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COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

Athlete's Heart Revisited: Historical, Clinical, and Molecular Perspectives

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ABSTRACT: The athlete's heart, formally introduced by Henschen and Darling in 1899 through observations of cardiac enlargement in endurance athletes, has evolved from a clinical curiosity to a recognized physiological adaptation. Even before this naming, similar constructs such as the soldier's heart in military recruits and the runner's heart in distance athletes suggested early observations of exercise-associated cardiac remodeling—often pathologized or mischaracterized. Today, this phenomenon is understood as exercise-induced cardiac remodeling, comprising structural, functional, and electrical changes that support the demands of sustained athletic performance. This compendium review examines the full spectrum of exercise-induced cardiac remodeling. We begin by tracing the historical context of how the athlete's heart was discovered and progressively understood. We then explore the morphological and functional adaptations that arise with different exercise modalities, distinguishing between endurance and resistance training effects. The review further investigates the molecular and genetic underpinnings of exercise-induced cardiac remodeling, leveraging data from both human subjects and experimental animal models. We also address the clinical challenges posed by exercise-induced cardiac remodeling, including its phenotypic overlap with cardiomyopathies, such as hypertrophic, dilated, and arrhythmogenic right ventricular cardiomyopathy. These overlaps complicate athlete evaluation and risk stratification, particularly in preparticipation screening and return-to-play decisions. Finally, we explore concerns regarding the long-term effects of high-volume endurance training, including potential maladaptation. Together, this review offers a synthesis of current knowledge and a window into the athlete's heart. By integrating perspectives from history, physiology, molecular biology, and clinical cardiology, we aim to highlight the distinctiveness of this phenotype and why it warrants focused scientific inquiry.

Key Words: athletes ■ cardiomegaly, exercise-induced ■ endurance training ■ exercise ■ hypertrophy

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The athlete's heart, first documented by Henschen[1] and Darling[2] in 1899 through observations of cardiac enlargement of endurance athletes, has since evolved from a clinical curiosity to a well-defined physiological phenomenon. Before Henschen's[1] formal naming, kindred constructs had emerged—the soldier's heart observed in military recruits and the runner's heart described in distance athletes—each an early recognition of exertion-associated cardiac remodeling, although often pathologized or misunderstood. Advances in imaging and cardiovascular physiology have clarified that this phenomenon—now aptly recognized as exercise-induced cardiac remodeling (EICR)—reflects adaptive structural, functional, and electrical changes that enable the heart to meet sustained athletic demands.[3]

This compendium review outlines the spectrum of EICR, beginning with historical perspectives and the physiological adaptations associated with different modes of training. We then examine the molecular and genetic mechanisms that govern these changes, drawing from both human and animal studies. Comparative evolutionary insights are presented to contextualize the athlete's heart within broader physiological adaptation. Finally, we address areas of clinical complexity, including the overlap between physiological remodeling and pathology, and the emerging risks of high-volume

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AKT1	protein kinase B
bZIP	basic leucine zipper
C/EBPß	CCAAT/enhancer–binding protein ß
CAC	coronary artery calcium
CITED4	Cbp/p300-interacting transactivator with a Glu/Asp–rich carboxy-terminal domain 4
CMR	cardiac magnetic resonance
CPhar	cardiac physiological hypertrophy-associated regulator
EF	ejection fraction
EICR	exercise-induced cardiac remodeling
HCM	hypertrophic cardiomyopathy
IGF1	insulin-like growth factor 1
IRS	insulin receptor substrate
LA	left atrial
LDL	low-density lipoprotein
LGE	late gadolinium enhancement
lncExACT	long noncoding exercise-associated cardiac transcripts
LV	left ventricular
m6A	N6-methyladenosine
MoTrPAC	Molecular Transducers of Physical Activity Consortium
PDK1	pyruvate dehydrogenase kinase 1
PGC-1α	peroxisome proliferator–activated receptor gamma coactivator-1α
PI3K	phosphoinositide 3-kinase
PPARα	peroxisome proliferator–activated receptor alpha
RV	right ventricle
SCD	sudden cardiac death
STAT3	signal transducer and activator of transcription 3
TTE	transthoracic echocardiography

endurance training. Our aim is to provide a framework for understanding how exercise remodels the heart—and when it may potentially go too far.

HISTORICAL PERSPECTIVES ON THE ATHLETE'S HEART

Ancient Foundations: Exercise and the Heart in Antiquity

Early notions linking physical activity to heart health can be traced to ancient Greece and Rome. The Greeks emphasized physical excellence, and physicians such as Herodicus and Hippocrates advocated for exercise as a cornerstone of health. Hippocrates notably emphasized the balance between exertion and intake—an early articulation of training principles. Galen later expanded on these ideas, arguing that exercise had therapeutic value and contributed to physiological resilience.[4]

Historical accounts, including the legend of Pheidippides—who ran from Marathon to Athens before collapsing—convey early recognition that extreme exertion could pose cardiovascular risks.[5] Although details of that story are likely apocryphal, they reflect a long-standing tension: does sustained exertion strengthen the heart, or strain it? This question, debated even in antiquity, would resurface with new urgency in later centuries.

Industrialization and the Emergence of the Athlete's Heart Debate

The 19th century ushered in major lifestyle shifts. As industrialization reduced physical activity, physicians became concerned not only with the effects of sedentarism but also with the perceived dangers of extreme exertion. During the American Civil War, Jacob Mendez Da Costa described Soldier's Heart—a syndrome of tachycardia, breathlessness, and fatigue. Although likely related to anxiety, it signaled a growing awareness of how sustained stress, physical or psychological, could affect the heart.[6]

With the rise of organized sports, particularly among the social elite, medical skepticism deepened. British surgeon Skey[7] warned that competitive rowing might produce permanent cardiac injury, describing the Oxford-Cambridge Boat Race as barbarous. The Clinical Society of London echoed these concerns, citing overstrain of the heart and aorta among athletes.

At the same time, sports were viewed as a crucible for moral and physical development. In elite British and American institutions, athletic participation was seen as a marker of discipline and character. That concern for cardiovascular consequences only gained traction once elite men took to sport underscores the class lens through which early athlete's heart debates emerged.[8]

Marathon Craze and Early Scientific Investigations

The revival of the Olympic Games in 1896 brought long-distance running into the public consciousness. The first modern Olympic Marathon rekindled both admiration and concern over extreme endurance events. Reports of runners collapsing at the finish line fueled fears about the risks of prolonged exertion. The case of Dorando Pietri, who famously staggered across the finish line in the 1908 London Olympics and was later disqualified for receiving assistance, further intensified concerns about the Runner's Heart.[5]

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Clarence DeMar, a 7-time Boston Marathon champion, was among the first athletes to be scientifically examined. DeMar was warned by physicians that marathon running could damage his heart. However, an autopsy conducted after his death from unrelated causes revealed that his coronary arteries were exceptionally large (with a large lumen despite atherosclerosis), suggesting that prolonged training might induce beneficial vascular adaptations rather than harm.[9]

These cases signaled a transition: from anecdote to inquiry, from myth to measurement. The athlete's heart was no longer just a cultural or clinical concern—it was now a subject of scientific interest.

Mid-20th Century: Defining the Athlete's Heart

In 1899, Swedish physician S. Henschen coined the term athlete's heart after noting cardiac enlargement in cross-country skiers using percussion-based techniques. Although primitive by modern standards, his observations anticipated the structural adaptations later confirmed by imaging.[10]

In the United States, Paul Dudley White[11] advanced a more nuanced view. A pioneer in preventive cardiology, White studied bradycardia in athletes and concluded that low resting heart rates were not pathological but adaptive. His work helped shift the narrative—casting the athlete's heart as a marker of fitness rather than disease. This period laid the foundation for reframing athletic cardiac remodeling from a potential liability to a physiological response, though uncertainty about its boundaries persisted.

Second Half of the 20th Century: Clarifying Risks and Adaptations

The 1960s and 1970s marked a turning point. Large-scale observational studies, particularly in Italy, quantified cardiac remodeling in athletes and helped define its limits. In one such study, Pelliccia et al[8] found that left ventricular (LV) hypertrophy and chamber enlargement were common in elite athletes but rarely exceeded thresholds concerning pathology.

At the same time, the emergence of sudden cardiac death (SCD) in young athletes—most notably linked to hypertrophic cardiomyopathy (HCM)—reintroduced uncertainty. The work of Maron et al[12] in 1980 identified HCM as a leading cause of SCD in this population, emphasizing the need to differentiate physiological adaptation from pathology. Importantly, the leading causes of athletic SCD have shifted over time, with autopsy-negative sudden unexplained death now increasingly recognized, particularly in younger athletes.[13] This evolving understanding underscores both the limits of current diagnostics and the need for continued investigation into environmental, arrhythmic, and molecular contributors to SCD.

These dual threads—refinement of normal athletic adaptation and awareness of its potential mimicry of disease—established the conceptual tension that defines sports cardiology today.

EXERCISE PHYSIOLOGY AND ITS ROLE IN CARDIAC REMODELING

Understanding the physiological basis of exercise is essential to contextualize EICR.[14] With increasing workload, oxygen consumption (VO_2) rises proportionally, reflecting greater metabolic demand. Peak VO_2—the highest oxygen uptake measured during testing—is a central marker of cardiovascular fitness and performance capacity.

To meet this demand, cardiac output increases via elevations in both heart rate and stroke volume. Although maximal heart rate is largely fixed—determined by age, sex, and genetic factors,[15,16]—stroke volume exhibits marked plasticity with training. Endurance athletes develop enhanced ventricular filling and reduced end-systolic volume, resulting in high-output physiology. This capacity for large stroke volumes is a defining feature of EICR and a cornerstone of endurance performance (Figure 1).

Sport-Specific Adaptations in EICR

The nature of cardiac adaptations varies depending on the type of exercise performed. Sporting disciplines can be broadly categorized based on their hemodynamic demands into isotonic (dynamic) and isometric (static) exercise, although most involve a combination of both.[17]

- Isotonic exercise (endurance training): Activities such as long-distance running, cycling, swimming, and rowing impose a primary and sustained volume challenge on the heart. The prolonged elevation in cardiac output with normal or reduced peripheral vascular resistance leads to the balanced dilation of all 4 cardiac chambers. Variations exist between endurance sports; for example, rowers tend to develop eccentric LV hypertrophy due to increased pressure stress, whereas long-distance runners exhibit eccentric LV remodeling with normal LV mass.[18,19]
- Isometric exercise (strength training): Strength-based activities, such as weightlifting and wrestling, are characterized by increased peripheral vascular resistance and relatively modest elevations in cardiac output. These activities induce a pressure overload, leading to mild LV wall thickening without chamber dilation.

