Why Are We Having This Debate?
The health effects of exercise are undeniable, both on cardio-
vascular and noncardiovascular mortality.1 But just as tennis
players can overuse their tendons and runners can develop
stress fractures, it may also be that endurance athletes may
develop sports-related cardiac injuries. Despite exercise being
our oldest and most efficacious therapy, there is an incomplete
understanding of the entire dose–response relationship. Faced
with the modern inactivity pandemic there has been an appro-
priate focus on the harm associated with too little exercise.
However, at the other extreme, intense exercise training can
result in profound cardiac remodeling, termed the “athlete’s
heart,” and the prognostic significance of the resulting struc-
tural, functional, and electric changes remains uncertain.

Response by Levine p 1002
Popular speculation and rumor regarding the risks of exer-
cise have persisted since the collapse of Pheidippides, an event
which has itself been altered and fabricated through centuries
of social media,2 and the topic cannot simply be dismissed on
account of a lack of evidence. Indeed, there are no random-
ized, controlled trials assessing the health effects of intense
prolonged exercise but this works both ways—there is no
definitive evidence of harm, nor definitive evidence of safety.
Thus, using cohort studies, surrogate end points and preclini-
cal data we seek to illuminate wider debate by highlighting
the substantial evidence suggesting that intense exercise, par-
ticularly intense endurance exercise, can be associated with
adverse cardiac remodeling and an excess of arrhythmias. We
will definitely not argue that any potential harm from more
extreme exercise negates the overwhelming benefits of mod-
erate and regular exercise.

Case 1
A 23-year-old professional cyclist was assessed with a clini-
cal evaluation, ECG, and echocardiogram as per International
Cycling Union licensing requirements. He had been com-
peting for a decade, had exceptional physical conditioning
(VO2max = 81 mL/min/kg), and had no symptoms of cardio-
vascular disease. The only family history of relevance was that
his father, also a competitive cyclist, had suffered from atrial
fibrillation from age 40. His ECG was remarkable for extreme
bradycardia with isorhythmic dissociation, incomplete right
bundle-branch block and T-wave inversion extending to V2,
all of which may be considered within the limits of an ath-
lete’s heart.3,4 Severe enlargement of all 4 cardiac chambers
and low-normal biventricular function were observed on a
resting echocardiogram (Figure 2), but there were no specific
features to suggest an inherited cardiomyopathy. Exceptional
exercise tolerance and good augmentation of systolic function

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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Intensive Exercise Can Harm the Heart

La Gerche and Heidbuchel

Figure 1. Relationship between cardiac remodeling and exercise capacity (VO₂max). Data derived from a mixed cohort of athletes and nonathletes demonstrates a strong correlation (r = 0.79, P < 0.0001) between left ventricular (LV) mass measured by cardiac MRI (x axis) and maximal oxygen uptake at maximal exercise intensity (VO₂ max y axis). Above the graph are representative examples of a 23-year-old nonathlete with average cardiac dimensions and VO₂ max, a 23-year-old international footballer with a modest increase in cardiac size and VO₂ max (middle), and the elite cyclist detailed in Case 1 with a markedly increased LV mass and a VO₂ max in excess of 80 mL/min/kg. BSA indicates body surface area. Adapted from La Gerche et al with permission of the publisher. Copyright ©2012, Springer.

in both ventricles was confirmed on stress echocardiography. Thus, the profound cardiac enlargement was attributed to “athlete’s heart” and the cyclist was reassured. Five years later, having remained asymptomatic and having undergone another similarly comprehensive screening evaluation, he experienced a cardiac arrest during a regular training ride. An autopsy confirmed significant cardiac enlargement and nonspecific patches of myocardial fibrosis but no evidence of coronary vessel disease, myofibrillar disarray, or fibro-fatty infiltration. Comprehensive testing of first-degree relatives revealed no evidence of a hereditable channelopathy or cardiomyopathy,5,7 of SCD cases are caused by an underlying inherited condition (cardiomyopathy, coronary anomaly, or channelopathy).5,7 Scenarios such as that in Case 1, we may argue that his severe ventricular dilation and reduced ejection fraction placed him at greater risk of arrhythmias in virtually all clinical settings,15 and it seems reasonable to question the orthodox view that the athlete’s heart is somehow different.

