Cardiac magnetic resonance imaging characteristics for the differentiation of athlete's heart from inherited cardiomyopathies

Benedikt Bernhard¹ · Babken Asatryan¹ · Christoph Gräni¹

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Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM) represent a group of inherited cardiomyopathies with highly variable phenotypic features [1]. Especially in early stages of the disease, an asymptomatic course is common, often accompanied with incidental diagnosis during routine clinical examination. Myocardial alterations may lead to left-, right- or biventricular structural and/or functional abnormalities, especially in the advanced stages of the disease and potential consecutive life-threatening ventricular arrhythmias with sudden cardiac death (SCD) [1–3]. However, a sizeable proportion of SCD occurs in previously asymptomatic, apparently healthy individuals, underlining the need for early diagnosis, adequate risk-stratification and correct indication for implantable cardioverter defibrillator (ICD) [4].

Over the past two decades, advances in noninvasive imaging and genetic sequencing have contributed importantly to our understanding of cardiomyopathies, and resulted in increased recognition of these potentially life-threatening but manageable conditions and their remarkable prevalence, conservatively estimated to be as high as 1/250 for DCM, 1/500 for HCM and 1/2000–1/5000 for ACM [5–8]. In addition, phenotypic mimics previously misdiagnosed as an inherited cardiomyopathy have been increasingly recognized in parallel to the implementation of more high-resolution imaging technologies. Nevertheless, diagnosis remains challenging due to the lack of specific clinical, electrocardiographic and imaging characteristics. Whilst genetic testing

helps in identifying asymptomatic family members of individuals confirmed to have a genetic cardiomyopathies, the incomplete penetrance, variable disease expressivity and to-date partial knowledge of the genetic architecture of cardiomyopathies are some of the challenges limiting the use of genetic testing for primary diagnosis [9]. In this setting, cardiac magnetic resonance imaging (CMR) has emerged as a key tool for the differential diagnosis of cardiomyopathies thanks to its high spatial resolution and excellent soft-tissue characterization [10]. However, inherited cardiomyopathies can show CMR features resembling non-pathological structural changes of the myocardium. This is particularly the case in exercise-induced cardiac remodeling, often referred to as ‘athlete’s heart’ (AH). Repetitive intense exercise, the core to the increasingly enhanced athletic activities, can result in long-term remodeling of the cardiovascular system and increases in cardiac dimensions and cardiac mass [11]. Male sex, endurance sports and higher training volumes were found to be associated with the extent of adaptations [12]. Endurance sports (e.g. cycling, long-distance running), associated with a volume overload, predominantly impact cavity sizes, while static sports (e.g. weight lifting), associated with pressure overload, have a disproportional higher impact on left ventricular (LV) wall thickness [13]. Structural, electrical and functional changes often include both ventricles and the atria, and AH may mimic DCM, HCM, and rarely ACM.

An accurate and timely delineation among these overlapping phenotypes is central to the patient’s management. While in HCM and ACM, exercise restriction is part of SCD prevention strategy; this can have severe and devastating impact on the career and quality of life in athletes incorrectly diagnosed with a heritable cardiomyopathy. Of note, the need for exercise restriction in patients with HCM is discussed controversially with recent evidence indicating that systematic exercise restriction is not fully justified [14–17]. In ACM families, cessation of competitive exercise activities

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✉ Christoph Gräni
christoph.graeni@insel.ch

¹ Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland

remains crucial not only for prevention of SCD in probands, but also in asymptomatic, pathogenic variant-carrier family members [14, 18]. Endurance sports can not only lead to features mimicking ACM, but also trigger the progression from carrier status to penetrant disease fulfilling the structural and electrical criteria of ACM, with ensuing increased arrhythmic risk [18, 19]. Data on the effect of static sport restriction is scarce [20].

Apart from its therapeutic considerations, sports restriction can also be a part of the diagnostic approach. Reversible LV hypertrophy after detraining, indicate an AH and makes the presence of HCM less likely [21]. Despite from the lack of evidence for a generalization of this approach, de-training elite athletes also impacts their career, underlining the need for precise non-invasive diagnostic modalities. On the other hand, missing the diagnosis of an inherited cardiomyopathy can delay appropriate prevention measures and therapy, in the worst-case scenario exposing the patient to the occurrence of a malignant ventricular tachyarrhythmia without ICD-protection.