The Morganroth hypothesis, proposed in the 1970s, first encapsulated these ideas with the suggestion that dynamic and static training produce distinct remodeling patterns—eccentric and concentric hypertrophy, respectively. Although this framework remains conceptually useful, it oversimplifies the physiological diversity of modern sports.[17,20,21]

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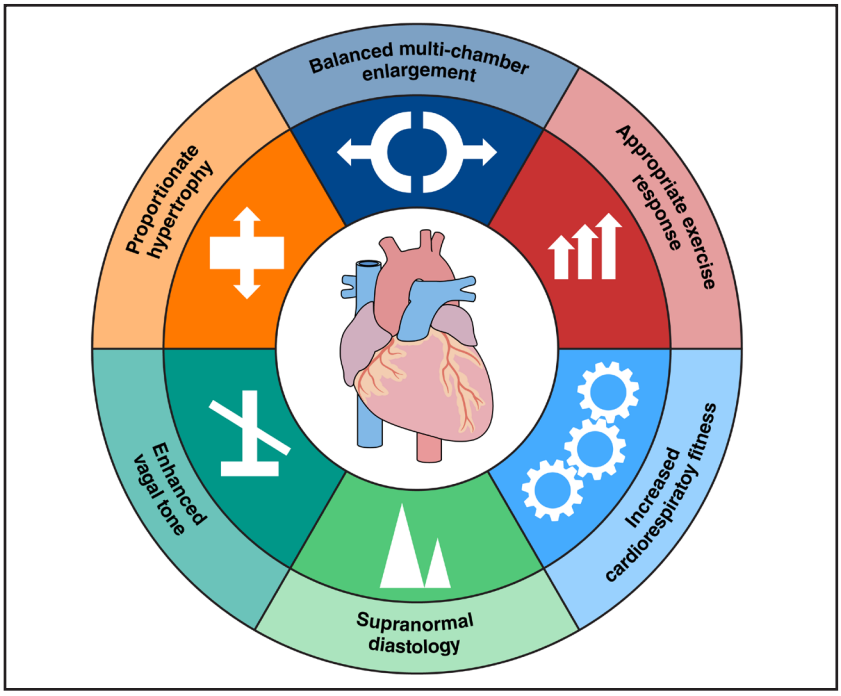

Figure 1. The hallmarks of exercise-induced cardiac remodeling (EICR). This schema sets forth tentative hallmarks generally recognized in humans engaging in chronic, primarily endurance, physical activity. We propose 6 candidate hallmarks as common denominators of EICR that together identify the EICR phenotype or athlete's heart. These include balanced multichamber enlargement, proportionate hypertrophy, enhanced vagal tone, supranormal diastology, increased cardiorespiratory fitness, and appropriate exercise response (eg, augmented stroke volume). Importantly, no one hallmark confirms the EICR phenotype, and not all of the hallmarks are present in every type of exercise or sport. Illustration credit: Sceyence Studios.

Determinants of EICR

The extent and pattern of EICR seem influenced by sex, ancestry, training duration, and genetic predisposition:

Sex differences: Female athletes generally exhibit less pronounced cardiac remodeling than male athletes. In a study of 600 elite female athletes, LV end-diastolic cavity dimensions and wall thickness were significantly greater than sedentary controls but were smaller compared with male athletes.[22–25] These differences persist even after adjusting for body size with some data suggesting that hormonal influences could potentially contribute to cardiac remodeling,[24,26,27] although causal mechanisms remain speculative. Ancestry and genetic influences: Athletes of African ancestry often exhibit greater LV wall thickness than athletes of European ancestry, with some individuals exceeding thresholds that overlap with HCM.[28,29] However, many studies rely on a binary comparison of Black versus White athletes, which may obscure relevant variation and oversimplify ancestral diversity. Broader ancestry-informed analyses are needed. Genetic polymorphisms—particularly in the renin-angiotensin-aldosterone system—have been associated with interindividual variability in EICR, though their predictive utility in clinical settings remains limited.[30,31] Exercise exposure (dose): The duration and intensity of training influence the trajectory of cardiac remodeling. Studies of individuals undergoing progressive training protocols reveal an initial concentric hypertrophy phase followed by eccentric remodeling with sustained exposure.[32,33] Training-related ECG changes are thought to require 4-8 hours of intense training per week in young athletes.[34] In older adults, the most pronounced changes are associated with >5 hours per week (Figure 2). Further research is needed to refine our understanding of the dose-response relationship in EICR.[35,36]

Clinical and Imaging Assessment of EICR

Accurate differentiation of physiological remodeling from pathological cardiac conditions is critical in clinical practice. Noninvasive imaging modalities, including transthoracic echocardiography (TTE), cardiac magnetic resonance (CMR), and computed tomography angiography, provide valuable insights into structural and functional cardiac adaptations.[37–39] TTE remains the primary imaging tool for assessing EICR, although CMR offers superior tissue characterization and allows for the assessment of volumes and fibrosis. CMR-based studies indicate that EICR is characterized by myocyte hypertrophy with minimal fibrosis, whereas the presence of late gadolinium enhancement (LGE) suggests underlying pathology.[40,41]

LV Adaptations in EICR

LV remodeling in athletes commonly involves chamber dilation, mild wall thickening, and preserved function—features that support enhanced stroke volume and aerobic performance. LV end-diastolic diameters frequently exceed normative cutoffs. In one large cohort of Italian athletes, 45% had LV diameters ≥55 mm, and 14% exceeded 60 mm.[42] Similar findings have been reported in US-based university athletes.[43] These data emphasize that LV dilation alone should not be used to differentiate EICR from cardiomyopathy.[44–46]

Mild LV wall thickening may also occur, particularly in strength-trained athletes, but rarely exceeds 12 to 13 mm.[8,47] When wall thickness approaches this threshold, careful evaluation is warranted to exclude HCM, infiltrative disease, or other forms of pathological hypertrophy.

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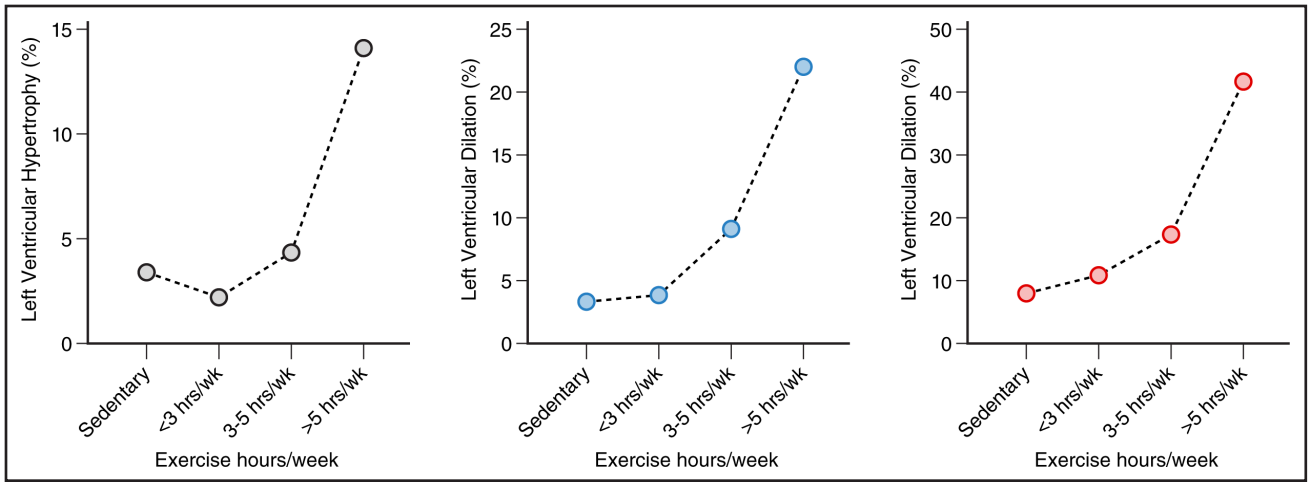

Figure 2. How much exercise is required?

Dose-response relationship between exercise volume and cardiac remodeling as assessed by cardiac magnetic resonance imaging. Left ventricular (LV) hypertrophy, LV dilation, and right ventricular (RV) dilation—defined as exceeding published reference values for LV mass index, LV end-diastolic volume index, and RV end-diastolic volume index, respectively—are plotted by weekly exercise duration. Exercise categories were based on the Copenhagen scale: sedentary, <3 h/wk, 3 to 5 h/wk, and >5 h/wk or competitive athletics. A dose-response relationship is observed, with the most pronounced chamber dilation in those exercising >5 h/wk. All data were derived from 1158 healthy adults (54% female; median age, 39.2 years) enrolled in the UK Digital Heart Project. Illustration credit: Sceyence Studios.

Key distinguishing features include the presence of asymmetrical hypertrophy, abnormal diastolic function, myocardial fibrosis, and impaired contractile reserve.[48–51] Importantly, the wall thickness in the 13–15 mm range exists in a diagnostic gray zone and may require longitudinal follow-up or detraining to clarify the cause—although even apparent normalization with detraining does not definitively exclude underlying pathology.

In cases of diagnostic uncertainty, integration of structural data with function—such as stress imaging, cardiopulmonary exercise testing, or serial assessments—can be useful. The clinical context, including athletic discipline, training history, and family history, should guide interpretation. Diagnostic certainty often requires synthesis across modalities and time.[52–54]

Right Ventricular Adaptation in EICR

EICR is not confined to the LV. Endurance training imposes substantial hemodynamic demands on both ventricles. However, during exercise, the right ventricle (RV) is exposed to a disproportionate increase in afterload due to the limited vasodilatory reserve of the pulmonary circulation. Unlike the systemic arterial tree, which can markedly reduce resistance during exercise, the pulmonary vasculature operates near maximal capacitance at rest and exhibits a relatively fixed resistance. Consequently, pulmonary artery pressures rise during exercise, increasing RV afterload.[55–60]

In response, the RV typically undergoes eccentric remodeling—mild to moderate dilation without significant hypertrophy. CMR imaging studies confirm that RV enlargement is a common and expected feature among endurance athletes.[61] As with the LV, mild reductions in RV systolic function at rest may be seen but should be accompanied by preserved or enhanced contractile reserve on stress imaging.[62] Speckle-tracking echocardiography may help differentiate physiological RV remodeling from pathology, but normative data remain limited and consensus on diagnostic thresholds is lacking.[63]

The effects of strength training on the RV are less well characterized. One echocardiographic study comparing endurance and strength athletes found that although RV dimensions were larger in the endurance group, RV systolic and diastolic function did not differ significantly between groups.[64] A longitudinal study of RV structure in collegiate athletes before and after 90 days of team-based exercise training showed significant RV dilation in endurance athletes but no changes in RV architecture in strength athletes.[65] These findings reinforce that RV remodeling in EICR is driven primarily by sustained volume load, rather than pressure load alone.

