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STATE-OF-THE-ART PAPER

Cardiac Imaging and Stress Testing Asymptomatic Athletes to Identify Those at Risk of Sudden Cardiac Death

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Sudden cardiac death in young athletes is rare but tragic. The cardiology community is faced with the challenge of providing a sensible strategy for the prevention of SCD while simultaneously reaffirming that the benefits of regular exercise far outweigh potential risks. At present, there is a broad range of screening recommendations dependent upon country, sporting discipline, and competition level. While much recent debate has focused on the efficacy of screening with electrocardiography, a number of sporting bodies also mandate the inclusion of exercise testing and echocardiography in screening protocols. Cardiac magnetic resonance imaging, coronary calcium scoring and computed tomography coronary angiography have also been promoted as potentially valuable screening tools for competitive athletes. This review will examine the controversial topic of utilizing cardiac imaging for athlete pre-participation screening. Specifically, the limitations of screening for relatively rare disorders using imaging tools with uncertain or imperfect accuracy will be addressed. Current evidence suggests that the accuracy of all cardiac imaging modalities is insufficient to justify their use as primary screening modalities in athletes. Atypical findings such as marked cardiac dilation, reduced deformation, or small patches of delayed gadolinium enhancement may be commonly encountered in well-trained athletes, but, at present, the prognostic significance of such findings is unknown. Resulting uncertainty for the clinician and athlete has the potential for psychological stress, further testing, and unnecessary exclusions from competition. However, these concerns must not be confused with the extremely useful applications of cardiac imaging for the assessment of athletes with symptoms, an abnormal electrocardiogram or a positive family history. As modern imaging further enhances our understanding of the spectrum of athlete's heart, its role may expand from the assessment of athletes with suspected disease to being part of comprehensive pre-participation screening in apparently healthy athletes.   (J Am Coll Cardiol Img 2013;6:993–1007) © 2013 by the American College of Cardiology Foundation

The sudden death of a young healthy athlete is a tragedy that leaves unanswered questions that can complicate the family's grief and produce emotive debate in the community. *What was the cause? Could it have been prevented? Could I be at risk?* The public demands a response and, as qualified spokespeople on the issue, medical practitioners have the opportunity to both educate and learn. It is important to provide perspective and reassure the public of the overwhelmingly favorable risk-benefit profile of exercise, but we must also develop better strategies for preventing sudden cardiac death (SCD) in athletes. However, it can be extremely challenging to accurately identify conditions predisposing to SCD, all of which are uncommon, among a cohort that is self-selected for cardiovascular health. This review focuses on the promise and limitations of multimodality cardiac imaging in identifying at-risk athletes. As an illustrative example, we will use the case of a 36-year-old marathon runner who, as is now mandated at some major city marathons, requires a medical certificate stating that he is medically fit to participate. Thirty-six years represents the approximate median age of participation in marathon events and also represents an age at which both inherited and acquired causes of SCD are prevalent. The issues discussed in relation to this case are relevant to a broader group of athletes, from the recreational enthusiast wishing to join a sporting club to elite professional athletes. However, it is the latter that frequently present the greatest dilemmas due to the diagnostic overlap between

profound athletic cardiac remodeling and cardiac pathology. Furthermore, the consequences of diagnostic inaccuracy are greater in professional athletes given the potential for lost careers and aspirations if an athlete is inappropriately disqualified or, on the other hand, a potentially greater exposure to exercise triggered SCD if an underlying pathology is missed.

Sport and exercise are an important part of daily life and should be encouraged for a multitude of reasons, including improved health outcomes and reduced SCD risk (1,2). Thus, a paradox exists whereby exercise is associated with substantial health benefits in the vast majority but may serve as a trigger for arrhythmias in a small minority with an underlying pathologic substrate. Therefore, the challenge for broad-based screening programs is to identify those at risk while minimizing harm through unnecessary exclusions from sport. In 1982, with this goal in mind, cardiologists lobbied government policy makers in Italy resulting in a law mandating pre-participation screening for all athletes age 12 years or older. Since this time, all Italian athletes have been required to undergo screening comprising clinical history, physical examination and an electrocardiogram (ECG) prior to acceptance in competitive sport (3). This policy has been both lauded and criticized in equal measure. Proponents cite proof of long-term efficacy among those screened under the Italian system (3,4), while others have argued that the incidence of SCD is extremely low in unscreened athletic populations and the less than perfect specificity of ECG screening has potential for harm through unnecessary investigations, psychological stress, and disqualifications (5–7). As the debate continues to rage, it is becoming increasingly clear that an opportunity has been missed. In 1982, when evidence for ECG screening was scarce, the medical fraternity and legislators could have insisted on a randomized trial (screening with vs. without ECG) in preference to uniform policy. Had this occurred, it might well have provided the definitive experience on which informed policy making could now be based. Similar lessons can be extrapolated to the topic of screening with cardiac imaging. Perhaps the foremost priority should be for evidence to lead the debate rather than opinion.

Potential Causes of Sudden Cardiac Death in a 36-Year-Old Marathon Runner

The incidence of sudden death in young athletes (≤35 years) is 0.6 to 3.6 per 100,000 population per year and the majority of deaths are due to cardiovascular causes (3,5,8–10). For reasons that remain unexplained, the risk is approximately 10-fold greater among males than females and is higher among competitive athletes when compared with nonathletes (8,9). Although considerable attention has focused on young athletes, the risk of SCD is greater among sports participants older than 35 years and is greatest in the fifth decade (9). Prevention strategies aim to identify cardiac pathologies that may serve as a substrate for arrhythmias triggered by exercise. In general, inherited cardiomyopathies are the most frequent cause of SCD in young athletes while acquired heart disease, principally coronary artery disease, is most frequent in athletes of middle age and older (5,8,9,11–13). However, there is considerable overlap, particularly among 30- to 50-year-old athletes and it may also be that the incidence of inherited cardiomyopathies is underestimated in this group as autopsies are less often performed and coronary disease causation more frequently presumed. It would seem important that each of the conditions predisposing to SCD be considered in potential screening strategies for our 36-year old marathon runner under consideration (Fig. 1).

Anticipating Screening Efficacy

The predictive value of a screening test may be anticipated according to Bayes' Theorem:

$$PV_{test} = \frac{P_{pathology} \times Sensitivity_{test}}{\left(P_{pathology} \times Sensitivity_{test}\right) + \left(P_{nopathology} \times false\,positive_{test}\right)}$$

where PV_{test} is predictive value of the screening test, $P_{pathology}$ is prevalence of a condition predisposing to sudden cardiac death, $Sensitivity_{test}$ is sensitivity of the screening test, and false positive$_{test}$ is 100% − specificity% of the screening test, respectively.

