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JACC FOCUS SEMINAR: EXERCISE, CARDIOVASCULAR DISEASE, AND THE ATHLETE'S HEART

JACC FOCUS SEMINAR

The Athlete's Heart—Challenges and Controversies

JACC Focus Seminar 4/4

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ABSTRACT

Regular exercise promotes structural, functional, and electrical remodeling of the heart, often referred to as the "athlete's heart," with intense endurance sports being associated with the greatest degree of cardiac remodeling. However, the extremes of exercise-induced cardiac remodeling are potentially associated with uncommon side effects. Atrial fibrillation is more common among endurance athletes and there is speculation that other arrhythmias may also be more prevalent. It is yet to be determined whether this arrhythmic susceptibility is a result of extreme exercise remodeling, genetic predisposition, or other factors. Gender may have the greatest influence on the cardiac response to exercise, but there has been far too little research directed at understanding differences in the sportsman's vs sportswoman's heart. Here in part 4 of a 4-part seminar series, the controversies and ambiguities regarding the athlete's heart, and in particular, its arrhythmic predisposition, genetic, and gender influences are reviewed in depth.
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Exercise has a powerful effect on cardiac structure and function. Although it would seem that the tremendous cardiac capacity of the trained athlete should be easily distinguishable from heart disease, there are several instances in which exercise-induced "physiological" myocardial remodeling, including changes in ventricular chamber size and wall thickness, can mimic pathological structural changes associated with inherited and acquired cardiac disorders. Recently it has also been appreciated that exercise-induced cardiac remodeling includes electrical molecular remodeling, and that exercise may induce myocardial inflammation and even scarring, leading to an array of rhythm changes from

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HIGHLIGHTS

- Regular exercise promotes structural, functional, and electrical remodeling of the heart, with significant exercise-related remodeling referred to as the "athlete's heart."
- Significant exercise-related remodeling is rarely associated with adverse clinical effects, such as AF and other arrhythmias.
- Both sex and genetics influence the cardiac response to exercise, and there are marked disparities in research and understanding of female vs male athletes' hearts.

bradycardia to an increased propensity for ventricular and atrial arrhythmias.[1] Collectively, these data suggest that physiological remodeling may sometimes be difficult to distinguish from pathology and cannot necessarily be regarded as benign in all athletes.

It is undeniable that, on average, athletes have superb health outcomes and survival,[2-4] but in the era of precision medicine, we strive to dissect this prognostic advantage and to identify those few athletes who may be at risk of serious cardiac events. In this final part of our *JACC* Focus Seminar series on Exercise, Cardiovascular Disease, and the Athlete's Heart, we highlight areas of evolving ambiguity and other controversies that, in some instances, challenge the assumption that the effects of exercise are always beneficial and protective. We discuss questions such as whether exercise-induced cardiac remodeling is a proarrhythmic condition, and explore the hypothesis that the overlap between physiological and pathological remodeling may be due, at least in some cases, to a genetic predisposition to cardiomyopathy and gene-environment interactions (**Central Illustration**). Finally, we address the knowledge gap that exists with respect to the female athlete's heart. Although some of these concepts are theoretical and anticipate future areas of discovery, there are also some very practical implications for the general cardiologist, sports cardiologist, and broader scientific and sports communities.

EXERCISE-INDUCED CARDIAC REMODELING

Exercise-induced cardiac remodeling, often termed the "athlete's heart," is an adaptive increase in cardiac chamber size and wall thickness that is promoted by the volumes and pressure loads of exercise. These changes are accompanied by enhancements in lusitropic and contractile function that enable the heart to fill and eject larger volumes than nonathletes during exercise. Maximal heart rates in athletes are similar to nonathletes, and thus, the greater exercise cardiac outputs observed in athletes are entirely caused by this ability to generate larger stroke volumes.

Exercise can have a profound influence on cardiac size and mass, and this is dependent on the type and duration of exercise. In 1975, Morganroth et al[5,6] provided a description of the electrical, structural, and functional changes in the athlete's myocardium that has largely remained the orthodox model for appreciating the physiology and consequence of athletic training. They compared athletes of differing endurance and strength-based training regimes and observed that cardiac mass was approximately 35% greater in athletes than nonathletes, and that cardiac volumes were up to 60% to 80% greater. They noted that endurance athletic training resulted in marked increases in volume with preservation of wall thickness, and thus, an overall increase in mass, whereas strength training resulted in an increase in wall thickness and cardiac mass but minimal change in volumes. These changes were likened to the hemodynamics and remodeling associated with regurgitant valvular heart disease for endurance athletes and aortic stenosis or hypertension for strength athletes.[5] A plethora of studies have validated these observations in endurance athletes, but prospective and cross-sectional studies in strength-trained athletes have reported only modest remodeling.[7,8] This has led to a re-appraisal of the "Morganroth Hypothesis" and an appreciation that although the description of marked remodeling in endurance athletes has proved accurate, significant increases in wall thickness or cardiac mass in strength-trained athletes should raise suspicion of an underlying pathology or the use of anabolic steroids.[7,9-11] It is well-established that habitual intense endurance exercise, such as that of competitive cycling, rowing, running, or cross-country skiing, has the greatest impact on cardiac structure, function, and electrophysiology. Previous analyses of athletic cardiac remodeling have sought to contrast the extent of cardiac remodeling according to sporting discipline. However, it can also be argued that the factors that determine cardiac remodeling are likely to relate to the severity of the hemodynamic challenge (exercise intensity) and the amount of time that the heart is exposed to this challenge (total exercise duration).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ARVC = arrhythmogenic right ventricular cardiomyopathy