Pathological Versus Physiological Remodeling—Not So Black and White

When assessing an athlete like our cyclist in Case 1, the clinical implications of his profound cardiac remodeling are often discussed in the context of whether it is physiological or pathological. This dichotomous approach to the issue would imply that the eccentric hypertrophy is either attributable to exercise stimulation of trophic signaling pathways such as IGF1-PI3K (p110α)-Akt with a resulting increase in cell size, improvement in contractility, and an absence of fibrosis or, conversely, pathological hemodynamic stressors inducing pathways involving ANGIOTENSIN II, protein kinase C, and calcineurin, in which myocyte apoptosis and extracellular fibrosis dominate.16 Descriptions of these distinctly different pathways have been derived from a murine model in which aortic constriction was contrasted with regular exercise. However, although both interventions may increase cardiac mass, they are not at all similar in terms of the hemodynamic load or the patterns of hypertrophy. Although also only an approximation, progressive aortic or pulmonary valve regurgitation better reflects the predominant volume load of aerobic exercise and in such patients the physiological IGF1 pathway is upregulated, just as it is with exercise.17 If we then extrapolate the clinical associations of severe valvular regurgitation to the cyclist in Case 1, we may argue that his severe ventricular dilation and reduced ejection fraction placed him at greater risk of arrhythmias and sudden death.18 This is an assumptive line of reasoning which almost certainly overstates any potential risk. However, we would argue that the wall stress imposed on the ventricles during exercise approximates the resting wall stress of some pathologies with proarrhythmic potential. Therefore, if high intensity exercise is performed too frequently, the hemodynamic stimulus for remodeling may be similar. Even physiological adaptations like dilatation, hypertrophy, and autonomic modulation may increase the chance for a stochastic process like arrhythmias.

Inherited Versus Acquired Heart Disease—Not Black and White Either

Recent approaches aimed at preventing SCD in young athletes have been predicated on evidence suggesting that the majority of SCD cases are caused by an underlying inherited condition (cardiomyopathy, coronary anomaly, or channelopathy).5,7 Thus, exercise is thought to trigger arrhythmic death in susceptible individuals, rather than to cause it per se. However, SCD may remain unexplained after autopsy in as many as one-third of young athletes.13,14 Scenarios such as that in Case 1 highlight the potential dilemma faced by the pathologist trying to decide whether the profound hypertrophy and small patches of myocardial fibrosis suggest a specific diagnosis. The limits of expected remodeling among highly trained athletes are ill-defined, and although the cardiac dilation in Case
1 is profound, it is consistent with previous descriptions of apparently healthy professional cyclists in whom left ventricular (LV) diastolic dimensions of up to 73 mm and ejection fractions as low as 41% have been observed. Thus, a cardiomyopathy cannot be diagnosed by cardiac dimensions alone. Distinguishing between athlete’s heart and hypertrophic or arrhythmogenic cardiomyopathy can be very challenging despite modern imaging and this uncertainty may be incompletely resolved at autopsy. For example, fibro-fatty infiltration of the right ventricle may not be as specific for the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) as has previously been thought, whilst hypertrophic cardiomyopathy and athlete’s heart may also be indistinguishable on histology. Although the reproducibility of autopsy diagnoses has seldom been scrutinized, recent data suggest that experts may reclassify the cause of death in as many as 41% of cases. An open-minded observer may conclude that in some cases of SCD in athletes, exercise-induced cardiac remodeling may be erroneously attributed to cardiomyopathy and sudden unexplained death may be presumptively attributed to a channelopathy. Thus, the possibility that athlete’s heart may represent an arrhythmogenic substrate may have been overlooked.

It may also be that the separation between cardiac remodeling attributable to genetic and athletic factors is somewhat artificial. Many, if not most, physiological and pathological adaptations are a result of interaction between genetic traits and environmental exposure. Twin studies, linkage analyses, and genome-wide association studies suggest that cardiac hypertrophy is determined in approximately equal measure by hemodynamic factors such as blood pressure and exercise, and genetic determinants such as single-nucleotide polymorphisms in regulatory genes. Thus, some of the variance in cardiac remodeling that has been described among athletes with similar training exposure is likely explained by genetic factors. Furthermore, given the relatively strong association between the extent of eccentric cardiac remodeling and maximal oxygen consumption during exercise, the genetic traits may confere a performance advantage. Could it be possible that polymorphisms in genes encoding titin,
desmosomes, or connexins could promote cardiac dilation and enhanced sporting performance in the short-term, but predispose to arrhythmias in the longer-term? This is a grossly speculative hypothesis, but it may be important to challenge the paradigm of mutual exclusivity between athlete’s heart and inherited cardiac disease. In Case 1, the cyclist’s father developed atrial fibrillation at a young age and we may speculate that a mild genetic predisposition (for example, multiple uncommon polymorphisms in genes associated with myocardial integrity) combined with the hemodynamic stress of years of intense cycling might explain the family’s propensity to arrhythmias.

