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The Exercise Rehabilitation Paradox: Less May Be More?

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Background: Debatably, the most commonly prescribed lifestyle modification for cardiovascular health involves daily exercise training (ET) and physical activity. Exercise has numerous known health benefits on blood pressure, lipid profile, weight loss, and glucose metabolism. However, controversy exists regarding the link between excessive endurance ET and harmful cardiac effects.

Methods: We review the current literature and discuss the numerous known adverse effects of endurance ET on cardiac function.

Results: Excessive endurance ET may negatively affect cardiac anatomy, play a role in osteoarthritis and coronary artery disease development, and increase the risks of cardiac arrhythmia and sudden cardiac death.

Conclusion: More ET may not always be better when it comes to endurance ET, and optimal ET dosing regimens are clearly needed.

Keywords: *Arrest–sudden cardiac, arrhythmias–cardiac, death–sudden cardiac, exercise, exercise therapy*

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INTRODUCTION

Daily exercise training (ET) and physical activity (PA) have long been praised as necessary components of lifestyle changes in the promotion of cardiovascular (CV) health. In association with a healthy diet, ET has known benefits such as lowering blood pressure, improving lipid profiles and glucose metabolism, and aiding weight loss.[1,2] Studies have also reported the association of improved morbidity and mortality with increasing cardiorespiratory fitness levels and PA.[3-6] The most recent evidence-based guidelines on PA, presented by the World Health Organization, recommend at least 150 min of moderate intensity aerobic ET or 75 min of vigorous intensity aerobic ET per week.[7] Even with this evidence, most of the US and global populations (>50%) do not meet the PA levels recommended by these guidelines.[3-6] On the opposite side of the spectrum, excessive ET and specifically excessive endurance ET (EEE), defined as ET >60-90 min in 1 session, occur in a much lower subset of the population (≤5%).[3,8]

In contrast to popular belief, more ET may not always be better, and current research has provided evidence of EEE being associated with deleterious cardiac effects. We discuss the evidence regarding the benefits of regular ET and PA on the heart and the adverse effects of EEE. We summarize structural changes that occur both acutely and with chronic exposure to ET, including the association with cardiac arrhythmia and the risk of sudden cardiac death (SCD). We also present data regarding the role that high intensity ET plays in the development of osteoarthritis (OA) and coronary artery disease (CAD) and the likely mortality benefits. Finally, we provide recommendations on the optimal ET dosing regimen and suggest screening tests for various populations.

CARDIAC FUNCTION AND STRUCTURE DURING EXERCISE TRAINING

Increases in cardiac output occur with ET in healthy adults from resting levels of approximately 5 L/min to >20-25 L/min with maximal effort and as high as approximately 40 L/min in elite athletes.[9-11] Additionally, left ventricular stroke volume also increases with elevations in end-diastolic volume and myocardial contractility.[9,12] Although in the acute setting variable increases in stroke volume are influenced by factors such as age, sex, and genetics, the adaptations seen in chronic ET occur irrespectively.[9,13-16] Both left ventricular dilatation and hypertrophy have been reported with chronic aerobic ET, termed ET-induced cardiac remodeling. Similar adaptations have also been seen in the right atrium and right ventricle that collectively have positive effects on physiologic performance and lead to increased cardiac output with ET.[9,15]

With the sustained increases in cardiac work required by certain athletes and sports (such as running, swimming, rowing, and cycling), the structural adaptations that would otherwise be considered to hold poor cardiac prognosis have been described to be typical findings in "athlete's heart."[17-21] Unfortunately, some of the remodeling that occurs does not completely regress to normal levels, even after prolonged periods of deconditioning when the athlete has retired from sustained EEE.[17,22] Marathon running is an

