Athlete's heart: diagnostic challenges and future perspectives

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ABSTRACT

Distinguishing between adaptive and maladaptive cardiovascular response to exercise is crucial to prevent the unnecessary termination of an athlete's career and to minimize the risk of sudden death. This is a challenging task essentially due to the substantial phenotypic overlap between electrical and structural changes seen in the physiological athletic heart remodeling and pathological changes seen in inherited or acquired cardiomyopathies. Stress testing is an ideal tool to discriminate normal from abnormal cardiovascular response by unmasking subtle pathologic responses otherwise undetectable at rest. Treadmill or bicycle electrocardiography, transthoracic echocardiography, and cardiopulmonary exercise testing are common clinical investigations used in sports cardiology, namely among participants presenting with resting electrocardiographic abnormalities, frequent premature ventricular beats or non-sustained ventricular arrhythmias. In this setting, as well as in cases of left ventricular hypertrophy or asymptomatic left ventricular dysfunction, stress imaging and myocardial tissue characterization by cardiovascular magnetic resonance show promise. In this review, we aimed to reappraise current diagnostic schemes, screening strategies and novel approaches that may be used to distinguish adaptive remodeling patterns to physical exercise from early phenotypes of inherited or acquired pathological conditions commanding prompt intervention.

Key points

- The diagnosis of athlete's heart is an important challenge due to the phenotypic overlap between the cardiac adaptive remodeling and early pathological changes seen in inherited or acquired cardiomyopathies.
- Cardiovascular magnetic resonance imaging has a central role in the assessment of cardiovascular diseases in athletes.
- Stress imaging is an emerging tool with high diagnostic yield to unmask reduced cardiac functional reserve and covert pathological changes that are not evident at rest.

1. Introduction

Sport and exercise are an integral part of the daily life of millions of people around the world. Physical, mental and social health benefits of exercise are well established, with both physically active men and women showing lower cardiovascular morbidity and mortality, as well as higher cognitive abilities and better quality of life compared with sedentary individuals [1]. Moderate intensity exercise is strongly recommended in guidelines for prevention and treatment of cardiovascular disease, though a linear dose-response relationship between intensity of exercise and cardiovascular health is still a controversial issue [2]. Importantly, athletes commonly exercise in vast excess of the recommended minimum doses for healthy individuals. Intensive physical training is known to add significant burden on the cardiovascular system, particularly in individuals affected by cardiovascular disease, in whom vigorous exertion could aggravate and accelerate disease progression, eventually increasing the risk for sudden cardiac death (SCD).

Accordingly, there is growing interest to promote effective risk stratification algorithms for the early identification of sport participants with underlying cardiovascular disease at risk of SCD. Differentiating between the so-called athlete's heart (AH) - a general term that encompasses all the cardiovascular changes secondary to physical exercise and training - and cardiovascular subclinical disease is a challenging task, also because findings consistent with exercise-induced cardiac remodeling should be viewed as the norm, and not the exception, in response to training [3].

Although much has been debated, clinical history and physical examination should be used to detect or raise suspicion of cardiovascular abnormalities, with twelve-lead ECG as the first line test for the diagnosis of heart disease in sport participants [4].

Standard echocardiography plays a pivotal role because of its wide availability, relative low cost and high diagnostic and prognostic yield. Further downstream, cardiovascular magnetic resonance (CMR) allows precise assessment of cardiovascular anatomy, function, and myocardial tissue characterization. These characteristics make CMR imaging a unique opportunity in the evaluation of AH, especially when results from first-line methods are equivocal or raise the suspicion of heart disease.

Although the distinction between AH and cardiac pathology might be better appraised during exercise [5], when it would be easier to unveil reduced functional reserve in pathological situation, most imaging studies continue to be performed at rest. This also involves the absence of reference values for morphologic and functional parameters under stress and uncertainties about the most effective stressor to be used. However, the increasing availability of faster and more advanced technologies enables the opportunity to accurately assess biventricular function during exercise, myocardial and extracellular matrix remodeling, bringing us closer to tackle critical controversies in the field of sports cardiology.

2. Cardiovascular adaptation to exercise: The Athlete's Heart

According to the scientific statement of the American Heart Association/American College of Cardiology (AHA/ACC), a competitive athlete is defined as one who participates in an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic and usually intense training [6]. Of note, it is important to recognize that several people who practice sports only for recreational purposes achieve training levels comparable to those of professional athletes.

In response to chronic high-intensity physical activity, the cardiovascular system develops a series of adaptive mechanisms defining the AH, including a constellation of changes with increased biventricular mass, volume, and wall thickness. Notably, different sports with distinct training patterns are known to induce different adaptive phenotypes, hence athletic cardiac remodeling results in a spectrum of morphological changes that should be carefully interpreted on the basis of different peak static and dynamic components achieved, the amount of haemodynamic stress exposure and the level of previous training, and cautiously distinguished from structural cardiac pathology.

Sports can be classified according to their strength component, expressed as the relative intensity of static muscle contractions, and their endurance component, reflected by the relative intensity of dynamic exercise or percentage of maximal aerobic power [6]. It is essential to underscore that all types of sports include both components, albeit with markedly different relative contributions (Table 1). Both dynamic and static exercise result in increased myocardial oxygen demand, but this distinction is relevant for the different cardiac adaptation induced.