This equation for calculating probabilities provides an instructive framework for evaluating the accuracy of diagnostic tests for rare conditions. When the disease prevalence is low, the probability of the test accurately identifying that pathology (the predictive value of the screening test) is exquisitely dependent on the test specificity. Unless the test is highly specific then an abnormal result on screening is most

Figure 1. Age-Dependent Changes in Incidence and Etiology of Sudden Cardiac Death

This figure represents an interpretation of the combined experience from studies that have assessed the causes of sudden cardiac death in athletes (3,5,8,9,11–13). While the majority of deaths may be attributed to inherited cardiomyopathies and channelopathies in those younger than 30 years old, there is no absolute cutoff. Thus athletes in their thirties and forties (the median age in many competitive sports) are at greatest risk of sudden cardiac death caused by inherited and acquired causes. RV = right ventricular; VT = ventricular tachycardia.
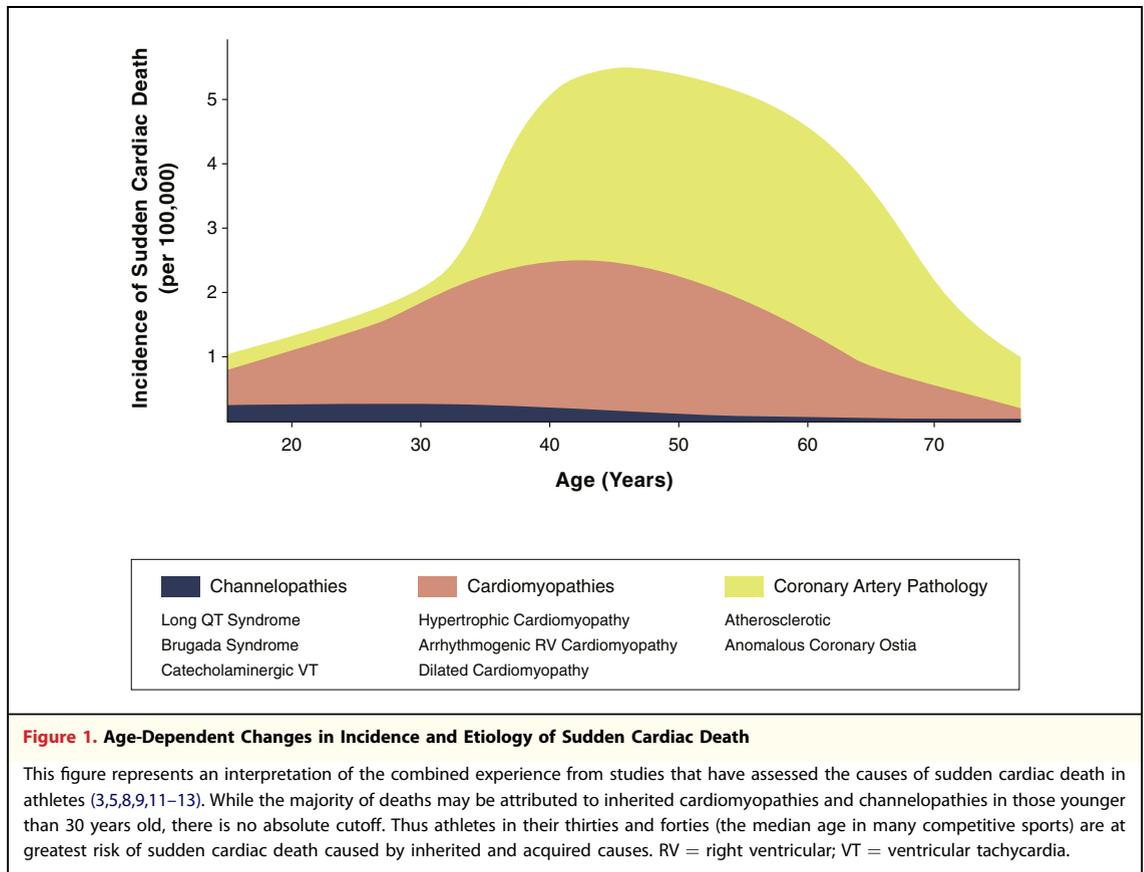
likely a false positive, prompting further testing with potential for emotional and financial harm.

Prevalence Estimates

The goal of screening is to identify pathology that may predispose to SCD. Further risk stratification of those with a pathological finding to determine those at greater or lesser risk of SCD is extremely challenging because most of our knowledge of prognosis is derived from symptomatic patients.

Estimates for the community prevalence of conditions predisposing to SCD are provided in Figure 1. The most common inherited or congenital pathologies associated with SCD in athletes are hypertrophic cardiomyopathy (HCM; prevalence ~0.05 to 0.2%) (14–16), anomalous coronary arteries (~0.2%) (17), arrhythmogenic right ventricular cardiomyopathy (ARVC; ~0.1%) (18), and ion-channel disorders (~0.007 to 0.2%) (16,19). It is noteworthy that these prevalence estimates have been derived from unselected populations and may be greater than among athletes in whom a "healthy cohort" effect tends to select out individuals with underlying cardiovascular disease. For acquired

heart disease, approximately 0.5% of an asymptomatic population with a median age of 51 years was identified as having significant coronary artery disease (20) but this may overstate the risk for our 36-year-old marathon runner with well controlled coronary risk factors. Thus, we may conservatively estimate that there is a 1 in 200 (0.5%) risk of any underlying cardiac condition that may represent a substrate for SCD in our marathon runner. The predictive value of any imaging modality is likely to be poor given this very low disease prevalence. For example, if the imaging modality were 95% sensitive and specific, the predictive value of the test would only be 9%. In other words, 91% of "abnormalities" identified on screening could be expected to represent a false positive (i.e., they would *not* represent a risk for SCD).

These calculations are dependent on speculative estimates of the sensitivity and specificity of cardiac imaging tests for the identification of causes of SCD in asymptomatic populations. There are limited studies that have assessed the accuracy of imaging modalities in diagnosing cardiomyopathies and none of these have been performed in cohorts of asymptomatic athletic adults. This largely reflects the fact

that clinical diagnoses are seldom based on imaging alone. ARVC, for example, cannot be diagnosed solely on the basis of imaging yet can be diagnosed despite normal appearance on cardiac imaging (21). The remainder of the review will aim to highlight the promise and limitations of established and novel imaging modalities for this purpose.

