The Athlete’s Heart vs. the Failing Heart: Can Signaling Explain the Two Distinct Outcomes?

Cardiac remodeling is typically associated with disease and can lead to heart failure. In contrast, remodeling that occurs in the athlete’s heart is considered an adaptive physiological response. This review provides an overview of signaling mechanisms responsible for inducing left ventricular hypertrophy in the athlete’s heart and in settings of pathological hypertrophy and heart failure.

The Athlete’s Heart vs. the Hypertrophied Failing Heart

In response to regular exercise training, the heart may undergo cardiac remodeling (i.e., changes in left ventricular geometry) to enhance performance. The resulting phenotype is referred to as the “athlete’s heart” and is most frequently observed in elite athletes who participate in regular, high-intensity training regimes. A fundamental component of exercise-induced remodeling is physiological cardiac hypertrophy, a process that increases muscle mass by increasing cardiac myocyte size. Physiological cardiac hypertrophy is associated with normal or enhanced cardiac function. In contrast, pathological cardiac hypertrophy occurs in settings of disease, such as hypertension. These events reduce cardiac output and contribute to the progression to heart failure.

Concentric vs. Eccentric Cardiac Hypertrophy

Exercise-induced physiological hypertrophy can be broadly defined as concentric or eccentric (66). Eccentric cardiac hypertrophy is induced by increases in volume load. Volume overload occurs during dynamic endurance exercises such as swimming and running. Eccentric cardiac hypertrophy is characterized by an increase in the longitudinal dimension of cardiac myocytes, which leads to dilatation of the left ventricle, accumulation of collagen (cardiac fibrosis), and loss of cardiac myocytes. These events reduce cardiac output and contribute to the progression to heart failure (see Ref. 12). In contrast, physiological cardiac hypertrophy that occurs in the athlete’s heart is not typically associated with fibrosis, cardiac dysfunction, or the development of heart failure (see Ref. 59).

Morphological and Functional Characteristics of the Athlete’s Heart and the Failing Heart

Left Ventricular Hypertrophy

The heart adapts to sustained increases in blood pressure or volume by increasing muscle mass. Since the rate of cardiac myocyte turnover is very low, this is largely achieved via an increase in cardiac myocyte size (i.e., cardiac myocyte hypertrophy) rather than an increase in myocyte number (95). Physiological heart growth occurs during development and pregnancy, and is a key feature of the athlete’s heart. In contrast, pathological cardiac hypertrophy occurs in settings of disease, such as hypertension (46, 86). There are distinct structural, functional, and metabolic differences between physiological and pathological cardiac hypertrophy (see Ref. 6 for extensive review). In settings of cardiovascular disease, left ventricular (LV) hypertrophy is initially an adaptive response that allows the heart to maintain cardiac output (“compensated hypertrophy”) (32). However, chronic pressure or volume overload can lead to further remodeling, which involves dilatation of the left ventricle, accumulation of collagen (cardiac fibrosis), and loss of cardiac myocytes (34). These events reduce cardiac output and contribute to the progression to heart failure (see Ref. 12). In contrast, physiological cardiac hypertrophy that occurs in the athlete’s heart is not typically associated with fibrosis, cardiac dysfunction, or the development of heart failure (see Ref. 59).
output (26); stroke volume of untrained individuals increases from ~70 ml/beat at rest (11, 19) to ~100–135 ml/beat during exercise (11, 104). Concentric cardiac hypertrophy occurs in response to pressure overload and is characterized by thickening of the left ventricle walls and minimal LV dilatation. Pressure overload occurs during isometric exercises, such as resistance training. During heavy weightlifting training, peak blood pressure can exceed 320/250 mmHg (52).

Training regimes vary from athlete to athlete and typically incorporate both strength and endurance exercises. In addition, volume overload does not occur in the absence of increases in pressure and vice versa (see Ref. 79). Thus, although LV hypertrophy of the athlete’s heart can be broadly classified as eccentric or concentric, there is a high degree of heterogeneity in the size and shape of the athlete’s heart. In general, endurance-trained athletes (such as runners and swimmers) display increased LV wall thicknesses and significant dilatation of the left ventricle. Strength-trained athletes (such as weightlifters and wrestlers) display thickening of the LV walls and mild to moderate LV dilatation. “Combination” athletes, who undertake strength and endurance training (such as rowers, canoeists, and cyclists), display the greatest degree of LV dilatation and wall thickening (78) (see FIGURE 2).

