Arrhythmogenic right ventricular remodelling in endurance athletes: Pandora’s box or Achilles’ heel?

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This editorial refers to ‘Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes’¹, by A. La Gerche et al., on page 1998.

The vessel coming from the right ventricle goes into the lungs to distribute spirits necessary for their nutrition. The left ventricle . . . closes more tightly, because the human intelligence is born of this left part of the heart, and controls the rest of the soul . . .

Hippocrates (460–375 BC)

The sudden death of a young athlete is a highly tragic event that has major emotional repercussions on society. Efforts to understand and prevent such catastrophes have witnessed half a century of scientific enquiry into left ventricular adaptation and disease in athletes. In contrast, the right ventricle, perceived in the early medical literature to be of little clinical consequence, has been largely neglected in sports cardiology. However, a growing number of persuasive studies have emerged in recent years to indicate that the right ventricle may hold far greater significance for the cardiac health of athletes than has been previously appreciated. Whilst it is well recognized that individuals harbouring cardiac diseases risk fatal arrhythmias during exercise,¹ the idea that intense, repetitive training might promote an abnormal cardiac substrate in a previously healthy heart is relatively novel. A burgeoning body of literature has raised the possibility of irreversible cardiac remodelling, myocardial fibrosis, ventricular arrhythmias, and even sudden death in some former endurance athletes.² This notion has been received with caution by the mainstream scientific community, perhaps driven by justifiable fears of generating an erroneous public perception that even modest exercise might be harmful. This controversial topic has become all the more relevant given the paradoxical societal increase in obesity and cardiac morbidity due to lack of habitual exercise, paralleled by a simultaneous increase in the number of individuals participating in gruelling ultra-endurance events which are well in excess of the exercise recommendations for general well-being. Questions relating to the optimal ‘dose’ of exercise for long-term health have therefore become the subject of intense scientific scrutiny.³

The concept of exercise-induced arrhythmogenic right ventricular cardiomyopathy (ARVC) has been pioneered by a decade of research from the group of Heidbüchel and La Gerche. Through a series of elegant studies, they have demonstrated that the thin-walled right ventricle is subject to far greater haemodynamic stresses during exertion than the left ventricle at similar workloads,⁴ and that prolonged exercise is associated with transient right ventricular (RV) dysfunction and elevated biomarkers of myocardial damage.⁵ The hypothesis has emerged that repeated haemodynamic insults to the right ventricle may eventually lead to an acquired, genotype-negative RV cardiomyopathy, phenotypically indistinguishable from the inherited condition.⁶ In support of this notion, further studies by the same group have revealed that only a small fraction of athletes with such a phenotype harbour desmosomal mutations to indicate primary ARVC,⁶ and that potentially fatal arrhythmias frequently arise from a dysfunctional right ventricle.⁷ In clinical practice, the difficulty in identifying endurance athletes at risk of sudden death from RV arrhythmias lies in the fact that many such individuals reveal increased biventricular dimensions or mild systolic impairment; as many as 14% may exhibit anterior pre-cordial T-wave inversion, and ventricular extrasystoles of RV origin are also relatively common.⁸,⁹ Risk stratification techniques such as the induction of ventricular tachycardia during electrophysiological testing are contentious to say the very least, and, therefore, more reliable, ideally non-invasive, methods are required in the assessment of endurance athletes with phenotypic features overlapping with ARVC.

In the current issue, the study by La Gerche et al. attempts to elucidate this complex diagnostic ‘grey zone’.¹⁰ Seventeen endurance athletes with established ventricular arrhythmias, 10 apparently healthy athletes, and 7 relatively sedentary control subjects were investigated using echocardiography, cardiac magnetic resonance...
imaging (CMRI), and invasive haemodynamic monitoring. Echocardiographic RV dimensions, fractional area change, systolic tricuspid annular velocities, and estimated pulmonary artery systolic pressures were assessed at rest and during exercise. The RV pressure–area ratio was used as an echocardiographic surrogate of systolic reserve during rest and exertion. Cardiac magnetic resonance imaging (CMRI) was performed in all individuals except for eight athletes with an implantable defibrillator in situ. Systolic reserve at rest and during exertion was estimated according to CMRI-derived right and left ventricular pressure–volume ratios, measured with the assistance of catheters in the pulmonary and radial arteries, respectively. The study revealed similar resting measures of biventricular function across groups. However, the ability to augment RV function during exercise was attenuated in athletes with established arrhythmias, whilst left ventricular function was augmented to a similar degree during exercise in all cohorts. Serum levels of natriuretic peptides correlated inversely with the capacity to augment RV function during exercise. Importantly for the applicability of the results to routine clinical practice, exercise echocardiography identified athletes at risk of arrhythmias with greater accuracy than exercise CMRI combined with invasive haemodynamic monitoring. The authors conclude that ventricular arrhythmias in endurance athletes are associated with RV dysfunction which is most evident during the haemodynamic stress of exercise. They further postulate that exercise echocardiography and CMRI may represent potent non-invasive tools for the identification of endurance athletes at risk of arrhythmias and sudden death (Figure 1).

