ABSTRACT: Regular exercise is effective in the prevention and treatment of conditions such as hypertension, coronary artery disease, and diabetes. Studies have investigated ideal amounts or “doses” of exercise to decrease risk factors associated with disease, as well as the minimum amount of exercise required to reduce mortality. With the increase in individuals participating in ultra-endurance events, recent research has focused on the high end of the exercise dose-response range and found that chronic endurance training can cause transient myocardial changes, possibly due to repetitive transient pressure and volume overload on the thin-walled left atrium and right ventricle. Some evidence suggests that years of endurance training can lead to long-term adverse consequences, including myocardial fibrosis, atrial fibrillation, and coronary artery calcification. Evidence suggests that years of training can lead to long-term adverse cardiac consequences in some individuals. This article has been peer reviewed.

REGULAR EXERCISE IS EFFECTIVE IN THE PREVENTION AND TREATMENT OF CONDITIONS SUCH AS HYPERTENSION, CORONARY ARTERY DISEASE, AND DIABETES. STUDIES HAVE INVESTIGATED IDEAL AMOUNTS OR “DOSES” OF EXERCISE TO DECREASE RISK FACTORS ASSOCIATED WITH DISEASE, AS WELL AS THE MINIMUM AMOUNT OF EXERCISE REQUIRED TO REDUCE MORTALITY. WITH THE INCREASE IN INDIVIDUALS PARTICIPATING IN ULTRA-ENDURANCE EVENTS, RECENT RESEARCH HAS FOCUSED ON THE HIGH END OF THE EXERCISE DOSE-RESPONSE RANGE AND FOUND THAT CHRONIC ENDURANCE TRAINING CAN CAUSE TRANSIENT MYOCARDIAL CHANGES, POSSIBLY DUE TO REPETITIVE TRANSIENT PRESSURE AND VOLUME OVERLOAD ON THE THIN-WALLED LEFT ATRIUM AND RIGHT VENTRICLE. SOME EVIDENCE SUGGESTS THAT YEARS OF ENDURANCE TRAINING CAN LEAD TO LONG-TERM ADVERSE CONSEQUENCES, INCLUDING MYOCARDIAL FIBROSIS, ATRIAL FIBRILLATION, AND CORONARY ARTERIOSCLEROSIS. THE LAW OF DIMINISHING RETURNS APPEARS TO APPLY AS EXERCISE EXTENT INCREASE, AND IT IS LIKELY THAT AN UPPER LIMIT EXISTS WHERE ADDITIONAL PHYSICAL ACTIVITY PROVIDES NO FURTHER MORTALITY BENEFIT.

Evidence suggests that years of training can lead to long-term adverse cardiac consequences in some individuals. The possibility that years of endurance training could lead to long-term consequences, such as myocardial fibrosis, atrial fibrillation (AF), ventricular arrhythmias, and coronary artery calcification, naturally leads us to three related questions: How...
much exercise is enough? When does endurance exercise become “excessive”? What are the potential impacts of excessive endurance exercise?

**How much exercise is enough?**

With obesity and associated comorbidities on the rise, several prospective studies have investigated ideal amounts or “doses” of exercise to decrease risk factors associated with these diseases, as well as the minimum amount of exercise required to decrease mortality. Wen and colleagues examined 416,175 healthy individuals age 20 years or older who participated in a standard medical screening program with an average follow-up of 8.05 years.5 The low-volume activity group exercised for the equivalent of about 15 minutes per day and had a 14% reduced risk of all-cause mortality and a 3-year increase in life expectancy. Every additional 15 minutes beyond the minimum amount further reduced all-cause mortality by 4%. However, more than 100 minutes per day of moderate activity or 50 to 60 minutes per day of vigorous activity conferred no additional health benefits.

The Copenhagen City Heart Study observed 1878 joggers and 10,158 non-joggers for up to 35 years.6 They found that both male and female joggers had a 44% lower risk of mortality during follow-up, with an increase in survival of 6.2 years in men and 5.6 years in women. In a subset of 5048 patients, a U-shaped mortality curve was observed with respect to frequency, pace, and quantity of jogging.⁷ When joggers were compared with sedentary non-joggers, 1.0 to 2.4 hours of jogging per week was associated with a reduced hazard ratio (HR) and the lowest mortality (HR 0.29; 95% CI, 0.11-0.80). The optimal amount of jogging was 2 to 3 times per week at a slow or average pace. Interestingly, those jogging at a strenuous pace did not exhibit a mortality rate statistically different from that of the sedentary group.