CACS = coronary artery calcium score

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

LV = left ventricular

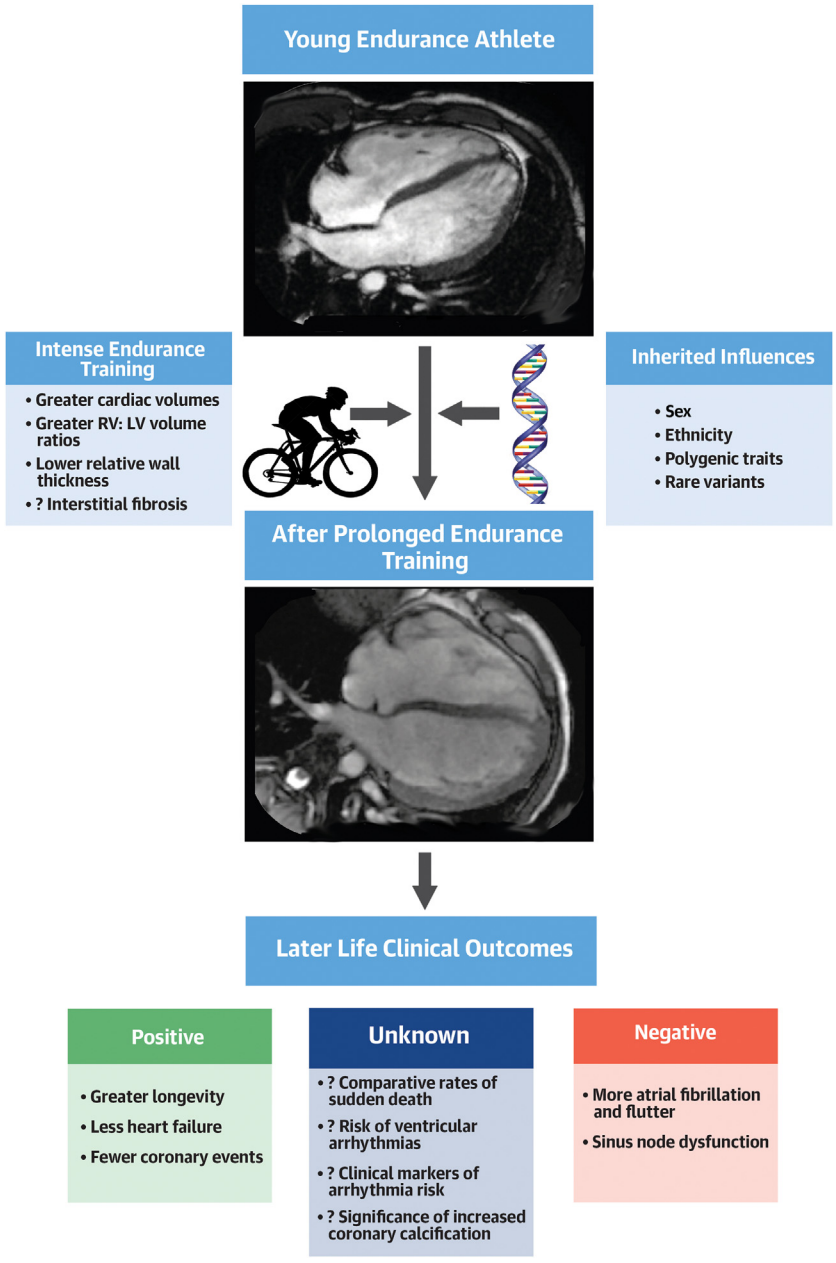
RV = right ventricular

SCD = sudden cardiac death

***TTN*tv** = truncating *TTN* variants

TWI = T-wave inversion

CENTRAL ILLUSTRATION **Potential Influences on Exercise-Induced Cardiac Remodeling and the Clinical Consequences**



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Cardiac magnetic resonance images of a professional cyclist before and after 3 years of intense competition and training that resulted in a cardiac arrest caused by rapid ventricular tachycardia. The environmental and genetic influences on cardiac remodeling are presented above the potential range of health benefits and possible risks.

It is probable that the cardiac remodeling is more greatly influenced by the total exercise burden (intensity × time, often quantified by metrics such as metabolic equivalent hours) than by the sporting discipline.[12] To put this simply, the heart cannot see what shoes you are wearing, but it can feel the effects. The primary focus in the following text concerns exercise-induced cardiac remodeling resulting

from endurance sports. There are several frequently encountered clinical conundrums, and these are listed and discussed in the following text.

IS IT POSSIBLE TO HAVE TOO MUCH ATHLETIC REMODELING? The sports cardiologist addresses questions such as: Is this athlete's heart too big or too slow? There is an established association among athletic performance, greater cardiac volumes, and lower resting heart rates,[13-15] but is there a degree of extreme remodeling at which physiological advantage may indicate future clinical sequelae? These questions are largely unresolved. Attempts at defining the limits of athletic structural and electrical remodeling have been published but have not tended to adequately encompass the full athlete spectrum, especially the most elite endurance athletes in whom more extreme measures may be encountered, such as left ventricular (LV) end-diastolic volumes exceeding 140 mL/m^2 or resting heart rates <30 beats/min. Long-term studies of athletes with these more extreme phenotypes are needed to determine whether they signify a susceptibility for disease.

DOES ATHLETIC REMODELING RESOLVE? Although there are a plethora of observational and prospective intervention studies documenting increases in cardiac volumes and mass associated with habitual endurance exercise, there are relatively few addressing the extent of reverse remodeling associated with detraining. A recent narrative review by Petek et al[16] noted significant heterogeneity in the findings to date, but some important themes included the observation that LV remodeling appears to occur within weeks of forced detraining, although return to normal cardiac dimensions may not occur even after decades of training, and that right ventricular (RV) reverse remodeling may occur at a slower rate than for the LV. There are 2 main clinical reasons for the interest in reverse cardiac remodeling. The first is the hypothesis that physiological exercise-induced cardiac remodeling should resolve with detraining, whereas pathological hypertrophy related to inherited conditions such as hypertrophic cardiomyopathy should persist. Although this theory would seem logical, it has never been tested and there are several case reports of athletes in whom inherited heart disease has appeared to resolve with detraining.[17-19] Thus, one must use significant caution if detraining is to be considered as a diagnostic test. Second, the incomplete regression of athletic cardiac remodeling challenges the concept that the increases in cardiac mass are caused exclusively by myocyte hypertrophy. Pelliccia et al[20] studied elite endurance athletes more than a decade after retirement from competitive sport and documented persisting cardiac dilation that in some cases remained profound. Incomplete regression raises the question as to whether there may be an expansion of the extracellular matrix, which, at least in theory, could be a potential explanation for some of the increase in prevalence of some arrhythmias observed in athletes. The current evidence base is insufficient to draw sound conclusions.

CLINICAL OVERLAP BETWEEN THE ATHLETE'S HEART AND INHERITED CARDIOMYOPATHIES. In prior decades, the potential clinical overlap between the athlete's heart and hypertrophic cardiomyopathy (HCM) had been frequently cited. Although this can be a diagnostic dilemma, significant increases in wall thickness are not a prominent feature of the athlete's heart. Deep inferolateral T-wave inversion (TWI) on electrocardiogram (ECG), characteristic changes on cardiac magnetic resonance (CMR) imaging, and genetic studies can usually be used to address uncertainty. More problematic is the distinction between the athlete's heart and the dilated or arrhythmogenic cardiomyopathies. Profound cardiac enlargement in combination with low-normal or mildly reduced measures of LV and RV systolic function is not infrequently encountered in elite endurance athletic populations,[21] raising the question in such athletes as to whether they may have an underlying dilated cardiomyopathy (DCM). Similarly, the common observation of ventricular ectopy in association with significant RV dilation may be difficult to distinguish from arrhythmogenic right ventricular cardiomyopathy (ARVC).[22] There are several comprehensive reviews that provide clinical guidance on the ambiguous "gray zone" cases in which there is phenotypic overlap between the athlete's heart and these cardiomyopathies.[23,24] Elucidating these diagnostic dilemmas is not the primary aim of this review, but the subsequent discussions highlight how complex the potential overlap may be, while other parts of this *JACC* Focus Seminar series provide clinical guidance for athletes in whom a genetically determined cardiomyopathy is identified.