Atrial Adaptations

Atrial remodeling is another well-established component of EICR. Initial echocardiographic studies demonstrated that endurance athletes have larger left atrial (LA) dimensions compared with sedentary controls.[66] Subsequently, in a study of over 600 athletes, the LA volume index confirmed a high prevalence of LA enlargement in trained athletes, particularly endurance athletes.[67] A meta-analysis involving over 7000 athletes and 1000 controls quantified these differences: compared with sedentary individuals, LA diameter was 4.6 mm larger in endurance athletes, 3.5 mm larger in athletes combining strength and endurance, and 2.9 mm larger in those engaging primarily in strength training.[68] As with morphological ventricular changes, atrial size

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should also be qualified in the context of fitness; in a cross-sectional study comparing 205 athletes with an average predicted VO_{2peak}>125% to 354 healthy controls, although LA volume index was associated with greater cardiorespiratory fitness, atrial deformation measures (eg, speckle tracking) were not, suggesting that negative associations of LA enlargement may be less relevant for exercise-conditioned patients.[69]

Right atrial dilation has also been documented. Similar to the RV, right atrial remodeling is more pronounced in endurance athletes and appears to follow the same volume load–driven physiology. Normative datasets for right atrial size in athletes have been published, although remain less commonly used in clinical practice.[70]

Although structural atrial adaptation is well documented, functional consequences are less clearly defined. A longitudinal study of elite female athletes showed that after 16 weeks of training, LA global peak longitudinal strain and peak atrial contraction strain declined significantly.[71] However, other studies comparing athletes to controls have not consistently demonstrated functional impairment in atrial strain.[72] Whether these changes reflect physiological adaptation or subclinical myopathy remains an open question.

Genetics of EICR With Low Ejection Fraction

Although most endurance athletes exhibit preserved or enhanced cardiac function, a subset—estimated at ≈10%—demonstrates a mildly reduced resting LV ejection fraction (EF<50%).[73,74] These athletes typically maintain excellent exercise capacity and contractile reserve, raising the question of whether low EF in this context reflects benign adaptation or early cardiomyopathy.

Recent work suggests a genetic contribution to this phenotype.[74] In a cohort of elite endurance athletes, those with low EF had significantly higher polygenic risk scores for LV end-systolic volume index, consistent with a genetic predisposition toward greater chamber dimensions and reduced EF. This pattern echoes findings in genome-wide association studies linking similar polygenic profiles to dilated cardiomyopathy.[75]

These observations raise the possibility that intensive training may unmask subclinical genetic variants, creating an extreme subphenotype of EICR. Analogous interactions have been described in arrhythmogenic cardiomyopathy, where variants in PKP2 (plakophilin 2) or LMNA (lamin A/C) are potentiated by endurance activity. Importantly, although low EF in athletes with high LV end-systolic volume index–polygenic risk scores may reflect a physiological extreme, whether it portends vulnerability under stress or with aging remains unclear. Longitudinal follow-up of these athletes is necessary to determine whether those with reduced EF and high polygenic risk scores are at increased risk for cardiovascular disease later in life.

Despite these insights, key uncertainties remain. The observed phenotype may represent a classic gene-environment interaction, in which high training loads unmask latent genetic susceptibility to specific remodeling patterns. Polygenic risk score–based models are not yet clinically actionable in routine practice, and longitudinal data are needed to clarify whether low EF in genetically predisposed athletes carries increased long-term risk. As genetic testing becomes more accessible, its role in distinguishing physiological from pathological remodeling may emerge but will require careful integration with clinical, imaging, and functional data. In addition, further research is needed to explore genetic predispositions for other conditions commonly seen in endurance athletes, such as atrial fibrillation (AF) and exaggerated coronary artery calcification.

EICR VERSUS PATHOLOGY: A GRAY ZONE

Clinical and Imaging Assessment of EICR

Distinguishing physiological adaptation from underlying cardiomyopathy remains one of the most important and challenging aspects of evaluating the athletic heart. EICR shares features with various pathological entities, and a systematic approach that integrates clinical context with imaging and functional data is essential (Table; Figure 3).[22,76–79] Components of the tool kit include a detailed clinical history, physical examination, electrocardiography, imaging, and, in select cases, genetic testing.

TTE remains the first-line imaging tool and provides most of the normative data that define the expected scope of EICR. CMR imaging, increasingly used in both clinical and research settings, offers superior resolution for wall thickness and tissue characterization and is considered the gold standard. Recent guidelines now explicitly address imaging in young adult competitive athletes.[37–39]

The LV dilation that occurs as a component of EICR may need to be distinguished from pathological overlaps, like the LV dilation seen in dilated cardiomyopathies of many causes (eg, familial or idiopathic, tachycardia-mediated, toxic cardiomyopathy (eg, alcohol), myocarditis and regurgitant valvular disease). The magnitude of LV dilation should not be used in isolation to attempt to distinguish EICR from pathology. Physiological LV dilation in EICR is typically accompanied by dilation of other cardiac chambers with normal or enhanced LV diastolic function, preserved LV systolic strain, and preserved RV systolic function.[45,46,80,81] Notably, LV systolic function as assessed by LV EF may demonstrate mild reduction (eg, LV EF 45%–50%) in EICR.[82] The presence of regional wall motion abnormalities, impaired contractile reserve during stress imaging, and impaired exercise capacity on cardiopulmonary exercise testing favor pathological cardiomyopathies.[83] As with all forms of EICR, the

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Table. Differentiating Features Between Physiological EICR and Pathological Growth

Physiological characteristics of EICR	Likely pathological Features
Morphological changes	
Synchronized multichamber enlargement	LVEDD>66 mm[22,76]
	LVESD men >50 mm; women >40 mm[22,76]
	Isolated RV enlargement
Eccentric wall thickening	Concentric wall thickening (RW>0.42; can be seen with strength training)[77]
	Wall thickness >15 mm
Lack of LGE on MRI imaging	LGE (including septal) outside of RV focal insertions*
Regression with reduction in exercise	Lack of regression with cessation of activity†
Systolic function	
Normal to low-normal EF	EF<45%
Proportional augmentation of EF and stroke volume with exercise	<10% augmentation of EF with exercise[78]
Elevated cardiorespiratory fitness	Reduced peak VO_2
Diastolic function	
Enhanced early diastolic filling	Lateral annular tissue Doppler velocity <10[79]
Increased lusitropy	

EF indicates ejection fraction; EICR, exercise-induced cardiac remodeling; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MRI, magnetic resonance imaging; RWT, relative wall thickness; and RV, right ventricle.

*LGE at the RV insertion points is currently accepted to be a physiological finding, with various proposed explanations. Septal LGE is not always a nonspecific finding and merits caution.

†Historically, lack of regression in detraining was considered supportive of pathological hypertrophy. However, detraining-related regression is not specific for EICR. Furthermore, patients with known pathological hypertrophy (eg, HCM) can exhibit reduced LV thicknesses with detraining even while the disease entity still exists.

assessment begins with whether the athlete participates in a sporting discipline or training regimen that explains the physiology and imaging phenotype (eg, primary isotonic versus isometric exercise). In addition, an unremarkable 12-lead ECG and a negative family history of cardiovascular disease/SCD often favor EICR over a cardiomyopathic state.[84]

LV wall thickening attributable to EICR rarely leads to measurements that exceed 12 to 13 mm. In an echocardiographic study of 947 elite Italian athletes, only a small number (1.7%) had LV wall thicknesses ≥13 mm.[8] Similarly, a low incidence (0.4%) of LV wall thickness >12 mm was reported in 720 elite junior athletes.[47] In a study of nearly 500 collegiate athletes, not a single healthy university athlete had LV wall thickness >14 mm.[85] LV wall thickness in the range of 13-15 mm is a rare finding in healthy athletes and is often confined to individuals with large body size with some enrichment in those with African Ancestry.[29] Unlike LV chamber dilatation in EICR, cutoff values are helpful when evaluating wall thickness and the finding of LV wall thickness >15 mm should be considered pathological until proven otherwise.

EICR-associated LV wall thickening may have phenotypic similarities to several cardiomyopathic states, including HCM, hypertensive heart disease, infiltrative cardiomyopathy, and valvular heart disease (eg, aortic stenosis). Isolated asymmetrical or focal LV hypertrophy with impairment of diastolic function, myocardial strain, or the presence of other anatomic abnormalities including mitral valve leaflet elongation, anomalous papillary muscle insertion, and myocardial crypts or recesses should raise suspicion of myocardial pathology.[48,50,51,86] Functional implications of concentric LVH stimulated by EICR are incompletely understood as longitudinal studies of male American-style football players showed the development of concentric LVH was associated with relative impairments both of early diastolic relaxation velocity, and systolic function, raising uncertainty about the adaptive nature of this form of EICR[65,87] (Figure 4). Importantly, although, the presence of normal diastolic function does not exclude a diagnosis of HCM. These findings regarding myocardial function make the distinction between EICR and pathology more challenging, although as noted above the magnitude of LV wall thickening can be helpful.

