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Review

Differentiating Exercise-Induced Cardiac Adaptations From Cardiac Pathology: The "Grey Zone" of Clinical Uncertainty

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ABSTRACT

Exercise-induced cardiac remodelling (EICR) refers to the cardiac structural and functional adaptations that occur in response to the hemodynamic stress of strenuous exercise. Differentiating physiological cardiac hypertrophy as a result of EICR from structural cardiac pathology may be challenging in clinical practice because of the phenotypic crossover between extreme forms of the "hearts of athletes" and mild forms of cardiomyopathy. This structural phenotypic overlap equates to a grey zone of clinical uncertainty. Specifically, asymptomatic athletes presenting with extreme left ventricular (LV) dilatation, LV wall thickening, or right ventricular (RV) dilatation require a systematic and integrative diagnostic approach to achieve accurate clinical differentiation. The combination of a careful clinical history and examination, appropriately used multimodality cardiac imaging, functional exercise testing, ambulatory rhythm monitoring, and occasional detraining typically provides the necessary data for diagnostic purposes and sports participation recommendations. Further clinical distinction of the hearts of athletes from cardiac pathology may emerge from future clinical and translational research efforts establishing exercise-related biomarker profiles and mechanisms underlying EICR adaptations.

RÉSUMÉ

Le remodelage cardiaque induit par l'exercice (RCIE) fait référence aux adaptations cardiaques structurelles et fonctionnelles qui se produisent en réponse au stress hémodynamique de l'exercice vigoureux. La différenciation de l'hypertrophie cardiaque physiologique à la suite du RCIE de la pathologie cardiaque structurelle peut être difficile dans la pratique clinique à cause du mélange phénotypique entre les formes extrêmes de « cœurs d'athlètes » et les formes légères de cardiomyopathie. Ce chevauchement phénotypique structurel équivaut à une zone grise d'incertitude clinique. Particulièrement, les athlètes asymptomatiques qui présentent une dilatation extrême du ventricule gauche (VG), un épaississement de la paroi du VG ou une dilatation du ventricule droit (VD) nécessitent une approche diagnostique systématique et intégrée pour parvenir à une différenciation clinique précise. La combinaison de l'anamnèse et de l'examen clinique minutieux, de l'imagerie cardiaque multimodalité utilisée de manière appropriée, de l'épreuve fonctionnelle à l'effort, de la surveillance ambulatoire du rythme cardiaque et du désentraînement occasionnel fournit habituellement les données nécessaires aux fins de diagnostic et les recommandations en matière d'activité physique. Une distinction clinique plus poussée entre les cœurs d'athlètes et la pathologie cardiaque peut ressortir des futurs efforts en recherche clinique et translationnelle établissant les profils et les mécanismes des biomarqueurs associés à l'exercice qui sous-tendent les adaptations du RCIE.

Sustained and repeated episodes of vigorous exercise lead to structural and functional cardiac adaptations, a process referred to as exercise-induced cardiac remodelling (EICR).[1-3] Although 1 cardinal manifestation of EICR, global cardiac enlargement, was first recognized more than a century ago,[4,5] more recent technological advancements in cardiac imaging have provided a more comprehensive understanding of the complex process of EICR. Moreover, diagnostic imaging tools have had a substantial impact in clinical sports cardiology practice by assisting in the differentiation of exercise-induced cardiac adaptations from occult cardiac pathology in athletes and highly active patients.

In clinical practice, there is often substantial overlap between physiological and pathologic cardiac hypertrophy, and the distinction between these 2 processes may be challenging, particularly in asymptomatic athletic patients. Practitioners charged with the care of such patients must balance the obvious need to accurately diagnose cardiac disease with the substantial negative consequences of misclassifying exercise-induced cardiac hypertrophy as occult pathology.

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Specifically, misinterpreting physiological cardiac hypertrophy leads to a myriad of undesirable and unnecessary consequences, including psychological stress, additional diagnostic testing, inappropriate implantable defibrillator placement, and exclusion from sports. Effectively navigating the "grey area" that exists between healthy exercise-induced cardiac adaptations and underlying pathologic cardiomyopathies requires an integrated and systematic diagnostic approach.

This review provides an overview of the physiology underlying EICR, sport-specific patterns of EICR, and a detailed summary of specific clinical areas of uncertainty (left ventricular [LV] dilatation, LV wall thickening, and right ventricular [RV] dilatation). Finally, a proposed clinical algorithm to assist in the differentiation of EICR adaptations from pathologic RV and LV cardiomyopathies will be discussed along with important areas of future research.

