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There has been long-standing debate as to whether intense endurance exercise provokes acute myocardial damage and whether cardiac remodeling associated with long-standing endurance training is entirely physiological. Despite the lack of concrete evidence on either side, the potential for serious clinical consequences, including life-threatening arrhythmias, elevates the importance of the debate. Studies have taught us that elite athletes enjoy excellent health, and athletic animal models consistently show up-regulation of molecular pathways, which are free of fibrosis and entirely different from those induced through pathological cardiac loading. On the other hand, extreme exercise has been associated with biochemical and functional evidence of acute damage, and some recent imaging techniques raise the possibility of small areas of myocardial scar. Moreover, some arrhythmias appear to be more prevalent amongst endurance athletes. Only large prospective trials will enable us to really assess the health benefits and risks of regular intense endurance sports.

Regular intense exercise is associated with structural, functional, and electrical changes of the heart, which are referred collectively to as the “athlete’s heart” (29). The most profound cardiac remodeling typically occurs in endurance athletes as a cause and effect of the sustained oxygen demands and requirements for very high cardiac outputs (27). The result is an increase in the volume of all four cardiac chambers and an increase in ventricular wall thickness and mass. Classically, the greater cardiac mass is believed to be due to an increase in myocyte size (hypertrophy) and number (hyperplasia) with little or no increase in extracellular matrix deposition (fibrosis), the latter being more characteristic of cardiac remodeling secondary to disease processes such as heart failure, hypertension, and valvular heart disease (22).

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terptrophy with patchy fibrosis of undetermined etiology. Natural causes." Although tragic, it is important not to amplify the significance of these exceedingly rare events. However, it was somewhat surprising that such a high-profile event did not stimulate inquiry as to why an elite 28-year-old athlete would be found to have "patches of myocardial fibrosis." Is this the exception or the rule in highly trained athletes? Were the patches of fibrosis a substrate for the arrhythmia that caused the sudden death? What other factors (*e.g.*, a subclinical viral infection) may have been responsible for this fibrosis? How can we identify risks for fibrosis and/or arrhythmias prior to such a tragic event? These are all contentious but extremely important questions. Although sudden cardiac death in young athletes is rare (0.6 to 3.6 in 100,000) (11,12,31,32), the impact on the wider community perceptions are profound. One strategy would be to retreat to the position of emphasizing that all such events are so rare as to not warrant further consideration. The other would be to evaluate intensively the interaction between endurance sports practice and cardiac remodeling so as to identify athletes at risk and prevent future events. The start of this process is to appraise openly the current evidence relating cardiac health to extreme exercise, thus identifying those areas that most likely are to provide the greatest future insights into whether exercise-induced cardiac remodeling represents an arrhythmogenic substrate.

