Published in final edited form as:

Life Sci. 2015 February 15; 0: 100–106. doi:10.1016/j.lfs.2015.01.007.

Evidence for distinct effects of exercise in different cardiac hypertrophic disorders

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Abstract

Aerobic exercise training (AET) attenuates or reverses pathological cardiac remodeling after insults such as chronic hypertension and myocardial infarction. The phenotype of the pathologically hypertrophied heart depends on the insult; therefore, it is likely that distinct types of pathological hypertrophy require different exercise regimens. However, the mechanisms by which AET improves the structure and function of the pathologically hypertrophied heart are not well understood, and exercise research uses highly inconsistent exercise regimens in diverse patient populations. There is a clear need for systematic research to identify precise exercise prescriptions for different conditions of pathological hypertrophy. Therefore, this review synthesizes existing evidence for the distinct mechanisms by which AET benefits the heart in different pathological hypertrophy conditions, suggests strategic exercise prescriptions for these conditions, and highlights areas for future research.

Keywords

aerobic exercise; cardiac hypertrophy; exercise prescription; pathological hypertrophy; physiological hypertrophy; myocardial infarction; diabetic cardiomyopathy

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CONFLICT OF INTEREST STATEMENT

None.

INTRODUCTION

Cardiac hypertrophy is enlargement of the heart that occurs in response to metabolic stress, hemodynamic insults, or inherent genetic defects. It is characterized by increases in ventricular wall thickness and/or internal chamber dimensions. With the exception of the physiological hypertrophy that occurs in response to pregnancy or exercise, hypertrophic cardiac remodeling is a response to a pathological condition, and precedes or causes impaired cardiac function (Bernardo et al. 2010). However, the prognoses as well as the structural, metabolic, and functional phenotypes of different hypertrophic disorders are distinct, and depend on the initial insult as well as the presence of cardiovascular comorbidities (**Figure 1**).

Aerobic exercise training (AET) reduces the risk of cardiac events with an efficacy comparable to pharmacological therapy (Naci et al. 2013). Increasingly, AET is prescribed for the prevention, management, or rehabilitation of those cardiovascular diseases that are characterized by cardiac hypertrophy, including hypertension, myocardial infarction (MI), and diabetic cardiomyopathy (Hordern et al. 2012, Mezzani et al. 2012). The rationale for prescribing AET is based on evidence that it reduces cardiovascular mortality and cardiac event recidivism rates, and improves cardiovascular risk factors such as high blood pressure and overweight (Nohria et al. 2002, Taylor et al. 2004, Clark et al. 2010, Lawler et al. 2011). Translational studies have shown that improvements in cardiovascular risk factors can be improved by both interval-based and continuous AET (Haram et al. 2009, Tjønnå et al. 2009, Wisloff et al. 2009). Therefore, a key question is what modes and intensities of exercise elicit the greatest benefit in individuals with various hypertrophic conditions.

Evidence for the effects of exercise training in humans with cardiovascular disease is mixed, and the exercise programs that have been used to investigate these effects use highly varied methods and outcome measures (Mishra et al. 2012, Seron et al. 2014). The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) Trial is the largest clinical trial to date examining the effects of AET in patients with reduced ejection fraction or New York Heart Association class II-IV heart failure who were randomized to exercise training or usual care (Flynn et al. 2009, O'Connor et al. 2009). Thirty-six weeks of supervised cardiac rehabilitation followed by home-based AET until the median follow-up point of 30 months was associated with modest but significant reductions in rehospitalization and all-cause mortality, after these outcomes were adjusted for key prognostic indicators such as atrial arrhythmias (O'Connor et al. 2009). Similarly, exercise training improved self-reported wellbeing assessed by the Kansas City Cardiomyopathy Questionnaire (Flynn et al. 2009).

These data indicate that AET is an effective therapy for improving outcomes in patients with pathological cardiac remodeling and cardiac dysfunction. However, evidence for the structural and functional effects of aerobic exercise on different types of pathological cardiac hypertrophy is lacking, and the effects may differ depending on the mode or duration of training. Therefore, the purpose of this review is to summarize current evidence for the therapeutic mechanisms and efficacy of AET in different types of cardiac hypertrophy.