In this context, Kübler et al. [22] aimed to identify imaging features that allow distinguishing AH from inherited cardiomyopathies by comparing CMR characteristics of patients with DCM, ACM and HCM and individuals with AH [22]. We congratulate the authors on this important study, that included a systematic analysis of 40 athletes and patients suffering from DCM ($n = 48$), ACM ($n = 18$) and HCM ($n = 14$). In line with previous studies, the authors were able to highlight several overlapping, as well as delineating features among the various entities. DCM was characterized by severely impaired LV ejection fraction (LVEF), and LV dilatation, while LVEF and LV end diastolic volume index (LVEDVI) were only slightly reduced in AH. Athletes showed reduced right ventricular EF (RVEF), RV enlargement and elevated LV myocardial mass. In contrast, HCM patients showed increased interventricular septum thickness and LV remodeling index, but lower RV myocardial thickness. In accordance with the recent knowledge establishing ACM as a mostly biventricular disease [20], the authors identified reduced LVEF, reduced LV stroke volume index (LVSVI), presence of LV late gadolinium enhancement (LGE) and LV wall motion abnormalities in patients with ACM. LGE showed high utility in delineating physiological remodeling from pathological alterations. Whilst it was only present in one patient with AH (5%), evidence for LGE was found in 57% of patients with HCM, 56% with ACM and 44% with DCM. Other studies have also found an association between LGE and outcomes in DCM [23], HCM [24], and ACM [25], underlining the prognostic value of this marker in inherited cardiomyopathies. As mentioned by the authors, LGE can be considered as a pathologic finding, indicating fibrotic changes of the myocardium.

Incidental findings of scar can indicate a ‘healed’ disease, such as myocarditis [26], ischemia [27], or corrected structural heart disease, as may be the case in the one athlete in whom Kübler et al. found LGE. Etiologies can be further defined according to the LGE distribution and localization. Similarly, LV and/or RV wall motion abnormalities such as hypo- and akinesia are often identified in all cardiomyopathy subtypes but, as shown in this study, are not seen in AH. Concomitant proportional enlargement of all cavities in the absence of other structural or functional abnormalities can be considered as a sign of AH. This form of remodeling allows for increased stroke volumes and hence higher cardiac output in athletes.

Strengths of the presented study are the multicenter design with a predefined image acquisition approach and the well-defined patient population with histologic confirmation of the diagnosis in the majority of participants. The study is limited to patients with pathological findings with an unequivocal definitive diagnosis and signs of advanced disease and elite athletes whose fitness can be expected to be in the highest percentile of the exercising general population, hence the study prevents drawing stronger conclusions. Furthermore, mostly endurance athletes were included while static sports were under-represented. Delineation between athlete’s heart, DCM, ACM and HCM will remain a challenge in patients with less clear diagnosis and overlapping phenotypes first presenting with unknown conditions. Prospective studies investigating such cases in the intermediate zone could help better define features distinguishing AH from early stages of inherited cardiomyopathies.

Besides the CMR characteristics identified by Kübler et al., previous work in this field found functional cardiac evaluation during exercise and parametric mapping, including extracellular volume (ECV) fraction to be useful in differentiating AH from structural heart disease [28, 29]. ECV has been shown to decline in individuals exposed to repetitive exercise since the cellular compartment expands with hypertrophy of myocytes [30]. On the contrary, ECV increases in several cardiomyopathy subtypes, thus it should also be taken into account in unclear cases. With regard to reference values, a recent meta-analysis including 983 athletes provides “normal ranges” on the distribution of LV/RV dimensions and LVEF in individuals classified as “healthy” and could help to define the maximum limit of cardiac adaptations estimated to be physiologic [11].

In conclusion, detailed analysis of CMR features can help to distinguish physiologic adaptation in elite athletes from inherited cardiomyopathies. Nevertheless, diagnosis cannot be made solely on imaging findings and all information on clinical presentation, personal and family history, and electrocardiogram findings should be implemented in differentiating athlete’s heart from inherited cardiomyopathies.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

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