ATHLETES AND CORONARY ARTERY DISEASE. There is a well-established inverse relationship between cardiorespiratory fitness and the risk of coronary events, and this seems to be true regardless of the extent of coronary disease. Radford et al[25] assessed cardiovascular events (fatal and nonfatal myocardial infarction, stroke, and revascularization) over 8 years' follow-up in 8,425 men according to absent, low, moderate, or high burden of coronary calcium. As expected, there were more incident events in those with a higher coronary artery calcium score

(CACS), but this was greatly attenuated with fitness such that each metabolic equivalent increase in fitness was associated with an 11% risk reduction. This exemplifies the paradox whereby athletes have fewer cardiovascular events and enhanced overall survival, and yet, male endurance athletes have been reported to have a greater burden of atherosclerotic disease.[26-28] In cohorts of middle-aged athletes, the prevalence of coronary disease (CACS >0) was similar to nonathletes with matched risk factors. However, in those with evidence of coronary disease, the CACS was consistently higher in athletic cohorts. This could be caused by "hardening" of coronary plaques with more calcified lesions being more clinically stable. The reason for the greater coronary calcium remains incompletely understood, although it may relate to greater shear stress associated with higher coronary flow and pressure. It is also notable that athletic women are not more prone to higher coronary calcium than nonathletic women. Given that coronary events remain the most common cause of death and morbidity, there is a need to determine whether coronary risk evaluation and treatment should be managed differently in athletes.

AMBIGUITIES IN DECISION MAKING CAUSED BY ATHLETIC CARDIAC REMODELING. The athlete's heart also complicates the management of individuals with established pathology. For example, significant LV dilation or low-normal systolic function would normally serve as a marker of severity and certain imaging-based cutpoints serve as indicators for intervention in an individual with mitral or aortic regurgitation. However, a substantial proportion of athletes have ventricular dimensions that exceed these cutoffs even in the absence of additional loading from valvular pathology. Thus, in an endurance athlete with valvular disease, what values should be set to indicate the point at which remodeling may be irreversible after surgical intervention? How do we determine optimal surgical timing? Another common dilemma is created at the intersection between the athlete's heart and atrial fibrillation (AF), a topic that will be discussed in greater detail in subsequent sections of this paper. The athlete's heart phenotype almost always involves a degree of atrial enlargement, often in the moderate or even severe range. Given that atrial enlargement is an adverse predictor for the success of electrophysiological treatment with pulmonary vein isolation, should more liberal selection criteria be adopted for athletes?

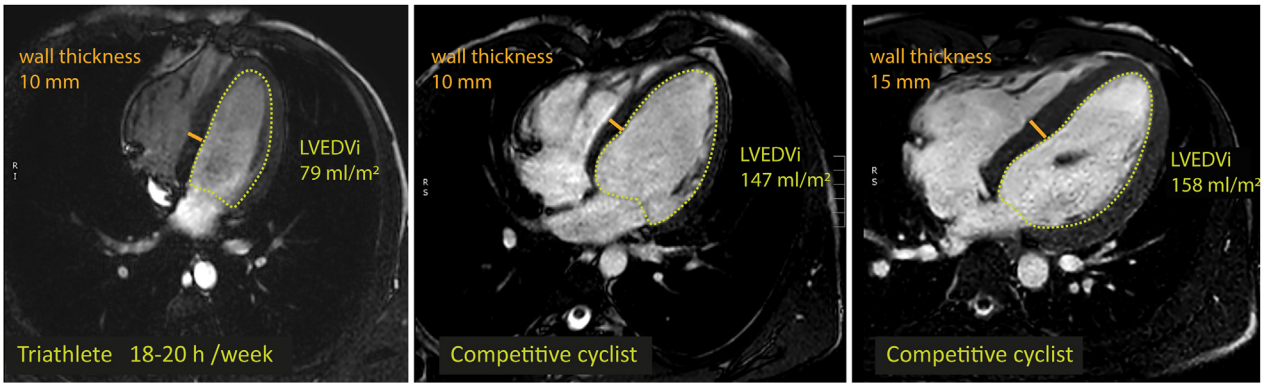
These clinical questions highlight some of the many situations in which an appreciation and understanding of athletic cardiac remodeling affects clinical cardiology care. Over recent decades, great advances have been made in understanding the spectrum of the athlete's heart. However, like most worthwhile endeavors, these discoveries have raised as many questions as they have answered.

IS ATHLETIC CARDIAC REMODELING A PROARRHYTHMIC CONDITION?

There is a clear association between high volumes of intense exercise and some types of cardiac arrhythmia. The clearest association has been established with AF, for which a U-shaped relationship has been demonstrated, with both a deficit and excess of exercise being associated with increased risk of developing this arrhythmia.[29-31] It is possible that cardiac remodeling mediates this risk of AF, given that atrial enlargement can be observed at both ends of the exercise spectrum. In an elegant series of lifestyle intervention studies, Pathak et al[32,33] demonstrated that factors including weight loss and increased exercise activity not only were associated with a marked reduction in AF recurrence, but also resulted in reverse remodeling and normalization of atrial volumes. At the other extreme, atrial volumes in athletes greatly exceed those of nonathletes. Trivedi et al[34] observed that athletes' left atrial volumes were 60% larger than those in age- and sex-matched nonathletes (27 mL/m^2 vs 43 mL/m^2).[34] Significant atrial enlargement and reduced atrial strain were observed in nonathletes with paroxysmal AF and also in athletes both with and without a history of AF. This might suggest that athletic atrial remodeling is not entirely physiological and that it may contribute to the proarrhythmic substrate, along with other associated consequences of athletic conditioning that affect the function of the sinus node and atrial myocardium, including changes in autonomic tone and molecular remodeling of ion-channels and mechanoreceptors.[35-37] As such, even physiological adaptation may set the stage for increased arrhythmogenicity ('the athletic heart is an arrhythmic heart'), further blurring the line between "normal" and "abnormal."[1] It is yet to be determined whether detraining may result in a reduction in atrial volumes and attenuation of AF burden, although randomized trials are underway.[38]

The fact that high volumes of intense exercise are related to certain arrhythmias raises the question as to whether this may be mediated by factors other than simple physiological hypertrophy of myocytes, like an expansion or interruption of the extracellular matrix. Preclinical athletic models have consistently demonstrated an association between high-intensity endurance training and myocardial inflammation,

FIGURE 1 **Individual Variance in Exercise-Induced Cardiac Remodeling**



Horizonal long-axis cardiac magnetic resonance images from 3 competitive endurance athletes. Despite similar training volumes, there is a marked difference in the extent of cardiac remodeling. The reasons for this individual variance have not been determined and may be caused by genetic traits. The **orange line** represents wall thickness and the **dotted yellow line** represents LVEDVi. LVEDVi = left ventricular end-diastolic volume index.