Static exercise results in large and sustained changes in blood pressure with relative small modification in heart rate and ventricular volumes whereas during dynamic exercise the modification of heart rate and ventricular volumes is predominant, with some evidence of more relevant strain on right heart [7, 8]. In 1975, Morganroth raised the now-obsolete hypothesis of a dichotomous morphological cardiac adaptation matching the different patterns of haemodynamic strain upon the heart during exercise[9]. According to Morganroth observation, chronic endurance (dynamic, aerobic or isotonic) training should lead preferably to eccentric hypertrophy, characterized by marked balanced biventricular dilatation paralleled by modest hypertrophy similar to that which occurs in patients with mitral or aortic regurgitation, whereas chronic resistance (static, anaerobic or isometric) training would be usually associated with

pronounced concentric left ventricular (LV) hypertrophy (LVH) with major changes in LV wall thickness and little effect in cavity dimensions, mimicking pressure overload conditions such as systemic hypertension or aortic stenosis [10]. However, this hypothesis has been challenged by recent studies suggesting that the increase in LV mass is proportional to the increase in LV volume (balanced remodeling) irrespective of the sport discipline [11-14]. Of note, the balanced nature of ventricular remodeling does not appear to be altered by the level of physical activity even in the general population[15]. Furthermore, it has been consistently shown that low-dynamic-high static sports yield very little cardiac adaptation, not exceeding ventricular volume and mass index of non-athletic controls. Accordingly, a key factor unique to exercise-induced cardiac remodeling, but not considered in the Morganroth's hypothesis, is that the hemodynamic load imposed by exercise is a transient phenomenon, and the temporal dimension needs to be gauged when drawing analogies between cardiovascular pathology where the load is constant and the athlete's heart where the load is intermittent [16]. It is also important to recognize that patterns of biventricular remodeling may differ according to age, sex[11], ethnicity (with prominent changes in male and black athletes), use of anabolic androgenic steroids [17], intensity, duration, and dose of the exercise performed [18].

In addition to the growing need for distinguishing athletic cardiac remodeling from early manifestations of cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), left ventricular non-compaction (LVNC) or excessive trabeculation (ET) cardiomyopathy, little is known about whether physiological cardiac morphological and functional changes secondary to exercise are per se a completely benign condition [19].

3. Implications of differentiating athlete's heart from heart disease

The diagnostic overlap between exercise adaptation and heart disease in professional athletes does represent a major clinical challenge (**Figure 1**). In patients with overt cardiovascular structural disease, intense training is actively discouraged due to increased risk of SCD and disease progression. However, there is no established exercise threshold associated with adverse outcome in patients with known cardiovascular disease, and data considering harmful effects of different types of exercise are lacking. Importantly, improper overdiagnosis of heart disease may lead to unnecessary disqualification of competitive athletes, depriving these individuals from psychological and economic benefits of professional sport practice. Conversely, missing the diagnosis of covert or early stage cardiovascular diseases may expose athletes to unacceptable risk of SCD and physicians to potential legal consequences. Further, competitive and leisure athletes are accustomed to an active lifestyle and are often concerned about detraining and exercise restrictions recommended in the treatment guidelines during the past decade

Heart diseases contributing to SCD in athletes <35 years of age generally fall into three categories: electrical, acquired and structural cardiac abnormalities. Most of these abnormalities are inherited cardiac disorders that may be quiescent but can predispose the athlete to SCD primarily through ventricular arrhythmias. In older athletes, atherosclerotic coronary artery disease is the recognized dominant cause of SCD.

In the presence of a pathological substrate of cardiomyopathies such as HCM, DCM, AC and ET cardiomyopathy, intense exercise with consequent alterations in hydration, blood volume, electrolytes, acid-base imbalance and catecholamine release can represent the trigger for the development of ventricular arrhythmias.

The true incidence of sports-related SCD in younger athletes (<35 years) is still debated. According to various US and European studies and registries, it ranges from 0.6 to 6.8 per

100,000 per year and is much more common in males (male-to-female ratio 5:1) and black athletes (black-to-white ratio 8:1), in most cases secondary to inherited heart disease, whereas in older athletes acquired heart disease becomes predominant. Landry and colleagues [20] reported data from the Rescu Epistry cardiac arrest database, a prospective registry of consecutive out-of-hospital sudden cardiac arrest in the Ontario region, Canada. The incidence of SCD between athletes aged 12 to 45 years occurring during or within 1 hour from competition or training, including both survivors and non-survivors, was 0.76 per 100,000 athletes-year.

Regardless of its true incidence, sports-related SCD is less common than many other causes of death in the same age group [6]. Nevertheless, the death of a professional, often young athlete in the athletic field remains a tragic event with a noticeable emotional impact, drawing media attention, and with relevant impact on health care system responsible for cardiovascular pre-participation screening.

4. Strategies for differential diagnosis

A step-wise approach to cardiovascular assessment of athletes is essential in order to make sense of overlapping clinical phenotypes and eventually provide a correct differential diagnosis between adaptive and maladaptive cardiac response to exercise (**Table 2)**. In this setting, it is possible to identify two distinct clinical contexts: the pre-participation screening of asymptomatic competitive or leisure athletes, and the assessment of athletes reporting specific symptoms, positive family history and/or abnormal physical examination.

The obligation for pre-participation screening of professional or leisure athletes remains controversial. This is because according to several studies the annual incidence rate of SCD is low, both in related and unrelated to sports [21], similar between non-competitive and

competitive athletes [20, 22], and nearly three times lower than that of SCD in the general population [23-25]. However, although no randomized controlled clinical trial has been or is likely to be performed due to low event rates and ethical considerations [26], pre-participation screening of all subjects embarking in sports activity has the potential to identify asymptomatic competitive athletes or asymptomatic individuals engaged in leisure-time sports activity at increased cardiovascular risk and potentially reduce mortality [27, 28]. Other potentially significant effects of screening that extend beyond the clearance for sports eligibility would include additional benefits of pre-participation history and physical examination on injury reduction, general health awareness, updating vaccination status, positive lifelong health-care interactions in young people, eventually favoring the beneficial effects of sports in the long run [29], where safe sports activity represents an important health issue [30].

The AHA/American College of Cardiology 2014 initiative [6] recommends that the AHA's 14-element screening guidelines should be used by examiners as part of a comprehensive history taking and physical examination to detect or raise suspicion of genetic/congenital cardiovascular abnormalities [31]. However, history and physical examination screening has a recognized limited diagnostic yield to detect potentially lethal cardiovascular abnormalities.