**Differences in the Athlete’s Heart Due to Sex and Ethnicity**

In absolute terms, female athletes do not develop as marked LV hypertrophy as male athletes. In a study of 947 elite athletes participating in a range of sports, mean values for absolute LV mass, wall thicknesses, and cavity dimensions were greater in male athletes compared with females (76, 78). A study of male and female cyclists, matched for training and competition history, found that LV mass normalized to fat-free mass was at least 30% greater in men compared with women (83). Indeed, maximal LV wall thickness in female athletes rarely exceeds the accepted upper limit for a normal adult (12 mm) (76, 81). However, in relative terms, female athletes develop significantly greater LV dilatation compared with male athletes (76). Black athletes also develop greater LV hypertrophy than white athletes (5, 81). Thus sex and ethnic differences exist in the athlete’s heart and need to be taken into consideration when screening for abnormalities indicative of HCM or dilated cardiomyopathy.

**Is the Athlete’s Heart Truly Physiological?**

There has been some debate over whether the athlete’s heart is a truly physiological phenomenon or whether long-term, chronic exercise training is maladaptive and leads to heart disease or sudden cardiac death (see Ref. 24). There may be a threshold above which exercise training may increase the risk of arrhythmias or sudden cardiac death (SCD) (41). However, a study of 114 world-class endurance athletes who had undergone uninterrupted exercise training over a 4- to 17-year period and competed in two to five consecutive Olympic Games has demonstrated that long-term, high-intensity exercise training does not lead to pathological LV remodeling, cardiac dysfunction, or adverse clinical events (75). Furthermore, LV hypertrophy in the athlete’s heart is reversible following detraining (27, 60, 77, 89), suggesting that physiological exercise-induced hypertrophy is a benign adaptation.

**SCD in Young Athletes**

SCD in athletes has not been extensively examined but is considered relatively rare, occurring at a frequency of ~1:200,000 in young athletes (58). Exercise-induced SCD has usually been associated with congenital cardiovascular disease (55, 90). HCM is the most common underlying cause of SCD in young athletes, accounting for 36% of all sudden deaths in an American cohort (57). HCM is characterized by gross thickening of the LV walls [maximal wall thickness ≥13 mm, typically 15–52 mm (39)] in the absence of LV dilatation (see Ref. 54). Since patients with HCM are more susceptible to SCD, it is recommended that HCM patients refrain from participating in competitive sport or high-intensity exercise (56). Indeed, some countries (i.e., Italy) have implemented prescreening programs to identify athletes at risk of SCD. Such programs have successfully lowered the incidence of SCD among young athletes (14).

**Myocardial Injury During Exercise**

Several investigators have studied myocardial injury in athletes during or immediately after  

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**FIGURE 1.** Key morphological and functional differences between the athlete’s heart and the failing heart

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**THE ATHLETE’S HEART**
- Increased heart mass
- Normal cardiac function
- Reversible

**THE FAILING HEART**
- Increased heart mass
- Reduced cardiac function
- Irreversible
- Cell death and fibrosis
- Increased mortality
prolonged exercise (18, 29, 40, 82). La Gerche et al. (40) assessed 27 athletes participating in a 10-h ironman triathlon. At the completion of the event, athletes displayed right ventricular dysfunction and had elevated circulating levels of cardiac troponin I and B-type natriuretic peptide (BNP), biomarkers that are typically elevated in settings of LV failure. Seven of the 27 athletes also displayed abnormal wall motion and had impaired systolic function, indicating that ultra-endurance exercise can cause myocardial damage. However, all abnormalities were transient and were not evident 1 wk postrace (40). Furthermore, it has been suggested that increases in circulating BNP following chronic exercise may be a protective mechanism rather than an indicator of myocardial injury (87). Thus, unlike pathological hypertrophy, physiological remodeling of the athlete’s heart is generally beneficial and does not progress to heart failure. Further evidence that exercise and physiological remodeling induce a protective phenotype comes from clinical studies demonstrating that regular exercise training is beneficial in patients with heart failure, improving functional capacity and quality of life (see Refs. 17, 74, 94). A comprehensive understanding of signaling pathways involved in both pathological and physiological cardiac hypertrophy may help to identify critical signaling events in the transition from pathological cardiac hypertrophy to heart failure.