Most screening algorithms propose imaging as a "second-line" strategy reserved for those with abnormal ECGs at rest. Indeed, cardiac imaging is invaluable for evaluating any athlete with symptoms, a positive family history, or abnormalities on screening examination or ECG. However, some international sporting bodies, such as the International Federation of Association Football (FIFA), the International Cycling Union (UCI), and the U.S. National Basketball Association (NBA) mandate echocardiography as part of primary screening tests in asymptomatic athletes. The rationale for combining ECG and imaging to screen athletes is that pathologies such as channelopathies and accessory pathways will be identified with ECG while coronary anomalies, aortopathies and some cardiomyopathies may be identified with imaging despite a normal ECG. In addition, it may be argued that in the middle-aged athlete screening should also address the increasingly appreciable risk of coronary heart disease. Thus, in the 36-year-old marathon runner exemplified in this review, comprehensive screening would need to include an ECG, imaging of cardiac structure and function, and some assessment of coronary risk. The following discussions address whether current imaging techniques have the accuracy to effectively predict athletes at greatest risk of SCD while minimizing the psychological, physical, and financial cost associated with false findings.

Echocardiography

Echocardiography is a logical candidate as a screening modality. It is relatively inexpensive and accessible, and is free of any direct adverse effects. However, adverse financial and psychological side effects caused through misdiagnosis should not be overlooked. Thus, it is important to appraise the accuracy of echocardiography in successfully diagnosing pathology among an athletic cohort in whom profound cardiac remodeling is common.

The greatest body of evidence pertains to the diagnosis of HCM, which, in most series, is the predominant cause of SCD in young athletes. Among others, Maron and Pelliccia (22,23) have provided extensive data to enable better discrimination between "physiological" and "pathological" hypertrophy, creating an algorithm in which ventricular dilation, a maximal oxygen uptake (VO_2max) >110% of predicted and a reduction in hypertrophy with detraining all suggest physiological "athlete's heart" while asymmetry of hypertrophy, left atrial enlargement, and abnormal diastolic function suggest hypertrophic cardiomyopathy. However, most of the experience used to formulate these criteria is derived from comparing athletes and patients with HCM whereas athletes with HCM frequently do not follow the rules, and this is especially true of endurance athletes. Sharma et al. (24) performed 1 of few studies which compared 8 highly trained athletes to 8 athletes with phenotypically mild, genotype positive HCM and found a considerable difference in VO_2max (66 vs. 33 ml/min/kg, p < 0.001). However, it is difficult to quantify how much of this difference was due to the altered cardiac function and how much was due to differences in athletic conditioning and training volume. Perhaps surprisingly, it seems that some athletes with HCM can achieve high levels of cardiovascular conditioning and can be very competitive in endurance sports (25,26). For example, despite significant pathology, all 3 athletes in Figure 2 competed at an elite or sub-elite level in triathlon and athlete 3 was documented as having a VO_2max of nearly twice that predicted for his age.

Of promise is the accumulating evidence base for tissue Doppler and strain measures in the evaluation of athletes in whom HCM may be suspected. D'Andrea et al. (27) have provided a guide for normal ranges in a moderate sized athletic cohort and others have extended this experience by comparing athletes to patients with HCM (28). However, the study cohort of relatively severe HCM phenotypes was easily distinguished using the simplest echocardiographic measures (e.g., septal thickness 23 vs. 11 mm, p < 0.0001) such that the incremental value of strain imaging was difficult to assess.

An increasing number of athletes may be diagnosed with HCM as a result of genotyping or with more sensitive diagnostic tools such as delayed gadolinium enhancement (DGE) identified with magnetic resonance imaging. These milder phenotypes may be compatible with high-level exercise performance and seem to be associated with few of the classical diagnostic hallmarks of HCM (25,26). A recent study by Maron et al. (29) reported that 10% of 114 young patients with asymptomatic HCM, largely diagnosed by means of DGE and/or familial studies, had a mild phenotype including a normal ECG. Thus, while we may easily identify
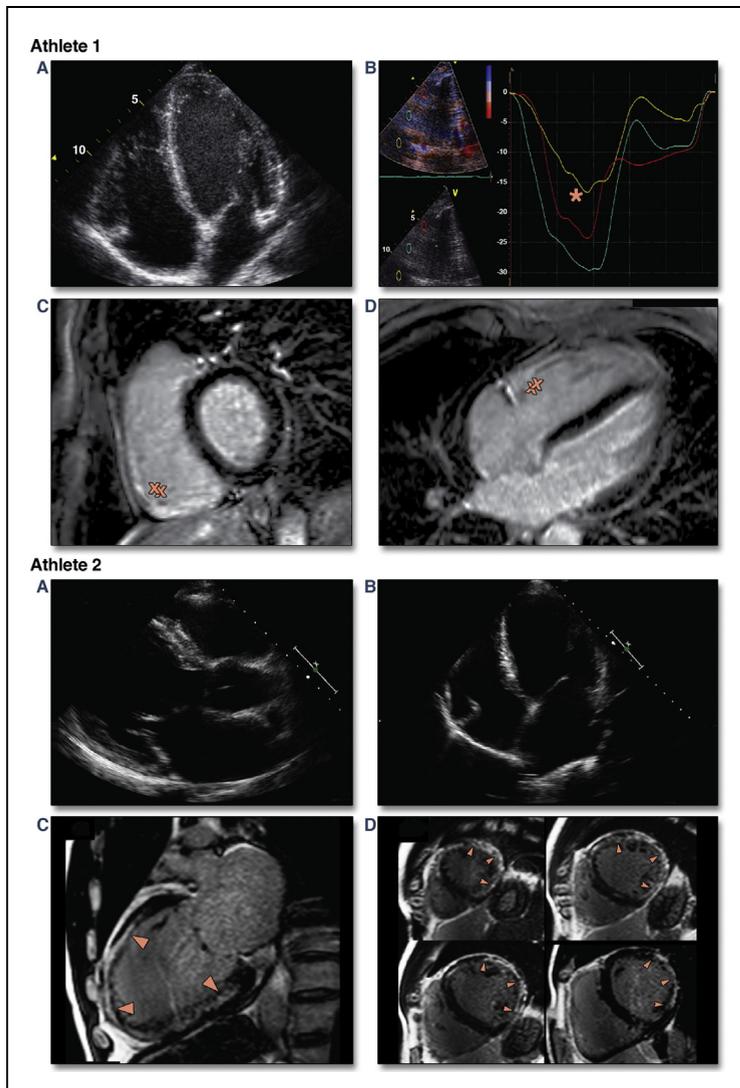
Figure 2. Increased Sensitivity of Cardiac Magnetic Resonance in Identifying Pathology