Exercise-Induced Cardiac Remodelling

Relevant exercise physiology

During exercise, the body's demand for oxygen increases in proportion to the intensity of exercise. To meet the increased metabolic demand of exercising skeletal muscle, pulmonary oxygen uptake increases (oxygen consumption [Vo_2]) along with the increased systemic transport of oxygen-rich blood, which is quantified as cardiac output (L/min). Peak oxygen consumption (peak Vo_2) is defined as the amount of oxygen uptake that occurs at an individual athlete's maximal volitional level of exercise. The Fick equation [Vo_2 = cardiac output $\times$ Δ (arterial $-$ venous O_2)] can be used to quantify the relationship between cardiac output and Vo_2. In the healthy human, there is a direct and inviolate relationship between Vo_2 and cardiac output.

Cardiac output, the product of stroke volume and heart rate, may increase upward of 5- to 6-fold during acute maximal exercise effort. The rise in cardiac output is attributable to a combination of parasympathetic nervous system withdrawal, sympathetic nervous system activation with subsequent heart rate increase, and increased preload. For the endurance athlete, stroke volume both at rest and during exercise may significantly increase with prolonged exercise training. Stroke volume is defined as the quantity of blood ejected from the heart during each contraction. Thus, cardiac chamber enlargement and the accompanying ability to generate a large stroke volume are direct results of endurance exercise training and are the cardiovascular hallmarks of the endurance-trained athlete. The stroke volume increase during exercise is a result of increases in ventricular end-diastolic volume and, to a lesser degree, sympathetically mediated reduction in end-systolic volume.[6]

The hemodynamic alterations associated with exercise and athletic training represent the stimulus for EICR and cardiac enlargement. Importantly, exercise-related hemodynamic alterations, specifically changes in cardiac output and peripheral vascular resistance, vary according to sporting discipline. Although overly simplistic, sporting disciplines can be generally categorized as isotonic/dynamic or isometric/static.[7] Isotonic exercise incorporates endurance sports and is associated with sustained elevations in cardiac output that affects all 4 cardiac chambers with reduced peripheral vascular resistance. Examples include long-distance running, swimming, and cycling. Isometric exercise incorporates primary strength training. In these activities, cardiac output remains relatively stable, but peripheral vascular resistance increases in short repetitive bursts. It must be emphasized that isotonic exercises vary with respect to the amount of concomitant isometric exercise, and sports with a combination of high isotonic/high isometric loads (eg, rowing) are typically associated with the most marked EICR. On the other end of the spectrum, sports including American-style football, power lifting, and track and field throwing events are characterized by a relatively isolated isometric load, during which marked rises in peripheral resistance equate to increased systemic arterial pressure/LV afterload with little impact on pulmonary vascular resistance or RV afterload.

EICR Structural and Functional Adaptations

Although crossover between sporting disciplines occurs, primary endurance and strength exercise are associated with relatively distinct forms of EICR,[8] as summarized in Figure 1. The relative "volume challenge" associated with endurance exercise typically leads to biventricular and biatrial dilatation, preserved systolic function, and enhanced diastolic properties.[9] In contrast, the relative "pressure challenge" inherent in strength exercise, and in some cases the mild to moderate resting hypertension that is common among strength-trained athletes,[10] is often associated with mild isolated concentric LV hypertrophy and preserved systolic function.[9] The right-sided chambers and left atrium are unaffected with pure strength training. The impact of vigorous isometric exercise on diastolic function remains an active area of research. Although preliminary longitudinal data from our group demonstrated a mild decrease in tissue Doppler–derived mitral annular velocities recorded in collegiate American-style football players after 1 season of competitive training (N = 24 American-style football players; basal septum E' [10.3 $\pm$ 1.6 vs 9.6 $\pm$ 1.7 cm/s; $P = 0.02$]; basal lateral LV E' [11.6 $\pm$ 1.3 vs 10.2 $\pm$ 1.4 cm/s; $P < 0.001$]),[11] the significance of these results is uncertain and represents an area of ongoing research.

Clinical Uncertainties

Clinical uncertainty 1: LV wall thickening

Although concentric LV wall thickening is not the most common manifestation of EICR, this pattern represents a "hypertrophic cardiomyopathy (HCM) mimicker" and thus represents the more challenging clinical scenario encountered in practice. The basis for this area of uncertainty lies in the small percentage of athletes and patients with HCM who overlap in measurements of LV wall thickness.[12,13] This overlap falls between 13 and 16 mm and has been termed the "grey zone" of concentric LV hypertrophy.[13]

To exclude the presence of pathologic LV hypertrophy, it is essential to define the incidence and magnitude of grey zone concentric LV hypertrophy.[13] In an early cross-sectional study of 947 elite, primarily white, Italian athletes, none demonstrated LV wall thickness in excess of 16 mm.[12] In addition, only 1.7% of the cohort measured in the grey zone, and all of these athletes demonstrated concomitant LV dilatation.[12]