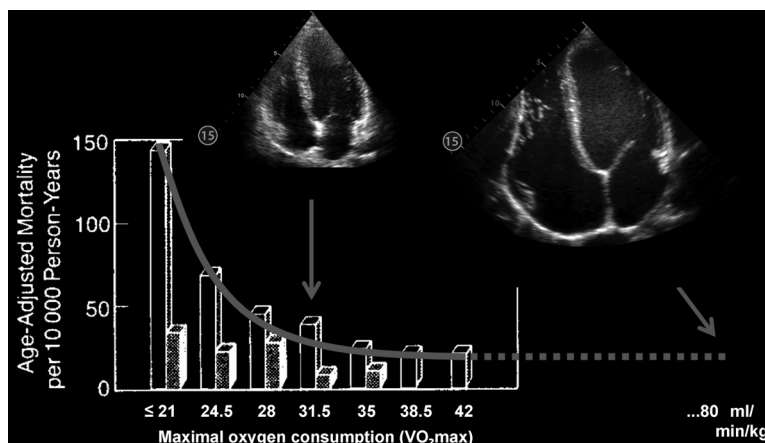


Figure 1: Epidemiological studies have failed to assess the extreme exercise loads and cardiac adaptation characteristic of highly trained endurance athletes. Data are presented from a study assessing mortality according to fitness levels in men (open bars) and women (closed bars) demonstrating an “asymptote of benefit” at a $\text{VO}_{2\text{max}}$ of approximately $35 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ (adapted from Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989; 262: 2395–401). Representative echocardiograms are superimposed. A 23-yr-old accountant with normal cardiac size and a $\text{VO}_{2\text{max}}$ of $33 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ is compared with a 23-yr-old elite cyclist with a $\text{VO}_{2\text{max}}$ of $81 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ and a heart that is more than twice as large. The data derived from populations in which exercise-induced cardiac changes are minimal cannot be extrapolated to include populations with an entirely different exercise-induced phenotype.

Epidemiology: Do Endurance Athlete’s Live Longer?

There is good evidence that elite athletes live longer and enjoy better health than the average person. A group of excellent studies detailed the health outcomes of Finnish athletes who had competed at an international level between the years 1920 and 1965. As compared with referents who had been certified sufficiently healthy for military service, endurance athletes lived longer (75.6 vs 69.9 years, $P < 0.05$) as a result of reductions in cardiovascular and cancer deaths (45). However, important confounders were detailed. Former athletes far more likely were to have never smoked (58.7% vs 26.5%), drank less alcohol, had gained less weight, and enjoyed a higher socioeconomic class. The extent to which these confounders may have effected outcomes is best illustrated in subsequent data from the same cohort, which identified that reductions in death were greatest in smoking-related diseases (100% and 86% reduction in deaths due to chronic pulmonary disease and lung cancer, respectively) (25). Thus, it is possible to conclude that it is healthy being an athlete but not necessarily that the health benefit is derived from exercise itself, as opposed to all of the other favorable lifestyle factors.

To isolate the health effects of endurance exercise, the ideal would be to compare “standard of care” with and without the addition of larger doses of strenuous endurance exercise. The standard of care is well established relatively and includes a healthy diet, abstinence from smoking, and regular moderate exercise. There is consistent data demonstrating that the benefits of moderate levels of exercise exceed those of less intense or less regular exercise (8,46,48), but unfortunately, the upper limits of the exercise studied is well below that applicable to endurance athletes. As an example, Blair *et al.* (8) described a delay in all-cause mortality in men and women with “high levels of fitness” but estimated an “asymptote of benefit” equivalent to a maximal oxygen uptake ($\text{VO}_{2\text{max}}$) of $35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. As illustrated in

Figure 1, such a finding is of very limited relevance to the current debate. Well-trained endurance athletes will commonly have a $\text{VO}_{2\text{max}}$ way in excess of this “asymptote of benefit.” Moreover, there is a strong association between $\text{VO}_{2\text{max}}$ and cardiac size (27,49), and the “asymptote of benefit” approximates the value at which exercise-induced cardiac remodeling becomes appreciable. This is a major limitation of the literature to date. Most studies that have assessed exercise dose have done so within a range insufficient to illicit the “athlete’s heart” phenotype, and yet, we frequently extrapolate the positive associations between exercise and health to presume that the cardiac remodeling also must be a manifestation of health.

There are no studies that have assessed health outcomes in relation to the presence or absence of the athlete’s heart phenotype. If exercise-induced cardiac remodeling includes a degree of fibrosis that is sufficient to result in clinical sequelae, then this would seem an important line of inquiry. In other words, is “too much of a good thing” indicated by the presence of profound remodeling? In one of the only studies to address this question, Pelliccia *et al.* (41) studied 114 athletes who had competed in two or more consecutive Italian Olympic teams. Over 8 years of follow-up, they found minimal changes in cardiac morphology or function and detected ventricular arrhythmias in only 5 athletes, none of which were serious. Whilst these results are reassuring, the incidence of cardiac arrhythmias in the general population of this age group (20 to 30 years) is exceedingly low, and hence, a far larger population needs to be studied through till middle age or later to have sufficient power to properly exclude an excess of clinical events. The importance of assessing arrhythmic risk in an appropriate age group is well illustrated by Baladesberger *et al.* (2) who reported an excess in sinus node disease, atrial fibrillation (AF), and nonsustained ventricular tachycardia amongst 62 ex-elite cyclists with a mean age of 66 years when compared with