**Keep It Real, Endurance Athletes Live Longer!**

Landmark studies described a 2- to 4-year greater life expectancy among Finnish national representative athletes when compared with referents from military recruitment records. More recently, investigators compared longevity among Tour De France cyclists with that of the general population and concluded that the cyclists’ mortality was 41% lower and life expectancy was increased by 8 years. These studies offer reassurance but need to be interpreted with caution because the reference groups (military recruits or the general population) differ substantially from the athletes in many respects other than just the amount of physical activity performed. The ‘healthy worker’ effect is used to describe the fact that people with severe chronic disease, terminal illness, and disabilities are less likely to be able to work or, in this case, perform sport at the highest level. The magnitude of the healthy worker effect has been estimated at 40% and might therefore account for all of the reported mortality differences between the Tour de France cyclists and the general population. Athletes are typically exposed to fewer risk factors for illness such as smoking, alcohol excess, and obesity and are more likely to be educated and be of a higher than average socio-economic status. This may explain, for example, why smoking-related illnesses (chronic obstructive pulmonary disease and lung cancer) were responsible for the greatest differences in cause-specific mortality between the elite Finnish athletes and the military recruit referents. Thus, the longer life expectancy of athletes may not be attributable to exercise training per se. As a means of attempting to isolate the effect of exercise, some investigators have compared professional endurance athletes with leisure-time athletes and reported that the survival benefit over the general population may be less and the incidence of arrhythmias may be more among those athletes performing the largest volumes of endurance exercise training.

Finally, it is possible that high doses of exercise have beneficial effects on some aspects of the cardiovascular system but have a negative impact on others. Exercise improves blood pressure control, lipid profiles, and insulin sensitivity and so it is not surprising that exercise has been associated with a reduced incidence of myocardial infarction. Considering that myocardial infarction accounts for the majority of cardiovascular deaths, it is plausible that exercise could be associated with improvements in all-cause cardiovascular mortality but also an excess in cardiovascular diseases of lesser prevalence or lesser lethality, such as arrhythmias (see Figure 3). The Finnish group of Karjalainen, Sarna, and Kujala realized this paradox and followed their descriptions of improved longevity among elite athletes with subsequent reports of more frequent atrial fibrillation among the same demographic.

**Case 2**

During a 120-mile road race, a 28-year-old professional cyclist with a history of ventricular arrhythmias of disputed prognostic significance developed rapid ventricular tachycardia (270 beats per minute) requiring prompt cardioversion.

At 20 years of age he had developed palpitations while competing in a major European stage race. Electrocardiograms revealed inverted T-waves in V1 and V2 and imaging revealed moderate enlargement of all four cardiac chambers, consistent with ‘athlete’s heart’ (Figure 4). Exercise testing provoked brief runs of ventricular tachycardia with a morphology consistent with a right ventricular outflow tract (RVOT) origin, but also some ectopics of variable right ventricular (RV) morphology. He underwent endocardial ablation and was nondiendible by programmed stimulation. After 6 months, his symptoms recurred and he underwent 3 subsequent electrophysiological studies and ablations of a larger arrhythmogenic area in the RVOT, with only transient relief of his symptoms. After further cardiac imaging, which failed to show any definitive evidence of pathology, and opinions from 5 independent cardiologists, the cyclist was reassured as to the benign nature of the ‘idiopathic’ RVOT tachycardia and advised that he could continue cycle racing.