Distinguishing Hypertrophic Cardiomyopathy from the Athlete’s Heart

Because HCM patients are more susceptible to exercise-induced SCD, it is critical to be able to distinguish HCM from the athlete’s heart; however, this can be challenging. Criteria that are assessed and considered when distinguishing HCM from the athlete’s heart include ventricular wall thickness, ventricular chamber dimensions, atrial size, diastolic function, ECG, gender, ethnicity, family history of HCM, peak oxygen consumption, and regression with detraining (44). However, overlap between many of these parameters can make diagnosis difficult. For example, the lower cut-off for maximal wall thickness in patients with HCM is 13 mm (54). Only 2% of male athletes in an Italian cohort had a maximal wall thickness ≥13 mm (78). However, 18% of black male athletes had a maximal wall thickness ≥13 mm, and 3% had a maximal wall thickness ≥13 mm.

FIGURE 2. Physiological remodeling of the athlete’s heart and pathological remodeling in settings of disease lead to different cardiac morphologies
thickness ≥15 mm (5), indicating that a significant number of elite male athletes have a maximal wall thickness consistent with that observed in patients with HCM. In contrast, the maximal wall thickness of female athletes is unlikely to fall within the expected range for HCM; a study of 600 female athletes identified 12 mm as the upper limit for maximal wall thickness in female athletes (76), whereas another study showed that ∼3% of black female athletes have a wall thickness of 12–13 mm (81).

**Stimuli and Signaling in the Athlete’s Heart vs. the Pathological Heart**

Understanding the signaling mechanisms underlying the pathological or failing heart and the athlete’s heart may lead to identification of new therapeutic strategies to treat the failing heart and identification of biomarkers that could be used in conjunction with echocardiography and ECG data to distinguish HCM from the athlete’s heart.

**Stimuli for Exercise-Induced Heart Growth**

Exercise causes the release of growth factors and neurotransmitters, which stimulate receptors on various cell types to mediate a biological response.

![Diagram showing effects of chronic exercise on PI3K and IGF1R activity](image)

- Normal mouse heart
- Chronic exercise
  - PI3K activity (dnPI3K Tg mice)
  - IGF1R activity (IGF1R Tg mice)
- 20% ↓ in heart mass due to ↓ in PI3K activity
- 20–40% ↓ in heart mass; mimics the “athlete’s heart”
- Chronic exercise
- IGF1R activity (IGF1R-dnPI3K Tg mice)
- No change in heart mass (blunted IGF1R-induced heart growth)
- Blunted hypertrophic response to exercise

FIGURE 3. Transgenic (Tg) mouse models have helped to identify key signaling proteins involved in inducing physiological hypertrophy of the athlete’s heart.

- caPI3K, constitutively active PI3K transgenic mouse; dnPI3K, dominant negative PI3K transgenic mouse; IGF1R, insulin-like growth factor 1 receptor; PI3K, phosphoinositide 3-kinase p110α.

A study of growth factors in the coronary sinus blood of professional soccer players found that cardiac formation of insulin-like growth factor 1 (IGF1), but not endothelin-1 (ET-1) or angiotensin II (Ang II), was elevated in athletes compared with healthy sedentary controls (69). Furthermore, IGF1 levels positively correlated with LV mass index and LV end-diastolic dimension index, suggesting a role for IGF1 in the induction of physiological heart growth (69).

Studies in transgenic mice have confirmed the importance of IGF1 signaling in physiological cardiac hypertrophy. Transgenic mice overexpressing the IGF1 receptor (IGF1R) in cardiac myocytes developed physiological cardiac hypertrophy, characterized by a 35–40% increase in heart size (see FIGURE 3) and enhanced systolic function (63). IGF1R transgenic mice displayed a greater hypertrophic response to swim training compared with controls (63), whereas mice with cardiac myocyte-specific ablation of the IGF1R gene were resistant to exercise-induced increases in heart size (38). This demonstrates the importance of IGF1 in mediating exercise-induced physiological heart growth. Activation of IGF1R leads to downstream signaling events including activation of phosphoinositide 3-kinase p110α [PI3K(p110α)] and Akt1, key mediators of cell growth and survival (see FIGURE 4).

Norepinephrine (NE) is a neurotransmitter that is released during exercise (25, 69). In the study of professional soccer players, cardiac NE spillover did not correlate with LV wall thicknesses or chamber dimensions but was positively correlated with ventricular contractility (69), implicating NE in the regulation of cardiac myocyte contractile function but not cardiac myocyte size. Local release of NE induces vasoconstriction by binding to α1-adrenergic receptors (α1-AR) (25). α1-ARs play an important role in protecting the heart against maladaptive remodeling in settings of disease (see Ref. 109). A study in mice deficient for both the α1A- and α1B-AR subtypes demonstrated that α1-ARs play a role in postnatal physiological heart growth in male mice but not in female mice (72). It is unclear whether this has relevance for the athlete’s heart in humans.