62 age-matched golfers. The other highlight of this study was the choice of golfers as the referents given that they were active, though not excessively, and similarly had matched cardiac risk factors. van Saase *et al.* (51) similarly were able to compare the effect of exercise doses in the more extreme ranges by assessing longevity amongst participants in a Dutch skating race comparing amateur participants against highly trained elite skaters. As compared with the general Dutch population, they described a longer life expectancy amongst amateur participants but that the life expectancy of the elite skaters was no better than the general population, even in spite of the potential for a “healthy cohort” bias. The elite cohort was small and may have been underpowered to detect a benefit, but the study adds some weight to the concept that it may be possible to have “too much of a good thing.”

Is Endurance Exercise Associated With an Increased Prevalence of Arrhythmias?

There is now reasonably compelling evidence that some cardiac arrhythmias are associated with long-standing endurance training. In the general population, AF is the most common sustained arrhythmia, with a prevalence of approximately 0.5% in middle-aged subjects increasing to 10% in those in their 80s (44), and is responsible for considerable morbidity conferring an increased risk of heart failure and a fivefold increased risk in stroke (44). Increased cardiac mass and left atrial size are well-established risk factors for AF in nonathletic populations (52), but their relevance to AF in athletes is less well established. Pelliccia *et al.* (43) documented atrial enlargement in 20% of a large cohort of elite athletes ($n = 1,777$, 71% men, aged 24 ± 6 years) and found that only 0.8% had evidence of AF. However, like the aforementioned study from this group, the study's conclusions are limited by the fact that arrhythmic risk was ascertained at an age when AF is extremely rare. In contrast, almost every study conducted in endurance athletes of middle age or greater has observed an increase in AF risk, and left atrial enlargement frequently has been identified as an important risk factor for its development (2,14,16,19,24,35,36). In a meta-analysis, Abdulla and Nielsen (1) determined a 5.3-fold relative risk for the development of AF amongst studies matching athletes (almost exclusively men) to nonathletic controls.

Evidence for an excess in other cardiac arrhythmias is less well established. Biffi *et al.* (6,7) reported that ventricular ectopic beats were common amongst athletes but were a benign and potentially reversible phenomenon so long as underlying cardiac disease was excluded. In contrast, Heidbuchel *et al.* (20) observed a high incidence of major arrhythmic events (39%) including sudden cardiac death (20%) amongst 46 athletes who presented with frequent ventricular ectopy or nonsustained ventricular tachycardia who were followed for 5 years. Many of these athletes had structural and/or functional changes of the right ventricle (RV), which the authors argued may have been a result of extreme exercise training rather than an underlying familial predisposition (20,21,28). Other groups are finding it similarly difficult to exclude a potential for life-threatening

arrhythmias amongst athletes presenting with ventricular ectopy. Dello Russo *et al.* (13) studied athletes presenting with ventricular arrhythmias in the context of normal structure and function on cardiac imaging. Despite apparently normal hearts, electroanatomical mapping and guided RV biopsy was performed in 13 athletes and revealed myocardial inflammation, fibrosis, and/or fatty infiltrates in all. The authors attributed these findings to inherited heart disease (arrhythmogenic right ventricular cardiomyopathy), infectious myocarditis, or substance abuse, but it is impossible to exclude exercise as a potential confounding etiological factor. It would be intriguing to know what percentage of the larger study cohort ($n = 1,644$) might also have had evidence of myocardial inflammation and scarring. Such a study would be impossible to justify in a healthy athletic population, but it is important to recognize that the association between myocardial inflammation/fibrosis and cardiac disease is based on the assumption that fibrosis is not present in the average endurance athlete's heart. We seem happy to accept that extreme exercise is associated with skeletal muscle inflammation, damage, and myocyte regeneration (18) and yet seem resistant to considering that a similar process may occur within the myocardium.

Cardiac Remodeling in Athletes, Reversible or Fixed?