Twelve-lead ECG enhances the sensitivity of the screening process by allowing early detection of cardiovascular conditions distinctively manifesting with ECG abnormalities, but only few countries developed comprehensive pre-participation screening protocols including 12-lead resting ECG in addition to careful family history information and physical examination.

While in Italy the adoption of such a pre-participation screening protocol led to a 90% reduction SCD in young athletes [28], no reduction of sports-related SCD has been observed in Israel and in the Unites States [32, 33]. Recent data from the mandatory screening program of the English Football Association, evaluating since 1996 more than 11,000 adolescent high-ranking

soccer players, aged 15 to 17 years, who completed a health questionnaire, physical examination, ECG, and echocardiogram, identified a SCD rate of 1 case per 14,794 athlete-years, or 6.8 per 100,000 athletes, that is approximately three-fold higher than previously estimates of 0.3 to 2.0 in 100,000 athletes, depending on the population studied and method used[34]. Overall, during a follow-up period of 118,351 person-years, there were 23 deaths from any cause, of which 8 (35%) were SCD. Of these, 6 (75%) athletes with SCD had had normal cardiac screening result, and most of these deaths were due to concealed cardiomyopathies. This makes clearly the point that one-off cardiac screening during adolescence is not enough to detect a relevant proportion of athletes who have or will eventually have a cardiomyopathy due to a number of possible reasons, including the fact that the disease is not yet manifest at that young age, when the player may harbor subtle or incomplete expressions of cardiomyopathy that age-related penetrance and intensive training may well contribute to unmask later on [34-36]. Accordingly, longitudinal prospective data from serial evaluation of footballers will help shed light onto the issue of if and when a cardiomyopathy may manifest. Further research is also needed to investigate the reasons behind a six-fold higher incidence of sudden cardiac arrest among black footballers than white footballers[36], in line with previous SCD reports among US black basketball players from the National Collegiate Athletic Association[37].

Currently, the European Society of Cardiology, most European Cardiologic Societies and Sports Medical Federations, and the International Olympic Committee ('Lausanne Recommendations'), recommend the 12-lead ECG screening as a part of pre-participation screening of competitive athletes [38], whereas within the US cardiology and sport medicine community there is no consensus[39], and the routine use of 12-lead ECG screening in both competitive and leisure athletes remains controversial. Although there is general agreement

that ECG screening improves the sensitivity for detecting unsuspected cardiac disease among asymptomatic athletes, arguments against universal ECG screening include the low prevalence of disease in a very large population with expected high false-positive rate, the financial sustainability, the potentially difficult interpretation that requires specific expertise, the logistical challenges and costs related to second-tier confirmatory screening with imaging and/or other testing should primary evaluations raise the suspicion of cardiac disease[40].

Analysis of costs and financial sustainability of screening programs aimed to the prevention of SCD in athletes is a very complex issue. Cost-effectiveness analysis should ideally be based on randomized controlled trials, or at the very least, on observational studies for which consensus exist[41]. Nevertheless, because reimbursement rates vary widely in different regions, because the epidemiology of SCD differs across different countries and sports categories, and given that the clinical effectiveness of screening has not been unequivocally determined, the quality and robustness of cost-effectiveness analyses require careful interpretation. A decision-analysis model showed that when assuming a high threshold for ECG positivity the incremental life years saved by including ECG are significant, overall suggesting that that pre-participation screening of young athletes with ECG can be both reasonable in cost and effective at saving lives [29]. Conversely, a cost-projection model suggested that replicating the Italian strategy in a 20-year program of ECG screening of young competitive athletes in the United States would result in enormous costs-per-life-saved ranging between $10.6 million and $14.4 million [41]. Both analyses have been modelled on the Corrado data[28], and applied them to the U.S. population, but the former was based on the assumption that one-off screening would result in a mortality reduction similar to that observed in Italy with 20 years of annual screening, thereby reducing the true costs of screening and artificially enhancing cost-effectiveness. However, the application of more contemporary ECG interpretation guidelines

[42], the implementation of ECG screening programs performed at less frequent intervals [43] and in targeted high-risk groups [37, 44] are viable alternative solutions to be tested in order to achieve financial sustainability. In the meanwhile, more training in cardiopulmonary resuscitation and better access to automated external defibrillators should be promoted in order to weave the best possible safety net for sports participants [45].

Abnormal ECG patterns are commonly observed in competitive athletes (nearly 15%), and more frequently seen in men than in women, in black than in Caucasian and in endurance than in strength athletes. The most common alterations reported are early repolarization, increased QRS voltage, incomplete right bundle branch block, and T-wave inversion. Trained athletes may also experience bradyarrhythmias - such as sinus bradycardia, junctional bradycardia and low-grade atrio-ventricular conduction blocks - or tachyarrhythmias - such as frequent premature ventricular complexes. However, these events are considered benign in patients with structurally normal hearts, particularly if they suppress with exercise, and are generally reversible with detraining. Bizarre and distinctly abnormal ECG patterns, including striking increase in R or S wave (≥35 mm) in any lead, pathological Q waves >4 mm in ≥2 leads, T wave inversion >2 mm in ≥2 leads, left bundle branch block (LBBB), high-grade atrio-ventricular conduction blocks, marked QRS axis deviation and pre-excitation pattern, are relatively rare in trained athletes [46].

In 2012, an international panel of experts convened in Seattle in order to develop a consensus on the distinction between normal and abnormal ECG findings in athletes [47]. The aim of this meeting was to provide a useful and practical guide to identify athletes requiring further testing limiting unnecessary secondary evaluation compared with previous ESC recommendation [48]. More recently, in a consensus document for ECG interpretation in athletes, Sharma et al. [4] proposed the distinction between normal, borderline and abnormal ECG findings in competitive

athletes, where normal or isolated borderline findings do not require downstream investigations, whereas abnormal or multiple borderline findings should prompt to ECG stress testing and cardiac imaging assessment.