The study is novel and important in several regards. As with so much of their previous work, the group combine an intricate understanding of basic science, cardiac pathophysiology, and the use of avant garde diagnostic techniques. The study design and execution is bold, innovative, and elegant, and supports the notion that exercise assessment of cardiac function, including the previously neglected right ventricle, should become a standard component of cardiac evaluation in athletic individuals. Physicians will be familiar with the phenomenon of the healthy athlete with a dilated left ventricle that appears mildly dysfunctional at rest, but which rapidly augments to normal contractility as resting myofibrils are recruited with gentle exercise. In a similar manner, La Gerche et al. have previously utilized exercise strain rate imaging to demonstrate normalization of apparent regional RV dysfunction in healthy endurance athletes. The present study reveals the utility of exercise imaging in the reciprocal

![Figure 1](image-url)
scenario of unmasking subtle cardiac dysfunction which appears ostensibly normal at rest. Recent data from Perrin et al. have demonstrated the potential of exercise testing to expose latent electrical instability in asymptomatic ARVC gene carriers. The results of the present study may therefore find application in identifying subclinical myocardial abnormalities in similar individuals. Finally, the study adds further credence to the argument for a ‘gene-elusive’ or exercise-induced form of ARVC in former endurance athletes. Until recently the subject of scepticism and even derision, evidence for what is known by many as the ‘Leuven syndrome’ has now become almost irrefutable, and is supported by similar reports in high impact publications from other reputable researchers.

The study is, however, not without its shortcomings. Methodological questions surround the observations that peak power output and exercise heart rate did not differ between healthy endurance athletes and supposedly detained arrhythmic athletes, as well as the potential influence of background beta-blocker therapy on functional capacity in the latter cohort. The athletes presenting with RV arrhythmias are described by the authors as exhibiting mild disease, yet a large proportion had implantable defibrillators in situ. More than a third fulfilled imaging criteria for ARVC, which by definition requires the presence of RV regional wall motion abnormalities that would automatically place them in a clearly abnormal category. Detailed results of simple investigations such as the 12-lead electrocardiogram are not reported, yet comparisons between ARVC patients and healthy athletes with RV dilatation and concomitant T-wave inversion suggest that isoelectric ST segments, low amplitude QRS complexes in the precordial leads, and deep Q waves favour pathology. Hence whilst receiver-operator curves for functional RV imaging revealed impressive diagnostic ability, it remains to be seen how much incremental information these complex measures would provide over inexpensive, widely accessible tests such as resting, exercise, signal-averaged, and ambulatory electrocardiography. Consequently, as with any study of risk stratification techniques derived retrospectively from proven high risk clinical cohorts, the prospective applicability to truly ‘grey zone’ individuals, such as asymptomatic athletes detected through pre-participation screening, cannot be assumed. Validation of the results in larger cohorts may be difficult to achieve in view of the invasive nature of the study protocol. Finally, whilst the authors, who are undoubtedly world leaders in RV imaging, report high reproducibility for their exercise parameters, measures such as RV fractional area change during exertion are likely to prove challenging in non-expert echocardiography laboratories, whilst simultaneous invasive haemodynamics with exercise CMRI must surely reside within the realms of ‘science fiction’ for most.

Despite these limitations, the study by La Gerche et al. is an important and unique addition to the scientific literature. Comprehensive evaluation for cardiac pathology predisposing to ventricular arrhythmias in athletes must aim to replicate the intense haemodynamic stresses during which risk is at its greatest. Importantly, assessment of the right ventricle should form an integral component of risk assessment in athletes presenting with potentially lethal rhythm disturbances. Until only recently considered to be a Pandora’s box of spurious and detrimental public messages, the right ventricle and its potential for adverse remodelling is increasingly acknowledged to represent the true Achilles’ heel of the endurance athlete.

Conflict of interest: none declared.

References