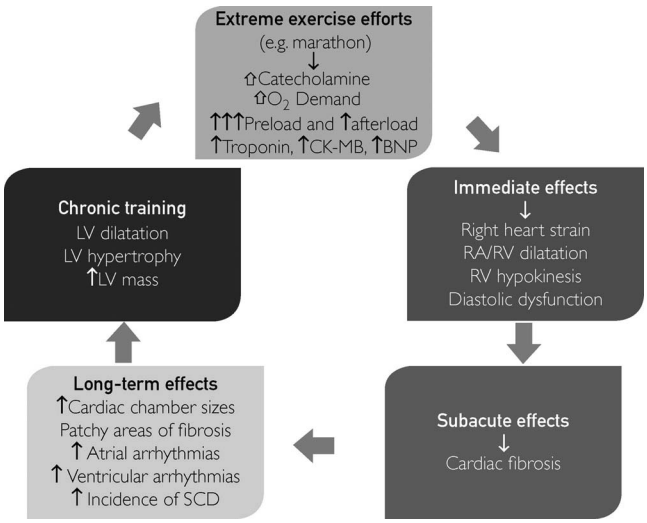

Figure 1. Proposed pathogenesis of cardiomyopathy in endurance athletes.[17] BNP, B-type natriuretic peptide; CK-MB, creatine kinase-MB; LV, left ventricular; O_2, oxygen; RA, right atrium; RV, right ventricular; SCD, sudden cardiac death. Reproduced with permission of Elsevier.

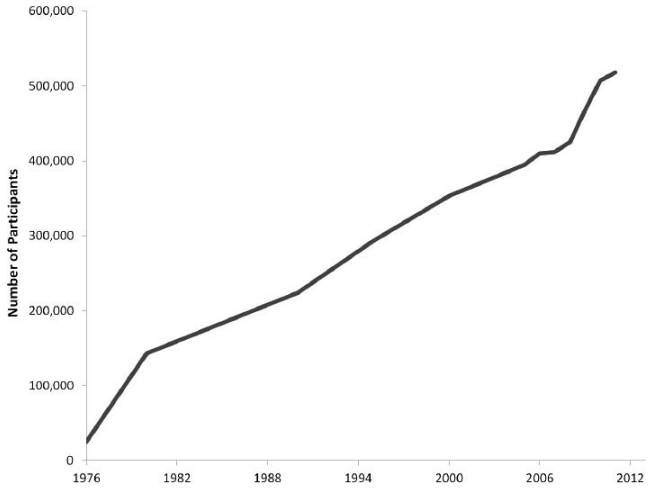

Figure 2. Marathon running trends in the United States from 1976-2011.[1] Copyright Missouri Medicine. Used with permission.

example of a prolonged demand endurance sport; although of uncertain clinical significance, cardiac serologic markers associated with damage (troponin T, creatinine kinase-MB, B-type natriuretic peptide) are elevated in >30% and up to half of the athletes both during and after marathon running.[17,23-27] Approximately one-third of marathon runners experience acute dilatations in cardiac chambers along with right ventricle and ventricular septum dysfunction that are restored at rest.[3,8,17,28-30] However, the continuous exposure to strenuous ET and the resulting volume overload and strain cause dilatations within the cardiac chambers and may lead to patchy myocardial scarring within the right ventricle and right atrium in the long term.[17-19,31-33] O'Keefe et al propose a potential pathogenesis of cardiomyopathy in endurance athletes (Figure 1).[17]