During TTE imaging, care must be taken to avoid the inclusion of RV septal trabeculations and the posterolateral chordal apparatus to avoid over measurement of the septal and posterior LV wall, respectively. In addition, careful attention must be paid to the LV apex when assessing for apical variant HCM and the use of an ultrasound contrast agent may be required. Athletes with LV wall thickening of unclear cause by TTE should undergo CMR imaging. CMR evaluation should include comprehensive assessment of LV wall thickness, chamber volume, and tissue characterization by LGE and mapping techniques.[41] Limited data suggest that LV hypertrophy among athletes develops as a function of myocyte enlargement with minimal fibrosis.[40] In contrast, the presence of LGE or interstitial fibrosis is highly suggestive of HCM or alternative myopathies (eg, Fabry disease). In a CMR study comparing patients with HCM to athletes and sedentary controls, markers of interstitial expansion, commonly referred to as extracellular volume by T1 mapping, were higher in patients with HCM than in athletes and controls and demonstrated excellent discriminatory capacity across the groups.[88]

Despite the use of a systematic approach integrating clinical history, family history, electrocardiography, and noninvasive imaging, gray-zone hypertrophy (13–15 mm) may remain ambiguous. When the distinction of LV hypertrophy due to EICR or pathology remains unclear after such an approach, a strategy of prescribed detraining

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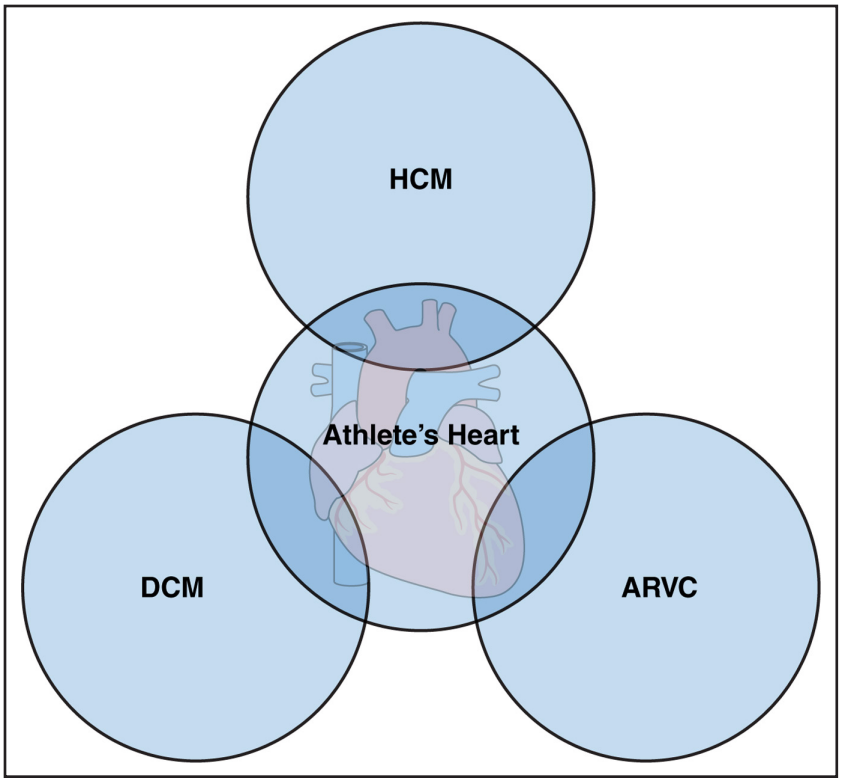

Figure 3. Conceptual overlap between the athlete's heart and cardiomyopathic phenotypes. Exercise-induced cardiac remodeling (athlete's heart) can share imaging features with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). HCM overlaps in the range of left ventricular (LV) wall thickness (13–15 mm), DCM in LV dilation and at times mildly reduced ejection fraction (45%–50%), and ARVC in right ventricular dilation. These shared phenotypes create diagnostic ambiguity, emphasizing the need for a comprehensive approach that incorporates clinical context, functional testing, and advanced imaging. Illustration credit: Sceyence Studios.

and follow-up cardiac imaging to assess LV hypertrophy regression may be considered. Despite the theoretical role of prescribed detraining, the time course and degree of expected regression of hypertrophy have not been well described.[52–54] Further investigation is required to delineate the expected structural and functional changes in athletes with LV hypertrophy and patients with cardiomyopathy undergoing a period of exercise cessation.

Other phenotypes add complexity. Hypertrabeculation of the LV with normal LV wall thickness can be seen in athletes[89] and must be differentiated from noncompaction cardiomyopathy which should be considered among athletes with malignant ventricular arrhythmias or a family history of sudden death. The use of standard diagnostic criteria for noncompaction may lead to overdiagnosis of disease in athletes as evidenced by a study in which at least one diagnostic criterion for LV noncompaction was common in a population-based cohort.[90] Physiological hypertrabeculation is usually accompanied by preserved systolic function and normal or enhanced diastolic function. Hypertrabeculation with a thin compacted layer (<5 mm), marked impairment of LV systolic function, and LGE on CMR are more suggestive of a true noncompaction cardiomyopathy. In the absence of corresponding LV systolic dysfunction or clinical syndrome, recent guidelines do not recommend a diagnosis of LV noncompaction cardiomyopathy and prefer the term LV hypertrabeculation.[21,91]

RV dilation in the endurance-trained athlete is typically associated with LV remodeling and the finding of isolated RV enlargement should raise suspicion of a pathological process. Furthermore, RV dilation in endurance athletes tends to be a global process, without sacculation, aneurysmal dilation, or segmental dysfunction. Similar to LV dilation, strict cutoff values for RV end-diastolic diameter are generally not helpful in distinguishing EICR and pathological cardiomyopathy. In a study of 102 endurance athletes, RV chamber dimensions on echocardiography were larger than normal values in over one-half of the athletes and 28% had an RV outflow tract dimension that met the proposed major size criteria for the diagnosis of arrhythmogenic RV cardiomyopathy.[92] Differentiating exercise-induced RV changes from the diagnosis of arrhythmogenic RV cardiomyopathy is one of the most important clinical challenges in sports cardiology, and awareness of the diagnostic criteria for arrhythmogenic RV cardiomyopathy which integrate family history, electrocardiography, and cardiac imaging is essential.[93,94]

In sum, distinguishing EICR from pathology requires more than pattern recognition. The overlap in phenotypes, limits of diagnostic thresholds, and variability with detraining suggest that some cases lie along a continuum. Interpreting why certain athletes remodel more than others may ultimately depend on understanding the heart's molecular response to exercise and how these pathways govern structural adaptation.

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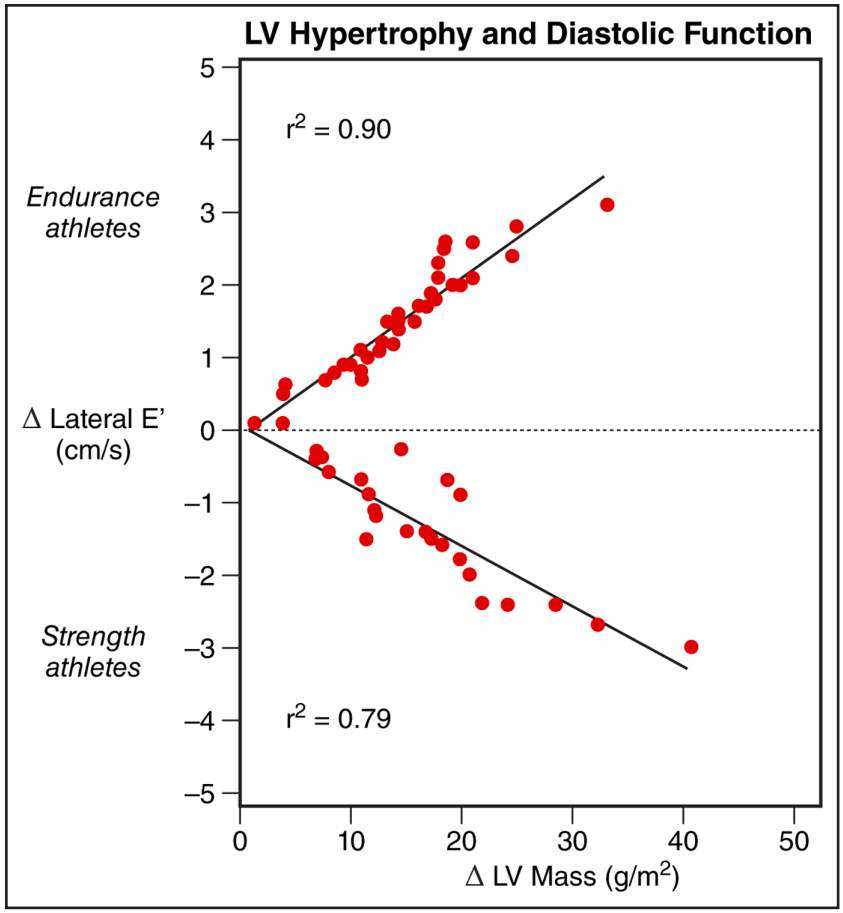

Figure 4. Divergent relationships between left ventricular (LV) hypertrophy and diastolic function in endurance and strength athletes. Change in LV mass index is plotted against change in lateral mitral annular early diastolic tissue velocity (E′), a marker of diastolic relaxation. Among endurance athletes, increases in LV mass are associated with improved diastolic function (r^2=0.90), whereas in strength athletes, similar increases in LV mass are associated with reduced diastolic function (r^2=0.79). Illustration credit: Sceyence Studios.

MOLECULAR FEATURES OF THE ATHLETE'S HEART: CARDIAC REMODELING

Although the structural features of EICR, described by various imaging modalities, can resemble and even overlap with true pathology, this is not true at the cellular and molecular level. Depending on the nature of the stimulus, the heart develops either pathological or physiological cardiac hypertrophy, each with distinct causes, characteristics, and outcomes. Pathological cardiac hypertrophy, caused by conditions, such as hypertension or myocardial infarction, progressively leads to adverse cardiac remodeling, fibrosis, and loss of cardiomyocytes, which eventually result in heart failure.[95,96] By contrast, physiological cardiac hypertrophy, seen in response to physiological stimuli such as exercise, leads to adaptive and reversible cardiac growth that does not generally cause adverse outcomes and protects the heart against stress.[95–97]

Structurally, pathological stimuli cause concentric cardiac hypertrophy, typically characterized by LV thickening and a slight reduction in chamber size (sometimes defined by relative wall thickness exceeding 0.42), usually accompanied by cardiac fibrosis, cell death, and the induction of fetal gene expression patterns (eg, ANP [natriuretic peptide A], BNP [natriuretic peptide B], βMHC [β-myosin heavy chain]).[95,96] In comparison, endurance training (eg, swimming or running) leads to eccentric cardiac hypertrophy, typically marked by proportional changes in ventricular wall thickness and enlargement of the ventricular chamber.[95,96] This exercise-induced physiological cardiac hypertrophy maintains normal or enhanced cardiac function without causing cardiac fibrosis, cell death, or the induction of fetal gene expression.[95,96] Despite the traditional view that the adult heart has a limited capacity for cardiomyocyte proliferation or renewal, accumulating evidence from animal models suggests that exercise-induced physiological cardiac growth is accompanied by increased cardiomyogenesis.[98–101] This raises the possibility that some of the structural gains from exercise derive from cellular growth as well as new cell formation. Further studies are needed to investigate the contribution of cardiomyogenesis to physiological cardiac growth in response to exercise.