Cardiac imaging is not usually recommended as a first-line test, but it represents a very useful tool, both at rest and during exercise, in the assessment of athletes with positive family history, symptoms and/or abnormal resting 12-lead ECG. Echocardiography has a pivotal role in differentiating physiological and pathological response to exercise, namely athlete's heart from pathologic LVH [5]. Combining different methods, such as 2D and 3D measurements of cardiac size, volumes, wall thickness, mass index, tissue velocity and myocardial strain imaging, cardiac ultrasound allows comprehensive morphological and functional evaluation of the heart and distinction between physiological and pathological remodeling [5]. So far, several clinical criteria and algorithms for the differential diagnosis between AH and cardiomyopathies have been proposed [5, 49] **(Figure 2).** In the presence of abnormal, uncertain, and/or controversial findings from the upstream diagnostic work-up, CMR imaging can be helpful to distinguish between exercise-induced cardiac remodeling and cardiovascular pathology. CMR represents the current gold standard in the noninvasive assessment of cardiac morphology and quantification of volumes and flow and offers the unique opportunity of advanced myocardial tissue characterization with excellent accuracy and precision. CMR cine images allow morphological and functional evaluation of cardiac chambers, with clear delineation of ventricular endocardial and epicardial borders, while other specific sequences are useful in the evaluation of replacement/scarring fibrosis, myocardial ischemia, edema, interstitial fibrosis, quantification of cellular and extracellular volume and assessment of iron overload [50]. Further, tissue tracking module allows measurement of strain and strain-derived parameters, while

native whole-heart CMR permits visualization of the origin and course of coronary arteries without need for paramagnetic contrast agents.

4.1 Hypertrophic cardiomyopathy

HCM is believed to be the most relevant cause of death in young athletes, responsible of about one third of sports-related SCD in this population [51]. Patients with HCM are discouraged from participating in competitive sports, as the risk of ventricular arrhythmias and SCD may increase during exercise [52]. However, exercise may not be necessarily harmful for HCM patients, and has been found to be associated with potential beneficial effects [1, 53]. Accordingly, previous reports have indicated adverse clinical outcome in overweight HCM patients, highlighting the importance of avoiding adverse effects of a sedentary lifestyle. Further, in patients with phenotypic HCM, vigorous exercise has been shown to be associated with favorable diastolic function, greater LV and stroke volumes with no excess risk of ventricular arrhythmias [52]. This was in line with a recent prospective randomized study which found no defibrillator shocks, sustained ventricular arrhythmias or sudden cardiac deaths in an exercise intervention group of phenotypic HCM patients [54]. Further research is needed to confirm these recent findings, and explore the impact of exercise intensity, duration, and dose on outcome of HCM patients, aiming to develop safe thresholds of physical exercise in HCM.

HCM is characterized by increased LV wall thickness and reduced left ventricular end-diastolic diameter (LVEDD) leading to asymmetrical LVH. LV wall thickness falling inside the “grey zone” ranging between 13 and 15 mm is expected in about 4% of males, and more frequently in African/Afro-Caribbean athletes. In these cases, the presence of normal or increased LVEDD, normal systolic and diastolic function, normal atrial size, and the reduction in LV wall thickness

after a period of detraining are in keeping with a diagnosis of AH [55]. However, it has been suggested that HCM in athletes might be slightly different from sedentary patients. Athletes with HCM are more likely to have LV wall thickness falling in the grey zone, with larger LV cavity and normal diastolic filling. Tissue Doppler imaging and strain are promising diagnostic tools for the differential diagnosis between AH and HCM, but the incremental diagnostic value of these methods is yet to be proven [56]. Although resting ECG and echocardiography are sensitive techniques for the diagnosis of more severe HCM phenotype, the presence of overt disease is relatively rare in highly trained athletes. However, diagnostic accuracy of echocardiographic parameters is currently limited by the lack of validated clinical cut-offs stratified by age, gender, ethnicity, and sport types. Furthermore, available reference ranges are largely restricted to relatively sedentary HCM patients and athletes with physiological ventricular hypertrophy.

Cardiopulmonary exercise testing (CPET) represents the gold standard in the evaluation of cardiovascular, pulmonary, muscular and cellular oxidative systems. CPET is being increasingly used in combination with echocardiography in order to integrate functional and structural data. Maximal oxygen uptake (VO_2 max) - a surrogate marker of cardiac output - has been proposed in the differential diagnosis of the AH, being a VO_2 max>45 mL/kg/min or >110% of predicted peak VO_2 in keeping with AH rather than early stage cardiovascular disease [49]. Sharma et al. [57] performed CPET evaluation in 8 highly trained athletes and 8 athletes with mild phenotypes HCM. Although differences in athletic conditioning and training volume could be responsible of different results, VO_2 max was considerably reduced in athletes with pathological LVH. However, in a recent study VO_2 max was unable to distinguish between healthy endurance athletes and endurance athletes with evidence of subclinical LV damage

defined by the presence of significant LGE (>10% of LV mass), thus questioning the usefulness of this functional parameter [58].

CMR performs better than echocardiography in the differential diagnosis of LVH and exercise-induced cardiac remodeling. In this setting, LGE imaging provides robust diagnostic and prognostic information, though present in only about 50% of HCM patients, so that the absence of LGE does not exclude HCM. On the other hand, non-specific small clustered patches LGE are frequently encountered in the heart of otherwise healthy athletes, especially after long-standing endurance training [7]. Of note, the presence of balanced remodeling (specifically assessed based on sex-specific reference values of RV/LV end-diastolic volume ratio and LV end-diastolic volume/mass ratio[59]), and a LV-diastolic-wall-to-volume-ratio <0.15 mm x m2 x ml(-1) have been shown to accurately confirm physiological rather than pathological LVH [60]. Parametric mapping now gives the opportunity for more detailed LVH characterization, enabling accurate quantification of cellular and extracellular volume [61] and distinction between physiological and pathological patterns of LVH. ECV analysis allows left ventricular mass to be split into its cellular and matrix components. It has been reported how physiological cellular hypertrophy is the prevalent adaptive mechanism in AH, whereas progressive matrix expansion features other pathological conditions such as HCM, aortic stenosis, Fabry disease and cardiac amyloidosis.