RUNNING AND OSTEOARTHRITIS

Susceptibility to OA has been linked to genetics, age, ethnicity, diet, obesity, and female sex.[34,35] Weight loading and joint injury exacerbated by obesity and repetitive overuse can increase the progression and development of OA.[34,35] The perception that, over time, running has negative effects on joints and joint function is common, and running has been proven to increase the risk of knee trauma and injuries, contributing to the development of OA.[35,36] However, running also leads to weight loss, likely cartilage thickening, and prevention in cartilage proteoglycan loss, factors that offset the risk of OA development.[36-42] Williams studied 74,752 runners and 14,625 walkers during a 5-7 year period and found that compared to those who ran less than 1.8 metabolic equivalent of task (MET)–hours per day (MET-h/d), those who ran 1.8-3.6 MET-h/d had 18% and 35% reductions in the risk of OA and hip replacement, respectively.[36,42] The risk reductions seen by exceeding 1.8 MET-h/d did not differ significantly. More important, body mass index (BMI) was strongly associated with OA (5.0% increase for every kg/m^2, $P=2\times10^{-8}$). Exercises other than running increased the risk of OA by 2.4% ($P=0.009$) for each MET-h/d, independent of BMI. As such, one can reasonably assume that the significant risk reduction for OA seen with running may largely be a result of the association with lower BMI.[36]

Kujala et al evaluated the risk of OA in 2,049 ex-professional athletes during a 21-year period who were involved in endurance sports (long-distance running, cross-country skiing), mixed sports (soccer, ice hockey, basketball, track and field), and power sports (boxing, wrestling, weight-lifting, and throwing sports).[43] The risk of OA was increased in all forms of competitive sports: in endurance athletes (odds ratio [OR] 1.73, 95% confidence interval [CI] 0.99-3.01, $P=0.063$), in mixed sports athletes (OR 1.90, 95% CI 1.24-2.92, $P=0.003$), and in power sports athletes (OR 2.17, 95% CI 1.41-3.32, $P=0.0003$). However, the authors noted that the endurance athletes seemed to require hospitalization for OA at older ages compared to the other groups.[35,43]

Marti et al retrospectively compared former long-distance runners to bobsleigh riders and healthy untrained controls and found that subchondral sclerosis, osteophyte formation, and joint space narrowing were significantly increased in the runners compared to the other groups.[44] Additionally, running pace was a stronger predictor of subsequent degenerative hip disease than running mileage, suggesting that long-term, high-intensity running, along with high-mileage running, may be a potential risk factor for hip OA.[44]

SUDDEN CARDIAC DEATH

Cardiac arrhythmia and SCD have long been associated with endurance sports. Partly driven by awareness and promotion of the beneficial effects of regular ET, the number of Americans taking part in marathons and half-marathons has increased as much as 25 times in the past 40 years (Figure 2).[1,3,17,25,28,45] Kim et al reported incidence rates of cardiac arrest and SCD during marathon and half marathon races as 1 in 184,000 and 1 in 259,000, respectively.[25] Although this study may have underestimated actual rates by including half-marathon runners and only including events during the marathon itself and not during the postrace period, the fatalities nevertheless remain relatively

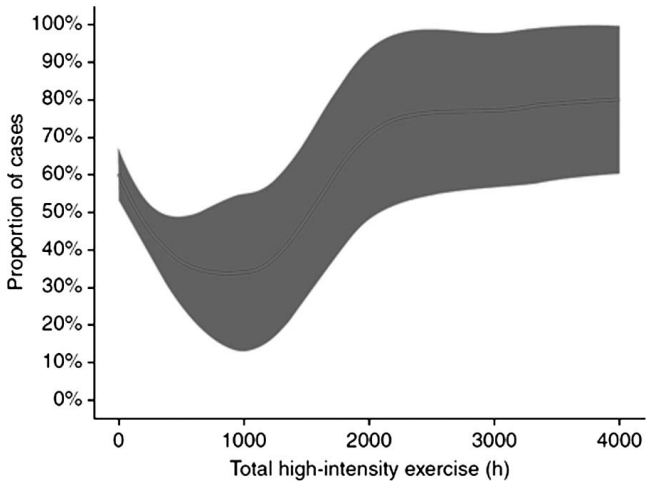

Figure 3. The percentage (95% confidence interval) of participants with lone atrial fibrillation according to accumulated high-intensity physical exercise. Reproduced with permission from Calvo et al.[57]

