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Are There Clinical Cardiac Complications from too Much Exercise?

Thijs M.H. Eijsvogels, Ph.D.^{1,2}

Paul D. Thompson, M.D.³

Affiliations:

¹Research Institute for Sports and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom. ²Department of Physiology, Radboud University Medical Center, Nijmegen, The Netherlands. ³Division of Cardiology, Hartford Hospital, Hartford, Connecticut.

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Author for correspondence:

Dr. Thijs Eijsvogels, Research Institute for Sports and Exercise Sciences, Liverpool John Moores University, Tom Reilly Building, L3 3AF, Liverpool, United Kingdom
E-mail: T.M.Eijsvogels@ljmu.ac.uk. Tel. +44 151 904 62 64. Fax: +44 0151-904-6284

The dose-response association between physical activity and cardiovascular outcomes is well described (10). As little as 15 min/day of moderate-intensity exercise significantly lowers the risk for cardiovascular morbidity and mortality. Greater volumes yield greater cardiovascular benefit. However, the impact of extreme volumes of exercise on cardiovascular health is under debate (9), since some studies present evidence of adverse clinical outcomes in endurance athletes who perform exercise volumes at the extreme upper end of the physical activity continuum. These observations raise the possibility that high doses of exercise have deleterious cardiac effects.

Potential acute cardiac complications

Among the early evidence of adverse cardiac effects in athletes was the observation that joggers in Rhode Island had a 7 times higher risk of sudden cardiac death (SCD) during exercise compared to rest (26). Nevertheless, the relative risk (RR) of an exercise-induced SCD was significantly higher in men with low levels of habitual physical activity (RR=56, 95%CI: 23-131) compared to men who perform the highest level of habitual activity (RR=5, 95%CI: 2-14) (24). The incidence of cardiac arrest among athletes is considered low, and estimated at 1 per 200,000 during marathon running (12). The risk appears to be higher in men (0.9 per 100,000 runners) *versus* women (0.16 per 100,000 runners), and bystander cardiopulmonary resuscitation and a non-hypertrophic cardiomyopathy cause of SCD are significant predictors of survival in collapsed runners (12).

SCD with exercise is rare, but exercise-induced increase of cardiac troponin concentrations is common (23). In fact, every runner participating in a Boston Marathon study demonstrated a post-exercise increase in cardiac troponin subunit I, and 54% of the study population exceeded the cut-point for diagnosing a myocardial infarction (8). Although an increase in cardiac troponin concentrations is associated with non-reversible cardiac damage in clinical populations, it is possible that this exercise-induced release does not represent cardiac damage (23). The observation that troponin concentrations return to baseline values below the clinical threshold within 24 – 72 hours post-exercise reinforce this hypothesis (21).

Performance of endurance exercise also affects structure and function of the cardiac chambers. A study in triathletes found a reduction in left ventricular and left and right atrial sizes following the Hawaii Ironman Triathlon (6). Furthermore, significant reductions in left and right ventricular ejection fraction have been observed in athletes performing prolonged exercise (14, 17), with larger decrements in the right heart. The greater vulnerability of the right

ventricle is due to the exposure of a substantial exercise-induced increase in wall stress ($\approx 125\%$) imposed on its thin wall compared to a moderate increase in wall stress ($\approx 4\%$) of the thick wall of the left ventricle (15). All changes in cardiac function are believed to be transient, with a recovery to normal function within 24 to 48 hours post-exercise.

Potential long-term cardiac complications

The possibility that high volumes of lifelong exercise training may lead to adverse cardiac remodeling and subsequent development of cardiovascular diseases is known as the “*Too much exercise hypothesis*”. Although evidence is conflicting (7), some observations are noteworthy. For example, myocardial fibrosis (i.e. scarring of cardiac tissue) have been found in endurance athletes. A total of 14 studies used cardiac magnetic resonance imaging to assess the presence of cardiac scarring and found myocardial fibrosis in 30 of the 509 athletes (5.9%) (27). Interestingly, the prevalence of myocardial fibrosis varied between 2.1% and 50% of the study population. More years of exercise training and a greater number of completed marathons and ultramarathons were associated with the risk for myocardial fibrosis (28). The majority of the athletes demonstrated fibrosis near the right ventricular insertion points or within the intraventricular septum. The location of the areas may suggest that the development of myocardial fibrosis results from repetitive exposure to myocardial micro-trauma and/or to exercise-induced dilatation of the right ventricle (27).