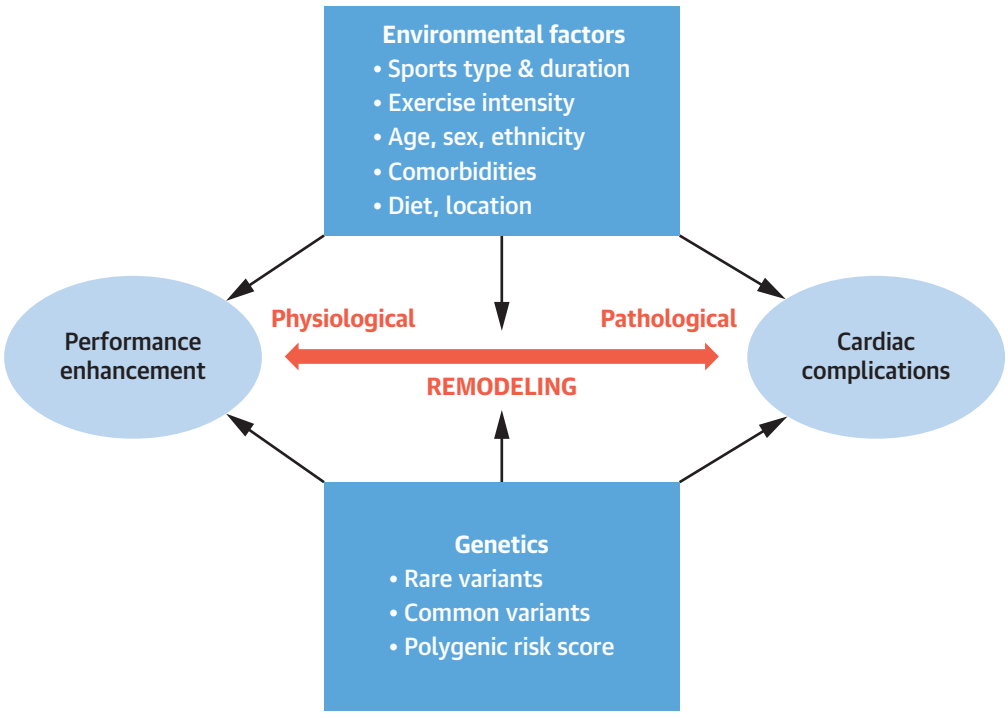
both of the atria and of the ventricles.[37,39,40] As a further similarity between exercise deficiency and excess that may contribute to the observed U-shaped clinical sequelae, it is intriguing that obesity and inactivity promote similar pathways of cytokine-induced myocardial inflammation as extreme exercise.[40-43] There is some controversy as to whether cycles of exercise-induced inflammation, mechanical stress, or other mediators could result in scarring of the myocardium.[44,45] Systematic reviews incorporating several studies have reported a high prevalence of discreet late gadolinium enhancement on CMR imaging among middle-aged endurance athletes, a marker that is usually associated with interstitial inflammation or scar.[46-48]

There is also evolving evidence for an association between myocardial scar and ventricular arrhythmias in some athletes. It is yet to be determined whether this scar is related to habitual intense exercise, or whether it may reflect an underlying inherited or acquired cardiomyopathy. It is important to note that small patches of delayed gadolinium enhancement on CMR imaging are relatively common in middle-aged endurance athletes, whereas serious ventricular arrhythmias are rare. However, there may be patterns of enhancement that are more concerning. Several groups have described cohorts of athletes presenting with subepicardial LV scar and complex ventricular arrhythmias.[49-51] Of importance, each of these studies noted prevalent myocardial scar in athletes presenting with arrhythmias. The predictive value of delayed gadolinium enhancement that is identified incidentally, or as part of screening, has not been determined.

The athlete's RV has also been the focus of attention, with the potential for adverse remodeling to result in serious arrhythmias. Relative to the LV, the athlete's RV is placed under a disproportionate hemodynamic load that has been demonstrated in both human and murine models,[52,53] resulting in acute RV dysfunction in response to prolonged exhaustive exercise[45,52] and slight asymmetric chronic remodeling with a greater RV to LV volume ratio in male and female athletes relative to nonathletes.[53-55] A more extreme phenotype can be observed in some athletes with more profound RV dilation associated with mild dysfunction, reduced contractile reserve during exercise, and a predisposition to arrhythmias of RV origin.[56-58] Heidbuchel et al[56] were the first to identify prevalent RV dilation, dysfunction, and arrhythmias in endurance athletes. Noting phenotypic overlap with ARVC but an absence of clinical or genetic evidence of inheritance,[59] Heidbuchel et al[56] termed this condition "exercise-induced ARVC." Differentiating between healthy athletic remodeling and proarrhythmic RV remodeling can be complicated. The finding of complex arrhythmias always requires a thorough assessment that may include CMR assessment of scar,[49,50] exercise assessment of RV contractile reserve,[57,60] and electrophysiological evaluation.[61]

The limits of athletic remodeling remain ill-defined. A strong association between cardiac size and fitness (maximal oxygen consumption - VO_2max) has been established,[12] but is there a point at which the heart can be too big? Should we be closely monitoring those athletes with the most profound remodeling? Are these athletes at greater risk of

FIGURE 2 **Influences on the Extent and Nature of Exercise-Induced Cardiac Remodeling**



Several environmental and genetic factors may influence the remodeling process and promote either a healthy physiological response or a pathological response with a potential for adverse clinical events. Although this has previously been considered a dichotomous response, it may represent a spectrum of change.

