Tackling an unmet need in sports cardiology: understanding exercise-induced cardiac remodelling and its clinical consequences

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The field of sports cardiology has surpassed many hurdles over the past decades. From initial findings of cardiac enlargement by clinical examinations and chest radiographs, through the better phenotyping of exercise-induced cardiac remodelling (EICR) on electrocardiography, echocardiography and cardiac MRI, our understanding of the spectrum of the athlete's heart has greatly advanced.

THE LIMITS OF RESEARCH ON EICR

Prior scientific endeavours have largely focused on describing EICR in healthy athletes and contrasting this with pathological mimics. For example, early studies contrasted the 'physiological' left ventricular wall thickening associated with athlete's heart to hypertrophic cardiomyopathy.[1] These studies provided some invaluable clinical tools enabling better discrimination of physiology from pathology, although recent observations have questioned the dichotomous separation between healthy 'physiological' myocardial hypertrophy and disease.

Several questions exemplify current knowledge gaps and the limits of our understanding of EICR. Why does EICR incompletely resolve on detraining? Why does myocardial scar exist in some of the fittest athletes? Why are arrhythmias more prevalent in ostensibly healthy athletes? Could certain features of EICR predispose some athletes to arrhythmias and thus discriminate between athletes with a lower and higher arrhythmic risk?

DEFINING THE DETERMINANTS OF EXERCISE-INDUCED CARDIAC REMODELLING

Despite all the advances, there are persisting uncertainties regarding the determinants and prognosis of EICR. Foremost is the need to dissect the relationship between environmental and genetic influences on EICR and the potential for arrhythmias. This requires a detailed assessment of the prevalence of rare genetic variants as well as more common genetic traits that are likely to influence cardiac structure. To facilitate this, cardiac remodelling needs to be measured as accurately as possible but, in addition, the environmental stimulus for remodelling needs to be quantified more rigorously than it has in the past.

Some studies have provided a gold standard assessment of fitness through quantification of maximal oxygen consumption. However, this does not necessarily reflect the duration, intensity and volume of training. Describing athletic performance has mainly been limited to the type of sport, level of competitiveness and reported training hours. As an example, the finding of myocardial delayed gadolinium enhancement has been associated with longer cumulative times and distances of training and competition.[2 3] However, a more precise measurement of exercise load could provide the necessary granularity against which to assess genetic influences. Accurate quantification of training load is now possible through the analysis of personal activity tracking devices that are ubiquitous among athletic populations.

The hypothesis that athletes with extreme EICR are destined to become successful is attractive but has yet to be investigated. Moreover, the extent to which this is driven by genetic predisposition remains unknown. The genetic background of cardiac structure is complex as highlighted by the amount of genes associated to cardiomyopathies.[4] Moreover, greater cardiac remodelling is associated with a family history of hypertension which is another polygenic trait.[5] Arrhythmias such as atrial fibrillation may also have a (poly)genetic predisposition.[6] Atrial fibrillation is more prevalent among athletes but it is unclear whether this is a result of independent or synergistic influences of exercise and genotype. A careful quantitative approach for genetic predisposition is of critical importance.

Another limitation in the evidence regarding the determinants and significance of EICR is the scarcity of prospective data, especially long-term follow-up data. Only few carefully conducted prospective trials in sports cardiology have been published. Their results have added tremendous value to our understanding on how exercise dose determines cardiac remodelling.[7–9]

Finally, it also known, yet incompletely understood, that sex and ethnicity influence EICR and athletic performance.

INTRODUCING A PARADIGM SHIFT AND THE PRO@HEART STUDY

In order to provide unbiased and meaningful insights on the prognosis of the athlete's heart, the field of sports cardiology will need to shift away from cross-sectional trials and redirect focus into large-scale and long-term prospective trials, performing in-depth cardiovascular phenotyping in athletes from a young age and providing follow-up for structural, functional and electrical abnormalities until elderly age, irrespective of how their competitive career evolves.

Figure 1 illustrates our proposed view of future sports cardiology trials comprehensively evaluating and monitoring athletes from a young age, while identifying the different clinical phenotypes and investigating their potential determinants.

In a quest to fuel the field of sports cardiology with a second wind, we have initiated the Pro@Heart (Prospective Athlete's Heart) trial. The Pro@Heart trial is an international multicentre prospective cohort study with collaborators in Australia and Belgium. The long-term prospective design and comprehensive multimodality cardiovascular assessment will describe the

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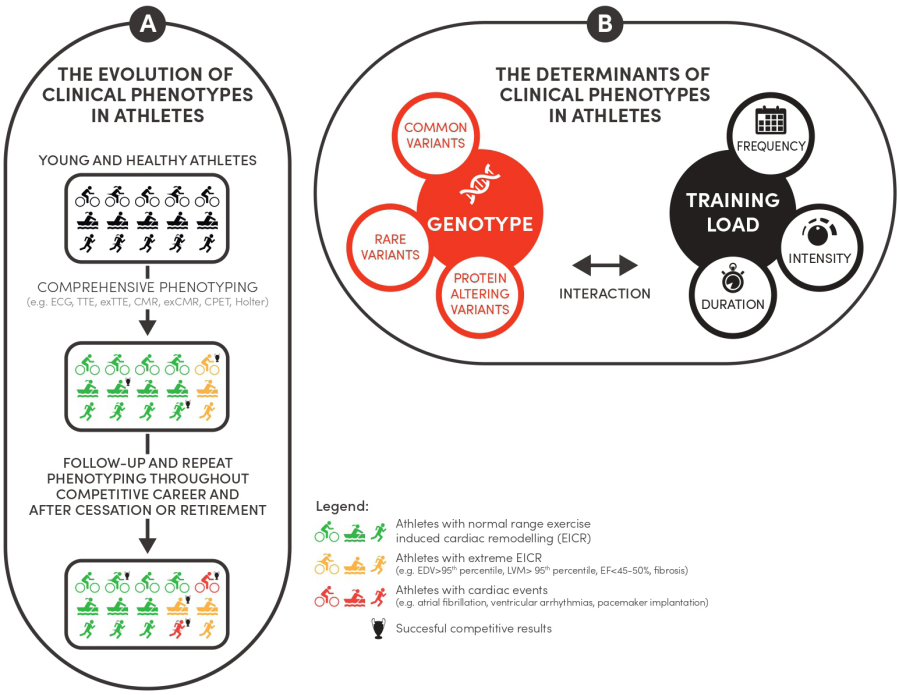

Figure 1 A proposed design of future trials in sports cardiology focusing on (A) a comprehensive and repeated assessment of young athletes in order to identify the different clinical phenotypes and (B) investigate the potential determinants of the clinical phenotypes such as genotype, training load and their interaction. CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; EDV, end-diastolic volume; EF, ejection fraction; exTTE, exercise transthoracic echocardiogram; LVM, left ventricular mass; TTE, transthoracic echocardiogram.

variability in structural, functional and electrical EICR in competitive endurance athletes; investigate the impact of training load, genotype, sex and ethnicity; and evaluate the associations with atrial and ventricular arrhythmias.

The future of sports cardiology will hopefully be enlightened by large, comprehensive, prospective and collaborative clinical trials accurately assessing training load while accounting for genetic factors.

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