Another intriguing observation is the potential risk for accelerated atherosclerotic coronary artery disease in athletes. A German study found increased coronary artery calcification (CAC) scores in middle-aged runners who participated in ≥ 5 marathons compared to an age and Framingham risk score matched control group (18). These findings were reinforced by an American study, which showed that total coronary plaque volume (200 *versus* 126 mm³, $p < 0.01$), calcified plaque volume (84 *versus* 44 mm³, $p < 0.0001$) and non-calcified plaque volume (116 *versus* 82 mm³, $p = 0.04$) were all higher in marathoners compared to controls (22). The underlying mechanisms responsible for the increased coronary artery calcification in runners are currently unknown, but exercise-induced disruption of laminar flow and/or acute, exercise-induced increases in parathyroid hormone levels (3) may contribute to accelerated calcification. It is also not clear that the increased CAC score are threatening since dense coronary calcification is associated with a lower risk for future cardiovascular events (4).

The association between physical activity patterns and the risk for atrial fibrillation (AF) appears to be a J-shaped curve. Data from the CARDIOrespiratory FITness study demonstrated that fit AF patients had a lower risk for AF recurrences during follow-up compared to unfit AF

individuals (20). Also, AF patients who increased their physical fitness during an exercise program had a greater ablation-free drug-free freedom from AF compared to AF patients who failed to improve their fitness (20). In contrast, among those athletes at the upper end of the physical activity spectrum, there appears to be an increased risk of AF. Swedish cross-country skiers who participated in more cross-country races (hazard ratio (HR): 1.29, 95%CI: 1.04 – 1.61) or had faster finishing times (HR: 1.20, 95%CI: 0.93 – 1.55) were at greater risk for AF (1). Furthermore, others have reported a significant association between years of exercise training and the risk for AF and atrial flutter in Norwegian cross-country skiers (19). These observations clearly show that both physically inactive individuals and high exercise volume endurance athletes are at an increased risk for AF, whereas moderate exercise training reduces AF risk. The exercise training induced increase in vagal tone and left atrial enlargement may contribute to the higher AF risk in athletes (25).

Genetic vulnerability to exercise

There is also evidence that exercise may accelerate the development of cardiac complications in individuals with genetic mutations. A retrospective study including 87 desmosome mutation carriers for arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) found that mutation carriers who were endurance athletes (n=56) developed symptoms at a younger age, were more likely to meet the ARVD/C disease criteria (82% *versus* 35%, $p < 0.001$), and had a lower lifetime survival free of ventricular arrhythmias ($p = 0.013$) and heart failure ($p = 0.004$) compared to non-athlete mutation carriers (n=31) (11). These findings are consistent with several animal studies. Age-related increase in right ventricular volume was significantly greater in heterozygous plakoglobin-deficient mice compared to wildtype mice (13). Furthermore, the presentation of ARVD/C phenotype appeared to be accelerated by exercise training in plakoglobin-deficient mice but not in wildtype mice. Similar findings were observed in plakophilin-2 (5) and desmoplakin deficient mice (16), suggesting that exercise training accelerates ARVD/C development in mutation carriers. Whether genotype to phenotype development is also accelerated in other genetic cardiac diseases such as hypertrophic cardiomyopathy and long QT syndrome is currently unknown.

Conclusion

The performance of endurance exercise has direct effects on the heart. Most potentially deleterious responses appear to be transient (troponin release, cardiac dysfunction) or very rare (sudden cardiac arrest/death). There is increasing interest in the cardiac effects of lifelong

exposure to high volumes of exercise training. Recent studies suggest that lifelong endurance athletes have an increased prevalence of myocardial fibrosis and coronary artery calcification compared to non-exercising peers. The clinical implications of these observations are unknown, but the causes and significance of these findings may differ between athletes and patients. Although exercise improves cardiovascular health and longevity for the majority of the (athletic) population (2), it may accelerate the genotype to phenotype development in mutation carriers of some genetic cardiac diseases.

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