PHYSIOLOGICAL HYPERTROPHY

Chronic AET, such as running, rowing or cycling, is associated with 12-lead electrocardiogram (ECG) changes indicative of increases in ventricular mass (Venerando et al. 1964, Arstila et al. 1966). Echocardiographic studies unequivocally support the existence of an “athlete’s heart” (Baggish et al. 2011), characterized by eccentric ventricular remodeling, an increase in septal thickness and ventricular wall thickness (Left ventricular hypertrophy in athletes), and normal or improved ejection fraction (EF) (Pelliccia et al. 1991). In male athletes, left ventricular wall thickness may be between 12 and 16 mm in male athletes (Rawlins et al. 2009); in females, this increase is about 23% less (Pelliccia et al. 1996). This remodeling is beneficial to cardiac function and is associated with improved oxygen delivery, angiogenesis, and nitric oxide sensitivity (Gielen et al. 2010).

Classic “physiological” hypertrophy results from AET and not from resistance exercise training. Indeed, it is important to clarify that resistance strength training actually result in concentric cardiac hypertrophy, and a reduction in internal ventricular chamber dimensions (Barauna et al. 2007, De Souza et al. 2014). The resistance-trained heart is therefore morphologically similar to a heart with pressure overload-induced pathological hypertrophy, although the important distinction is that resistance training-induced hypertrophy does not result in cardiac dysfunction in healthy human subjects (Hurley et al. 1984, Hagerman et al. 2000). This review will focus on the effects of endurance AET on physiological hypertrophic remodeling in the heart.

It is probable that a relatively high exercise intensity, frequency, and duration are required to induce the actual “athlete’s heart.” Therefore, it is unlikely that patients with pathological hypertrophy or post-infarct remodeling will achieve the phenotype of the “athlete’s heart” or a clinically relevant level of physiological hypertrophy. However, an eight-year longitudinal study in mildly hypertensive individuals showed that chronic moderate physical activity did not actually induce physiological hypertrophic remodeling, but merely prevented pathological remodeling (Palatini et al. 2009). Therefore, AET may improve or prevent cardiac remodeling following cardiac insults.

Physical activity or exercise training is actually the result of repeated exposures to individual exercise sessions, and translational studies suggest that the effects of exercise at the molecular level occur immediately and have acute effects on hypertrophic signaling. We recently reported that 15 minutes of moderate-to-high intensity treadmill running in mice reduces the association of the histone deacetylases (HDACs) 4 and 5 with the mSin3A/REST corepressor complex in the mouse heart, an event that may permit transcription of pro-hypertrophic genes (Medford et al. 2013). This is consistent with the findings of McGee and Hargreaves, who showed that 60 minutes of cycling at 70% peak oxygen consumption (VO_2) decreases the association of histone deacetylase 5 (HDAC5) with myocyte enhancer factor 2 in skeletal muscle, permitting hypertrophic signaling and sarcomeric protein expression (McGee et al. 2004). Though preliminary, these data suggest that physiological cardiac hypertrophic signaling occurs with moderate- to high-intensity exercise, and begins either during or immediately after an exercise session.

The chronic effects of exercise on physiological cardiac hypertrophy are mediated, at least in part, by several required growth factors, although insulin-like growth factor 1 (IGF-1) and its receptor, IGF-1R, appear to be a primary stimulus in vivo. Ligand-bound IGF-1R induces growth signaling in cardiomyocytes by phosphorylating ERK and the insulin-like growth factor receptors 1 and 2 (IRS-1 and -2). Phosphorylated IRS-1 and IRS-2 mediate activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and AKT, which increase protein synthesis by activating ribosomal protein S6 kinase and eukaryotic translation initiation factor 4E-binding protein 1. (For an excellent review, see (Troncoso et al. 2014).) Circulating IGF-1 is elevated in exercise-trained mice (Kodama et al. 2000), rats (Yeh et al. 1994), and humans (Neri Serneri et al. 2001, Meckel et al. 2011, Mason et al. 2013), and IGF-1 signaling is essential for physiological cardiac hypertrophy in mice (Kim et al. 2008).