Although the heart grows in response to both physiological and pathological stimuli, the underlying molecular mechanisms are largely distinct between these 2 types of cardiac hypertrophy. The mechanisms of pathological cardiac hypertrophy have been extensively studied, and multiple signaling pathways have been identified, such as the angiotensin II/ATR (angiotensin II type 1 receptor), endothelin 1/EndoR (endothelin receptor),

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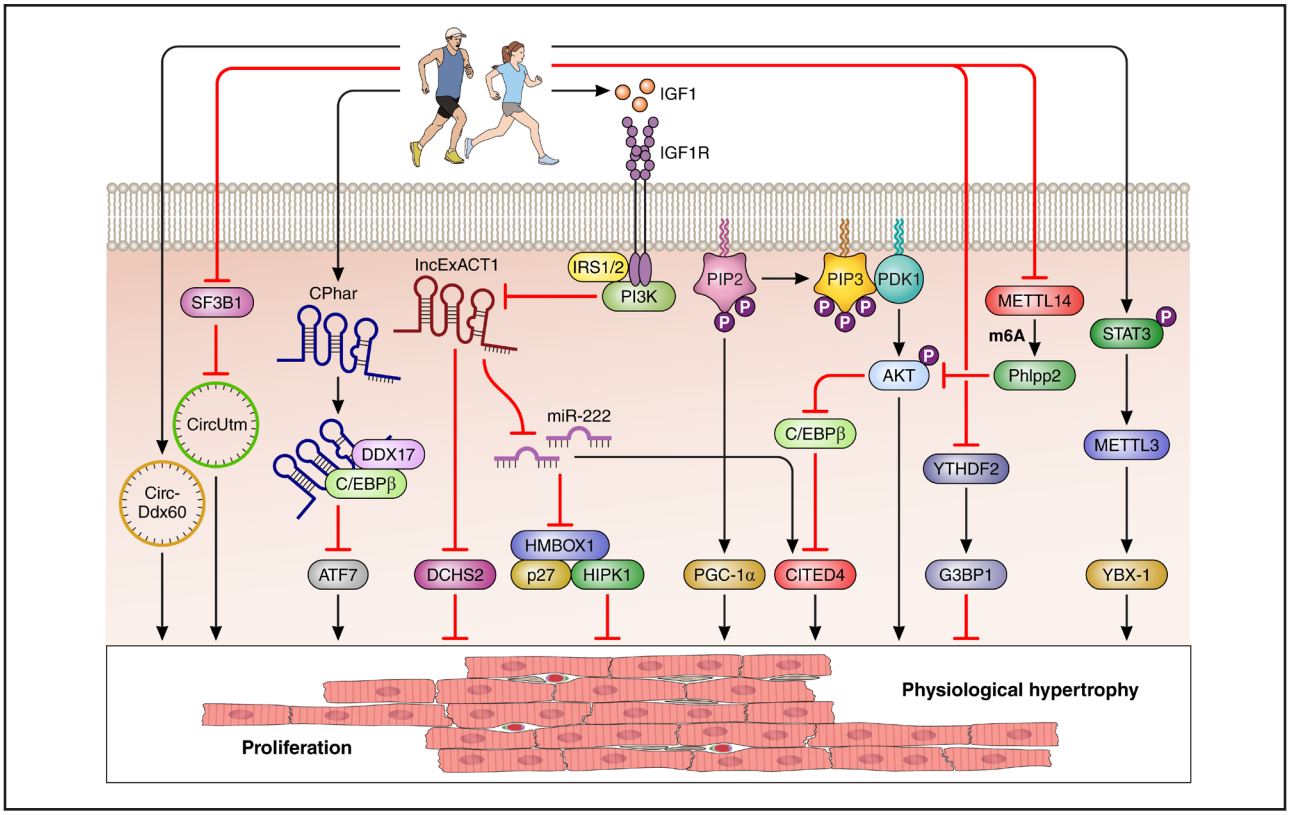

Figure 5. Molecular pathways driving physiological cardiac remodeling in response to exercise.
Exercise induces a coordinated set of molecular responses that promote cardiomyocyte proliferation and physiological hypertrophy. Central to this process is IGF1 (insulin-like growth factor 1)/PI3K (phosphoinositide 3-kinase)/AKT1 (protein kinase B) signaling, which stimulates adaptive cardiac growth. Noncoding RNAs—including miR-222 (microRNA 222), lncExACT1 (long noncoding exercise-associated cardiac transcript 1), CPhar (cardiac physiological hypertrophy-associated regulator), circUtrn (exercise-induced circular RNA), and circDdx60 (circular RNA Ddx60)—modulate key transcriptional regulators such as C/EBPβ (CCAAT/enhancer-binding protein β), CITED4 (CREB-binding protein/p300-interacting transactivator with a Glu/Asp -rich carboxy-terminal domain 4), and downstream effectors (eg, PDK1 [pyruvate dehydrogenase kinase 1], HMBOX1 [homeobox containing 1], HIPK1 [homeodomain interacting protein kinase 1]) to support growth and regeneration. Epitranscriptomic mechanisms such as N6-methyladenosine (m6A) RNA modification, mediated by METTL3 (methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit), METTL14 (methyltransferase 14, N6-adenosine-methyltransferase non-catalytic subunit), and read by YTHDF2 (YTH N6-methyladenosine RNA binding protein F2), further regulate this response. Together, these pathways underlie the structural and functional adaptations of the athlete's heart. IRS indicates insulin receptor substrate; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator-1α; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; and STAT3, signal transducer and activator of transcription 3. Illustration credit: Sceyence Studios.

catecholamine/α-AR/β-AR (α-/β-adrenergic receptor), and natriuretic peptides pathways (ANP or BNP/natriuretic peptide receptor [NPR]).[102–105] In contrast, our understanding of the drivers of physiological cardiac hypertrophy is still emerging.[96] Several signaling pathways have been proposed to contribute to physiological cardiac hypertrophy, including the IGF1 (insulin-like growth factor 1)/PI3K (phosphoinositide 3-kinase)/AKT1 (protein kinase B) pathway, and the C/EBPß (CCAAT/enhancer–binding protein ß)/CITED4 (CREB-binding protein/p300-interacting transactivator with a Glu/Asp–rich carboxy-terminal domain 4) pathway.[106–110] The roles of noncoding RNAs and RNA modifications have also been proposed, though further studies are needed to fully elucidate their contributions to physiological cardiac hypertrophy.[111–113] Importantly, virtually every functional pathway activated in the heart's response to exercise also protects the heart against pathological stress. Thus, deciphering the molecular mechanisms of exercise-induced physiological cardiac hypertrophy will provide unique opportunities to discover novel targets for treating pathological hypertrophy, heart failure, and myriad forms of heart disease.

Animal Models of Exercise

Much of what is known about the mechanisms mediating exercise-induced cardiac remodeling comes from rodent models of chronic exercise. These models—swimming, treadmill, and wheel running—provide complementary insights into how the heart adapts to chronic aerobic training.[114]

Swim training is a widely used aerobic animal exercise model due to its relatively low cost and controlled, uniform exercise conditions, which help avoid potential confounders when comparing animals with different genetic

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backgrounds. Across various experimental conditions, swim training reliably induces physiological cardiac hypertrophy and markers of cardiomyocyte proliferation.[109,112,115] However, its limitations include being stressful for the animals and time-consuming for the investigators. Treadmill training is another widely used forced exercise model in which exercise speed and intensity can be precisely controlled. It is one of the most commonly used animal exercise models for studying cardiac adaptation to exercise due to the availability of commercial treadmills that allow speed and intensity adjustments and can reliably induce physiological cardiac hypertrophy.[112,116] However, like swim training, treadmill training can also be stressful for animals due to the use of electric shocks or air puffs as motivators. Acclimatization can help reduce stress, though pretraining may confound results. Wheel running is a voluntary, nonstressful exercise model that aligns with rodents' natural circadian activity. Although it requires individual housing for accurate tracking, it allows for long-term studies with minimal supervision, making it less stressful for animals and less time-consuming for investigators. However, there is variability in running distance across strains and sexes, although this model effectively induces physiological cardiovascular adaptations.[111,117,118]

There is a longstanding practice of examining exceptional human athletes to better understand the physiology of exercise and performance. In a similar vein, studying animals with extreme exercise or extreme cardiac adaptation could offer valuable insights into key aspects of exercise physiology. The Burmese python (*Python bivittatus*) is one such model. After consuming large meals, Burmese pythons exhibit a rapid and profound increase in metabolic rate, cardiac output, and organ growth, particularly in the heart, liver, and intestines.[119] Remarkably, the python's heart undergoes physiological hypertrophy, characterized by a significant increase in ventricular mass and enhanced contractility, similar to endurance-trained mammals.[120] This reversible organ enlargement is driven by molecular pathways that are also implicated in EICR, including upregulation of fatty acid transport and oxidation.[121] As such, the Burmese python provides a unique platform for identifying conserved and potentially targetable mediators of adaptive cardiac growth.

Key Signaling Pathways Mediating Exercise-Induced Physiological Cardiac Remodeling

IGF1/PI3K/AKT Pathway

The IGF1/PI3K/AKT1 pathway is well recognized as a key mediator of exercise-induced physiological cardiac growth and is among the most extensively studied pathways (Figure 5). IGF1 is a growth hormone that can be released by both the liver and the heart. Exercise stimulates the release of IGF1 in the heart and serum in both animals and athletes.[106,107,122,123] IGF1 then binds to and activates the IGF1 receptor, which recruits IRS (insulin receptor substrate) proteins (IRS1/2) and activates the PI3K/AKT pathway. Among PI3K isoforms, class 1A PI3K, which contains the p110α catalytic subunit, was the first gene implicated in exercise-induced physiological cardiac growth.[124] In transgenic mice expressing a dominant-negative PI3K mutant specifically in cardiomyocytes, 4 weeks of swimming training failed to induce physiological cardiac hypertrophy, suggesting a necessary role of PI3K in this process.[124] Once activated by exercise, the p110α catalytic subunit of PI3K catalyzes the phosphorylation of the 3-hydroxyl residue of phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol (3,4,5)-trisphosphate, which then recruits and phosphorylates PDK1 (pyruvate dehydrogenase kinase 1) and AKT, leading to physiological cardiac growth. Over the years, the involvement of the IGF1/PI3K/AKT1 signaling pathway in exercise-induced physiological cardiac growth has been demonstrated by numerous studies using animal models with loss- and gain-of-function mutations affecting different aspects of this pathway. In mice with cardiomyocyte-specific IGF1R knockout, the cardiac hypertrophy induced by 5 weeks of swimming training, which was observed in wild-type mice, was blunted.[125] In addition, adult cardiomyocytes with AKT1 knockout were resistant to IGF1-induced protein synthesis.[126] Similarly, AKT1 knockout mice were found to be resistant to cardiac hypertrophy induced by 20 days of forced swimming training, indicating that AKT1 is required for exercise-induced physiological cardiac growth.[126] However, it is worth noting that while short-term (acute) activation of AKT is cardioprotective, constitutive (chronic) activation of AKT is detrimental and can lead to heart failure,[127–129] highlighting the need for tight regulation of this pathway. Interestingly, exercise has been shown to induce physiological cardiac growth through PI3K-mediated upregulation of PGC-1α (peroxisome proliferator–activated receptor gamma coactivator-1α), a transcription factor with potent regulatory effects on mitochondrial biogenesis and cardiac metabolism.[130–133] However, mice with constitutive activation of AKT developed heart failure that was associated with downregulated cardiac PGC-1α gene expression.[134] Nevertheless, this reinforces the necessity of strict regulation of the IGF1/PI3K/AKT and its downstream pathways (eg, PGC-1α) in cardiac response to exercise.