The Aerobics Center Longitudinal Study reported a similar reduction in mortality in runners versus non-runners.¹⁰ Among 55,137 adults, runners had a 30% lower adjusted risk of all-cause mortality (HR 0.70; 95% CI, 0.64-0.77) and a 45% lower adjusted risk of cardiovascular mortality (HR 0.55; 95% CI, 0.46-0.65) than non-runners. The mortality benefits among runners were similar across quintiles of running time, distance, amount, frequency, and speed. The study found that running once or twice per week for as little as 51 minutes per week at a speed of 6 miles per hour was enough to reduce risk of mortality. In keeping with previous studies, researchers reported a U-shaped mortality curve and noted that the mortality benefit was slightly less with running for more than 176 minutes per week.

**When does endurance exercise become “excessive”?**

At what point does mortality risk increase with exercise and what are possible explanations for this? There is no exact definition of “excessive” endurance exercise. Well-known endurance events include marathons (42 km), ultra-marathons (50 to 150 km), ironman triathlons (3.9-km swim, 180-km bike ride, and 42.1-km run), and long-distance cycling races (more than 120 km). In preparation for these events, endurance athletes may train for several hours per day, often exceeding 300 MET hours (metabolic equivalent task hours) per week—20 to 30 times more than the amount of exercise recommended for mortality benefit.¹¹

**What are the potential impacts of excessive endurance exercise?**

The effects of long-term endurance exercise are still unclear; however, a growing body of data suggests such exercise may be harmful (Figure 1). Functional impairment of the right ventricle (RV) during and after activ-
Myocardial fibrosis

Extreme exercise has been associated with biochemical and functional evidence of acute myocardial damage and may also be associated with small areas of myocardial fibrosis secondary to episodic volume and pressure overload in the RV. La Gerche and colleagues investigated the potential relationship between endurance training and the effects on the RV and LV. They observed 40 asymptomatic athletes with structurally normal hearts who participated in either a marathon, endurance triathlon, alpine cycling race, or an ultra-triathlon. Study subjects had trained intensely for at least 10 hours per week, and had finished in the top 25% in a recent endurance event.

Echocardiography and biochemistry studies, including measurement of cardiac troponin I levels, were performed 2 to 3 weeks before the event (baseline), immediately after the event (post-race), and 6 to 11 days after the event (delayed). Cardiac magnetic resonance imaging (CMR) was performed at baseline. When compared with baseline measurements, the right ventricular ejection fraction (RVEF) decreased significantly by 9% \((P < .0001)\), while the left ventricular ejection fraction (LVEF) was preserved. All athletes had detectable cardiac troponin elevations post-race and levels correlated with depressed RV function. RVEF and biomarkers returned to baseline during the delayed measurements. Interestingly, there was a significant interaction between race duration, race completion time, and changes in RVEF. The change in RVEF correlated inversely with duration \((P < .0001)\) with the greatest reduction seen in those who completed the longest event. These findings suggest endurance exercise evokes transient declines in RV function.

CMR was used to assess fibrosis as a possible effect of endurance exercise. Five athletes (12.8%) had delayed gadolinium enhancement (DGE) confined to the interventricular septum and commonly at the site of RV attachment. These athletes had longer cumulative exposure to endurance events and had a lower ejection fraction than those without DGE. This finding adds support to the proposition that repeated bouts of intensive endurance exercise may lead to RV abnormalities. However, the study was not powered for the assessment of clinical events; therefore, it cannot be concluded that the short-term changes result in cumulative injury or that the fibrosis in the right ventricle results in development of a proarrhythmic substrate.

Ventricular arrhythmias

Studies have suggested that long-term high-level exercise might be associated with an increased risk of cardiac arrhythmias, mainly those originating from the right ventricle due to myocardial fibrosis, dysfunction, or underlying arrhythmogenic right ventricular cardiomyopathy (ARVC). Heidbuchel and colleagues investigated the prevalence of right ventricle dysfunction in 46 endurance athletes (median age 31 years, 80% cyclists) with ventricular arrhythmias. Eighty percent of the ventricular arrhythmias were of left bundle branch block morphology,
suggesting an RV origin. Thirty-six athletes presented with symptoms attributable to ventricular arrhythmias. Nine were asymptomatic but had a documented complex ventricular arrhythmia; this was defined as one or more run of three or more beats of 120 bpm or higher of nonsustained ventricular tachycardia (VT). While 27 athletes met the old diagnostic criteria for definite ARVC, 14 athletes met the new criteria for borderline or possible ARVC.20 Eighteen athletes developed a major arrhythmic event and sudden death occurred in nine—all of whom were cyclists. All but one episode occurred during light or moderate physical activity.7 Fifteen athletes with inducible sustained VT or ventricular fibrillation (VF) found on an electrophysiology study had a significantly higher risk for developing major arrhythmias during follow-up (RR 3.4; \(P = .02\)). This study demonstrates that endurance sport may be related to the development of an underlying proarrhythmic substrate, and that complex ventricular arrhythmias are not necessarily a benign finding.