The concept of purely physiological remodeling in response to exercise training implies that myocyte hypertrophy and, to a lesser extent, hyperplasia is stimulated in response to a hemodynamic load and is downregulated once that stimulus is removed (22). Thus, we would expect that cardiac size would return to normal in athletes who detrain. However, Pelliccia *et al.* (42) prospectively followed 40 elite male athletes and found that whilst cardiac dimensions did decrease with detraining, substantial cavity dilation persisted in nine athletes (22%). Whilst it is possible that this reflects the “baseline” cardiac dimensions of these athletes (*i.e.*, that their larger than normal cardiac size represents a sports advantage and is therefore overrepresented amongst the self-selection of athletes), it is perhaps more likely that this represents an extent of permanent structural change induced through many years of athletic training. This latter premise also is supported by observational studies, which have described enlarged ventricular and atrial dimensions amongst retired endurance athletes and related the extent of these changes to the development of arrhythmias (2,16,17,30). It may be that exercise induces physiological remodeling only to a certain point beyond which there is a capacity for “overstretching.” This concept is akin to regurgitant valvular heart disease where remodeling initially compensates for the greater volume load (as evidenced by the complete regression of hypertrophy following surgical correction) but a point is reached whereby compensation is overwhelmed and a vicious cycle of increased apoptosis and fibrin deposition prevents cardiac structure and function from normalizing following treatment. There are obvious limitations in comparing the continuous and intermittent hemodynamic loads of valvular heart disease and exercise, respectively. However, the concept of a short- and long-term compensatory threshold deserves some consideration

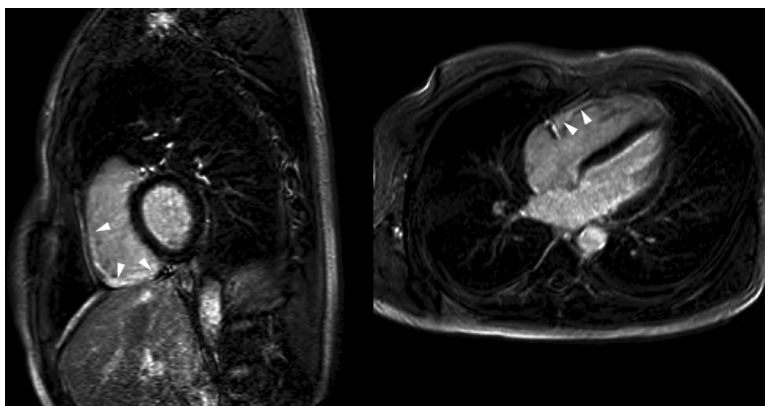


Figure 2: An example of right ventricular scar in a highly trained triathlete presenting with sustained ventricular tachycardia. Images are presented from a 40-yr-old ultraendurance triathlete who had competed for 20 yr prior to developing potentially life-threatening sustained ventricular tachycardia originating from the basal portion of the RV. Gradient-echo inversion recovery cardiac magnetic resonance images are presented following administration of gadolinium contrast. *Arrowheads* highlight the signal enhancement signifying fibrosis of the basal free wall of the RV. The question that cannot be addressed in such anecdotes is whether exercise contributes to, or causes, fibrosis such as this.

in the athlete with profound cardiac remodeling combined with fatigue, performance failure, and/or arrhythmias. Perhaps the concept of “over training” indeed can be extended to the heart.

Can Intense Exercise Cause Acute Myocardial Damage?