Images from 3 male middle-aged elite triathletes are presented. Athlete 1 presented with sustained ventricular tachycardia. He had changes consistent with athlete's heart on echocardiography **(1A)** including reduced basal right ventricular (RV) strain (indicated by * in **1B**), which is a common finding in endurance athletes. However, on cardiac magnetic resonance imaging there was akinesis of the basal lateral RV free wall corresponding to areas of delayed enhancement (indicated by ‡ in **1C** and **1D**) consistent with localized scarring suggestive of arrhythmogenic right ventricular cardiomyopathy, Athlete 2 presented with palpitations. He had marked cardiac enlargement on echocardiography **(2A and 2B)** but normal systolic function on echocardiography at rest and exercise. Cardiac magnetic resonance revealed large areas of delayed enhancement of the subepicardium and mid-myocardium **(arrowheads, 2C and 2D)** suggestive of a dilated cardiomyopathy. Athlete 3 survived a ventricular fibrillation arrest during a triathlon race. His left ventricular wall thickness on echocardiography was at the upper limits of normal **(3A)** and his diastolic myocardial velocities were normal **(3B)**. Cardiac magnetic resonance imaging revealed mid-cavity obstruction during systole **(3C)** and apical gadolinium enhancement (‡, **3D**) suggestive of hypertrophic cardiomyopathy.

Racial variance in cardiac morphology further complicates echocardiographic assessment. M-mode measures of septal wall thickness are the usual means by which HCM is suspected during an echocardiographic assessment and descriptions of the normal distribution of hypertrophy in male Caucasian athletes suggest that a dimension greater than 12 mm is rare and should be considered abnormal pending further investigations (30). However, 18% of male athletes of African/Afro-Caribbean have been found to have a septal thickness exceeding 12 mm and similar ethnic differences have also been reported for female athletes (31). It is likely that the specificity of echocardiography would be substantially reduced when screening athletic populations of age, gender and ethnic diversity in which our understanding of normal ranges is limited (32). As a result, we can be caught in the difficult situation of excluding athletes on a suspicion that they *may* have a disease that *may* cause SCD. This could be considered prudent by some and unacceptable by others.

The identification of other cardiomyopathies by echocardiography is similarly problematic. There is mounting evidence that intense endurance exercise results in morphological, functional and electrical remodeling of the right ventricle (RV), which may be equivalent, if not greater, than that of the left ventricle (LV) (33–36). Thus, distinguishing ARVC from the dilated athlete's heart can be extremely challenging. Our experience in screening elite endurance athletes is that the wide variance in structure and function of the RV creates significant diagnostic uncertainty. Echocardiograms from 4 professional cyclists from the same team are presented in Online Video 1 illustrating the frequency in which RV assessment provides clinical challenges. Important changes to the Task Force criteria for ARVC diagnosis have qualified RV enlargement such that *regional* abnormalities in structure or function are now required, thereby reducing the overlap with athlete's heart (21). However, identification of regional RV abnormalities is imperfect. Teske et al. (37) performed Doppler and 2D deformation analysis (strain and strain rate) on patients with ARVC and found poor agreement between RV wall motion scoring and identification of regional abnormalities by strain. Even in healthy patients, the specificity of regional wall motion analysis of the RV was insufficient to provide diagnostic confidence.

Myocarditis and dilated cardiomyopathy have been implicated in a minority of SCD cases (5,8,12). Once again, in an asymptomatic population with

severe HCM by ECG and echocardiography, these phenotypic extremes are probably very rare among highly trained athletes.

extremely high levels of fitness, the accurate identi-
fication of segmental or global ventricular dilation
and hypokinesis is extremely challenging. Abergel
et al. (38) performed echocardiographic assessments
on 424 cyclists competing in the Tour de France and
found that 51.4% exhibited significant LV dilation
and 11.6% had a LV ejection fraction <53%, which
could be compatible with a diagnosis of dilated
cardiomyopathy. Furthermore, Gati et al. (39)
recently reported that 8.1% athletes fulfilled con-
ventional criteria for left ventricular noncompaction
syndrome and yet only a very small minority of these
had any other features suspicious of an underlying
cardiomyopathy . Exercise echocardiography may
prove a useful discriminator in these settings. Plehn
et al. (40) reported that exercise caused a reduction
in end-systolic volumes among healthy controls but
not in patients with HCM or a dilated cardiomy-
opathy (40). Exercise echocardiography enables
assessment of cardiac structure, function, and con-
tractile reserve, which can be combined with real-
time ECG data, thus arguably providing greatest
promise as a single test for the exclusion of signifi-
cant pathology in athletes in whom there is clinical
suspicion. However, its predictive value in unselected
athletic populations is insufficient to accurately pre-
dict the rare athlete at risk of SCD.

Ischemic cardiac disease, either due to anomalous
coronaries or acquired atherosclerotic disease should
be excluded as a potential cause of SCD. It has been
demonstrated that the coronary ostia can be visu-
alized in 90% to 92% of athletes using echocardi-
ography and that the identification of anomalous
ostia is highly specific (41,42). However, the sen-
sitivity of echocardiography in detecting congenital
coronary anomalies (the ability to identify all cases)
has yet to be assessed, and it requires an experienced
sonographer and good image quality to confidently
identify the ostia and proximal course of the coro-
nary circulation. Outside the realm of screening, in
those athletes with exertional symptoms in which
coronary anomalies may be suspected, it is advisable
to consider computed tomography coronary angi-
ography (CTCA) and/or cardiac magnetic reso-
nance (CMR), which are highly accurate methods
for identifying the precise anatomy of coronary
anomalies (43).