**Arrhythmogenic right ventricular cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy has typically been described as an inherited condition, but RV arrhythmias may exist without genetic abnormalities. The hypothesis is that shear stress placed on the right ventricular myocardium during vigorous exercise “unmasks” ARVC in athletes due to disruption of the desmosomal proteins that anchor intermediate filaments between adjoining myocardial cells and impair the function of cell adhesion junctions. With abnormal desmosomes, adjacent cardiomyocytes detach from one another, die, and are gradually replaced by fat and fibrous tissue.18,21 This can result in a reduced RVEF and provide the substrate for malignant reentrant arrhythmias.

Ector and colleagues compared endurance athletes and nonathletes without ventricular arrhythmias to 22 endurance athletes with RV arrhythmias to determine whether these arrhythmias were associated with RV abnormalities.19 Athletes with ventricular arrhythmias had a significantly lower RVEF compared with the matched control groups, findings that suggest ventricular arrhythmias in endurance athletes likely originate from a mildly dysfunctional RV. Similarly, when La Gerche and colleagues investigated athletes with complex ventricular arrhythmias of RV morphology who performed moderate to intense exercise,22 they found lower than expected rates of desmosomal mutations, leading to the conclusion that RV changes from intense endurance exercise can occur independent of a genetic predisposition.

These studies suggest some athletes either have a forme fruste of ARVC that is unmasked by RV mechanical loading conditions during intense endurance exercise, or they have developed primary RV abnormalities from endurance exercise itself.11 In athletes with a genetic predisposition to ARVC, cell adhesion may be more vulnerable to shear stress—a vulnerability that only becomes clinically apparent under the conditions of repetitive endurance exercise. The six major genes involved in ARVC have immense natural variability; these allelic differences may predispose to desmosome dysfunction in the context of pressure or volume overload. Recent evidence from both exercise surveys in ARVC patients and animal models supports a strong interaction between exercise and severity of disease expression.23-25 ARVC is inherited with incomplete penetrance and has variable phenotypic expression, suggesting a role for environmental influences.21

When Sawant and colleagues studied 82 ARVC patients23 they found that the 43 patients who did not have desmosomal mutations (i.e., they were diagnosed with gene-elusive, nonfamilial ARVC) were more likely to be endurance athletes \(P < .001\) and to participate in more intense exercise prior to presentation than those with desmosomal ARVC \(P < .001\).

James and colleagues sought to determine how exercise might influence penetrance of ARVC among patients with known desmosomal mutations by looking at a group of 87 mutation carriers.21 After identifying 56 subjects who exercised at levels greater than 70% VO2 max for at least 50 hours per year, they found these endurance athletes were more likely than other study subjects to meet the ARVC 2010 Task Force Criteria at last follow-up (82% vs 35%, \(P < .001\)), and that this finding was associated with increasing hours per year of exercise \(P < .001\). Interestingly, a reduction in exercise after initial presentation actually decreased VT/VF risk \(P = .04\), and was one of several findings leading the researchers to conclude that frequent endurance exercise increases risk for VT/VF and ARVC in desmosomal mutation carriers.

In an animal model, rats developed eccentric LV hypertrophy, diastolic dysfunction, and atrial dilation after 16 weeks of vigorous running.17 The rats also had significantly greater collagen deposition and fibrosis markers in the RV and atria, and a greater likelihood of inducible VT \(P = .05\). After 8 weeks of detraining, most of the abnormal cardiac remodeling parameters exhibited by the rats returned to control levels. However, it is difficult to determine if an animal
model can accurately reflect the human response. The human equivalent to the intensity of the rats’ exercise would be approximately 10 years of daily exercise training at 90% of predicted maximal heart rate.17 Also, the study compared intense exercise with a complete cessation of exercise rather than with a decreased amount and intensity of exercise. This training and detraining pattern would be less likely to occur in humans, and thus the reversibility of the changes seen in the rats might not apply to humans.

