Exercise-induced arrhythmogenic right ventricular cardiomyopathy: fact or fallacy?

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This editorial refers to ‘Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes†, by A. La Gerche et al., on page 998

The cardiovascular benefits of regular exercise are established; individuals exercising regularly have an average life expectancy of 7 years longer than their sedentary counterparts. Indeed exercise is regarded as one of the most potent and cost-effective treatments dispensed by health professionals in the management of an adverse risk profile for generalized atherosclerosis. Such benefits are achievable with relatively modest doses of exercise amounting to 6–10 METS (metabolic equivalents) per day and are devoid of the side effects associated with usual drug therapy. Analogously to pharmacological treatments, it is recognized that exercise exhibits an inverted J-shaped dose–benefit response with respect to musculoskeletal injuries; however, the concept that intensive exercise may exert a detrimental effect in individuals with normal hearts is rarely entertained and has never been investigated in large cohorts. The majority of highly trained athletes exercise intensively for several hours per day, resulting in workloads of 200–300 METS per week which is 5–10 times greater than the exercise recommendations for preventing coronary atherosclerosis.

Cross-sectional studies in athletes demonstrate modest increases in cardiac size with preserved indices of systolic and diastolic function and high scores during objective assessment of functional capacity. Adverse cardiac events in athletes are also low and most frequently confined to those harbouring hereditary or congenital cardiac abnormalities. These facts support the widely held notion that exercise is beneficial irrespective of the dose and, contrary to the haemodynamic circumstances associated with cardiac pathologies, the paradigm has evolved that ‘the athlete’s big heart is beautiful’.

The past three decades have witnessed somewhat of a paradox consisting of an increase in obesity and cardiac morbidity due to lack of habitual exercise as well as a simultaneous rise in the number of individuals participating in gruelling ultra-endurance events which are well in excess of the usual exercise recommendations. There are > 500 marathon races in the USA and Europe and > 1 million participants each year, and this figure is projected to rise by at least 5% each year. Coinciding with high participation rates in ultra-endurance events, a plethora of studies have emerged demonstrating transient increases in serum concentrations of biomarkers of cardiac damage associated predominantly with impaired left ventricular (LV) myocardial relaxation; up to 50% of marathon runners exhibit raised serum cardiac troponin concentrations. The precise significance of this transient phenomenon is uncertain, but limited cardiac magnetic resonance imaging (MRI) studies in small cohorts immediately post-race have failed to demonstrate obvious features of myocardial inflammation. However, it is plausible that repeated myocardial injury may be associated with myocardial inflammation and fibrosis, resulting in a substrate for arrhythmogenesis and myocardial dysfunction. A small number of case reports in humans and experimental studies in animals have demonstrated myocardial fibrosis in individuals taking part in chronic intensive endurance exercise. The 5-fold increase in the prevalence of atrial fibrillation in veteran endurance athletes is probably the most compelling suggestion that too much exercise may be ‘cardio-toxic’ in predisposed individuals. The proposition is supported by reports of sino-atrial disease, heart block, and complex ventricular arrhythmias in apparently healthy athletes. Additionally, failure of cardiac dimensions to regress to baseline levels several years after retiring from competitive sport may be a marker of adverse cardiac remodelling.

The focus on the athlete’s heart has consistently centred on LV physiology and structure. The right ventricle is relatively neglected but is subject to the same preload as the left ventricle during exercise. Whereas resting pulmonary vascular resistance and right ventricular (RV) afterload are considerably low at rest, the substantial increase in cardiac output coupled with a relatively minimal decrease in pulmonary vascular resistance during exercise may be associated with exercise-induced pulmonary artery pressures exceeding 80 mmHg in some athletes. Hypothetically, repeated and prolonged bouts of massive surges in pulmonary arterial
pressure may result in adverse electrical and structural remodelling of the right ventricle.