Echocardiography may accurately identify prox-
imal aortic dilatation and/or bicuspid aortic valve
disease that may prevent some cases of SCD due to
aortic dissection. Data from large cohorts of ath-
letes have provided a clear definition of expected
normal ranges of aortic size (44,45). While aortic
dimensions are slightly increased in athletic cohorts

Athlete 3
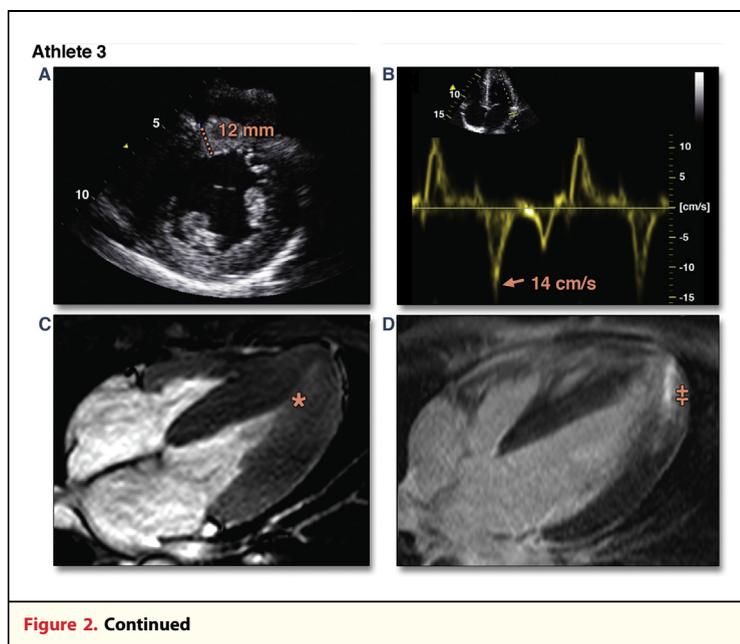
Figure 2. Continued

the difference is of minimal clinical significance
and aortic root dimension of >40 mm in males or
>34 mm in females should be considered
abnormal. These represent useful diagnostic cutoffs
for screening and may identify small numbers of
athletes with severely dilated aortas at significant
risk of dissection. On the other hand, some athletes
will be identified with milder dilation in whom
there is little evidence to direct advice on sports
participation. Posing similar management issues,
bicuspid aortic valve (BAV) pathology can be
identified in as many as 2.5% of athletes under-
going echocardiographic screening (46). Identifi-
cation of athletes with BAV may be helpful in
identifying athletes in whom regular follow-up may
prevent asymptomatic LV deterioration, particu-
larly in the context of severe aortic regurgitation,
although there is again limited evidence on the
degree to which exercise modifies the natural pro-
gression of the disease. One may also argue that the
majority of athletes with valvular complications
secondary to BAV would be identified on physical
examination and that progressive LV remodeling
may result in ECG changes. Thus, while echo-
cardiography will reliably identify aortopathies and
BAV, the number of lives saved as a result of
screening is likely to be very small. Although
focused echocardiographic studies using portable or
hand-held devices may minimize costs, echocardi-
ography still requires considerable resource infra-
structure and operator skill. This is likely to be
prohibitive in most settings, with the possible
exception of sports such as basketball in which

athletes with Marfan's syndrome may be more common.

Zeltser et al. (47) provide some insight into the potential limitations of a pre-participation screening program inclusive of an echocardiographic examination. They screened 2,051 high-school athletes with a "limited" echocardiographic examination comprising 2-dimensional measures of cardiac structure, volumes, and ejection fraction. Fourteen athletes (0.7%) were considered to have changes on echocardiogram suspicious of disease (10 HCM, 2 noncompaction, 1 dilated cardiomyopathy, and 1 subaortic stenosis), all but 3 of which had ECG changes that would have prompted further evaluation in any case. Of the 14 athletes with suspicious changes on screening echocardiography, 6 refused follow-up, 5 were considered normal after a more comprehensive echocardiogram, and 3 athletes were diagnosed with a cardiomyopathy (2 HCM, 1 noncompaction). However, none of these 3 diagnoses were subsequently confirmed by a blinded expert at an independent institution. Thus, this initial real-world experience would suggest that routine echocardiography has the potential to inappropriately exclude athletes while having limited or no efficacy in detecting pathological disease with potential for SCD.

Acquired atherosclerotic coronary disease may be identified using exercise echocardiography with moderate sensitivity and specificity (approximately 76% and 88%, respectively), comparing favorably with other stress-testing methods (48). However, few asymptomatic middle-aged athletes will have risk factors constituting intermediate pre-test likelihood by standardized criteria such as the Diamond-Forrester method or Duke Clinical Score (49,50), and thus exercise testing should not be recommended (51). Furthermore, while a positive stress test may be a good predictor of subsequent angina, it may not be a good predictor of subsequent myocardial infarction or SCD because the former requires an existing significant stenosis whereas the later generally occur in a nonobstructing lesion that experiences plaque disruption.

In the 36-year-old experienced marathon runner seeking medical clearance cited in this review, an echocardiogram was performed. As demonstrated in Online Video 2, there were typical features of athlete's heart with moderate enlargement of all 4 cardiac chambers, particularly of the right atrium and right ventricle (Fig. 3). There was mild hypertrophy of the septum (11 mm) and of the RV free wall (6 mm). Low normal systolic function was confirmed with 3D echocardiography. Strain and strain rate of the RV

free wall demonstrated considerable heterogeneity with reduced values for the basal and mid segments. While each of these values is within the ranges commonly seen in highly trained athletes, they differ considerably from that which we would consider normal for a nonathlete. The borderline systolic function and low regional deformation make it difficult to conclusively exclude pathology.

CMR

CMR has considerable promise in the evaluation of the heart of an athlete. As compared with echocardiography, CMR enables better assessment of the morphology and function of all cardiac chambers while also enabling tissue characterization by means of T2-weighted imaging of acute edema and DGE assessment of focal and diffuse fibrosis (52). Recent developments suggest CMR may also become a gold standard means of assessing cardiac function during exercise (53).

In the recent era in which familial cardiomyopathies are being diagnosed using cascade screening of effected family members, it is increasingly recognized that CMR represents a more sensitive diagnostic tool. As compared with ECG and echocardiography, CMR including DGE assessment can identify athletes when the ECG and echocardiography are normal (29) (Fig. 2). Thus, CMR should be considered the most comprehensive imaging modality for the exclusion of pathology, making it an extremely valuable imaging modality for assessing athletes with concerning symptoms. However, the relative expense and limited availability of CMR make it less suitable for broad-based screening and the specificity of CMR testing in athletes with little pre-test probability for disease is not sufficiently high to preclude a significant burden of false positive results.