C/EBPβ/CITED4 Pathway

C/EBPβ belongs to the bZIP (basic leucine zipper) C/EBP transcription factor family and is a complementary regulator of physiological hypertrophy.[135] It regulates gene transcription by binding to specific gene promoters, forming either homodimers or heterodimers with intrafamilial members, or heterodimers with other transcription factors.[136] C/EBPβ and its downstream effector, CITED4, have been identified as critical regulators of exercise-induced physiological cardiac growth. Cardiac

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C/EBPβ mRNA and protein expression were downregulated in mice after 2 weeks of swimming training but remained unchanged in mice with transverse aortic banding–induced pathological cardiac hypertrophy, an alternative model commonly used for inducing pathological cardiac hypertrophy due to pressure load on the heart.[109] In isolated primary rat cardiomyocytes, small interfering RNA-mediated gene knockdown of C/EBPβ induced cell hypertrophy and proliferation, as well as a gene expression pattern consistent with exercise-induced physiological cardiac growth.[109] In vivo, homozygous C/EBPβ knockout is lethal; however, heterozygous C/EBPβ knockout recapitulated many cardiac phenotypes of exercise, including increased heart weight, improved cardiac function, and elevated markers of cardiomyocyte proliferation,[109] suggesting that downregulation of C/EBPβ is sufficient to induce physiological cardiac growth. Interestingly, the physiological cardiac phenotypes observed in heterozygous C/EBPβ knockout mice were not further enhanced when these mice were subjected to swimming exercise training.[109] Mechanistically, C/EBPβ negatively regulates physiological hypertrophy by interacting with the transcription factor serum response factor, binding to promoters, and downregulating the cardiac genes GATA4 (GATA binding protein 4), αMHC (α-myosin heavy chain), and CITED4.[109] Further studies in cardiomyocyte-specific CITED4 knockout mice showed that cardiomyocyte CITED4 deficiency did not affect baseline cardiac size or function.[110] However, cardiomyocyte-specific CITED4 knockout led to a maladaptive cardiac response to 3 weeks of swimming exercise training, including a mild reduction in systolic function, increased cardiomyocyte size, and elevated expression of fibrotic genes.[110] In mice subjected to the same swimming exercise training, cardiomyocyte CITED4 appeared to be required for cardiac lymphangiogenesis-mediated physiological cardiac growth during exercise, as gene knockdown of CITED4 abolished the lymphatic endothelial cell–conditioned medium–induced cardiomyocyte hypertrophy.[137] Interestingly, the expression of CITED4 in the exercised heart was regionally heterogeneous, with a preferential increase in the lateral wall in mice after 8 weeks of voluntary wheel running.[117] Cardiomyocyte-specific CITED4 knockout prevented exercise-induced regional microstructural helicity remodeling.[117] These findings suggest a necessary role of CITED4 in exercise-induced physiological cardiac growth. Similar to what is observed in exercised hearts, transgenic overexpression of CITED4 in cardiomyocytes increased heart weight and cardiomyocyte size without affecting cardiac function, suggesting that CITED4 overexpression induces physiological growth.[108] Importantly, cardiomyocyte-specific CITED4 overexpression via AAV9 gene transfer, at a clinically relevant time frame (ie, after reperfusion), was sufficient to protect the heart against adverse cardiac remodeling, functional decline, fibrosis, and inflammatory responses after myocardial ischemia-reperfusion.[138]

Noncoding RNAs

Noncoding RNAs, which constitute the majority (≈98%) of the human transcriptome, are RNA molecules that lack protein-coding potential.[139] Based on their sequence length, noncoding RNAs can be categorized as small noncoding RNAs (<200 nucleotides) and long noncoding RNAs (lncRNAs, >200 nucleotides). Emerging evidence has linked noncoding RNAs to various aspects of cardiac pathophysiology, including exercise-induced physiological cardiac growth.

MicroRNAs are a class of highly conserved noncoding RNAs, typically 18 to 22 nucleotides in length. MicroRNAs are generally transcribed as primary transcripts by RNA polymerase II and processed into mature microRNAs by the endonucleases Dicer and Drosha.[140] In most cases, microRNAs degrade or suppress gene translation by binding to the 3′-untranslated regions of target mRNAs.[141,142] MicroRNAs in the heart are dynamically regulated by exercise and have been demonstrated to be functionally important in exercise-induced physiological cardiac growth.[143,144] miR-222 was the first microRNA identified and proven to be necessary for cardiac adaptation to exercise.[112] Cardiac miR-222 was consistently upregulated in 2 distinct exercise mouse models, voluntary wheel running and swimming training.[112] Cardiomyocyte-specific overexpression of miR-222 phenocopied exercise-induced physiological cardiac hypertrophy and cardiomyogenesis in adult mouse hearts, although its inhibition attenuated exercise-induced cardiac hypertrophy and cardiomyogenesis.[100,144] This highlights the necessary role of miR-222 in the cardiac response to exercise. Further studies demonstrated that mimicking the upregulation of miR-222 seen in exercised hearts protected against myocardial ischemia-reperfusion injury and transverse aortic constriction-induced adverse cardiac remodeling and heart failure, through context-specific mechanisms (p27/HMBOX1 [homeobox containing 1]/HIP1/2 [homeodomain-interacting protein kinase 1/2] in myocardial ischemia-reperfusion versus NFATc3 [nuclear factor of activated T cells c3]/PUMA [p53 upregulated modulator of apoptosis]/HMBOX1 [homeobox containing 1] in transverse aortic constriction).[100,112,145] Circulating miR-222 levels were increased in healthy young athletes after 90 days of team-based rowing training and in heart failure patients undergoing a symptom-limited cardiopulmonary exercise test on a bicycle ergometer, reinforcing the potential of miR-222 as a biomarker and therapeutic target for monitoring heart health and treating heart disease.[112,146] Other microRNAs, such as miR-143 and miR-133a, have also been implicated in cardiac adaptation to exercise, though further functional validation is needed.[147,148]

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LncRNAs are RNA molecules longer than 200 nucleotides, transcribed by RNA polymerase II, and constitute the majority of noncoding RNAs.[149] Unlike microRNAs and protein-coding genes, lncRNAs are expressed at relatively low levels and are much less conserved across species.[150] Despite these challenges, multiple lncRNAs have been identified and demonstrated to be functionally important in exercise-induced physiological cardiac growth. CPhar (cardiac physiological hypertrophy-associated regulator) was the first lncRNA identified as being required for cardiac adaptation to exercise.[151] Cardiac CPhar expression was increased in cardiomyocytes of mice after 8 weeks of swimming exercise, where it bound to DDX17 (DEAD-box helicase 17) and downregulated ATF7 (activating transcription factor 7) by sequestering C/EBPβ, thereby inducing cardiac hypertrophy and markers of cardiomyocyte proliferation.[151] Cardiomyocyte-specific *CPhar* gene knockdown via AAV9-shRNA (adenovirus serotype 9-short hairpin RNA) abolished exercise-induced cardiac hypertrophy and cardiomyocyte proliferation, indicating an essential role for CPhar in this process.[151] In a distinct animal exercise model, in which mice underwent 8 weeks of voluntary wheel running, a series of lncRNAs, termed long noncoding exercise-associated cardiac transcripts (lncExACTs), were shown to be dynamically regulated by exercise.[111] Among these, lncExACT1, a highly conserved lncRNA, was downregulated by exercise but upregulated in transverse aortic constriction-induced heart failure.[111] Cardiac lncExACT1 was downregulated by IGF1 through PI3K while upregulated by mitogen-activated protein kinases.[111] Inhibition of lncExACT1 using antisense oligonucleotides released microRNA-222 and downregulated DCHS2 (dachsous cadherin-related 2), resulting in cardiomyocyte hypertrophy and increased markers of cardiomyocyte proliferation without impairing cardiac function, effectively mimicking the cardiac response to exercise. Importantly, cardiac and circulating lncExACT1 levels were elevated in heart failure patients, and inhibition of lncExACT1 protected the heart against myocardial ischemia-reperfusion injury and transverse aortic constriction-induced heart failure.[111] These findings highlight the therapeutic potential of lncExACT1 inhibition in protecting against heart failure.

In addition to CPhar and lncExACT1, 2 circular RNAs (a subclass of lncRNAs that form closed loops), circUtrn (exercise-induced circular RNA), and Circ-Ddx60 (circular RNA Ddx60), have recently been identified as important regulators of the cardiac response to exercise.[152,153] circUtrn expression was increased in exercised hearts while downregulated by various cardiac stresses.[152] In cardiomyocytes, splicing factor 3b subunit 1, an RNA splicing factor, bound to the flanking inverted complementary sequences of circUtrn and downregulated its expression.[152] Cardiomyocyte-specific circUtrn gene knockdown via AAV9-shRNA abolished exercise-induced cardiac growth.[152] Similarly, inhibition of Circ-Ddx60 attenuated the hypertrophic preconditioning effects of exercise (3 weeks of swimming training, terminated 1 week before inducing heart failure), thereby reducing antipathological cardiac hypertrophy.[153] These findings underscore the functional importance of circUtrn and Circ-Ddx60 in physiological cardiac growth induced by exercise.