In almost all recent studies of athletes following intense endurance exercise, acute increases in troponin and B-type natriuretic peptide have been demonstrated, especially when using high-sensitivity assays (47). Although these are relatively specific markers of myocyte damage and strain, respectively, their identification does not automatically imply *permanent* myocardial injury. Training adaptation is underpinned by the physiological principal of “super-compensation” following exercise-induced injury. In most settings, this results in functional improvements, enabling the athlete to better tolerate the same physiological stress in the future. This is likely to also be true of the heart. However, it is also possible that following a more profound or more frequent exercise stimulus, the recovery processes may be insufficient to compensate for the extent of injury, thereby resulting in permanent alterations in cardiac structure and function. Of some intrigue is the disproportionate degree to which the RV seems vulnerable to exercise-induced fatigue or damage, as compared with the LV. A meta-analysis of 23 studies concluded that intense endurance exercise provoked only a mild decrease in LV ejection fraction, which was at least partially attributable to changes in cardiac loading in the postrace setting. In contrast, a number of recent studies have reported decrements in RV function, which are far more substantive than those observed for the LV (26,37,38,40,50). Also, whilst multiple studies have documented that there is no relationship between biomarkers of cardiac injury and changes in LV function (47), two recent studies have documented moderately strong inverse correlations between the decrease in measures of RV function and the increase in release of troponin and B-type natriuretic peptide (26,38). The potential mechanisms that may explain the susceptibility of the RV to exercise-induced strain and injury have been reviewed extensively elsewhere (21) and may be of

importance given the fact that exercise-induced arrhythmias are also most commonly of RV origin (4,20).

Is There Direct Evidence for Exercise-Induced Cardiac Fibrosis?

Histology provides the only direct evidence of fibrosis, and in the case of the heart, this involves an invasive procedure with significant risks. Thus, biopsies are performed in those athletes in whom there is a high pretest probability of identifying pathology, and hence, it is unsurprising that inflammation and/or fibrosis is identified in a considerable proportion (13,28,54). Although the commonly held perception is that a biopsy provides all of the answers, most commonly, inflammatory infiltrates and fibrosis are non-specific and the etiology can be deduced only by other clinical factors. Even findings such as fatty infiltration are not as specific as one might expect (3). The implication of this is that it can be difficult to deduce whether myocardial infiltrates are caused by viral infection, an inherited cardiomyopathy, or by exercise itself. The investigator should therefore maintain an open mind.

An accurate noninvasive surrogate of fibrosis would enable us to compare large populations of athletes and non-athletes to determine whether fibrosis is indeed more common in highly trained athletes. Perhaps the most promising tool for identifying fibrosis noninvasively is by combining cardiac magnetic resonance imaging following gadolinium contrast. Cell necrosis and fibrosis lead to leaking of gadolinium into the extracellular space, and this can then be identified using gradient-echo inversion recovery imaging as a bright signal contrasting with the normal myocardium, which appears black (Fig. 2). This delayed gadolinium enhancement (DGE) technique has been investigated in small cohorts of athletes, and whilst it appears that DGE tends to be absent in athletes with modest training histories (37,39,50), four recent studies have each reported DGE in 12% to 50% of extensively trained veteran athletes (9,26,34,53). We identified DGE in 5 of 39 well-trained endurance athletes and found that those with DGE had a more extensive history of training and had greater cardiac dimensions, particularly of the RV (26). However, in each of these studies, the patches

of DGE have been very small and have tended to be clustered around the septum and RV insertion points, a region that may indicate local mechanical stresses rather than extensive fibrosis. On the other hand, this technique may underestimate diffuse fibrosis because of the technique's reliance upon contrast in intensity between normal and abnormal tissue. Novel techniques may be more relevant for assessing whether low-grade diffuse fibrosis accompanies exercise-induced remodeling of the myocardium (15,23). However, of greatest importance is the fact that there are no studies in which DGE has been associated with arrhythmias or other clinical events in athletes, and until such a time, the clinical significance of these findings is limited.