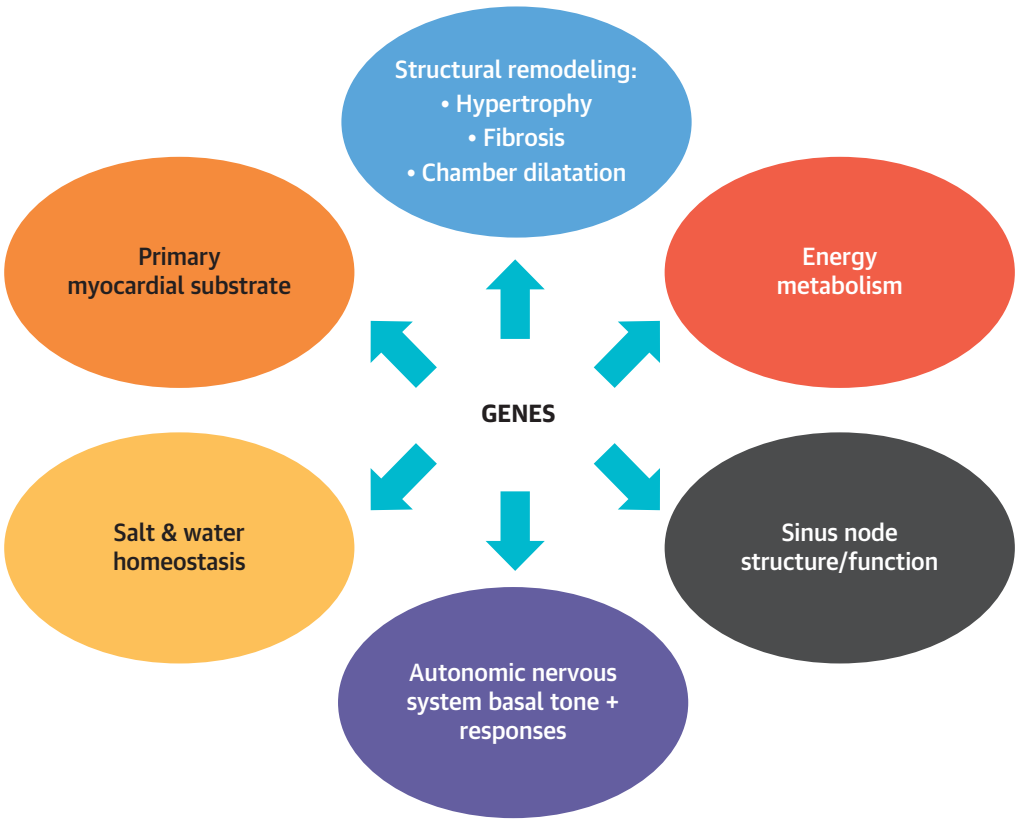
arrhythmias? These questions remain unresolved. Furthermore, additional critical questions include the degree to which these abnormalities are caused by repeated bouts of intense exercise, genetic predisposition, or an interplay of both? And finally, if profound athletic remodeling is problematic in a specific individual, to what extent can it be reversed with detraining and other measures?

GENES VS ENVIRONMENT

It is generally assumed that the degree of exercise-induced cardiac remodeling is determined primarily by the amount of hemodynamic stress that is imposed on the heart. In keeping with this, the most profound changes in cardiac volumes and mass are typically seen in well-trained endurance athletes who are engaged in sports such as rowing and cycling, which have both dynamic and static demands over prolonged periods of training and racing. However, although generalizations can be made for specific sports disciplines, there is often substantial heterogeneity in cardiac remodeling responses at the individual level (Figure 1). The extent to which these differences might be explained by environmental factors or genetic predisposition is currently unknown.

ENVIRONMENTAL FACTORS. Studies of athletic cardiac remodeling have tended to assume that the exercise load amongst elite athletes of varied sporting disciplines is equal, but this is not necessarily the case. For example, even amongst professional athletes, training characteristics vary between different individuals and from season to season. In addition to hemodynamic load (determined by sports type and training regimen), several other factors, including age, sex, ethnicity, diet, comorbidities, and location, contribute to the "environment" in individual athletes (Figure 2). The mechanisms by which these factors modify cardiac adaptation to exercise are incompletely understood but might include, at least in part, differences in training characteristics. Research in this field has been hampered by inconsistency and confusion about the definition of elite/expert athletes and by a lack of precise methods to

FIGURE 3 **Are Athletes Born or Created?**



Although far from a complete picture, there is emerging evidence linking genetic traits to several aspects related to athletic performance with multiple areas of overlap.

quantify training load and exercise conditioning. Resolution of these issues is needed to better stratify exercise exposure and to identify the full spectrum of environmental factors that modify exercise effects. It is possible that the evolving era of personalized training monitors and resulting "individual big data" may provide an opportunity to quantify the exercise component of the environmental determinants of cardiac remodeling more precisely.

GENETICS AND EXERCISE PERFORMANCE. It would seem appropriate to consider genetic influences as one of the key determinants of the variance in cardiac remodeling that is not explained by the intensity and duration of the exercise stimulus. Outliers such as those with profound remodeling with relatively modest training regimes or those with modest remodeling despite massive training loads would seem to be groups of great interest.

But beyond this, a longstanding question is: Are elite athletes born rather than made? This question is fundamental to the concept that early genetic testing might be used to inform sports choices in young athletes and even to potentially identify future champions. Understandably, extensive efforts have been made to investigate genetic determinants of sports performance. Hundreds of studies have identified variants that associate with parameters that affect muscle strength and endurance capacity.[62-64] Although data are often conflicting, these studies have implicated genetic influences on skeletal muscle properties such as muscle mass, fiber type, fiber size, and contractile speed, as well as on homeostatic functions such as regulation of salt and water balance, glucose uptake, and energy metabolism.[62]

Cardiac function is a key element of sports performance, particularly for endurance athletes. It is intriguing to speculate that some individuals might be predestined to excel as elite athletes because they have bigger, thicker, or more compliant hearts before exercise training. In support of this theory, elite

athletic hearts remain enlarged after long-term detraining,[20] and longitudinal training studies in previously nonathletic individuals have demonstrated improvements in fitness and changes in heart volumes that fall well short of those observed in elite athletes.[8]

There are numerous ways in which an athlete's genetic makeup could influence cardiac structure and function (**Figure 3**), but the extent to which genetic factors might contribute to individual variability in physiological cardiac remodeling is unknown. Genetic risk could be conferred by single rare variants or by combinations of low-frequency and/or common variants. Genome-wide association studies have recently identified genetic determinants of cardiac traits such as LV end-diastolic and -systolic diameters and volumes, LV and RV ejection fraction, and heart rate.[65-68] Polygenic risk scores derived from suites of common variants are yet to be evaluated in athletes but could provide an explanation for phenotypic variability in a subset of cases.