4.2 Dilated cardiomyopathy

DCM is characterized by increased LVEDD, LV and possibly RV volumes, in addition to an impaired overall systolic function. DCM is relatively rare in competitive athletes as compared with other cardiomyopathies due to fact that systolic function impairment preventing adequate cardiac output during exercise is not generally compatible with professional sports practice. A

structural overlap between early stage of DCM and endurance AH phenotype according - based on the Morganroth hypothesis - does exist. In this regard, it was reported that more than 10% of elite cyclists competing in the Tour de France fulfilled the diagnostic criteria for DCM [62]. In another series, approximately 15% of elite athletes were presenting with LVEDD >60 mm [63]. In these cases, an LVEDD >60 mm persistent after a period of deconditioning, also associated with impaired LVEF - particularly when <45% - and LV stroke volume is suggestive of DCM [49]. However, as morpho-functional adaptations typical of the AH have been described to persist over the long term, a brief period of detraining may not be sufficient to achieve a clear differential diagnosis. Preliminary data showed that native T_1, ECV and T_2 relaxation times were significantly higher in DCM patients as compared with healthy subjects and athletes, with native T1 and ECV providing the better discrimination between DCM patients and athletes. Of note, low-normal native T1 values have been also associated with increased VO_2 max. However, CMR during resting condition sometimes cannot be enough in case of LV dilation associated with mildly reduced LVEF and absence of LGE. This scenario may require downstream evaluation by stress-imaging, or repeated assessment after detraining.

Stress echocardiography and CMR are often effective to pick up abnormalities of both systolic and diastolic function that become more apparent on exercise, and to detect abnormal tissue characterization, i.e. replacement scar, increased extracellular volume. Furthermore, it has been showed that real-time CMR imaging performed during exercise can be used to quantify cardiac function - including biventricular and biatrial function - with very high accuracy and reproducibility [58]. Exercise CMR appears promising to become the gold-standard for ventricular volume quantification during high-intensity exercise in order to investigate differences in contractile reserve between normal and early diseased myocardium [64].

4.3 Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (AC) is an inherited cardiomyopathy - most frequently autosomal dominant - predisposing to ventricular arrhythmias, SCD, and more rarely ventricular dysfunction and heart failure. According to the Task Force Criteria, the diagnosis of AC requires multimodality assessment [65]. About 15% of athletes show V_1-V_3 T waves inversion, and nearly 40% show RVOT enlargement compatible with AC. Moreover, endurance athletes frequently display premature ventricular beats arising from the RVOT, along with reduced resting RVEF or RV fractional area change. Notably, the RV is exposed to a disproportionate increase in wall stress during exercise resulting in mildly asymmetric RV dilation, that should be considered normal and rather common in endurance athletes[16]. These findings impose distinguishing between AH and AC. Resting echocardiography still represents the first line imaging technique for the evaluation of right chambers. It can identify global and regional RV morphological (thinning, bulging or aneurysms) or functional (akinesia, dyskinesia) abnormalities in symptomatic athletes or with ECG findings suggestive of AC. In athletes, RV enlargement mainly involves the inflow tract, is usually associated with balanced LV enlargement, and RV diastolic function is normal (or supernormal). 3D echocardiography and advanced 2D echocardiographic methods can be useful in the evaluation of subtle RV dysfunction [66]. Subjects with unclear echo findings or with suboptimal echo images should be further evaluated with CMR, which has been shown to be significantly more accurate than conventional 2D echocardiography to detect subtle RV regional functional and structural wall abnormalities due to its higher spatial resolution. Importantly, great caution must be employed in suspecting AC when the only abnormality is found at the level of the RV on CMR, in patients with otherwise normal ECG and Holter monitoring.

CMR is more accurate than echocardiography in identifying regional RV wall motion abnormalities, volumes and function, and allows assessment of fibrosis and signs of fibro-fatty replacement/infiltration. CMR findings of reduced RVEF, unbalanced RV enlargement (RV/VL end-diastolic volume ratio >1.15 [59]), RV wall motion abnormalities and the presence of LGE are consistent with a diagnosis AC. LGE is also useful in the identification of early and/or predominant LV involvement which is increasingly recognized. Importantly, two key points should be borne in mind: i) evidence of fat by CMR is not a recognized imaging criterion for the detection of AC; ii) AC diagnosis cannot be based on imaging criteria alone.

4.4 Left ventricular non-compaction or excessive trabeculation cardiomyopathy

LVNC or ET cardiomyopathy is characterized by the presence of a double-layered wall structure with a thin compact epicardial layer and an inner trabeculated endocardial layer in the context of the LV wall. The interventricular septum is generally spared whereas the RV may be involved in isolation or in association to the LV. The genesis of this cardiomyopathy is still not fully established and previous hypothesis involving the embryonic arrest in coalescing of the trabeculation into the solid compact layer has been questioned [67]. Genetic inheritance has been found in about 30% of patients with involvement of sarcomeric and cytoskeletal proteins coding genes. Excessive trabeculation may occur in association with many other congenital diseases, but it is unclear whether excessive trabeculation per se represents a separate entity, or only a morphological trait shared by different pathologies [67]. ET cardiomyopathy has been associated with increased risk of heart failure, ventricular arrhythmias, heart transplantation, SCD and thromboembolic events. Nevertheless, the presence of excessive trabeculation does not seem to confer any added prognostic value in subjects without clinical symptoms or positive family history [68], and in patients with DCM [69].