However, the action of IGF-1 and IGF-1R appears to be mediated by IRS-1 and IRS-2, since IRS-1/2 knockout mice do not develop cardiac hypertrophy in response to exercise training (Riehle et al. 2014). Similarly, expression of a dominant negative PI3K in mice prevents physiological hypertrophy, but has no effect on the development of pathological transaortic constriction-induced hypertrophy (McMullen et al. 2003), indicating that PI3K specifically mediates physiological hypertrophic signaling. Translational studies also indicate that IGF-1 signaling is cardioprotective, and improves insulin sensitivity, cardiomyocyte depolarization, and endothelial dysfunction, and low circulating IGF-1 may be an independent risk factor for heart disease (Conti et al. 2004).

It is important to note that chronic AET induces metabolic changes in the myocardium that may underlie structural and functional changes to the whole organ. In mice, short-term high-intensity interval training reduces fatty acid oxidation and increases glucose utilization (Hafstad et al. 2011). However, ten weeks of treadmill training is associated with reduced glycolytic flux and higher rates of palmitate oxidation in isolated rat hearts (Burelle et al. 2004), and seven weeks of treadmill training increases cardiac expression of genes that regulate lipid metabolism such as peroxisome proliferator-activated receptor alpha (PPAR α) (Dobrzyn et al. 2013), fatty acid translocase (CD36) and uncoupling protein 2 (UCP2) (Strom et al. 2005). This metabolic phenotype of the endurance trained heart is clearly distinct from the phenotype of the pathologically hypertrophied heart, which is a preferential glucose consumer (Young et al. 2007, Taegtmeier et al. 2010, Kolwicz et al. 2011). Whether lipid and glucose metabolism influence hypertrophic remodeling is still unknown, but upregulation of fatty acid oxidation (FAO) protects the heart against pathological hypertrophy (Chatham et al. 2012), and increased glucose utilization is strongly associated with pathological hypertrophy and cardiac dysfunction (Wambolt et al. 1997). Therefore, it is possible that the therapeutic effects of AET on the pathologically hypertrophied heart are partly due to increased flexibility in substrate utilization and increased myocardial metabolic efficiency.

PATHOLOGICAL HYPERTROPHY

Pressure overload

Conditions that increase LV afterload, such as hypertension or aortic stenosis, induce concentric hypertrophy that is characterized by fibrosis (Bernardo et al. 2010), increased

ventricular wall thickness, and reduced ventricular cavity dimensions (Drazner 2011). Concentric LV hypertrophy in response to hypertension initially normalizes wall strain by increasing wall thickness (Dorn 2007). However, this increase in myocardial mass is not energetically sustainable, and progresses to decompensation and heart failure (Drazner 2011). Indeed, concentric hypertrophy is a strong positive risk factor for heart failure and cardiac-related mortality (Levy et al. 1990).

Treatment for concentric cardiac hypertrophy typically focuses on reducing the primary insult, i.e. the use of antihypertensives to reduce blood pressure resulting from high afterload (Gradman et al. 2006). Blood pressure reduction is clearly the most efficacious therapy for regression of hypertension-induced LV hypertrophy (Sheridan et al. 1999, Sheridan 2000), and reduces the risk of cardiovascular events by over 50% (Verdecchia et al. 2003). There are several classes of antihypertensives that can reduce pathological hypertrophic remodeling via different mechanistic targets; a meta-analysis concluded that efficacy of these compounds for the treatment of hypertension-associated hypertrophy, from most to least effective are: angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, calcium channel antagonists, diuretics, and beta-blockers (Klingbeil et al. 2003). However, epidemiological studies suggest that antihypertensives are associated with long-term complications such as idiopathic new-onset diabetes (Elliott et al. 2007, Ong et al. 2014). While AET lowers blood pressure with virtually no detrimental side effects, the efficacy of AET for LV mass reduction and attenuation or reversal of pathological hypertrophic remodeling in hypertensive individuals has not been systematically researched.