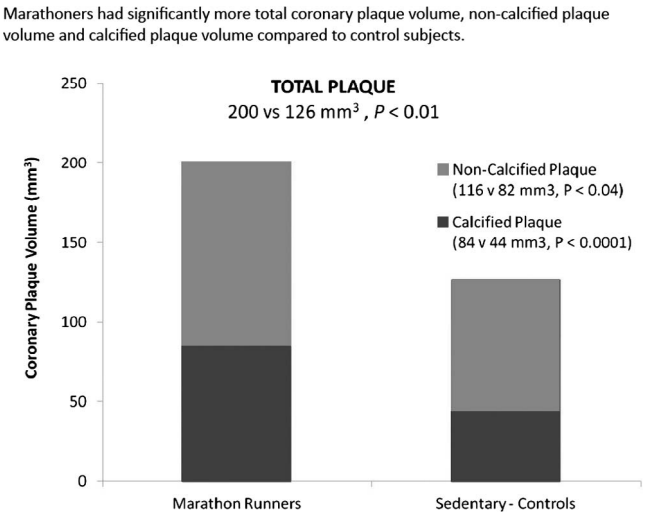

Figure 4. Total plaque burden in marathon runners vs control subjects shows that runners had significantly higher total coronary plaque volume, noncalcified plaque volume, and calcified plaque volume.[1] Copyright Missouri Medicine. Used with permission.

uncommon and much rarer than the incidence seen in collegiate athletes (approximately 1 in 40,000 per year for all athletes).[3,24,46,47] Interestingly, the final 1 mile of marathon courses has been shown to account for half of SCDs that occur during the race.[17,25,26]

EXERCISE TRAINING AND CARDIAC ARRHYTHMIA

When considering the changes in cardiac structure and the scarring that occur with long-term EET, one can reasonably presume that EEE promotes an arrhythmogenic environment, especially in the pliable chambers of the heart (the atria and the right ventricle).[17,48,49] Approximately a 5-fold increased risk of atrial fibrillation (AF) in athletes (marathon runners, ultramarathon runners, professional cyclists) has been documented in the literature.[17,19,48,50-53] Although speculative, some of the proposed mechanisms underlying AF development in chronic EEE are increases in atrial size, vagal tone, sympathetic tone, bradycardia, catecholamine fluxes, right ventricle cardiomyopathy, and atrial wall fibrosis and stretching.[3,17,54] Indeed, left atrial enlargement has been found in up to 20% of competitive athletes, possibly contributing to AF development.[17,54] Drca et al evaluated 44,410 men and reported an increased risk (risk ratio [RR] 1.19, 95% CI 1.05-1.36) of AF development later in life in 30-year-olds who had participated in intense ET for >5 hours per week and a decreased risk (RR 0.87, 95% CI 0.77-0.97) in those who participated in moderate ET (walking or bicycling).[55] The Cardiovascular Health Study reported a similar finding in adults >65 years.[56] ET intensity and lifetime quantity both showed a U-shaped relationship with AF (P=0.02), with light to moderate ET significantly associated with lower AF incidence and high-intensity ET significantly associated with increased risk of AF.[3,56] Calvo et al evaluated the impact of PA quantity in patients with lone AF and found a correlation between lone AF and vigorous endurance training (cumulative ≥2,000 hours) (Figure 3).[57]

Although electrocardiographic abnormalities in athletes are usually considered benign, complex findings may suggest a need for further investigation. A study of 46 high-level endurance athletes with ventricular arrhythmia reported a predominance for left bundle branch morphology with right ventricle arrhythmogenic involvement in 59%, and this abnormality was suggested in another 30%.[58] Even in the absence of familial arrhythmogenic right ventricle cardiomyopathy, ventricular arrhythmia in high-level athletes is frequently found to originate from mild right ventricle dysfunction, and EEE may possibly act as a trigger.[32]