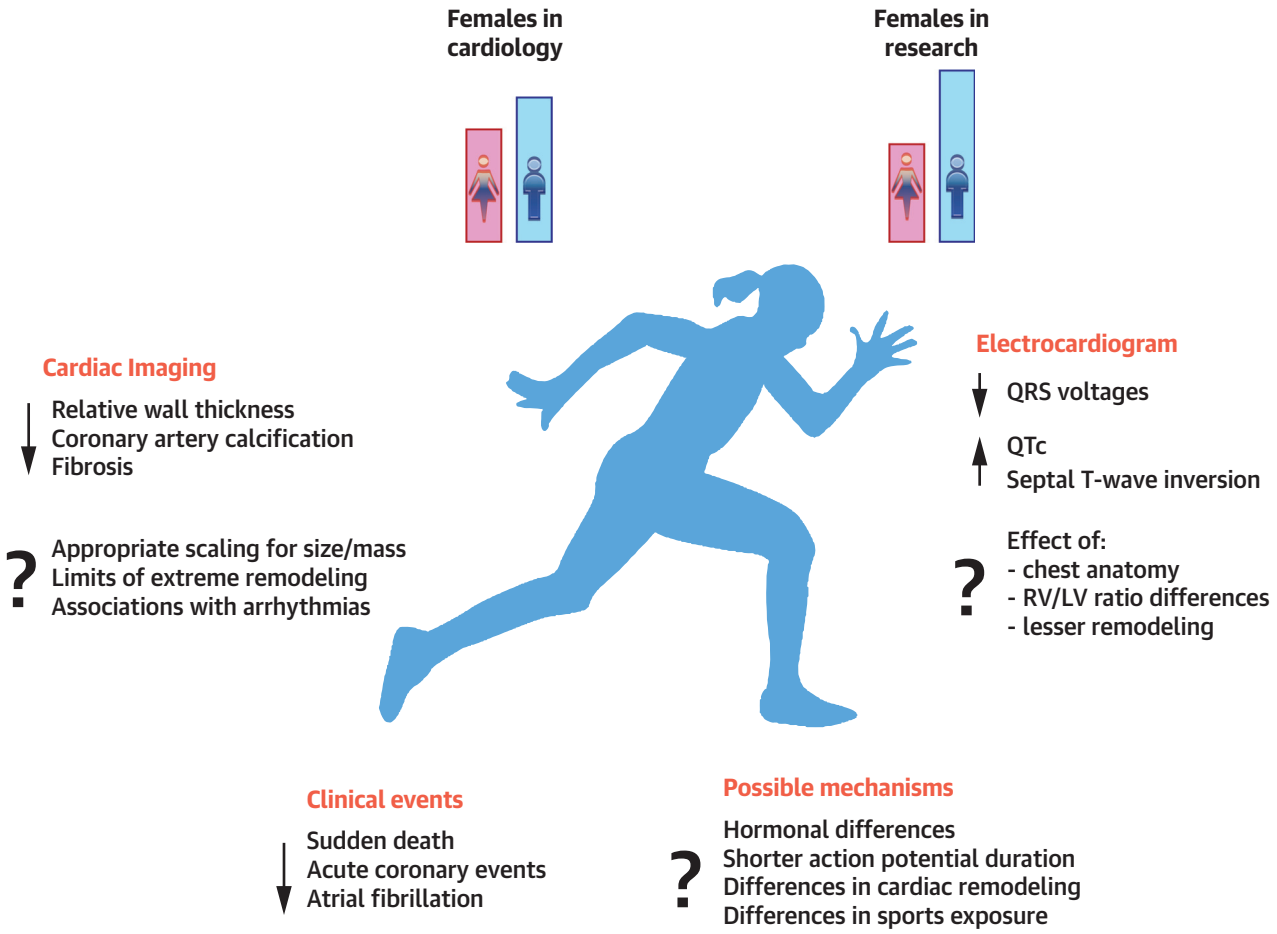
GENETICS AND EXERCISE-INDUCED CARDIAC COMPLICATIONS. Although big hearts might have intrinsic performance advantages, do these larger cardiac sizes also portend a higher risk of pathological structural and electrical remodeling and long-term cardiac complications? For athletes with marked remodeling changes, it may be challenging to differentiate clinically between the athlete's heart and disorders such as genetically mediated cardiomyopathies. As detailed earlier and also in the part 3 of this series, clinical features such as increased LV mass and chamber dilatation can mimic early stages of HCM and DCM. Chamber remodeling in athletes often disproportionately affects the RV rather than the LV, resulting in a phenotypic overlap with ARVC. Comparative analyses of the clinical features of the athlete's heart and these different cardiomyopathies have been reported elsewhere.[69]

It seems highly plausible that a subset of athletes might have both exercise-induced cardiac remodeling and a genetic cardiomyopathy. In 1 small study of 47 athletes who had arrhythmias of RV origin, 24 (51%) met clinical criteria for ARVC and 6 (13%) were found to carry a pathogenic variant in an ARVC-associated desmosomal gene.[59] Overall, however, there is a paucity of information on this topic, and comprehensive genetic testing of athletes to screen for rare variants in cardiomyopathy-associated genes has yet to be performed.

Although exercise and genetic factors could have independent and additive effects, there are emerging data to suggest that specific gene-environment interactions might have synergistic effects on cardiac function. This is particularly evident in patients with ARVC, in whom intensive endurance exercise has been shown to increase disease penetrance and arrhythmia risk.[70,71] Consequently, participation in high-intensity recreational or competitive sports is currently not recommended for these persons.[72] Similar precautions are advised for individuals with other genetic cardiomyopathies, but in many cases this is caused by exercise acting as a trigger for arrhythmias rather than the effect of exercise on the disease phenotype. There is much yet to be elucidated on the effect of exercise in those with a genetic alteration of cardiac structure. In patients with DCM, susceptibility to exercise effects may differ according to the type of underlying genetic defect. For example, variants in genes that contribute to the structural integrity of the myocardium, eg, cytoskeletal or Z-disc components, may be more prone to adverse effects of exercise-induced mechanical stress than variants in genes with other functions, eg, chaperone proteins and transcription factors. Mechanical stress is a potentially important "second hit" risk factor in the context of DCM caused by Lamin A/C cardiomyopathy in which active patients have been observed to have larger cardiac dimensions and lower systolic function when compared with less active patients with a pathological variant in the *LMNA* gene.[73] Similarly, increased hemodynamic stress may influence phenotype in individuals with truncating *TTN* variants (*TTN*tv). The hemodynamic stress of pregnancy may be less well tolerated in women with *TTN*tv, and this may precipitate peripartum cardiomyopathy.[74,75] Further, adult zebrafish carriers of a human A-band *TTN*tv showed impaired ventricular contractile reserve compared with age- and sex-matched wild-type fish when subjected to anemia-induced volume load.[76] Mechanical stress is also relevant to atrial size and the risk of arrhythmic disorders such as AF. We previously reported a cardiac ion channel gene variant in a family with AF and showed that gain-of-function effects were only present in conditions of cellular stretch.[77] Collectively, these observations have clinical implications for cardiomyopathic and arrhythmic risk in athletes who carry deleterious rare genetic variants.

As discussed in part 3 of this *JACC* Focus Seminar series, recommendations have advised caution against strenuous or competitive exercise in patients with HCM, although recent consensus statements have introduced some nuance enabling shared decision-making that weighs the risk of arrhythmic events against the psychological and metabolic health benefits of exercise.[78,79] The effect of exercise on cardiac remodeling and function in patients with

FIGURE 4 Time to End the Neglect: The Female Athlete, Researcher, and Clinician



Women are under-represented in sporting opportunity, cardiology, and research, which has resulted in a gap in our understanding of the female athlete's heart. Despite several clear sex-based differences in the effect of exercise on cardiac remodeling, electrophysiology, and clinical outcomes, there are a multitude of critical questions that remain. LV = left ventricular; RV = right ventricular.

HCM has yet to be fully elucidated. Murine models of exercise have raised the possibility that exercise may attenuate hypertrophy and increase cardiac compliance.[80] In a trial randomizing patients to exercise training or standard of care (exercise restriction), Saberi et al[81] demonstrated that HCM patients could improve cardiopulmonary fitness (VO_2peak) with regular moderate intensity exercise. This study did not detail changes in cardiac structure and function, and although it is possible that the changes in fitness were caused by peripheral adaptations, this experience should promote further studies into the effects of exercise in those with inherited hypertrophic heart conditions. If short-term arrhythmic risks prove not to be a barrier, then it is reasonable to hypothesize that improvements in cardiac remodeling may be associated with attenuated long-term arrhythmic risks.