Effects of exercise on hypertrophy and function—AET has both acute and chronic benefits in hypertensive individuals. Acutely, exercise elicits a transient unloading effect called post-exercise hypotension (PEH) (MacDonald 2002); this phenomenon may permit myocardial repair processes to occur while the heart is unloaded. Chronic AET lowers basal catecholamine concentrations and resting heart rate (MacDonald 2002, Appel et al. 2003), and generally reduces systolic blood pressure by 5-10 mmHg (Cleroux et al. 1999). The net effect of these acute and chronic unloading affects is a reduction in cardiac afterload, which reduces the stimulus for concentric remodeling.

Unlike pharmaceutical therapies, there is almost no uniformity in exercise regimens utilized in hypertension research, in which exercise is prescribed in highly varied modes, intensities, frequencies and durations. Therefore, it is perhaps not surprising that there is mixed evidence regarding the effects of AET on the morphology of the hypertensive heart. For example, 15 months of AET reduced blood pressure but did not change echocardiographically-determined ventricular mass in hypertensive individuals (Baglivo et al. 1990), while others reported that 26 weeks of AET had no effect on echocardiography or MRI estimates of heart size (Stewart et al. 2006). However, six months of AET decreased echocardiographically-determined LV wall thickness in hypertensive patients (Hinderliter et al. 2002), 16 weeks of AET in hypertensive African American males caused significant reductions in ventricular mass and wall thickness compared to sedentary controls (Kokkinos et al. 1995), and 12 weeks of supervised exercise decreased LV mass in mildly hypertensive sedentary humans (Zanettini et al. 1997). Nevertheless, one study showed that 10 weeks of military training increased LV mass as determined by MRI (Jamshidi et al. 2002), while

another reported that AET increased LV mass in hypertensive participants (Kelemen et al. 1990). These conflicting results highlight the need for additional research to identify more specific exercise regimens to improve afterload-induced cardiac hypertrophy.

Effect of exercise on molecular characteristics—The therapeutic effects of AET on concentrically hypertrophied hearts may also be mediated by changes in cardiac metabolism. As mentioned above, a distinguishing characteristic of concentrically hypertrophied hearts is preferential glucose utilization rather than FAO (Kolwicz et al. 2011). The preferential use of glucose is characteristic of fetal hearts, and is thought to be a stress response in adult hearts (Rajabi et al. 2007, Taegtmeyer et al. 2010). Translational studies have shown that treadmill exercise improves both glucose and fatty acid utilization in tandem in hypertensive and hypertrophied rat hearts (Kinney LaPier et al. 2001). However, there is very limited evidence for this effect, and additional studies are needed to confirm this hypothesis.

Myocardial Infarction (MI)

The process of ventricular remodeling after MI has been extensively reviewed elsewhere (Cohn et al. 2000). Briefly, the early phase of MI is characterized by inflammation of the infarcted area, expression of the stretch-responsive hormones atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), and increased expression of fetal isoforms of myosin heavy chain (Gidh-Jain et al. 1998, Yue et al. 1998). “Late” or long-term remodeling after infarction includes fibrosis and a loss of contractile activity in the infarcted area, increased wall stress in the ventricular region surrounding the infarct, and progressive decompensatory dilatation of the LV that predisposes the infarcted heart to failure (Sutton 1996, Sutton et al. 2000).

Effects of exercise on hypertrophy and function—AET training reduces MI-related mortality, regardless of whether training occurs before or after the infarct occurs (Thompson 2003). Outpatient cardiac rehabilitation programs that utilize AET after infarction improve LV performance and reduce mortality by 20-26% (O’Connor et al. 1989, Lawler et al. 2011, Acar et al. 2014, Deniz Acar et al. 2014). Six months of AET successfully attenuates ventricular remodelling after MI in humans (Giallauria et al. 2008). In rats, eight weeks of treadmill exercise improved ventricular fibrosis and systolic function, although it had no effect on ventricular dilatation (Xu et al. 2008). Similarly, voluntary wheel running in mice improved fractional shortening but not cardiac hypertrophy post-infarction (de Waard et al. 2010).