Evidence for and Against Exercise-Induced Myocardial Fibrosis in Animals

Animal models have been used successfully to illustrate the differences between cardiac remodeling secondary to exercise as opposed to pathological loading conditions. The molecular mediators of "pathological" hypertrophy (natriuretic peptides, vasoactive hormones, and catecholamines) are quite different from those that mediate hypertrophy as a result of exercise (trophic hormones such as insulin growth factor), possibly as a result of the chronic versus intermittent nature of the load excess (5). Pathological hypertrophy induced by aortic banding includes cellular apoptosis and expansion of profibrotic elements and frequently progresses to cardiac dysfunction, whereas the increase in myocyte mass is relatively "pure" in mice forced to swim regularly (33). However, against this backdrop of reassuring evidence are a number of small animal studies in which myocardial inflammation and fibrosis have been induced when more extreme exercise interventions have been introduced. Chen *et al.* (10) forced rats to swim strenuously for 5 h and found that this provoked myocardial necrosis and inflammatory infiltrates. Extending the evidence from a single bout of extreme exercise to a regular intense training load, Benito *et al.* (4) instituted a strenuous 18-wk treadmill running regime in young rats, estimating that this was the equivalent of 10 years of endurance exercise training in humans. As compared with the sedentary control rats, there was an increase in atrial and right ventricular inflammation/fibrosis in the "marathon rats," and perhaps most importantly, this was associated with a greater potential for inducible ventricular arrhythmias (42% vs 6%, $P = 0.05$). The similes with human data are important. As previously discussed, single bouts of extreme exercise in humans also can induce biochemical and functional evidence of myocardial damage, whilst decades of exercise training may result in permanent changes in cardiac structure. The other striking similarity between the human and murine data is the predilection for effects on the RV, as opposed to the LV. The difference is that there is no direct evidence linking chronic changes to arrhythmias in humans.

Important Questions That Remain to be Addressed

Beyond the current debate as to whether endurance exercise has the potential to cause cardiac damage, fibrosis, and arrhythmias, a critical clinical question is why some athletes are affected whilst others are not? It seems that very few

endurance athletes develop issues, whilst the majority thrives on massive volumes of high-intensity exercise without developing any adverse health consequences. What explains this individual variability? There are a number of hypotheses that are all plausible but largely unsubstantiated. Firstly, athletes frequently train through viral illnesses, and it may be that the combination of low-grade myocardial inflammation and exercise promotes minor degrees of cardiac damage that may become clinically relevant years later (possibly after accumulated episodes). Secondly, it may be that there are important genetic influences. We are used to associating genetic mutations with some cardiac disease phenotypes, but it is also possible that milder degrees of genetic risk, such as a combination of specific polymorphisms, may result in weakness of the cardiac structure only when combined with years of extreme hemodynamic stress. Thirdly, training practices may be influential. Just as excessive training and insufficient recovery may promote musculoskeletal damage, so might "overtraining" be associated with myocardial injury. Finally, there may be an element of chance. It may be that small patches of fibrosis are not so uncommon in athletes but only rarely form in such a manner as to manifest arrhythmogenic potential. It is likely that a combination of these risks may explain individual susceptibilities to exercise-induced damage and clinical events, and we have a long way to go before we will be able to understand these in a manner sufficient to enable risk prediction and preventive strategies.

A second important question is whether the excess of arrhythmias and potential for exercise-induced cardiac remodeling extends beyond intense endurance sports? The majority of the literature has focused on well-trained participants in sports such as marathon running, cycling, triathlon, and cross-country skiing because it is these athletes who sustain the greater exercise loads and in whom cardiac remodeling is most profound. However, this pertains to a minority of the regularly exercising public. Team sports, such as basketball and the football codes, are more popular, and there are little data on which to assess whether these athletes are placed at an excess risk of arrhythmias and/or exercise-induced cardiac damage. Similarly, we do not know whether the "weekend warrior" who trains only a few hours per week but then challenges his or herself with a major endurance event places him or herself at an increased risk of arrhythmias. These will be important questions for the future. When assessing whether extreme exercise may induce proarrhythmic remodeling, it makes some sense to start with those doing the most exercise. However, the public health implications will be better clarified as these investigations extend to a more comprehensive understanding of all sports, in all doses, in all people.

Conclusion

There is accumulating evidence that extreme exercise can cause short-term injury and chronic remodeling of the athlete's heart, but the clinical significance of these changes is uncertain. This should stimulate investment into large prospective studies adequately powered to evaluate clinical end points including arrhythmias. With an increasing proportion of today's society enjoying the challenges and benefits of endurance sport, it is time to more accurately quantify the potential risks.

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