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**Figure 3.** A potential hypothesis to reconcile observations of improved survival yet more arrhythmias among athletic cohorts. Athletes (solid lines) may have improved overall survival (red lines) because of the beneficial effects of exercise on cardiovascular risk factors and fewer vascular deaths (blue lines). Arrhythmias are a less common cause of death, and thus an excess of arrhythmias in athletes relative to nonathletes (solid and dashed green lines, respectively) may have minimal impact on total mortality because they do not outweigh the other cardiovascular benefits. Identifying individuals at risk, however, is the mission of medical science. (This is a hypothetical schema based on the authors’ interpretation of available data.)
At age 26, 2 years before his arrest, the athlete was evaluated at our institution and a potential causative link between his history of extreme exercise and arrhythmias was considered. Consistent with our previous descriptions of exercise-induced ARVC, we noted (1) recurrent and progressive RV arrhythmias from a large area in the RVOT and some from outside the RVOT, (2) prominent and disproportionate RV remodeling, with a relative increase in RV to LV size during periods of intense training, and (3) electrocardiograms that showed that T-wave inversion in V3 occurred during periods of heavy training, resolving within weeks of rest (Figure 4).

Although he met only 2 minor criteria for arrhythmogenic cardiomyopathy (nonsustained ventricular tachyarrhythmias [VT] of RVOT morphology and T wave inversion to V2) and remained noninducible on programmed stimulation, he was advised to retire from competitive sport. Nevertheless, he had returned to racing at age 27, a year before his arrest.

From Cardiac Plasticity to Arrhythmogenic Remodeling

Cardiac structure and function represent a balance between the requirements of metabolic efficiency at rest and the hemodynamic stress imposed during exercise. Cardiac outputs of 40 L/min or more have been recorded in elite endurance athletes, and this promotes significant stretching of the atria. During ventricular systole, the residual atrial volume and rapid venous inflow fill the atria with >200 mL to maintain these massive outputs. This is a very substantial volume load when one considers that atrial volumes of 80 mL or more are generally considered severely abnormal. This acute hemodynamic stress is reflected in chronic remodeling of the atria, which increase with the extent and duration of endurance exercise training.

The important question is whether the recurrent hemodynamic stress and resultant atrial remodeling represent an arrhythmogenic substrate. Multiple cohort and case–control studies have reported an increase in the incidence of atrial fibrillation or flutter among endurance athletes as compared with nonathletic controls. In a recent meta-analysis, Abdulla et al estimated that endurance athletes faced a 5.3-fold greater risk of atrial fibrillation (AF). Perhaps even more compelling are the data derived from the novel study design of Thelle et al, who assessed physical activity levels in relation to flecainide usage among >300,000 Norwegian men and women with the assumption that the majority of flecainide prescriptions would be for “lone” AF. They observed that men who reported intensive physical activity were 3.2-fold more likely to be prescribed flecainide than were sedentary males. Andersen et al provided further valuable insights into the dose–response relationship by demonstrating that the risk of AF among cross-country skiers increased progressively with shorter race completion time and with the number of races completed, surrogates of training volume and duration, respectively. Potential mechanisms underpinning the excess in AF in athletes were elegantly investigated by Wilhelm et al. In a cohort of 70 randomly selected athletes entering a 10-mile running race, they demonstrated an increase in left atrial volume and P-wave prolongation as evidence of altered atrial substrate, as well as increased vagal tone and atrial ectopy as potential modulators and triggers of arrhythmias, respectively. These data concur nicely with preclinical data from the “marathon rat” model of Nattel, Mont et al showing promotion of
AF in relation to an altered atrial substrate in the form of fibrosis, dilation, and vagal modulation. Athletic remodeling of the atria is not only associated with atrial fibillation but may also be associated with chronic adverse remodeling of the sino-atrial and atrio-ventricular nodes and a possible increase in the need for pacing among retired athletes.

There is less definitive evidence to suggest that intense exercise can promote arrhythmogenic remodeling of the ventricles, especially given that the low prevalence of VT makes it challenging to adequately power epidemiological studies. However, once again, considerable evidence from preclinical and clinical studies raises questions. Biffi et al detected ≥3 ventricular premature beats (VPBs) on a standard 10-second ECG in 2.2% of athletes, seemingly more than in nonathletic populations where ≥1 VPBs are found in <1% of ECGs. In 329 athletes with frequent VPBs but normal cardiac imaging, Biffi et al observed that there were no cardiac events and concluded that VPBs should be considered benign in athletes. However, a recent meta-analysis concluded that subjects with frequent VPBs but no evidence of cardiovascular disease were at 2.6-fold greater risk of SCD than those without frequent VPBs. Thus, more frequent triggering of multifocal VPBs and nonsustained VT arrhythmias could indicate the development of subclinical structural myocardial changes of clinical relevance. Balduzzi et al observed a greater prevalence of nonsustained VT among 62 retired professional cyclists when compared with age-matched golfers (15% versus 3%, P=0.05). The small size of the cohort raises the distinct possibility of a Type I error but, on the other hand, could also imply that the excess in arrhythmia prevalence is relatively substantial.