The accurate differentiation of normal athlete's heart from pathology is largely dependent upon our understanding of what constitutes normal. While we now have echocardiographic values from many thousands of athletes of differing demographics and sporting practices, normal CMR values are far less numerous, derived from few centers and from a less diverse sporting population. The largest experience describing the normal range of cardiac morphology and function is provided by the Utrecht group of Prakken et al. (54) who compared biventricular volumes, masses, and dimensions in 222 endurance athletes (79 elite and 143 recreational, 42% female) with 114 age and sex-matched nonathletes. They have also described morphological differences
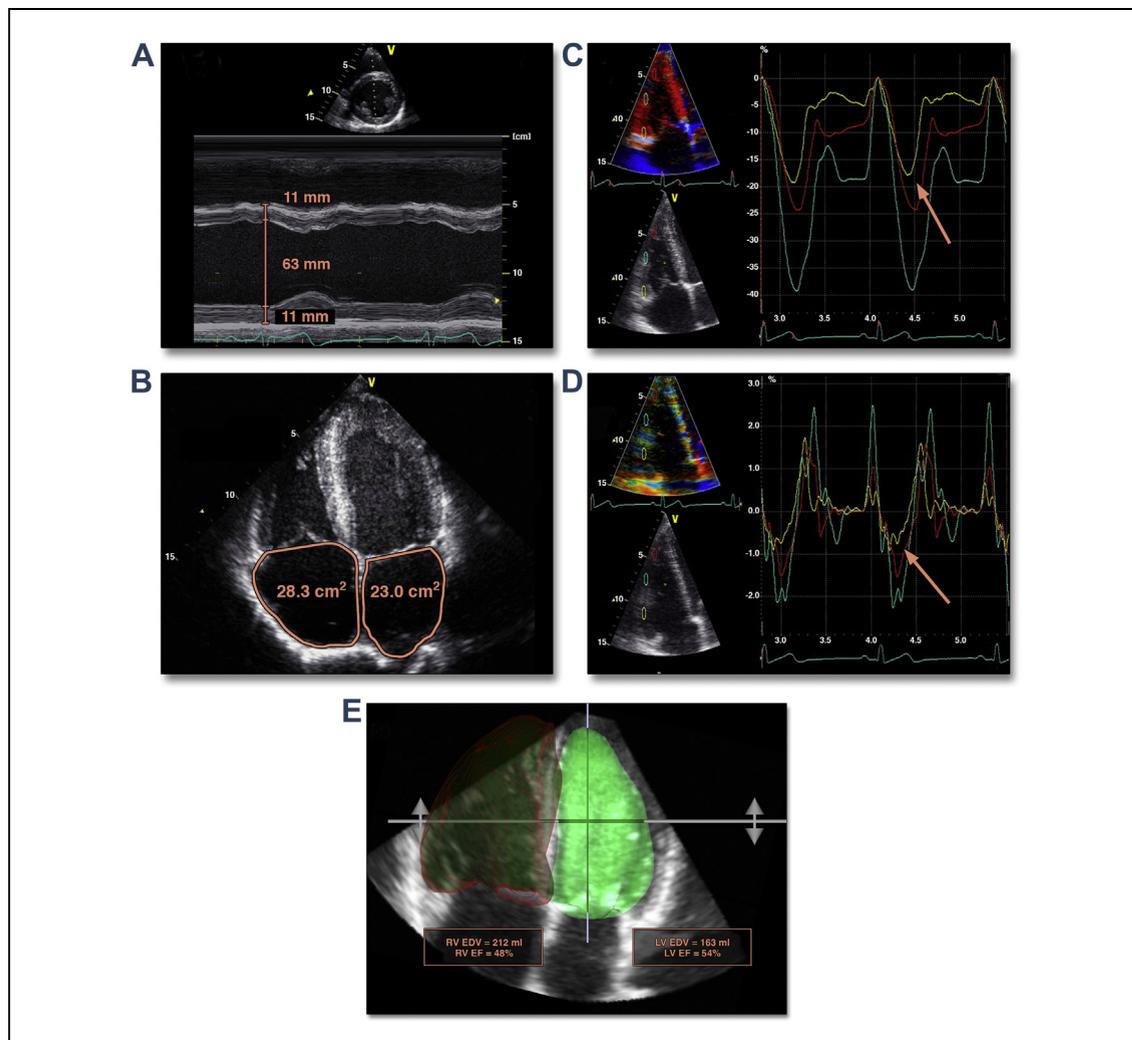
Figure 3. The "Gray Zone" in Established and Novel Echocardiographic Measures of a 36-Year-Old Well-Trained Marathon Runner

Echocardiographic measures are demonstrated for the healthy marathon runner exemplified in this review. As is common in athletes, all 4 cardiac chambers are enlarged. M-mode measures demonstrate moderate left ventricular dilation and mild hypertrophy **(A)**. The 2-dimensional atrial areas are mild to moderately increased **(B)**, while 3-dimensional volumes are moderate (LV) to severely (RV) enlarged when compared with reference ranges derived from nonathletic populations **(E)**. Color-coded Doppler derived strain **(C)** and strain rate **(D)** demonstrate mildly reduced basal strain and strain rate values (as indicated by the **orange arrows**). Many of these measurement values overlap with those of cardiomyopathies and there are currently very few diagnostic cutoff values that enable us to risk-stratify asymptomatic athletes with accuracy. Online Video 1 demonstrates unusual RV dilation and function in 4 professional cyclists, thus, further illustrating the difficulties in separating health from disease in asymptomatic athletes. Cardiac magnetic resonance imaging of our middle-aged marathon runner does not always resolve uncertainty, as illustrated in Online Video 2. EDV = end-diastolic volume; EF = ejection fraction; LV = left ventricle; RV = right ventricle.

in cardiac adaptation according to training and sport type in a manner similar to the experience with echocardiography (55,56). Interestingly, they report the only direct comparison between CMR and echocardiography in the assessment of athletes' cardiac morphology in which, similar to non-athletic findings, measures of cardiac volumes are consistently larger while wall thickness and mass were lower when measured by CMR (57). In total, this constitutes an impressive body of work but

the application of this single-center experience in clinical decision making may be confounded by operator-specific differences in image acquisition and analysis techniques. For example, considerable differences between ventricular volumes determined from axial, as compared with short-axis acquisitions, have been observed even when analyzed at 1 institution using the same software (58,59). Thus, a broader and larger experience of healthy athlete CMR values is required prior to being able to use

these to accurately identify athletes who have cardiac dimensions that may be considered abnormal.