La Gerche et al. have now attempted to progress their hypothesis that intensive exercise is associated with RV dysfunction and structural abnormalities. In a study of 40 healthy endurance athletes, the investigators used 2D and 3D echocardiography and echocardiographic parameters of myocardial deformation at baseline, immediately post-endurance race, and 1 week after the race to assess cardiac function. The results revealed enlarged RV dimensions associated with impaired systolic function post-race. In contrast, LV volume was slightly reduced due to septal shift from the stretched right ventricle and only LV filling was impaired. The investigators noted a correlation between biomarkers of cardiac damage and the magnitude of RV systolic function but not with LV systolic function, a relatively novel phenomenon that has not been observed in the majority of previous studies examining LV function post-endurance events. Race duration correlated with the level of RV dysfunction. Interestingly, left atrial filling pressure and pulmonary artery pressure were low, indicating that the main limiting cardiac factor for functional capacity may be a compromise in ‘forward surge’ from acute RV injury from a persistently high afterload. A small number of athletes (n = 5; 13%) also exhibited delayed gadolinium enhancement indicative of myocardial fibrosis in the interventricular septum just prior to racing, but the study did not provide an adequate explanation for the observation. Almost all parameters of cardiac function returned to normal within a week post-race. The study reveals transient and reversible RV dysfunction following intense exercise and begs the hypothetical question whether repetitive long-standing bouts of arduous exercise result in the development of an acquired form of arrhythmogenic right ventricular cardiomyopathy (ARVC) (Figure 1).

A study by Heidbuchel previously reported complex RV arrhythmias in 46 symptomatic athletes participating in endurance sports, predominantly cycling. Of these, almost 25% exhibited RV structural abnormalities following RV angiography, nearly 50% revealed RV structural abnormalities on MRI, and ~ 90% fulfilled diagnostic criteria for ARVC. A subsequent study by Ector et al. comparing RV structure and function using detailed RV angiography in endurance athletes with a history of symptomatic RV arrhythmias (n = 22) vs. matched endurance athletes without RV arrhythmias (n = 15) demonstrated a significantly reduced RV ejection fraction in athletes with arrhythmias. These observations have been persuasive enough for some to speculate the existence of a syndrome of ‘exercise-induced ARVC’, phenotypically identical to the familial disorder, but driven predominantly by training rather than a genetic substrate. In a recent paper, La Gerche et al. identified desmosomal gene mutations in only 12.8% of 47 athletes (42% fulfilling task force criteria for ARVC) presenting with complex ventricular arrhythmias of RV origin, a figure much lower than that reported for familial ARVC (27–60%), supporting the concept that the ARVC phenotype may be acquired and not necessarily attributed to a genetic predisposition relating to desmosomal proteins at least, although other unrecognized genetic factors could not be excluded. Further support for the notion was provided by a recent animal model study by Benito et al. demonstrating training-dependant RV fibrosis and increased arrhythmia inducibility after chronic endurance exercise.

Whereas the aforementioned appears to provide a convincing account in support of exercise-induced chronic RV damage, there are many pertinent prerequisites that require clarification before the concept can be unanimously accepted in the sports cardiology community. The athletes reported by Heidbuchel et al. and Ector et al. presented with ominous symptoms, including one case of aborted sudden cardiac death, and should not be considered to represent the usual asymptomatic endurance sportsmen. Furthermore, adverse events occurred in the youngest athletes, who would have expectedly trained for the lowest number of
cumulative life time hours, thus refuting the fact that chronic intensive exercise is the only mechanism for RV damage. The rat model reported by Benito et al. showed complete regression of fibrosis following a short period of detraining. Although electrophysiologic al studies to assess RV arrhythmia induction were not performed in the rats prior to sacrifice, these results indicate that the increases in the genetic and biochemical markers of fibrogenesis during exercise could represent a form of physiological super-compensation akin to that observed in skeletal muscle aimed to sustain wall stress during chronic intensive exercise (Figure 1). Finally, failure to demonstrate a high prevalence of ARVC causing desmosomal mutations in athletes with sinister RV arrhythmias should not automatically lead to an assumption that an acquired form of the disorder is possible. The yield for ARVC gene mutations in sporadic cases of the disorder is low; in a previous study by La Gerche et al., only 2 of 47 athletes who underwent genotyping had familial disease.

The current study by La Gerche et al. revealed transient, reversible RV dysfunction following an ultra-endurance event and may be regarded as another publication to raise the burgeoning speculations that regular participation in intensive endurance exercise may induce arrhythmogenic substrates in some athletes. The study is small in size by virtue of its design and methodology, and fails to provide information relating to electrocardiographic markers of RV damage or excitability, nor any intermediate follow-up data. Nevertheless, the results provide food for thought and the data should be embraced to galvanize more detailed and longitudinal assessment of large groups of endurance athletes. The potential for such projects is enormous considering the colossal increase in participation rates in endurance events such as the marathon. The long-term conclusions of the authors may appear preposterous to some, but could prove to be the retrospective ‘elephant in the room’.

Conflict of interest: none declared.

References

Corrigendum
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Regrettably, on p. 1834, line 33, the most prevalent sulphonylurea used in the ACCORD trial should have read ‘glimepiride’ instead of ‘glyburide’.

The authors would like to apologize for this error.

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