FEMALE REPRESENTATION IN SPORTS CARDIOLOGY: PRACTICE MAKES PROGRESS, BUT NOT PERFECT

In the landmark study of Morganroth et al[6] describing the sport-specific nature of exercise-induced cardiac remodeling in competitive athletes, the single sex of their cohort is betrayed by only one use of the descriptor of athletes as "male" in the Methods section. Although this is striking in the current era, the exclusion of female athletes in that study is not surprising given the social context when it was conducted ~50 years ago. Women were very

under-represented in competitive sport at that time, comprising only 20% to 30% of participants from high school up to the Olympic level.[82-84] The Morganroth study was published just 3 years after the passage of Title IX of the Education Amendments Act of 1972, which prohibited educational institutions receiving federal funds from excluding individuals from programming, including sport, on the basis of sex. Between 1972 and now, female sports participation has expanded enormously, with men and women now participating in nearly equal numbers in sport in the United States.[82-84] Although the balance of male and female athlete participants has become more equal over time, women are still under-represented in the research that informs sports cardiology practice. Furthermore, much of what appears to differ regarding the cardiovascular health of male and female athletes remains poorly understood (**Figure 4**).

Female under-representation in sports cardiology research is not unique and shares common roots as under-representation across medical research.[85] Specifically, women may be excluded from research caused by concerns about how the biological variability conferred by hormonal physiology, such as menstrual phase and menopausal status, might affect results. Differing body size and composition also complicate comparisons between sexes.[86] These inherent sex-based differences obligate increased complexity in study design and analysis, which is possible only with adequate research resources and expertise. Motivation for investigators to recruit women in studies and for women to join studies may be further reduced by the lower prevalence of certain outcomes and diseases in female athletes, such as sudden cardiac death[87-91] and AF.[31,92] Finally, both in sports cardiology and more broadly, nondiverse research teams may lead to failures to recognize the importance of including female participants or to effectively recruit both sexes.[85,93] Sex-based equality in sports cardiology research leadership suffers both because of the lower number of female cardiologists and trainees,[94] and the lower overall prevalence of funded female vs male investigators.[95]

Sports cardiology research also has distinct challenges because of reliance on athletes as research participants. Although the prevalence of female athletes may nearly equal male athletes at many levels of sport, inequality still exists with regard to the resources allocated to female vs male sports.[96] Even if equal resources were allocated to medical support and preparticipation cardiovascular screening starting today across all sports, the previously acquired data is skewed toward male athletes. Finally, even with equal access to female athletes for research, implicit or explicit bias on the part of research teams as to what constitutes an "elite athlete" may continue to foster unequal representation.

To address the previously mentioned issues, advocates outside of medicine must continue to push for equal participation and resources for women, and those inside medicine must continue to promote policies that orient research training, funding, and infrastructure around improving equal representation of women, participants and investigators alike, in research. Although not yet perfect, there has been progress over the last decade, with several sports cardiology research programs embracing rather than avoiding sex as an important biological variable. In the process, investigations have uncovered several instances in which there is important interaction between exercise exposure and sex with regard to impact on the cardiovascular system and outcomes. In most instances, this work has raised more questions than it has answered regarding the mechanistic underpinnings of these sex-based differences.

RECOGNIZING EXERCISE-INDUCED CARDIAC ADAPTATIONS IN THE FEMALE ATHLETE—1 SIZE DOES NOT FIT ALL. The normal physiological adaptation of the cardiovascular system to intense exercise training is most commonly assessed using the ECG and cardiac imaging. The ECG is widely used as a preparticipation screening tool for athletes, and international recommendations for athlete ECG interpretation have been refined and published multiple times over the past 12 years.[97-99] These guidelines are based largely on data from preparticipation screening programs in which female athletes are under-represented. For example, several national football codes have mandated screening of male but not female athletes. Although it may be argued that the lower incidence of sudden cardiac death in female athletes warrants a different approach to screening, this has not been communicated as the rationale between the different approaches to preparticipation evaluation. Other than the recognition of longer QTc intervals in women, no accommodation for sex is made in any of the guidelines, despite the ECGs of both athletic and nonathletic women having important differences from their male counterparts. Although female endurance athletes undertaking high-volume, high-intensity training demonstrate similar prevalence of many normal, training-related ECG changes as men,[100,101] female athletes have lower QRS voltages, shorter QRS duration, and lower prevalence of LV hypertrophy by voltage criteria, regardless of sporting discipline.[100-102] **Table 1** summarizes the current understanding regarding the

TABLE 1 ECG and Structural Changes in Female Compared With Male Athletes

	Female vs Male Athletes
Electrocardiogram	
Sinus bradycardia	↔
Early repolarization	↓
LVH on voltage criteria	↓
QTc interval	↑
Inferolateral TWI	↔
TWI V_1-V_2	↑
TWI V_3	↑
Structural changes	
Absolute LV dimensions	↓
LV dimensions indexed to BSA	↑
Absolute RV dimensions	↓
RV dimensions indexed to BSA	↑
LV wall thickness	↓
Relative wall thickness	↓
Coronary calcium score	↓

↔ = similar prevalence to male athletes; ↓ = lower prevalence than male athletes; ↑ = greater prevalence than male athletes; BSA = body surface area; CMR = cardiac magnetic resonance imaging, LV = left ventricle, LVH = left ventricular hypertrophy, RV = right ventricle, TWI = T-wave inversion.

differences in electrophysiological and structural differences according to sex.

The pattern of abnormal TWI suggestive of pathology also differs between male and female athletes. Whereas TWI in the lateral leads is rarely seen in White athletes of either sex (Table 1),[100,102-104] the prevalence of anterior TWI is around 3 times higher in female than male athletes.[100,105] Female endurance athletes demonstrate a prevalence of anterior TWI of up to 19%, although this is largely confined to TWI up to lead V_2 with TWI extending to lead V_3 seen in only 6%.[100,101] This difference in TWI according to sex is particularly important because anterior TWI is part of the diagnostic criteria for ARVC, and phenotypically evident ARVC has been variably reported to be either similar[106-108] or paradoxically less common[109,110] in women than men. The reason for the higher prevalence of anterior TWI in women in the absence of pathology is not clear, although differences in chest conformation, the placement of ECG leads around breast tissue, and the anatomical situation of the RV with respect to the ECG leads are possible explanations. Lateral displacement of the RV as assessed by CMR has been found to be strongly predictive of the presence of anterior TWI in predominantly male endurance athletes, with smaller thoracic size being a contributing variable.[111]

As another area of concern, female athletes, particularly elite female endurance athletes, have been under-represented in literature describing exercise-induced cardiac remodeling as manifest on cardiac imaging. Recent work has identified that the magnitude of exercise-induced cardiac remodeling is sport-specific among female athletes, just as it is among male athletes. Cardiac dimensions, including LV wall thickness, LV mass, RV outflow tract, and RV dimensions and right and left atrial size as well as inferior vena cava diameter have been demonstrated to be higher in female endurance compared with non-endurance athletes.[112] However, comparison of exercise-induced cardiac remodeling between women and men has produced variable results. There is a commonly held perception that exercise-induced cardiac remodeling is less profound in female than male athletes. Although female athletes have smaller absolute chamber dimensions, LV and RV cavity size is actually larger in women than men when indexed to body surface area (Table 1).[112,113] This difference is attenuated or even reverses when ventricular dimensions are normalized using other more sophisticated methods such as lean body mass or allometric scaling. It remains unclear which method is optimal to compare heart size across athletes with different body size and composition depending on sex.