RNA Modifications

Eukaryotic RNA chemical modifications, also known as RNA editing, are posttranscriptional biochemical modifications of nucleotides that regulate RNA metabolism and function.[154] More than 100 internal modifications have been identified on mRNAs and noncoding RNAs.[154] N^6-methyladenosine (m^6A) is the most prevalent and well-studied internal RNA modification, influencing RNA stability, protein binding, and interactions with other RNAs.[154] The role of m^6A in exercise-induced physiological cardiac growth is only beginning to emerge. In mice subjected to 4 weeks of swimming exercise, cardiac m^6A levels were decreased, accompanied by a reduction in the cardiac m^6A methyltransferase METTL14.[113] Inactivation of METTL14's methyltransferase activity or cardiomyocyte-specific METTL14 overexpression abolished exercise-induced cardiac hypertrophy and markers of proliferation.[113] Mechanistically, exercise-induced inhibition of cardiomyocyte METTL14 led to a reduction in Phlpp2 (PH domain and leucine rich repeat protein phosphatase 2) mRNA m^6A deposition. This resulted in Akt phosphorylation, thereby increasing cardiomyocyte hypertrophy and proliferation.[113] The same group also found that suppression of YTHDF2 (YTH N6-methyladenosine RNA binding protein 2), an m^6A reader (ie, an m^6A-binding protein that recognizes m^6A modifications on RNAs), was required for exercise-induced cardiac growth.[155] Cardiac YTHDF2 was downregulated by exercise in the hearts through lactylation, whereas YTHDF2 overexpression abolished exercise-induced cardiac growth.[155] However, it appears that this YTHDF2-mediated cardiac response to exercise was independent of its m^6A regulatory function.[155] Most recently, Wang et al[156] have found that cardiac METTL3, an m^6A methyltransferase, is downregulated in animals with diabetic cardiomyopathy and upregulated by 8 weeks of treadmill training. The cardioprotective effects of exercise were lost in a cardiomyocyte-specific METTL3 knockout, suggesting an essential role of cardiomyocyte METTL3 in the cardiac benefits of exercise in diabetic cardiomyopathy.[156] Exercise-mediated upregulation of METTL3 was mediated by transcription factor STAT3 (signal transducer and activator of transcription 3) phosphorylation, thereby increasing Y-box–binding protein 1, reducing oxidative stress, and ultimately protecting the heart against diabetic cardiomyopathy.[156] Nevertheless, these studies provide evidence of the involvement of RNA modifications in exercise-induced physiological cardiac growth. Further research is needed to fully uncover the role of RNA modifications in cardiac adaptation to exercise.

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The findings discussed above offer promising insights into the molecular mechanisms responsible for exercise-induced physiological cardiac growth. However, the upstream regulatory mechanisms (ie, how these targets and pathways are regulated in exercised hearts) remain less investigated and are active areas of study. Mechanosensors that can theoretically transduce hemodynamic stress to produce physiological cardiac remodeling have been identified in animal models. Melusin overexpression (a beta1 integrin-interacting protein) in mice induces concentric hypertrophy with preserved fractional shortening and is protective in models of pressure overload.[157,158] Neurohormonal signaling is also sensitive to biomechanical stress, as in cultured cells subjected to stretch, and in mice with transaortic constriction lacking angiotensin II, AT1 can be activated and induce cardiac hypertrophy.[159] Other mechanisms have been proposed, including sensing by myocardial sarcomeric Z-discs and paracrine signals from the extracellular matrix.[160,161] Advanced high-throughput omics technologies (eg, single-cell sequencing) along with existing resources, such as the large datasets generated by the MoTrPAC (Molecular Transducers of Physical Activity Consortium) are potentially valuable in ongoing efforts to uncover other upstream effectors.[162] The targets/pathways discussed above are mostly, if not entirely, located in cardiomyocytes—the cell type most extensively studied in the context of exercise-induced physiological cardiac growth. However, it is possible that exercise also regulates cardiac growth through other cell types (eg, endothelial cells), or via organ crosstalk mediated by circulating factors such as exerkines.[163–165]

Animal models of exercise require nuanced interpretation. There are significant pitfalls in translating observations made in artificial, albeit controlled, settings to the vast and subtle varieties of human athletic activity. Presumed physiological changes early in exercise models can quickly become pathological via animal stress or the type of induced cardiac growth (eg, transaortic banding). Complex and interrelated signaling pathways overlap and are activated at different times which confounds straightforward conclusions. Further, most models used for molecular studies use a single exercise dose—typically one that induces physiological cardiac growth. There are far fewer studies that investigate the dose-response relationship of the heart to exercise, particularly in response to extreme exercise. This is well demonstrated by one study in male Wistar rats subjected to long-term intensive treadmill exercise training (60 cm/s, 60 min/d, 5 d/wk for 16 weeks, corresponding to 85% VO_{2max}), which found that this long-term strenuous endurance training promoted deleterious vascular remodeling, tunica media fibrosis, and vascular stiffness, potentially through noncoding RNAs miR-212, miR-132, and miR-146b.[166] Extreme exercise or extreme cardiac adaptation warrants further study to decipher the distinct molecular mechanisms underlying the cardiac response (eg, Burmese python as mentioned above). Such studies will provide valuable insights into whether molecular mechanisms differ across exercise doses and whether specific targets/pathways are responsible for the cardiac phenotypes observed in the athlete's heart, as described in this review.

THERAPEUTIC PROMISE OF UNDERSTANDING THE ATHLETE'S HEART

The molecular characterization of the athlete's heart highlights a unique biological state—adaptive, regenerative, and resistant to disease. The same signaling pathways, metabolic shifts, and epigenetic changes that underlie physiological remodeling in response to exercise also counteract mechanisms driving pathological remodeling. As such, understanding these molecular features offers therapeutic promise—both as a blueprint for cardiovascular resilience and as a guide for targeting disease.

These findings take on a broader meaning when viewed through the lens of evolution. Human survival once depended on sustained physical activity. With the transition to bipedalism, our ancestors developed energy-efficient gaits for endurance-based foraging and migration. This behaviorally driven need for movement shaped cardiovascular adaptations that favored stamina and efficiency. Human peak VO_2 is nearly 5× greater than that of our closest primate relatives, whose cardiovascular systems support strength rather than endurance activities.[167,168] Modern populations like the Tsimane and Hadza, who still engage in subsistence lifestyles, exhibit low rates of atherosclerosis and hypertension, reflecting the physiological benefits of sustained exertion.[169,170]

Contemporary epidemiological data reinforce this biological and ancestral pattern. From the London bus study to modern cohort analyses, regular aerobic activity is strongly and consistently linked to reduced glycemic burden, lower atherosclerotic cardiovascular disease risk, and improved longevity.[171–179] Few phenomena in medicine are so well-supported and universally observed. These findings have been codified in professional guidelines, which endorse at least 150 minutes of moderate or 75 minutes of vigorous activity per week.[180,181]

In a sedentary modern environment, exercise restores a physiological state aligned with our evolutionary design. The athlete's heart reflects this restoration—offering a window into adaptations that may be harnessed therapeutically.

At the molecular level, exercise induces beneficial transcriptional and metabolic reprogramming. In mammalian animal models, training activates mitochondrial fatty acid oxidation and suppresses glycolysis—reversing the fetal metabolic shift seen in heart failure.[182–186] Many of these changes are mediated by PGC-1a, and its nuclear receptors (PPARα [peroxisome proliferator–activated

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receptor alpha]), ERR [estrogen-related receptor], and NRF-1 [nuclear respiratory factor 1].

Exercise also modifies neurohormonal tone. Training reduces circulating norepinephrine, angiotensin II, aldosterone, and natriuretic peptides,[187–189] improves heart rate variability,[190] enhances vagally mediated baroreflex response,[191–193] and restores calcium handling in models of sympathetic hyperactivity.[194–196] Vascular function improves via nitric oxide signaling and angiogenesis[197,198] and inflammation is attenuated.[199–203]

These changes translate clinically. In heart failure with preserved EF, exercise reduces LV volumes and wall stress comparably to pharmacological therapies.[187,204–207] The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial showed that moderate-to-high-intensity training reduced mortality and hospitalization by 11% after adjustment for confounders.[208–210]

Cardiac rehabilitation programs translate these findings into practice, improving outcomes across a spectrum of cardiovascular conditions—from ischemic heart disease to transplant recovery.[211–217] In one meta-analysis, early post-MI training produced the most robust reverse remodeling over 6 months.[206] Underlying mechanisms include attenuation of neurohormonal activation, RAAS (renin-angiotensin-aldosterone system) modulation, reduced fibrosis, and preserved contractile function.[218–220]

In sum, chronic exercise activates a coordinated set of structural, functional, and molecular responses that confer cardiovascular resilience. The athlete's heart serves as a model to identify, study, and translate these protective adaptations. Studying the effects of exercise offers both mechanistic and clinical insight, revealing molecular effectors that can be targeted to therapeutically induce the beneficial features of training. Although exercise cannot prevent all diseases, it renders the heart more resistant to it—and offers a roadmap to therapies that might mimic the trained state.

ENIGMAS OF EXERCISE: THE ATHLETE'S HEART IS NOT IMMUNE TO DISEASE

Although the athlete's heart offers a blueprint for physiological remodeling and therapeutic potential, it is not uniformly protective. At the extremes of exercise, patterns emerge that may blur the line between adaptation and maladaptation. This section explores the paradoxes of high-volume endurance training—highlighting arrhythmia risk, coronary artery calcification, and myocardial fibrosis—and considers how these phenomena challenge our understanding of cardiovascular adaptation.

AF Risk

Exercise is generally protective to cardiovascular health but exercise at extremes can generate structural changes that may increase the risk for arrhythmias in high-level endurance athletes.[221] Specifically, higher levels of exercise duration and intensity have been most closely linked to an increased risk of AF, with a notable dose-response phenomenon, as described in the Vasaloppet study.[222] This study analyzed 52 755 participants in a renowned 90-km cross-country ski race in Sweden and tracked athletes for cardiovascular outcomes. Athletes completing the race within 60% of the winner's time were 1.3× more likely to be diagnosed with AF than those who took more than twice as long to finish. Similarly, participants who had completed the race ≥5× exhibited a 1.3-fold increased risk of AF compared with those with only a single race completion. This study provided compelling evidence confirming findings from prior studies regarding the relationship between the extent and intensity of endurance sports and arrhythmia risk.[223]

Endurance athletes, a population typically absent of traditional AF risk factors (hypertension, sleep apnea, valvular heart disease, cardiomyopathy) have a 5-fold increased risk of AF, with a male predominance.[224] Habitual exercise itself leads to complex electrical and structural adaptations that play a critical role in the development of AF in this population. Repeated exposure to increased volume and pressure loads during prolonged exercise can lead to LA enlargement and fibrosis. This atrial remodeling, although beneficial in augmenting cardiac output during exercise, can also create a substrate for arrhythmias. Proinflammatory processes linked to prolonged and intense exercise may further exacerbate atrial remodeling and contribute to the development of fibrosis.[225] Fibrotic remodeling disrupts normal conduction pathways, fostering heterogeneous electrical activity and increasing susceptibility to reentrant circuits, a well-recognized mechanism underlying AF.[226–228]

Endurance training is also associated with increased vagal tone, which prolongs atrial refractory periods and promotes bradycardia, further predisposing athletes to AF. This interplay between cardiac remodeling and autonomic modulation underscores the paradox of exercise—although protective against cardiovascular disease, high-intensity endurance training may also heighten susceptibility to arrhythmias.