A relevant proportion of athletes fulfill the diagnostic criteria for ET cardiomyopathy [70]. It has been also hypothesized that this structural abnormality may be the result of chronic preload increase on cardiac chambers [71]. Actually, the diagnosis of this condition requires careful history and physical examination, 12-lead ECG and cardiac imaging. Echocardiography provide low specificity in the diagnosis of ET cardiomyopathy. It can detect the excessive endocardial trabeculation pattern and LV function abnormalities, but its spatial resolution does not allow accurate measures and the identification of crypts within the epicardium, especially when located in the LV apex. The most widely used echocardiographic diagnostic criteria were proposed by Jenni et al. [72], with a threshold of end-systolic trabecular/compact ratio ≥2 in adults and ≥1.4 in children.

CMR is often requested to confirm or exclude ET cardiomyopathy in symptomatic or positive family history patients with echocardiographic detection of ET pattern. Petersen et al. [73] reported the overall good diagnostic performance of an end-diastolic noncompacted/compact ratio ≥2.3 as measured by CMR in long-axis views. Other diagnostic CMR criteria for LVNC have been introduced by Jacquier, who recommended the short-axis end-diastolic trabecular mass>20% of the total LV mass[74], Stacey, who proposed the short-axis end-systolic noncompacted/compacted ratio ≥2 [75], and Captur, who provided evidence of measurement of fractal dimension of the endocardial border, and reported significantly higher fractal dimensions in LVNC patients compared with healthy subjects, as well as higher accuracy and reproducibility of this method when compared with Petersen and Jacquier's criteria[76]. Beyond morphology, CMR allows quantification of LGE burden, which has been associated with worse clinical status and outcome in ET cardiomyopathy, and accurate rule-out of LV thrombosis within the intertrabecular recesses.

5. The role of stress imaging

The absence of structural heart disease is a critical factor in determining the athlete's management and prognosis [77], but the best diagnostic work-up strategy by which structural heart disease should be excluded has not been established. Echocardiography and CMR are frequently used in these settings but emphasis tends to be placed on LV measures and imaging is performed at rest. Current evidence suggest that this is a flawed practice with poor sensitivity for identifying athletes at risk of adverse cardiac events[78]. Guidelines suggest that exercise assessments of cardiac function can be used to differentiate athlete's heart from cardiomyopathy when resting measures of function appear abnormal [5].

Stress imaging represents a useful tool to unmask reduced cardiac functional reserve and covert pathological changes that are not evident at rest, especially in athletes in whom arrhythmias and/or early stage cardiomyopathies are suspected. Stress can be performed either using pharmacological stressors or exercise. Exercise imaging has several advantages. Firstly, it avoids the administration of drugs, which, although generally well tolerated, may cause unwanted harmful side effects. Secondly, the use of dynamic exercise as a stressor has the advantage of obtaining a physiological activation of the cardiovascular system. Thirdly, exercise stress is the simplest modality that can induce both regional wall motion abnormalities and perfusion defects. Fourthly, exercise allows exertional symptoms to be reproduced, correlation of symptoms with ECG and stress imaging findings, and comparison of functional capacity and the extent of any ischemia.

On the other hand, it requires specific and sometimes expensive equipment. Moreover, motion artifacts may significantly limit the overall accuracy of the examination both with echocardiography and CMR during stress. To overcome this important limitation and obtain higher quality scans, it has been proposed to acquire images after temporary exercise

cessation. However, the time period of exercise cessation allows partial recovery, limiting the yield of detection of those abnormalities unmasked during effort. An undervalued method is represented by isometric stress imaging, e.g. static biceps contraction [79], which is known to be associated with well-characterized hemodynamic changes [80].

Stress echocardiography may play an important role in the assessment of ventricular function during exercise. This technique enables evaluation of cardiac structure and function combined with real-time electrocardiographic and CPET data. Moreover, wide availability, low cost and the absence of radiation also make it the ideal first-line method in the evaluation of AH during exercise. Several studies have investigated various systolic and diastolic functional parameters both at rest and under stress. Abernethy et al.[81] evaluated 156 healthy professional football players with rest and stress echocardiography and observed in all subjects an increase in LVEF during exercise irrespective of resting values. Tissue velocity imaging during exercise is an important tool in the evaluation of cardiac function. Interestingly, increased LV torsion, but reduced diastolic function and apical RV tissue Doppler derived strain have been reported in elite rowers after maximal intensity short-duration exercise, whereas enhanced diastolic function by tissue Doppler analysis has been described in athletes with a high-intensity mixed endurance and strength training program compared with non-athletes. Furthermore, while resting RV function by 2D and strain parameters was slightly reduced in weightlifters, a greater improvement under stress could be observed compared with sedentary subjects. Similarly, during isometric exercise greater stroke volume increase and enhanced diastolic function has been reported in highly-trained resistance athletes compared with sedentary controls [82]. Reduction of LV end-systolic volume during exercise has been described in both athletes and normal subjects, but not in DCM or HCM patients, suggesting LV function analysis during exercise as a promising tool in distinguishing AH from pathological conditions [83].

Technological improvements currently offer the possibility to perform exercise CMR imaging with high accuracy and reproducibility. This can become a key tool for the assessment of athletes with mild ventricular dilation, and/or mildly reduced LVEF or RVEF, and/or when rest imaging is inconclusive. First attempts with treadmill stress CMR imaging, performed in a timely fashion immediately after maximal exercise with the treadmill placed outside the scan room, showed good diagnostic and prognostic values in a small group of patients with known or suspected coronary artery disease [84, 85]. However, this technique assumes that regional wall motion abnormalities would persist long enough to be detected in the recovery phase, but when abnormalities do recover rapidly false-negative results occur. Indeed, the time needed for typical cardiovascular disease patients to go from outside the scanner room to the scanner table and then to isocenter may push post-exercise wall motion imaging beyond the 60 seconds advocated by guidelines [86], which show that exercise- induced functional abnormalities rapidly disappear after exercise.

Since CMR-compatible treadmill equipment was introduced, exercise stress perfusion CMR performed inside the scan room has become feasible [87, 88].