Although it is unclear to what extent chamber size relative to appropriate metrics of body size differs on the basis of sex, the geometric pattern of LV remodeling that occurs in healthy athletes does appear to be sex-specific. Although prior longitudinal work has shown that LV mass increases by a similar amount in men and women over a discrete period of intense exercise training,[114] women consistently demonstrate lower LV wall thickness and mass than men even when adjusted for body size and training exposure.[112,113] Importantly, this difference persists when wall thickness is considered in the context of chamber size (ie, relative wall thickness), with female athletes being far less likely than men to have relative wall thickness consistent with concentric hypertrophy. The reasons for these sex-related differences in exercise-induced myocardial hypertrophy are not known. Differences in maximal exercise blood pressure may provide a possible explanation, with lower peak systolic blood pressures observed in female athletes.[112,115] However, a direct relationship between exercise blood pressure and LV hypertrophy in athletes is yet to be demonstrated.

The importance of recognizing and defining sex-based differences in the athlete's ECG and exercise-induced cardiac remodeling lie in the ability to differentiate pathology from physiological cardiac adaptation. In the context of the preparticipation

examination or clinical assessment of athletes, the most difficult clinical conundrum is when observed changes lie in the gray zone between that which may be expected because of exercise, vs that which may represent early or mild pathological changes. Given that diseases such as HCM and ARVC can overlap structurally with exercise-induced cardiac remodeling, an understanding of what is normal for an athlete in the context of their exercise history and sex is fundamental. The data presented in the previous text support the conclusion that in female athletes, concentric LV hypertrophy or wall thickness >12 mm is very rare and should raise suspicion of underlying pathology such as HCM. In addition, although TWI in the anterior leads is more prevalent in women, TWI extending into lead V_3 is rarely seen, and when present, ARVC needs careful exclusion. With continued efforts to ensure that female athletes occupy a representative proportion of research work defining exercise-induced cardiac remodeling, we expect more data to emerge with respect to the sex-based differences of the impact of vigorous exercise on the heart.

IDENTIFYING ATHLETES AT RISK OF CARDIOVASCULAR DISEASE—IS FEMALE SEX PROTECTIVE? The incidence of sudden cardiac death (SCD) in female athletes is consistently and disproportionately lower in female than male athletes.[89-91,116-118] Although women have a slightly lower phenotypic prevalence of HCM and ARVC, with both of these being among the most common autopsy-proven causes of SCD in young athletes, this does not explain the 5- to 10-fold lower incidence of SCD in the young female athletic population. This sex-specific disparity in the incidence of SCD is not unique to the athletic population, with SCD in young (<35 years of age) women reported to be 2 to 3 times lower than that of men of a similar age in the general population.[119,120] This discordance suggests that young women with cardiac disease may be less likely to experience SCD than their young male counterparts with the same conditions.

Lower rates of sport-related SCD are also observed in older female athletes compared with males, as best demonstrated by data from endurance sport competition.[90,91,117,118] Most cases of SCD in older athletes during organized competition are caused by coronary artery disease. In this regard, sex-based differences in sport-related SCD among older athletes are better explained than those among younger athletes, given the known protection from atherosclerosis and associated myocardial infarction in middle-aged women until after menopause.[121] This pattern in the general population is mirrored in studies examining the presence and extent of coronary artery calcification in endurance athletes.[27,122]

Although in the past, sport-specific differences in SCD rates have potentially been attributed to different levels of exercise intensity or competition based on sex, the persistence of a lower incidence of SCD in women in contemporary cohorts suggests that the difference is caused by sex-based biology rather than caused by sex-based constructs. There remain myriad possible causes of lower SCD risk in women across the age span, including differences in phenotypic expression of genetic cardiac conditions, modification of arrhythmic risk by sex-specific hormonal or biochemical pathways, and relative protection from atherosclerosis and coronary artery disease until postmenopause. Research to define the contribution of these mechanisms to sex-specific SCD risk stands to improve the health of both those athletes who are highly exercise-exposed and the general population.

CONCLUSIONS AND LOOKING TO THE FUTURE

The average athlete lives longer and has superior health outcomes in virtually every domain when compared with the general population.[2-4] This important public health message should be promoted. On the other hand, it is critical that symptoms, abnormal signs, or investigations should not be overlooked in the athlete on account of the misnomer that they are "too fit" to have significant cardiovascular disease. As has been detailed, even the very fittest of athletes can have serious pathologies that require a sound knowledge of the athlete's heart to be able to appreciate those features that are atypical, extreme, or abnormal. Sports cardiology is a rapidly evolving subspecialty that combines niche physiology, imaging, and electrophysiology expertise, which aims to best understand and describe the spectrum of cardiovascular changes and consequences resulting from habitual sports training. This endeavor needs to consider sex, ethnicity, and age. In the modern precision medicine era, we are also starting to understand the influence of genetic variance on the athlete's heart phenotype.

In this paper, we have highlighted clear limitations within the sports cardiology evidence base. The accuracy of diagnostics and the effectiveness of therapeutic interventions are defined by the completeness of medical knowledge, and it follows that these research gaps need to be prioritized so that women can be afforded equal care. We have also highlighted several areas of ambiguity related to the extent to

which more extreme athletic cardiac remodeling may have the potential to evolve into cardiac disease. Although cardiovascular disease is less common among athletes than the general population, cardiovascular disease remains prevalent and presents unique challenges in terms of risk prediction, diagnosis, and management. Early identification of disease remains a major challenge, and there is much yet to be learned beyond the relative contributions of exercise and underlying genetic predisposition. Answers will require detailed quantification of environmental factors, deep phenotyping using imaging and electrophysiology, and an integrated assessment of genetic traits. These critical clinical questions will be best addressed with prospective studies of adequately sized populations of highly trained athletes. The athlete population is healthy, but some individual athletes may not be. The advance toward precision diagnostics and genetics will enable us to advance the goal of making exercise safe for everyone.

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