In athletes, ventricular arrhythmias tend to originate from the RV, thereby raising the intriguing hypothesis that exercise-induced stress and remodeling promote an arrhythmogenic substrate. Under resting conditions, more work is required of the LV, which has to generate output against the moderate afterload imposed by the systemic circulation. During exercise, however, pulmonary artery pressures and RV afterload increase disproportionately relative to the systemic circulation. Thus, RV wall stress exceeds that of the LV, making it more susceptible to acute injury during endurance exercise and, as a result, repeated small ‘hits’ may promote chronic remodeling of the endurance athlete’s RV. This, the hemodynamic stress, acute injury, and chronic remodeling all disproportionately favor the RV.

Heidbuchel et al first raised the concept of an exercise-induced RV cardiomyopathy when describing 46 high-level endurance athletes who were evaluated in the context of nonspecific symptoms like palpitations and dizziness, but that could later be attributed through work-up to ventricular arrhythmias, the majority of which were of RV origin. Despite the seemingly mild clinical presentations, the syndrome proved to have an ominous clinical course with 18 (39%) experiencing a major arrhythmic event, of which 9 were (aborted) sudden death. A majority of the athletes had structural, functional, and electric abnormalities of the RV, but not of the LV. Combining major and minor criteria of the 1994 ARVC diagnostic framework, 59% had manifest ARVC and an additional 30% had probable ARVC. However, in contrast to what would be expected with familial ARVC, evidence of familial disease was uncommon (only 1 of 46 athletes had a familial history). Thus, the syndrome was almost indistinguishable from ARVC except for the fact that the predisposing factor was intense endurance exercise rather than genetic inheritance, leading Heidbuchel to coin the term “exercise-induced right ventricular cardiomyopathy.”

The disproportionately greater wall stress in the RV during intense exercise provides a plausible link between the hemodynamic stressors of exercise and subsequent proarrhythmic remodeling of the RV. Once again, the “marathon rat” methodology of Benito et al shows remarkable similarities with the human data. A strenuous 18-week treadmill running regime in young rats was designed to approximate 10 years of endurance exercise training in humans. As compared with the sedentary control rats, there was an increase in atrial and RV inflammation/fibrosis whereas the LV was spared. Perhaps most importantly, this predominant RV remodeling was associated with a greater potential for inducible ventricular arrhythmias (42% versus 6%, P=0.05).

Some of the clinical features in Case 2 could be consistent with a diagnosis of ARVC. Intriguingly however, the extent of the T-wave inversion in the precordial leads and the severity of the RV dilation seemed to increase with training intensity and volume. In our experience, the slow progression from a syndrome suggestive of benign RVOT-tachycardia to a more diffuse RV process is a common feature of this exercise-induced syndrome. Ablation often consists of ‘debunking’ of a vast area of the RVOT (rather than a real focal ablation), while not addressing the causative factors. Most importantly, there was no evidence nor suspicion of ARVC within the family. This leaves 2 equally valid and overlapping explanations: either exercise can cause an ARVC-like syndrome in its own right, or there is an interaction between endurance exercise and predisposing genetic traits that are not currently identified by screening for known mutations in the desmosomal genes.

**Picking the Athlete at Risk**

At the end of the day, the question from the athlete is simple: “Can you tell me whether I am at risk of arrhythmias?” In both the asymptomatic athlete and the athlete complaining of lethargy, palpitations or presyncope, this can be a very difficult task.