PLAQUE BURDEN AND CORONARY ARTERY DISEASE

One of the potential benefits of ET, based on years of epidemiologic data, is the contribution to the reduction of risk factors for cardiovascular disease (CVD).[9,59-62] Despite popular belief and the presumption that running protects against coronary artery plaque formation, recent data suggest that long-distance runners are at increased risk of higher levels of atherosclerosis and CAD than those who engage in less-intense ET.[1,3,8] Möhlenkamp et al reported increased coronary event rates with elevated coronary artery calcium scores (CACs) (21% with CAC ≥400, P=0.002) and prevalent myocardial fibrosis in marathon runners compared to risk factor–matched controls.[3,63] A 2014 study evaluating long-term marathon running (completing at least 1 marathon per year for 25 consecutive years) found increased total plaque, calcified plaque, and noncalcified plaque volume in the group of marathon runners compared to the sedentary control group (Figure 4).[1,3] One explanation for these findings may be because of vascular function, oxidative stress, and the production of atherogenic particles induced with intense long-term repetitive ET.[1,64] In a 2011 randomized clinical trial, short ET duration (30 min) was associated with favorable antioxidant and vascular effects, while long (30-60 min) ET duration was associated with adverse effects on vascular function.[64]

MORBIDITY AND MORTALITY

The Copenhagen City Heart study reported a remarkable 44% lower risk of mortality for joggers compared to non-

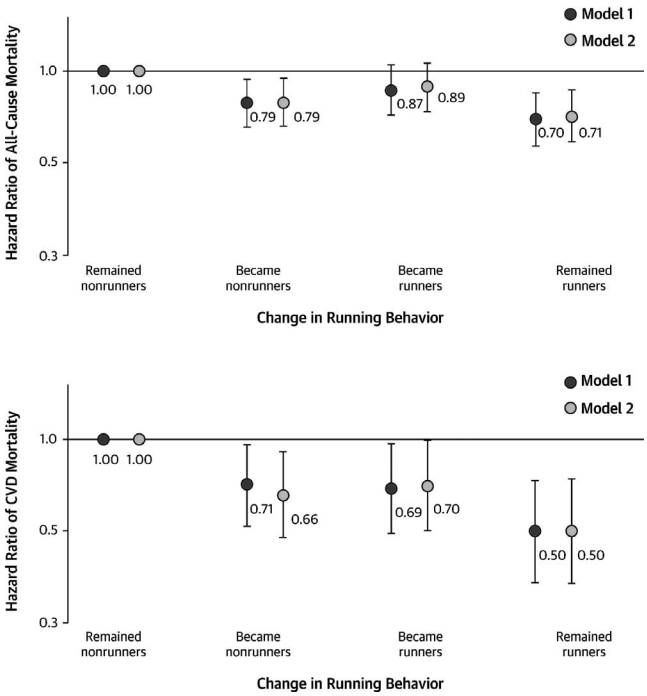

Figure 5. Hazard ratios of all-cause and cardiovascular disease (CVD) mortality by change in running behaviors. Model 1 adjusted for baseline age (years), sex, examination year, and interval between baseline and last examinations. Model 2 adjusted for model 1 in addition to baseline smoking (never, former, or current), alcohol consumption (heavy drinker or not), other physical activities except running (0, 1 to 499, or ≥500 metabolic equivalent of task–minutes per week), and parental CVD. The number of participants (deaths) in the groups of remained nonrunners, became nonrunners, became runners, and remained runners were 13,522 (1,013), 2,847 (141), 1,578 (131), and 2,700 (113) for all-cause mortality and 12,885 (376), 2,753 (47), 1,485 (38), and 2,616 (29) for cardiovascular mortality, respectively. The bars indicate 95% confidence interval, and hazard ratios are shown next to the bars.[66] Reproduced with permission of Elsevier.