Coupled with recent improvement in real-time imaging techniques, treadmill exercise CMR testing holds promise for accurate non-invasive assessment of myocardial ischemia, as further demonstrated in a large symptomatic patient population with known or suspected CAD enrolled in the prospective, multicenter EXACT trial [89].

In contrast to exercise treadmill, a supine cycle ergometer attached to the scan table will allow patients to exercise while in the magnet bore, and real-time imaging to be performed at every stage of exercise [90]. Although this approach has made hitherto limited inroads into clinical care [91], the ability to assess cardiac physiology and function at every stage of exercise provides a unique opportunity to characterize and differentiate the exercise profiles between

individuals [64]. Feasibility and reproducibility of supine bicycle exercise CMR has been demonstrated and validated against both invasive Fick method and cardiopulmonary exercise testing, with ungated real-time CMR imaging yielding excellent accuracy and precision in measuring cardiac output during maximal exercise [64, 92]. Importantly, peak exercise cardiac index assessed during in-scanner supine ergometry has been reported to outperform resting measurement in differentiating athletes from healthy volunteers [92].

Gradually increasing bicycle exercise with real-time phase-contrast CMR acquisition has been also demonstrated feasible and highly reproducible [93]. This simple method permits the evaluation of cardiac index at different stages from rest to intense exercise and was found to disclose pathological situations not apparent at rest. In a series of 24 individuals with resting LVEF between 40 and 52%, including 10 ostensibly healthy endurance athletes (EA), 5 EA with evidence of subclinical LV damage and 9 mild-phenotype DCM patients, who underwent CPET and exercise supine bicycle CMR, it has been showed that i) neither exercise capacity (VO_2 max) nor resting measures of cardiac function are helpful in differentiating between healthy EA from those with myocardial impairment or fibrosis; ii) augmentation of biventricular and atrial function during exercise can accurately differentiate between physiological and pathological LV adaptation; iii) exercise-induced LVEF increase >11% differentiated DCM and EA-fibrosis patients from healthy EA with 93% sensitivity and 90% specificity [58]. These findings are consistent with previous evidence in patients with severe DCM [94], suggesting that assessment of LV contractile reserve may improve risk stratification and guide optimal therapeutic management in the early course of the disease.

Consistent with the hypothesis that pro-arrhythmic remodeling predominantly affects the RV, it has been demonstrated that endurance athletes with ventricular arrhythmias and ostensibly normal cardiac function at rest, developed right ventricular dysfunction during exercise, while

healthy endurance athletes and non-athletic controls did not [78]. This evidence further highlights the importance of developing non-invasive clinical tools for risk-stratification of arrhythmic events in sports participants, and in this context both exercise-CMR and echocardiographic RV stress testing show promise.

Isometric exercise has been proposed as an alternative to dynamic exercise. The feasibility of combining CMR, which has the advantage of being the reference standard method of assessing flow and ventricular function, with isometric exercise has been demonstrated [79]. In a proof-of-concept study isometric exercise CMR using biceps contraction evoked specific age-, BMI-, and sex-related hemodynamic responses that were not apparent at rest, suggesting this technique might be tested to unveil covert pathology in different clinical settings, with the significant advantages of limited motion artifacts and relatively low cost [80].

Exercise stress imaging is becoming an active field of research, also because of recent developments in free-breathing real-time CMR imaging techniques and the availability of CMR-compatible exercise equipment [90]. Despite initial favorable results, further investigation is needed to assess the incremental diagnostic yield and cost-effectiveness of exercise cardiac imaging in distinguishing between early stage cardiomyopathies and exercise-induced cardiac remodeling.

6. Conclusions

The accurate diagnosis of athlete's heart from the differential diagnosis of early cardiomyopathy phenotypes or concealed cardiovascular pathology require comprehensive diagnostic work-up based on morphological, electrical, structural and functional information. Multimodality non-invasive cardiac imaging plays a central role to tackle this important diagnostic challenge. Stress imaging with exercise echocardiography and cardiovascular magnetic resonance hold

promise to improve current diagnostic schemes and enabling early detection of covert pathological situations not apparent at rest. As the question remains whether we can show that pre-participation screening is beneficial with regard to reducing mortality, further research is needed to appraise the efficacy and cost-effectiveness of adding imaging stress tests.

Compliance with Ethical Standards

Conflict of Interest: Carlo De Innocentiis, Fabrizio Ricci, Mohammed Y Khanji, Nay Aung, Claudio Tana, Elvira Verrengia, Steffen E Petersen, and Sabina Gallina declare that they have no conflicts of interest.

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Table 1. Classification of sports. The increase in dynamic component is defined in terms of percentage of maximal oxygen uptake (VO_2 max). The increase in static component is defined in terms of estimated percentage of maximal voluntary contraction. Modified from Levine et al. *Journal of the American College of Cardiology*, 2015.

DYNAMIC COMPONENT \ STATIC COMPONENT	Low (<10%)	Medium (10-20%)	High (>30%)
Low (<50%)	*Bowling* *Cricket* *Curling* *Golf* *Riflery* *Yoga*	*Archery* *Auto racing* *Diving* *Equestrian* *Motorcycling*	*Bobsledding/Luge* *Fields events (throwing)* *Gymnastics* *Martial arts* *Rock climbing* *Sailing* *Water skiing* *Weight lifting* *Windsurfing*
Medium (50-75%)	*Baseball/Softball* *Fencing* *Table tennis* *Volleyball*	*American football* *Fields events (jumping)* *Figure skating* *Rodeoing* *Rugby* *Running (sprint)* *Surfing* *Synchronized swimming* *"Ultra" racing*	*Body building* *Downhill skiing* *Skateboarding* *Snow boarding* *Wrestling*
High (>75%)	*Badminton* *Cross-country skiing (classic technique)* *Field hockey* *Orienteering* *Race walking* *Racquetball/Squash* *Running (long distance)* *Soccer*	*Basketball* *Ice hockey* *Cross-country skiing (skating technique)* *Lacrosse* *Running (middle distance)* *Swimming* *Team handball* *Tennis*	*Boxing* *Canoeing* *Kayaking* *Cycling* *Decathlon* *Rowing* *Speed skating* *Triathlon*

Table 2. Advantages and limitations of diagnostic tools involved in the assessment of the athlete's heart.