Recently, there has been considerable interest generated by a number of studies in which DGE has been observed within the LV myocardium of ostensibly healthy athletes (33,60,61). It has been hypothesized that these small patches of DGE found in 12% to 50% of extensively trained veteran athletes may represent fibrosis resulting from extreme physical training (33,61). However, there are still very limited data on which to assess causality and there are a number of studies that have reported that DGE is not a feature of athlete's heart, albeit in younger, less trained cohorts (62–64). The fact that the DGE has been observed in healthy athletic cohorts would suggest that it is of limited clinical significance and we have no long-term clinical data to suggest otherwise. Recently, Trivax et al. (65) described the case of a middle-aged runner in whom aborted SCD was attributed to proar-rhythmic myocardial fibrosis, as evidenced by a small patch of DGE (Fig. 4). However, if these changes may be identified in approximately 12% of asymptomatic "healthy" athletes then it may be presumptive to cite this as the probable cause of cardiac arrest. Moreover, if CMR with DGE is used to assess asymptomatic athletes then what advice do we offer the athlete in whom DGE is identified? We contend that there is a clear need to assess the long-term consequences of these findings but, in the meantime, there is no evidence on which to advise athletes of an increased risk of events. Perhaps more than anything, it highlights the need to have a good reason for doing a test which is expensive, time consuming, may include the use of contrast agents (with a small but definite risk) and, in some cases, may increase the level of uncertainty for the athlete and clinician.

Coronary Artery Calcium Scoring and CTCA

For the 36-year-old marathon runner featured in this review, acquired coronary vascular disease represents 1 of the greater risks for SCD. Kim et al. (66) reported that among marathons completed in the United States, 2 in every 100,000 male athletes (mean age 52 years) suffered SCD, an incidence that seems to have increased in recent years. Among the 8 survivors of cardiac arrest in this study, causation was attributed to nonobstructive athero-sclerotic disease in 5 athletes, none of whom had angiographic evidence of ruptured plaque. This raises the question as to whether otherwise stable coronary artery disease could constitute a risk for SCD among the milieu of hemodynamic, cate-cholaminergic, and other stresses during a marathon. In this context, if screening were to be performed in our 36-year-old athlete, it may be prudent to include evaluation of his coronary arteries with CACS and/or CTCA. Both have been pro-moted as "promising tools" for screening asymp-tomatic veteran athletes (60,67) on the basis that they have proven value over clinical risk factors in the prediction of myocardial infarction and SCD, particularly among those of intermediate risk (16,68). However, there are a number of arguments against screening asymptomatic athletes with coro-nary artery calcium scoring (CACS) and CTCA. Apart from the financial cost of screening a low-risk cohort and the potential to cause harm due to contrast reactions and radiation exposure (accepting that this has been substantially reduced and now constitutes a relatively small dose), 1 prime concern is whether a significant finding on CACS or CTCA changes the management of the athlete. It is frequently argued that informing an asymptomatic individual of the presence, or likely presence, of coronary artery disease will increase physician and patient motivation to aggressively adhere to phar-macological and lifestyle prevention interventions (69). There have been 2 randomized controlled trials that investigated this hypothesis. Rozanski et al. (70) randomized 1,424 subjects to risk factor management including CACS and 713 subjects to management without CACS and determined that scanned subjects had a slightly greater reduction in systolic blood pressure (−7 mm Hg vs. −5 mm Hg, p = 0.02) and low-density lipoprotein cholesterol (−17% vs. −11%, p = 0.04), but there was no dif-ference in medication adherence, smoking cessation or exercise and the CACS strategy tended to be more expensive ($US 4,053 vs. $3,649, p = 0.09). O'Malley et al. (71) randomized 450 asymptomatic middle-aged army personnel who underwent CACS to either have their results known or withheld. Knowledge of CACS did not influence treatment adherence, intervention initiation or the extent to which risk factor management improved. Despite this relatively modest evidence for incremental benefit of CACS beyond traditional risk factor guided management, recent American College of Cardiology/American Heart Association guidelines support its use in asymptomatic individuals with intermediate cardiovascular risk (10% to 90% Fra-mingham risk) but regard CACS as inappropriate for those of low risk (72). It would seem, therefore, that few athletes would benefit from CACS. If considering the study of Mohlenkamp et al. (60),

Figure 4. Delayed Gadolinium Enhancement in 2 Competitive Runners With Very Different Clinical Outcomes

Cardiac magnetic resonance images of consecutive short-axis slices following gadolinium contrast are demonstrated. The 3 images are taken from a case report of an athlete who survived sudden cardiac death. The authors speculated that the patch of delayed gadolinium enhancement in the anteroseptal wall of the left ventricle (LV) **(yellow arrows)** may represent pro-arrhythmic myocardial fibrosis resulting from extreme exercise training (65). On the other hand, similar findings have been found in 12 to 50% of well-trained endurance athletes (33,60,61). In the case of the apparently healthy 36-year-old marathon runner undergoing screening in this review, there is a similar small patch of delayed gadolinium enhancement in the posteroseptum of the LV. Given the uncertainty of the significance of these findings, identification of small patches of delayed gadolinium enhancement on screening may be of limited clinical value in older endurance athletes.

none of the 108 marathon runners age 50 years or older had a Framingham risk prediction of >10%.

According to American College of Cardiology/American Heart Association guidelines, there is no role for CTCA screening of asymptomatic individuals of low or moderate cardiovascular risk according to American Heart Association guidelines (72).

Exercise Testing

A number of studies have demonstrated that an abnormal exercise ECG test is associated with cardiovascular events, total mortality, and SCD in asymptomatic adults (1,73,74). However, it is also notable that the predominant risk factor is low fitness. An exercise capacity of greater than 8 to 10 METs (approximating a VO_2max of 28 to 35 ml/min/kg or the ability to run slowly) is associated with fewer cardiovascular events and greater longevity in men and women, the predictive value of which exceeds any information provided from ECG changes during the test (73,74). Even among adults with a moderate to high risk of coronary vessel disease, significant myocardial ischemia is uncommon among those with a maximal exercise tolerance >10 METs (75). Thus, the simplest and most cost-effective risk stratification would be to simply determine whether an adult is

able to swim or jog at low to moderate intensity and directing further assessment at those who cannot. Athletes, virtually by definition, pass this test and have an excellent prognosis. Further testing will have limited impact on further refining this risk and is not recommended except in those who are planning on entering vigorous competitive situations and who have moderate-to-high cardiovascular risk profiles (76,77). There is no evidence to guide recommendations in athletes already engaged in vigorous sporting activities, such as the seasoned marathon runner exemplified in this review. If we conclude that the most predictive feature on exercise testing is fitness, then the answer is apparent before the athlete steps on the treadmill and any abnormality is, statistically, most likely to be benign.