joggers, with an age-adjusted increase in survival of approximately 6 years in both men and women.[29,65] Interestingly, the authors discovered U-shaped curves for mortality with respect to speed, frequency, and quantity of jogging, suggesting that the optimal benefit from jogging is seen in those who jog at a slow to moderate pace, between 1.0-2.5 hours per week 2-3 times per week.[29,65] Jogging at higher intensity and quantity appeared to actually diminish the remarkable gains in longevity that were obtained by moderate levels of jogging.[29,65] Lee et al evaluated 55,137 adults during a 15-year period and found that compared to nonrunners, runners had lower adjusted risks of all-cause (30%) and CVD (45%) mortalities, in addition to a 3-year benefit in life expectancy and 4.1 years in CV life.[66] Even running at slow speeds (<6 miles/hour) for short periods of time (5-10 min/day) had markedly improved mortality benefits (Figure 5).[66] Prior investigations support higher mortality benefits in individuals achieving MET levels >10.[42,67-69] Interestingly, persistent runners appear to get full mortality benefits compared to those who were running but stopped and those who were not runners. The former runners and nonrunners achieved only half the benefit.[44,66] Williams and Thompson reported mortality benefits in patients with prior myocardial infarctions (MIs): a CVD mortality risk-reduction average of 15% per every MET-h/d up to 7.2 MET-h/d.[70] Beyond 7.2 MET-h/d, a significant risk increase was noted, suggesting that the mortality benefits for patients with known heart disease and prior MIs have a benefit threshold of approximately 7 MET-h/d, the rough equivalent of 30 miles per week of running and 46 miles per week of walking.[70]

OPTIMAL DOSING AND RECOMMENDATIONS

Regular aerobic ET and a heart-healthy diet are recommended often as lifestyle modifications. However, ET regimens should be prescribed at proper dosages and intervals, just as medications. As mentioned earlier, less than half of American adults meet the minimum ET requirements set forth by the most recent Physical Activity Guidelines for Americans by the US Department of Health and Human Services; on the opposite end of the spectrum, a small population (approximately 5%) may be overdosing with too much ET.[3-6,8,71] The data suggest that even at levels below the recommendation (150 min/week of moderate or 75 min/week of vigorous aerobic PA) significant health benefits are seen. [65,66,72-74] In a 2014 study, Wen et al found that a 15-min walk produces the same benefits as a 5-min run, and a 105-min walk produces the same benefits as a 25-min run.[75] The maximal benefits of running appear to occur at low levels and at approximately 40 min/day or less.[42,65,66,72-75] Although marathons and triathlons are associated with some risk, that risk is not high, and athletes should be not discouraged from participating.[42] Of note, the typical sports that most individuals are involved in during adolescence, and some during adulthood (ie, football, soccer, basketball), do not involve sustained intense aerobic PA, the main pattern of concern for cardiac overuse injury.[28]

Specific ET guidelines and recommendations do not exist for patients >50 years with known CAD and CVD risk factors or prior MIs. Some researchers recommend CAC scanning, exercise stress testing, low-dose aspirin therapy, and statin therapy for this population.[42,76] Individuals with these risk factors who are considering initiating EEE or vigorous PA may benefit from some of the same recommendations. No screening protocol exists for athletes partaking in EEE. However, an acceptable strategy may involve posttraining measurement of cardiac biomarkers to monitor cardiac muscle injury, aortic pulse wave velocity to evaluate for arterial stiffness, and periodic echocardiography or cardiac magnetic resonance imaging to help further risk-stratify patients with structural remodeling and myocardial scarring and identify proarrhythmic substrate.[30,77]

CONCLUSION

The benefits of regular ET and PA along with a healthy diet and lifestyle are clear. Although the motivation to exercise varies for each individual, the current PA guidelines provide reasonable recommendations for the general population. Educating athletes who choose to participate in EEE about the health risks is important, although the risks are relatively low. Furthermore, the overall benefits of running far outweigh the risks for most. Further studies

are needed to develop consensus-based guidelines regarding athletics in special populations.

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