Despite the increased AF risk among endurance athletes, it is important to contextualize these findings within the broader spectrum of exercise-related health benefits. The risk of AF must be weighed against the well-documented reductions in cardiovascular morbidity and mortality conferred by regular exercise.[221,229] Notably, follow-up Vasaloppet studies have shown that even after a diagnosis of AF, skiers had a 27% lower risk of stroke and 43% lower risk of mortality risk compared with nonskiers, confirming the long-term benefits of an active lifestyle.[230] Although high-intensity endurance training may heighten AF susceptibility, it does not negate the overall protective effects of exercise. Clinicians must, therefore,

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navigate a nuanced approach when counseling athletes—recognizing AF as a potential consequence of extreme endurance exercise while continuing to advocate for lifelong physical activity in line with current guidelines.[231]

Most research on AF in athletes has focused on predominantly male populations, leaving uncertainty as to whether similar risk patterns apply to women. Although AF has been most extensively studied in male endurance athletes, emerging evidence suggests important sex-specific differences in both the risk and underlying mechanisms of exercise-associated AF. Sex significantly influences EICR, with female athletes exhibiting distinct electrical and structural adaptations compared with their male counterparts.[232] Despite similar training exposure, women tend to demonstrate less LA enlargement and fibrosis, factors central to AF pathogenesis. A follow-up analysis of the Vasaloppet cohort found that female skiers had a lower incidence of both AF and stroke compared with male skiers, reinforcing the possibility of sex-based protective mechanisms.[230] Similarly, a large UK Biobank study revealed that women who engaged in physical activity well beyond guideline-recommended levels—exceeding 5000 MET-minutes per week—experienced a continued reduction in AF risk, a pattern not observed in men.[233] However, a recent analysis of older female endurance athletes reported a relatively high cumulative prevalence of AF, although rates were not significantly different from nonathletic women, suggesting that excessive endurance training may still carry some arrhythmogenic potential in female athletes.[234] These mixed findings underscore the need for further research with adequate representation of female athletes to elucidate sex-specific mechanisms of EICR and better define the relationship between endurance exercise and AF risk in women.

Coronary Artery Calcium in Athletes

Coronary artery calcium (CAC) scoring is a widely used marker of subclinical atherosclerosis and a predictor of future cardiovascular events. However, its interpretation of athletes presents unique challenges. Despite superior cardiorespiratory fitness and fewer traditional risk factors, endurance athletes frequently exhibit elevated CAC scores.[235,236] This paradox raises the question of whether such findings represent maladaptive atherosclerosis or benign vascular remodeling.

Multiple mechanisms may contribute to CAC development in athletes, though the underlying pathogenesis remains unclear. Repeated high-intensity exercise may alter coronary hemodynamics, leading to endothelial dysfunction and plaque formation. Additional contributors include chronic inflammation, sympathetic activation, mechanical vascular stress, and exercise-induced increases in parathyroid hormone, which may influence vascular calcification.[237,238] Although endurance training is generally associated with favorable risk profiles, extreme athletes often consume high-fat diets, contributing to elevated LDL (low-density lipoprotein) and oxidative stress. Together, these factors may promote calcific atherosclerosis even in the absence of overt clinical disease.[239] Some have postulated that this may represent a form of reparative calcification, similar to statin-associated plaque healing where increased calcification reflects stabilization.[240]

Coronary computed tomography angiography studies have shown that athletes with elevated CAC often exhibit more heavily calcified, stable plaques, distinct from the soft, rupture-prone morphology seen in traditional CAD.[235,241] However, a large European study of lifelong endurance athletes challenged this view, reporting a higher prevalence of noncalcified and mixed plaques in this population, suggesting more heterogeneous plaque composition than previously appreciated.[242] That same study also refuted earlier hypotheses that CAC in athletes predominantly localizes perivascularly, demonstrating instead that calcification is largely intraluminal—similar to patterns observed in nonathletic populations.

More recently, long-term data from the Cooper Clinic in Dallas helped clarify the clinical relevance of CAC in active individuals. In a cohort of over 26 000 participants followed for 2 decades, higher CAC scores were associated with increased rates of myocardial infarction and revascularization, even among those engaging in >3000 MET-minutes per week of physical activity. Although high-volume exercise was linked to lower all-cause mortality, it did not mitigate the cardiovascular event risk associated with CAC.[243] These findings challenge the notion that physiological fitness offsets the prognostic significance of anatomic disease.

Emerging data also suggest sex-specific differences in CAC prevalence among athletes. In one study, male endurance athletes exhibited higher CAC scores and greater coronary plaque burden than less active male controls, whereas female athletes showed no significant differences in CAC or plaque burden compared with less active women.[244] The pathophysiologic basis for this discrepancy may relate to hormonal influences, divergent shear stress responses, or sex-specific vascular remodeling. This may partially explain the lower incidence of exercise-associated SCD among female athletes and underscores the need for more sex-specific data in this field.[245]

Finally, although CAC is a surrogate for atherosclerosis, it does not capture the full spectrum of coronary artery disease. A low CAC score does not exclude hemodynamically significant disease, and in athletes, calcified plaque may represent a spectrum of biological processes with unclear clinical implications.[246] Traditional CAC scoring models were not developed for athletic populations and may not fully account for differences in plaque distribution, composition, or downstream risk. Further research is needed to refine risk stratification models

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that distinguish protective exercise-induced vascular adaptations from pathological atherosclerosis that may confer elevated major adverse cardiovascular events (MACE) risk.

Myocardial Fibrosis in Athletes

Endurance exercise induces several well-defined cardiovascular adaptations that are considered physiological and favorable to enable athletes to sustain high levels of activity by optimizing stroke volume, myocardial compliance, and overall cardiovascular performance. However, emerging evidence suggests that prolonged high-intensity training may also lead to myocardial fibrosis, a process that is traditionally associated with pathological cardiac remodeling but less defined in the athlete population. Myocardial fibrosis is characterized by the excess deposition of extracellular matrix proteins and can occur in response to repetitive mechanical stress, inflammation, ischemia, or oxidative injury. There have been several mechanisms proposed to lead to the development of myocardial fibrosis, but discrete evidence has been provided to support factors, such as genetic predisposition, silent myocarditis, pulmonary artery pressure overload, and prolonged exercise-induced repetitive microinjury as primary contributors.[247]

Conventionally, myocardial fibrosis is thought to serve as an arrhythmogenic substrate, increasing the risk of both atrial and ventricular arrhythmias. In addition to increasing arrhythmogenicity, diastolic dysfunction is a well-known consequence of myocardial fibrosis due to chamber stiffening and reduced compliance. In long-term endurance athletes, myocardial fibrosis particularly has been found to develop in the atria, RV, interventricular septum (ie, RV insertion points), and subepicardium, rather than the typical subendocardial pattern associated with ischemic heart disease.[248] Although myocardial fibrosis identified at RV insertion points is not traditionally associated with clinical significance, the presence of myocardial fibrosis in other areas requires further evaluation and conjunctive risk stratification.[21]

The imaging gold standard for determining the burden of myocardial fibrosis is CMR imaging with LGE and T1 mapping techniques. The distribution of LGE is useful in distinguishing ischemic fibrosis from nonischemic fibrosis. T1 mapping allows for the quantification of diffuse interstitial fibrosis, which may not be visible on LGE. Furthermore, extracellular volume fraction derived from T1 mapping provides a more objective and continuous measure of fibrosis burden, making it valuable in the evaluation of EICR, hypertensive heart disease, and early-stage cardiomyopathies.

There have been opposing thoughts shared in the literature regarding myocardial fibrosis and exercise exposure. A meta-analysis reported that 21% of high-intensity endurance athletes exhibited LGE compared with 3% of nonathletic controls.[249] A more recent 2023 study identified myocardial fibrosis in 48% of veteran endurance athletes, suggesting a higher prevalence than previously documented.[250] Conversely, a 2024 study demonstrated that there was no association between increasing exercise dose and extracellular volume fraction on magnetic resonance imaging, diffuse myocardial fibrosis had a low prevalence, and there was no adverse dose-response relationship between exercise and myocardial fibrosis in otherwise healthy endurance athletes.[251] Recent data from competitive athletes with COVID-19 indicate that myocardial fibrosis may also occur incidentally in young athletes and does not necessitate additional clinical evaluation.[252]

Sex-based differences have also been observed in myocardial fibrosis, with male athletes being more likely to exhibit imaging findings of fibrosis compared with females, even after adjusting for training volume and intensity.[232] This has been postulated to be attributed to differential blood pressure response to exercise as well as hormonal influence. Moreover, this difference in fibrosis burden may further contribute to sex-specific differences in arrhythmia risk and adverse cardiac events in endurance athletes.

Whether myocardial fibrosis in the context of extensive endurance exercise history is a distinct protective response to reinforce myocardial integrity, an early sign of pathological remodeling that increases the risk of arrhythmias or heart failure or falls on a phasic spectrum that imposes both physiological benefit and pathological risk remains unanswered. Further investigation to understand the complexity of this relationship between exercise and myocardial fibrosis, its potential mechanisms, and implications for sports cardiology and athlete safety are necessary.

CONCLUSIONS

The athlete's heart is a powerful model of human cardiovascular adaptation, reflecting the dynamic interplay between structure, function, and molecular signaling in response to sustained physical training. Across historical context, physiological insight, and molecular biology, the data converge on a central theme: although exercise induces beneficial remodeling that enhances performance and resilience, the boundary between adaptation and maladaptation can become blurred with extreme exposure. The same mechanisms that confer benefit—cardiac enlargement, vascular compliance, and enhanced metabolic flexibility—may under certain conditions contribute to arrhythmias, coronary calcification, or myocardial fibrosis. These phenomena do not negate the profound benefits of regular exercise but emphasize the need for personalized interpretation of findings in highly trained individuals. Emerging data on physiological molecular pathways offer a roadmap for identifying therapeutic targets that mimic or enhance adaptive remodeling. Moving forward, the athlete's heart provides both a model and a caution—a window into the upper limits

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of human cardiovascular potential and the thresholds beyond which adaptation may carry risk.

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None.

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