**Signaling Cascades Involved in Physiological Cardiac Hypertrophy**

As described previously, IGF1 levels are elevated in the athlete’s heart (69), and activation of IGF1R leads to physiological cardiac hypertrophy in mice (63). Two downstream effectors of IGF1R that are critical for the induction of physiological heart growth have been identified: PI3K(p110α) and Akt1 (also known as protein kinase B).
**PI3K(p110α)**

PI3K(p110α) is a lipid kinase that phosphorylates lipids in the plasma membrane to form phosphatidylinositol 3,4,5-trisphosphate (PIP3) (see Ref. 101). PIP3 acts as a second messenger to cause downstream signaling events, such as phosphorylation and activation of Akt (30). Generation of cardiac-specific transgenic mouse strains have confirmed that PI3K(p110α) is critical for physiological heart growth, both during normal heart development and in response to exercise training (51, 64, 91) (see FIGURE 3). In the adult heart, mice with elevated cardiac PI3K(p110α) activity due to expression of a constitutively active PI3K(p110α) construct (caPI3K mice) develop physiological hypertrophy (~20% increase in heart size) with normal cardiac function (64, 91). In contrast, mice with reduced cardiac PI3K(p110α) activity due to expression of a dominant negative PI3K(p110α) mutant (dnPI3K mice) or Cre-induced muscle-specific deletion of PI3K(p110α) have smaller hearts compared with non-transgenic littermates (15–20% reduction in heart size) (50, 64, 91). dnPI3K transgenic mice displayed a blunted hypertrophic response to exercise training (see FIGURE 3), confirming that PI3K(p110α) is important in the development of exercise-induced physiological hypertrophy (64). In addition, dnPI3K mice were more susceptible to heart failure when subjected to pressure overload (62, 64) or myocardial infarction (48), and more susceptible to atrial fibrillation in a setting of dilated cardiomyopathy (80). Thus PI3K(p110α) is not only critical for physiological hypertrophy but is important for protecting the heart against pathological insults. Finally, crossbreeding of dnPI3K mice with IGF1R transgenic mice (which overexpress IGF1R in adult cardiac myocytes) blunted the hypertrophic response normally observed in IGF1R transgenic mice (63). Thus PI3K(p110α) is an important downstream effector of IGF1 (see FIGURE 3 and FIGURE 4).

**Akt1**

Akt is a serine/threonine kinase that plays a central role in cardiac myocyte growth and survival via its effects on protein synthesis and apoptosis (16, 22, 28, 31, 42, 61). Akt is a downstream target of PI3K (30) and is activated (i.e., phosphorylated) in animal models of physiological hypertrophy (37, 63, 64, 73). The generation of transgenic mouse models (e.g., Refs. 10, 13, 20, 21, 92) has allowed examination of the physiological roles of different Akt isoforms in the heart. Akt1 is the predominant Akt isoform in mouse heart (31). The strongest evidence for involvement of Akt1 in exercise-induced cardiac hypertrophy comes from a study that examined the cardiac phenotype of Akt1 knockout mice (21). Akt1 knockout mice displayed a similar phenotype to dnPI3K mice when subjected to hypertrophic stimuli, i.e., a blunted hypertrophic response to a physiological stimulus (swim training) and an accelerated heart failure phenotype in response to a pathological stimulus (pressure overload) (21).

**Signaling Cascades Involved in Pathological Hypertrophy and Heart Failure**

**G Protein-Coupled Receptors**

Ang II and ET-1 are pro-hypertrophic hormones (4, 36, 84, 85, 93, 103, 110) that are upregulated in heart failure patients (88, 99) but not in the athlete’s heart (69). Ang II and ET-1 are secreted from cardiac myocytes during mechanical stress (i.e., stretch due to pressure overload) (3, 84, 97). Ang II and ET-1 signal by binding to Gq protein-coupled receptors (GPCR). The importance of Gq proteins in mediating pathological cardiac hypertrophy has been demonstrated in cardiac-specific transgenic
mouse models overexpressing wild-type or a constitutively active mutant of \( G_{q} \) (15, 65). In both models, mice developed significant pathological cardiac hypertrophy and dysfunction (15, 65). Furthermore, inhibition of \( G_{q} \) signaling in transgenic mice blocked pressure overload-induced hypertrophy (1, 106). \( G_{q} \) is thought to mediate pathological cardiac hypertrophy via downstream effectors such as calcineurin (65, 98) and mitogen-activated protein (MAP) kinases such as extracellular signal-regulated kinases 1 and 2 (ERK1/2) (7, 100).

