to ascertain the exact relationship between exercise and myocardial fibrosis. Indeed, some athletic cohorts more rigorously screened for coronary risk factors do not demonstrate any evidence of LGE.[51–53]

The strongest evidence for exercise-related myocardial fibrosis arises from the small minority of athletes who demonstrate an atypical pattern of LGE not consistent with either coronary artery disease or myocarditis. This is often localized to the interventricular septum, with a propensity toward the right ventricular insertion points.[49,54] Vigorous endurance exercise, with its attendant increase in pulmonary pressures and right ventricular afterload, may place disproportionate strain on the right ventricle,[55] leading to transient right ventricular dilatation and fatigue.[49] It is possible, though yet to be proven in rigorous fashion, that repetitive transient increases in hemodynamic right ventricular load and strain eventually cause scar formation at the interventricular septum and right ventricular insertion points. Although peak exercise pulmonary artery pressure does not necessarily correlate with peak exercise systolic blood pressure, the latter is an independent predictor of LGE presence in symptom-free middle-aged triathletes.[56]

However, if high levels of endurance exercise alone were to induce this pattern of scar distribution, we would expect to see this in most athletes, as opposed to only a small minority. Furthermore, LGE distribution in this pattern is also seen in patients with pulmonary hypertension[57] and roughly 10% of patients with hypertrophic cardiomyopathy.[58] In these patients, most scar formation in this distribution is not due to cell necrosis and replacement fibrosis and is not associated with an increased risk of adverse events or sudden death.[57,58] As studies examining the link between high levels of endurance exercise and myocardial fibrosis continue, it appears increasingly likely that most scar formation observed in athletes occurs in the setting of underlying cardiac disease. It is therefore important in athletes with LGE presence to address the traditional cardiovascular risk factors, highlight the importance of avoiding strenuous exercise during acute bouts of illness, and promote adequate recovery between training sessions.

CORONARY ARTERY CALCIFICATION

The most common cause of exercise-related sudden cardiac death in athletes >35 years old is coronary artery disease.[59,60] Coronary computed tomography scans in >100 accomplished male veteran marathon runners reveal a greater degree of coronary artery calcification compared with controls matched for age and risk factors.[61] Follow-up of these athletes demonstrated significant ischemic coronary events in 4 individuals with high coronary artery calcification scores. However, half of the marathon runners were former smokers and of the 4 runners that suffered coronary events, 3 were former smokers and had a history of hypertension, and 2 had elevated lipid profiles. Thus the degree to which exercise alone contributes to disease pathogenesis and adverse events is unclear.

Veteran endurance athletes devoid of conventional atherosclerotic risk factors appear to harbor a higher burden of coronary artery calcification and luminal irregularities compared with sedentary controls matched for age and risk factors.[62,63] Although emerging data document a convincing association between coronary artery calcification and high levels of exercise, the clinical significance of this association remains incompletely understood. In athletes, the morphology of coronary artery plaques are predominantly calcific,[62,63] which in nonathletic cohorts protects against plaque rupture and coronary events.[64,65] It also is important to note that most veteran endurance athletes do not have coronary artery calcification. Therefore, although it is possible that athletes with coronary artery calcification may be at higher risk of adverse coronary events than athletes without coronary artery calcification, it is equally plausible that high levels of exercise facilitate coronary plaque remodeling with a stabilizing effect that ultimately protects against acute coronary events. Luminal irregularities, however, still provide cause for concern in athletes due to risk of ischemic injury during exercise from a demand/supply mismatch. The data supporting this theory are limited, but in 5 marathon runners who survived cardiac arrest related to myocardial ischemia, immediate coronary angiography revealed high-grade stenosis without evidence of coronary plaque rupture.[66]

From a causation and mechanistic perspective, the evidence pertaining to coronary artery disease in endurance athletes remains unclear. Although recent studies attempted to screen for traditional atherosclerotic risk factors, this approach did not encompass all of the determinants of coronary artery disease. Dietary intake, sleep, psychosocial stressors, and genetic profiles were not captured in prior studies and likely contribute to the development of atherosclerosis. Of greater importance is the absence of outcomes data to help determine the clinical significance of coronary artery calcification in athletes. Although tempting to extrapolate from sedentary populations, it is conceivable that coronary artery calcification among athletes portends a more favorable prognosis. Longitudinal prospective outcome data in endurance athletes are essential to determine the cause-and-effect relationship between high-dose endurance exercise and clinically relevant coronary artery disease. Until such time as these studies become available, the presence of coronary artery calcification in athletes should not represent grave concerns; rather, it should direct the physician and athlete to address atherogenic risk factors in greater detail.

CONCLUSIONS

Most individuals who regularly exercise stand to derive all the benefit that physical training affords without any of the potentially adverse outcomes highlighted in this review. It is conceivable, however, that vigorous exercise may be

harmful if a cascade of additional insults were to occur simultaneously in an individual. This would represent the "perfect storm," which, by its nature, is a rare event and should not be used to warn individuals against engaging in regular exercise. Although the phenomenon of an exercise overuse phenotype remains a conjecture in the absence of well-designed longitudinal studies, it is important to maintain an open dialogue surrounding the ambiguities and implications of high-dose exercise.

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