Methods	Pros	Cons
Resting ECG	• Low cost • Widespread availability • Prognostic yield	• Nonspecific findings • False-positive results
CPET	• Accurate evaluation of cardiac, respiratory and metabolic functions • Gas exchange analysis • May be used with imaging	• Requires expert interpretation • False-negative results
Echocardiography	• Widespread availability • Accurate morpho-functional assessment • Diastolic function testing • Valvular heart disease assessment • High temporal resolution	• Poor visualization of apical segments • Limited reproducibility • Limited acoustic window • Need for LV contrast or TEE imaging
CMR	• High spatial resolution • Accurate and precise morpho-functional assessment • Tissue characterisation • RV assessment • Flow analysis	• Relatively expensive • Limited availability and expertise • Limited temporal resolution • Use of contrast agent • Artifacts
Exercise Imaging (echo, CMR)	• Assessment of biventricular function during exercise • Unmask pathology not apparent at rest • Physiological activation of cardiovascular system • Diastolic stress testing	• Specific and sometimes expensive equipment • Motion artifacts • Limiting skeletal muscle fatigue in individuals not accustomed to cycling

CMR, cardiovascular magnetic resonance; CPET, cardiopulmonary exercise testing; LV, left ventricle; TEE, transthoracic echocardiography.

Figure Legends

Figure 1. The diagnostic continuum between exercise-induced cardiac remodeling and pathology. CPET, cardiopulmonary exercise testing; CMR, cardiovascular magnetic resonance.

Figure 2. Clinical criteria used to distinguish cardiac pathology from athlete's heart in patients with overlapping phenotypic characteristics consistent with both diagnoses.

ECV, extracellular volume; FH, family history; LA, left atrium; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; RV, right ventricle; RWMA, regional wall motion abnormalities; TWI, T-wave inversion; VA, ventricular arrhythmia.

Figure 1

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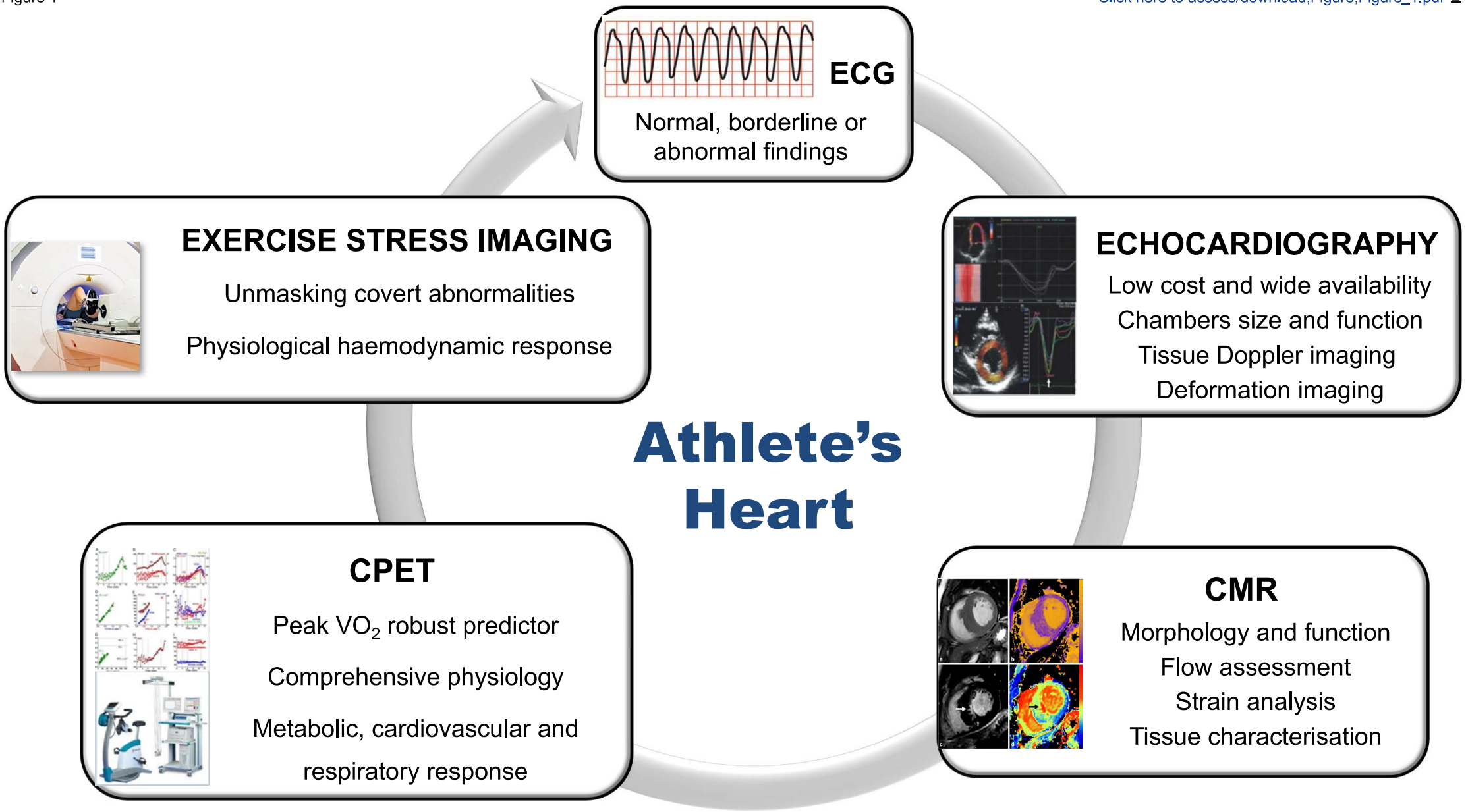

Figure 2