**Calcineurin and NFAT**

Calcineurin is a \( \text{Ca}^{2+} \)-dependent phosphatase that regulates hypertrophic gene transcription by dephosphorylating transcription factors such as nuclear factor of activated T-cells (NFAT; see Ref. 108). Calcineurin has been identified as a key enzyme involved in the induction of pathological, but not physiological, cardiac hypertrophy, since NFAT activity was upregulated in mouse models of pressure overload and heart failure but not in mice with exercise-induced physiological hypertrophy (107). Calcineurin activity was elevated in hearts of patients with LV hypertrophy and heart failure (33), and transgenic mice overexpressing calcineurin developed marked pathological cardiac hypertrophy, which rapidly progressed to dilated cardiomyopathy (68). Furthermore, inhibition of calcineurin prevented cardiac hypertrophy in rodent models of cardiomyopathy and pressure overload (96).

**Signaling Pathways in HCM**

Signaling pathways involved in the phenotype associated with HCM have not been extensively defined. It has been suggested that one mechanism by which HCM mutant proteins could stimulate hypertrophy is via associated contractile changes activating signaling pathways involved in mediating pressure overload-induced hypertrophy and the cellular response to mechanical stress (53) (see FIGURE 4). Consistent with this hypothesis, hypertrophic factors, including Ang II and ET-1, are elevated in HCM patients (9). Furthermore, blockade with losartan (an Ang II receptor antagonist) reversed interstitial fibrosis in a transgenic mouse model of human HCM (47).

**Signaling Pathways in Concentric and Eccentric Hypertrophy**

There are clear differences in gene expression and patterns of signal transduction between concentric and eccentric hypertrophy (33, 45, 67); however, it is still unclear whether the different phenotypes are due to activation of distinct signaling pathways or differences in temporal and spatial activation of the same signaling proteins. Activation of ERK5 has been implicated in the development of eccentric hypertrophy, since transgenic mice with elevated ERK5 activity developed eccentric cardiac hypertrophy, which rapidly progressed to dilated cardiomyopathy and resulted in premature death (70).

**Identification of New Therapeutic Strategies to Treat the Failing Heart**

As described earlier, physiological cardiac hypertrophy is mediated by the IGF1-PI3K(p110\(\alpha\))-Akt1 signaling pathway. Evidence from genetic mouse studies demonstrates that activation of the IGF1-PI3K pathway protects the myocardium in settings of disease, including pressure overload-induced hypertrophy, dilated cardiomyopathy, atrial fibrillation, myocardial infarction, and diabetic cardiomyopathy (35, 48, 62, 80). However, targeting the IGF1-PI3K signaling pathway with therapeutics is complicated due to the multiple actions of this signaling pathway in numerous tissues and cell types. We have identified cardiac-selective mRNAs and microRNAs (miRs) that are regulated by PI3K(p110\(\alpha\)) and that correlate with cardiac function in mice (48). These candidates may hold promise as novel therapeutic targets in the treatment of conditions such as heart failure.

**Identification of Biomarkers to Distinguish HCM and the Athlete’s Heart**

Identification of biomarkers associated with HCM or the athlete’s heart would assist clinicians in detecting cases of HCM in athletes displaying LV hypertrophy. Factors that are associated with the pathophysiology of HCM include Ang II, transforming growth factor-\(\beta\), ET-1, and interleukin-6 (9). IGF1 is not a good biomarker of the athlete’s heart, since circulating MMP-9 and MMP-2 levels were lower in marathon runners compared with sedentary controls (105) and elevated in patients with heart failure (2). MMP-9 and MMP-2 were also increased in patients with HCM (49, 71). A relatively recent area of research is the use of microRNAs (miRs) as biomarkers for disease (see Refs. 8, 102). We recently identified a number of miRs that are associated with physiological cardiac hypertrophy in the mouse heart (48). Investigation of the role of these miRs in regulating IGF1-PI3K(p110\(\alpha\)) signaling and the development of physiological hypertrophy may help identify biomarkers of the athlete’s heart.
Summary

Signaling pathways that induce physiological hypertrophy of the athlete’s heart are distinct from signaling pathways that are activated in cardiovascular disease. In animal models of physiological hypertrophy, exercise causes the release of IGF1, which leads to cardiac myocyte growth via activation of PI3K(p110α) and Akt1. In pathological settings, signaling molecules such as Ang II and ET-1 signal through GPCRs to induce heart growth. A comprehensive understanding of signaling in the athlete’s heart vs. the failing heart may provide a means to manipulate signaling pathways that are activated in the athlete’s heart to regress hypertrophy and improve outcome in settings of heart failure.

References