**Atrial fibrillation**
Recent data have documented a higher prevalence of atrial fibrillation cases in long-term endurance sport.26 Most are thought to be cases of lone atrial fibrillation (AF without any identifiable cause in individual younger than 60).27 Karjalainen and colleagues were the first to identify a relationship between endurance sport and AF in cross-country runners, with a 5.5 odds ratio for AF associated with vigorous exercise.28 Elosua and colleagues demonstrated similar results with a 3 times higher prevalence of lone AF and 5 times higher prevalence of vagal AF in those who reported current sport practice versus controls.27 In a prospective study of high-performance male participants in endurance cross-country ski competitions, there was a 12.8% prevalence of lone AF after approximately 30 years of follow-up.29 Furthermore, a comparison of former professional cyclists with a mean age of 66 (7) years with a control group found an AF rate of 10% for the cyclists and 0% for the control group.15

The mechanisms proposed for development of AF with excessive endurance exercise appear to be multifactorial. Volume overload, stretching of the thin-walled atria, and myocardial damage may all contribute to atrial remodeling and development of fibrosis over time.30,31 Other mechanisms that may contribute to AF include increased atrial ectopic beats, shifts in electrolytes, increased vagal tone and bradycardia, and inflammatory changes.19,31 The exact relationship between increased atrial size in endurance athletes and AF development has yet to be established in clinical studies.13

**Atherosclerosis**
Endurance exercise presumably protects against coronary artery plaque formation as marathon running has been shown to reduce cardiovascular risk factors.16 However, Mohlenkamp and colleagues quantified coronary artery calcification using computed tomography and found that despite having Framingham risk scores lower than age-matched controls, male marathon runners had calcium scores that were not significantly different from those of the controls.32 A coronary artery calcium score of 100 or higher was present in 36% of runners. Similarly, Schwartz and colleagues assessed 50 veteran male marathon runners and 23 sedentary control subjects using coronary computed tomographic angiography. The two groups were similar in age, resting blood pressure, height, smoking history, total cholesterol levels, and LDL cholesterol levels. Marathon runners had significantly lower resting heart rate, weight, body mass index, and triglyceride levels, and higher HDL cholesterol levels. However, compared with controls, the marathoners had higher total plaque volume, calcified plaque volume, and noncalcified plaque volume. As well, when the two groups were compared there was no difference in lesion prevalence, diameter of the stenosis, lesion area, or lesion length.16

The metabolic and mechanical stress to coronary arteries generated by excessive running offers a potential explanation for the increased coronary artery atherosclerosis in the marathoners.16 Michaelides and colleagues found that exercising for as long as 60 minutes resulted in higher oxidative stress and vascular endothelial dysfunction with deterioration of vascular elastic properties.33 Increased sustained levels of catecholamines, persistent and prolonged tachycardia, and elevated
blood pressure could also contribute to atherosclerosis. In addition, many of the runners started marathon running in middle age, which may have reduced their cardiovascular risk as measured by Framingham risk score but not their life-long risk exposure to poor lifestyle habits. More than half the runners in the Mohlenkamp study were former smokers and 5% were current smokers. Marathon runners may also believe that exercise negates the effects of a poor diet.

**Conclusions**

While we know the minimum amount of exercise needed to improve health and decrease comorbidities, many questions remain unanswered regarding the impact of endurance exercise on the heart. This is partly because invasive techniques to assess electrical and histological changes cannot be justified in healthy study subjects. In addition, the highest levels of performance often reflect an obsessive commitment to training that is akin to addiction, and competitive athletes are seldom willing to participate in comparative studies that require detraining.

There appears to be a law of diminishing returns that applies as exercise extent increases, and there is almost certainly a U-shaped curve with adverse cardiac effects at the highest levels of exercise duration and intensity. The reason some athletes are affected and others are not is likely multifactorial, with genetic, lifestyle, and environmental influences all playing a part.

Studies have indicated that the left ventricle is not vulnerable to the effects of long-term endurance exercise, while the precise effects of cumulative injury to the right ventricle remain to be elucidated. There are transient changes in the RV after endurance exercise, but it is uncertain if they result in development of a proarrhythmic substrate. RV fibrosis with intense exercise has been observed in humans and confirmed in animal models. At present, it remains unclear whether a separate exercise-induced acquired form of arrhythmogenic right ventricular cardiomyopathy exists in addition to familial ARVC, or if exercise unmask a genetically mediated predisposition to ARVC. The fact that atrial fibrillation is seen predominately in middle-aged athletes engaged in sport activities over a long period suggests that years of endurance training are necessary to develop AF. Further data are needed regarding the effect of endurance exercise on the risk and development of CAD.

Whether the evidence gathered so far will change the way endurance athletes train and practise is uncertain given that most high-level athletes do not engage in their sports for the health benefits alone, and may be motivated more by the need for an adrenaline "high," a desire to reduce stress, and a commitment to competition. Exercise addiction is not well defined in the literature; however, it is known to co-occur with substance dependence and eating disorders. In addition, there may be other exogenous factors not yet addressed in these studies, such as use of performance-enhancing drugs, which may have long-term adverse cardiac effects. Based on the evidence to date, however, we can say that some exercise is good but more is not always better.

**Competing interests**

None declared.

**References**


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