**Cardiac Biomarkers**

There has been speculation about whether noninvasive surrogates of cardiac injury may identify athletes at greater risk. Increases in cardiac troponin and B-type natriuretic peptide after endurance sporting events lead to speculation that this may reflect myocardial injury and predispose athletes to cardiac events through chronic structural remodeling. However, such speculation seems to ignore half of the concept of adaptive physiology. Cardiac muscle, like other muscles and indeed most biological tissues, adapts to injury by means of regenerative structural and...
functional changes which make the heart more able to withstand subsequent training stressors. Myocyte regeneration is a well-established phenomenon and partly explains why athletes develop larger hearts. There have not been any studies appraising the mechanisms, rate, and extent of cardiac recovery after intense endurance exercise. Although such investigations may be challenging, it may be more instructive to assess the completeness of repair rather than simply assessing the extent of damage (eg, via biomarkers). We have previously hypothesized that chronic adverse remodeling of the athlete’s heart may represent an imbalance between more substantive training-induced cardiac injury and inadequate time for regenerative recovery.

Akin to other models of overtraining, we suspect that this may explain why some athletes develop arrhythmias (Figure 5).

Amount of Exercise
How much exercise is too much? Although it is tempting to select some arbitrary exercise dose in terms of intensity, duration, or distance, we believe that this trivializes an extremely complex interaction between the environmental, personal, and genetic factors involved in stress and repair (Figure 6). As a useful analogy, running mileage is 1 risk factor for tibial stress fractures and yet many runners can develop fractures with minimal mileage, whereas others can run extreme volumes without incident. The multitude of factors involved make it impossible to define risk by training factors alone, and this very likely holds true for the heart as well.

Delayed Gadolinium Enhancement on Cardiac Magnetic Resonance Imaging
The presence of subclinical myocardial fibrosis in highly trained athletes could explain the association with arrhythmias as well as the observation that athlete’s heart may not completely resolve with long-term detraining. Thus, there has been great interest in noninvasive surrogates capable of assessing the extent of fibrosis in ostensibly healthy athletes. Delayed gadolinium enhancement (DGE) on inversion recovery cardiac magnetic resonance sequences enables accurate delineation of focal scar in some pathologies and, recently, small patches of DGE have been observed in 12% to 50% of extensively trained veteran athletes. However, there is still very limited data on which to assess causality and even less to assess its clinical significance. Recently, Trivax et al described the case of a middle-aged runner in whom aborted SCD was attributed to proarrhythmic myocardial fibrosis, as evidenced by a small patch of DGE, and suggested that this test may be useful in identifying athletes at risk. However, if DGE may be identified in ≥12% of healthy athletes then its positive predictive value seems poor. Although it may constitute part of the evaluation of athletes with arrhythmias, incidental findings of limited DGE should be interpreted with caution.

Electrophysiological Evaluation
Some electrophysiological techniques may be valuable when attempting to ascertain the risk of malignant arrhythmias in
athletes with frequent VPBs or nonsustained VT. In the study of athletes with exercise-induced ARVC, Heidbuchel et al.\(^7\) observed that the induction of re-entrant arrhythmias was the only test predictive for later arrhythmic events (relative risk, 3.4; \(P=0.02\)). Further evidence to support invasive assessment comes from Dello Russo et al.\(^7\) who assessed 57 athletes with complex ventricular arrhythmias from a population of 1644 screened athletes. Electro-anatomic mapping and guided RV biopsy was performed in 17 athletes in whom a diagnosis remained elusive after comprehensive cardiac imaging. Both electro-anatomic mapping and biopsy were normal in 4 athletes, whereas in the remaining 13 biopsies directed at abnormal low-voltage areas revealed myocardial inflammation, fibrosis, or fatty infiltrates in all. The extent to which exercise played a causative or incidental role remains unclear.

**Genotyping**

At present, our understanding of genetic traits predisposing to cardiomyopathies, arrhythmias, and SCD does not extend much beyond single mutations located within a limited number of disease-associated genes—coding structural proteins, contractile elements, ion-channels, etc. The phenotypic expression of these mutations can be influenced by environmental factors such as intensive exercise. Among 87 patients with a positive ARVC genotype, James et al.\(^7\) reported that clinical disease manifested at an earlier age in endurance athletes than nonathletes. At the other end of the spectrum, we systematically evaluated the 5 desmosomal genes for mutations in a cohort of 47 athletes, of whom 87% had definite or probable criteria for an ARVC phenotype.\(^3\) If RV arrhythmogenicity were the early expression of a latent underlying genetic (desmosomal) mutation, we would have expected a similar prevalence of mutations to that described in nonathletes with ARVC (≈50%),\(^7\) but rather the yield was a modest 12.8%. Moreover, clinical evidence of inheritance was even less common (2 of 47 athletes). Together these studies might suggest a spectrum of disease with genes explaining the majority of disease expression at one end (classical familial ARVC), and exercise proving the major factor at the other (exercise-induced ARVC). There is still an enormous amount of research required to enable us to better quantify the genetic and environmental hits required to reach the threshold for phenotype expression, and research will need to expand to include patterns of multiple polymorphisms and modifier genes. We will also need to consider personal and environmental factors other than exercise; for example sex, body-habitus, nutrition, and intermittent illnesses (Figure 6).