Sofi et al. (78) provide the only large-scale evaluation of exercise stress testing in pre-participation screening for competitive sports. Drawing from the Italian experience in which exercise ECG testing has been a mandated part of pre-participation screening since 1982, the study reported the results of over 30,000 referrals for screening. The unselected population included a very broad age range (5 to 92 years, mean = 31 years) and a combination of well-trained athletes and nonathletes seeking to commence sport. Abnormalities were detected in 4.9% leading to

disqualification from competitive sport in 0.6% of the total population. The efficacy of these exclusions in preventing SCD remains unknown.

Cardiac Imaging as a Second-Line Screening Tool

While there is no evidence to support cardiac imaging as a primary modality in screening asymptomatic athletes, it becomes of prime relevance in the evaluation of athletes in whom an abnormality is identified on ECG. Recently refined recommendations aim to increase the specificity of the screening ECG in athletes to >97% (79). If achieved, it may be expected that the prevalence of underlying cardiac disease will be far greater among those 3% of athletes with significant abnormalities on ECG. Thus, according to Bayes' theorem, the predictive value of cardiac imaging is much improved. Further testing should be applied on a case-by-case basis and should focus on appraising the differential diagnoses arising from the clinical examination, history and ECG. The flowchart provided in Figure 5 illustrates the manner in which a hierarchy of cardiac imaging modalities may enable differentiation of healthy athletes from those with conditions that require

further management to minimize the risk of SCD. This chart is unable to reflect the considerable flexibility required of clinical decision making. For example, in the athlete with deep T-wave inversion in anteroseptal leads (raising the suspicion of ARVC) or inferolateral leads (HCM), the clinician may be ill-advised to reassure the athlete even if the echocardiographic study were to appear normal. In this scenario, a subtle cardiomyopathy may be evident on CMR or may evolve with time, thus necessitating careful surveillance.

Conclusions

Athletes represent a group in whom the risks of cardiovascular events and SCD are extremely low. The causes of SCD are relatively diverse and are not accurately identified by any 1 imaging test, especially in the middle-aged athlete who represents a substantial proportion of competitive sports participation. At present, we have an incomplete understanding of what constitutes the normal range of cardiac morphology and function among athletes of all ages and ethnicities. This is especially true for novel techniques and imaging modalities other than
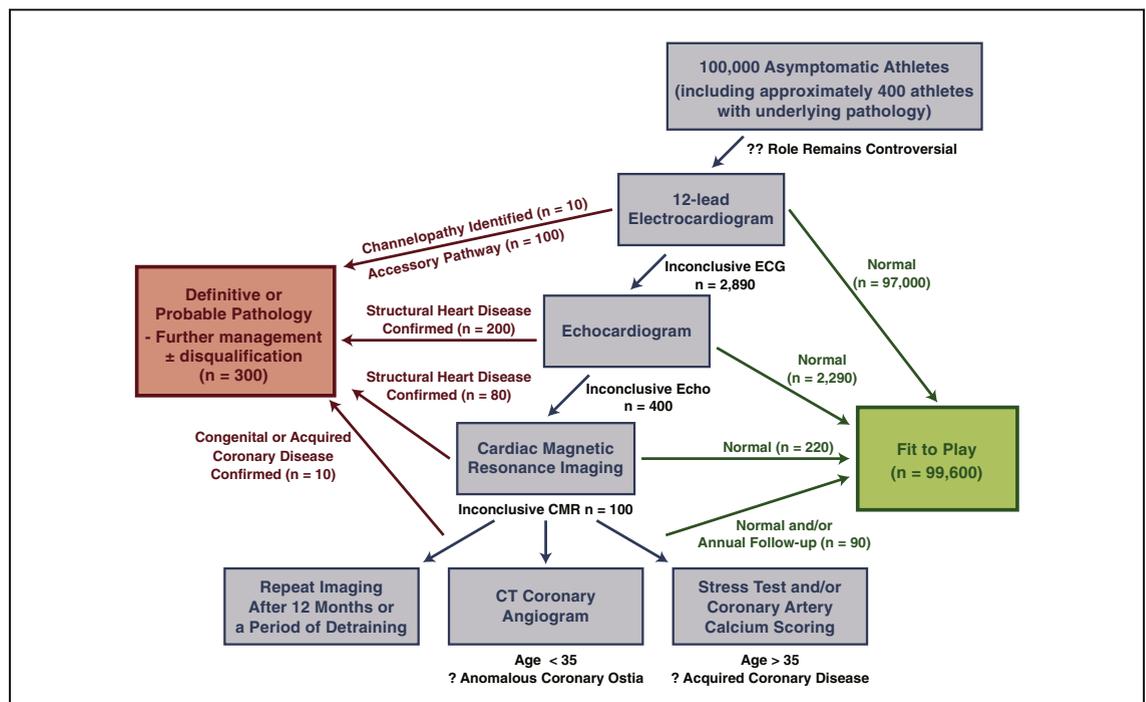
Figure 5. Screening 100,000 Asymptomatic Athletes Using a Hierarchy of Cardiac Imaging Modalities

This flowchart provides an algorithm whereby cardiac imaging may be employed as secondary screening modality following refinement of the "at-risk" population by means of electrocardiogram (ECG) screening. This flowchart represents an ideal scenario in which all potentially serious pathology is identified (100% sensitivity) and no healthy athletes are incorrectly diagnosed with pathology (100% specificity) following the cascade of tests. CMR = cardiac magnetic resonance; CT = computed tomography.

the most basic echocardiographic measures. As exemplified by the examples in this review, atypical findings such as marked cardiac dilation, reduced deformation or small patches of delayed gadolinium enhancement may introduce uncertainty in the asymptomatic athlete in whom the risk of SCD is extremely small. Therefore, we do not believe that cardiac imaging can be recommended as a first-line screening tool. Rather, patient specific investigations should be focused on evaluating those athletes in whom clinical suspicion is raised by symptoms, family history, clinical exam and/or abnormalities on ECG. While it is imperative that we continue our efforts to safeguard athletes, we must also recognize the current limitations of our tools in predicting SCD in low-risk populations.

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Key Words: athlete's heart ■ cardiomyopathy ■ cardiovascular screening ■ exercise ■ risk prediction ■ sudden cardiac death.

⊞ **APPENDIX**

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