**Performance Enhancing Drugs**

It is tempting to fall back on performance enhancing drugs (PEDs) to explain the many things that we do not understand about arrhythmias in athletes. History tells us that PEDs have at times been ubiquitous among professional endurance sports, but this does not necessarily mean that they are responsible for all proarrhythmic cardiac remodeling. There are limited data regarding the direct cardiotoxic effects of PEDs, and it is therefore difficult to speculate as to how likely they are to provoke adverse clinical events.\(^7\) Also, we should consider the indirect effects in which PEDs enable longer and more strenuous endurance activity and thereby exacerbate changes driven by exercise hemodynamics. Potentially important disease-causing mechanisms may be overlooked if we simply assume that all adverse events can be ascribed to PED usage.

**Conclusion**

Clinical decision-making demands concrete answers, whereas science needs balanced views. We look for a definitive ‘yes’ or ‘no’ answer when asked whether intense exercise can harm the heart. However, our current interpretation of the data would lead to an answer along the lines of the following: “endurance exercise most likely increases your chances of living longer but may increase your risk of some arrhythmias.” Unfortunately, this is a sentence full of qualifiers. After centuries of intrigue about the benefits and risks of intense exercise we have failed to arrive at definitive answers. Exercise, including intense endurance exercise, offers a plethora of population health benefits that likely exceed any excess risk of arrhythmias. However, the debate is of great relevance to the individual athlete who has profound myocardial remodeling or arrhythmias and needs us to understand the mechanism so that we can target our treatments and best prevent adverse outcomes. At present there is insufficient evidence to treat athletes with arrhythmias any differently from the general population,\(^8\) but if we start to accept that exercise may contribute to the disease substrate then it would seem relevant to assess whether changes in exercise practice may change clinical outcomes. We need open-minded investigators with the patience, will, and resources to conduct adequately powered prospective studies. This might seem daunting, but given that exercise is such an essential ingredient for good health, we should try and best understand the complete dose-response relationship.

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**Disclosures**

None.

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Response to La Gerche and Heidbuchel

Benjamin D. Levine, MD, FACC, FACSM, FAPS

My opponents and I mostly agree: (1) the cardiovascular response to intensive endurance training is primarily adaptive; young and old athletes alike have big, compliant hearts that pump large volumes of blood very quickly to support high rates of oxidative metabolism; (2) This cardiac enlargement (and associated autonomic adjustment) includes the atria, modestly increasing the risk for atrial fibrillation; (3) There is likely some degree of exercise training that is unsustainable even for the most highly trained athlete, leading to musculoskeletal injury, overtraining syndromes, and perhaps cardiac fatigue/injury; (4) When athletes do present with cardiovascular compromise, it is likely attributable to some combination of genes, toxins, and training that interact within a given athlete.

I would caution though, that the link with specific polymorphisms is at best tenuous. Except for a few specific mutations, there are many variations of unknown significance that have failed to live up to the hype surrounding genomic testing. Moreover, caution should be applied to generalizing conclusions from case studies and anecdotes; many other cases illustrate alternative interpretations. For example, Olympic swimmer Chad Carvin demonstrated that subclinical myocarditis may underpin many cases of athletes who develop “idiopathic” cardiac abnormalities. Ultimately, the epidemiologic evidence is compelling: ex-Olympians, Tour de France riders, Swedish skiers, Californian runners—all live longer and better; the physiological evidence is striking: Masters athletes have youthfully compliant hearts and blood vessels, and extraordinary coronary vasodilatory capacity; and the contrary evidence is weak, indirect, and anecdotal. I, for one, am heading out for a run!
Can Intensive Exercise Harm the Heart?: You Can Get Too Much of a Good Thing
André La Gerche and Hein Heidbuchel

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