Exercise consistently and significantly improves cardiac function after MI. Indeed, AET induces the same magnitude of improvement in EF as angiotensin-converting enzyme inhibitors or pacing with cardiac resynchronization therapy in humans with heart failure (Haykowsky et al. 2011). AET attenuates a decline in EF after MI (Andrews Portes et al. 2009, Batista et al. 2013), and six months of AET after MI improves the LV end-diastolic volume index (Giallauria et al. 2008), while as little as three months of AET post-infarction can improve early diastolic function (Giallauria et al. 2006, Giallauria et al. 2006). A recent meta-analysis indicates that EF is improved by aerobic cardiac rehabilitation programs, and clearly demonstrated that the sooner the program begins, and the longer it lasts, the greater

the improvement in EF (Haykowsky et al. 2011). Though limited, these data highlight exercise as a potential first-line therapy for preventing cardiac remodelling post-MI. There is a clear need for additional research to identify the ideal mode and duration of exercise for preventing cardiac remodelling and improving EF after MI.

Diabetic cardiomyopathy

Type 2 diabetes mellitus (T2DM) is associated with a distinct syndrome of cardiac hypertrophy and diastolic dysfunction known as diabetic cardiomyopathy (DCM) (Amour et al. 2008, Schilling et al. 2012, Miki et al. 2013). The existence of a distinct DCM in human patients is reasonably well established, and has been extensively reviewed in recent papers (Poornima et al. 2006, Boudina et al. 2010). Because insulin signaling is generally required for muscle protein synthesis after exercise (Farrell et al. 1998, Fedele et al. 2000) and is absolutely necessary for physiological hypertrophy in cardiomyocytes (Kim et al. 2008, Ikeda et al. 2009), it is possible that diabetes-associated hypertrophy is completely distinct from other types of pathological hypertrophy. For example, it has been proposed that DCM results from cardiomyocyte atrophy and apoptosis and cardiac fibrosis, rather than cardiomyocyte hypertrophy (Poornima et al. 2006). Indeed, although T2DM is associated with increased ventricular mass (Galderisi et al. 1991, Devereux et al. 2000, Eguchi et al. 2008, Lindman et al. 2014), hypertrophy in diabetic hearts is associated with an increase in echodensity of the ventricular wall (Di Bello et al. 1995), suggesting that the increase in mass may be due to fibrosis rather than actual hypertrophy of the myocardium. In general, the molecular mechanisms and phenotype of the diabetic heart are not well understood, partly because translational research studies in this field over the last 30 years have used widely varied methods of inducing diabetes in pre-clinical models, and have also reported many different indices of cardiac hypertrophy (Cox et al. 2014). However, the clinical characteristics of DCM are well characterized and have been recognized as a distinct entity for several decades (Schilling et al. 2012).

Clinically, DCM is characterized by increased LV wall thickness and mass, independent of other cardiovascular comorbidities (Galderisi et al. 1991, Devereux et al. 2000, Eguchi et al. 2008, Lindman et al. 2014). T2DM is often comorbid with hypertension; however, in normotensive humans, T2DM has comparable effects to hypertension on myocardial strain and strain rate (Masugata et al. 2009), as well as diastolic dysfunction (Liu et al. 2001, Russo et al. 2010). The early functional characteristic of DCM is diastolic dysfunction, which occurs in up to 70% of humans with diabetes (Shivalkar et al. 2006, Brooks et al. 2008), and although most cases of DCM are asymptomatic, subclinical diastolic dysfunction appears to underlie the development of systolic dysfunction and predisposition to heart failure in humans with diabetes (Boudina et al. 2010). DCM is not usually associated with systolic dysfunction, but humans with metabolic syndrome and diabetes are more likely to display exercise-induced impaired systolic function; the reason for this exercise-induced dysfunction is not clear at this time (Fournier et al. 2014).

The primary therapeutic focus for a patient with DCM is essentially diabetes management: glucose control, reduction of cardiovascular comorbidities such as hypertension, and preventing organ-specific complications of diabetes (Pappachan et al. 2013). Exercise,

therefore, is an ideal potential therapy for DCM because it improves not only the primary cardiac insult – hyperglycemia and insulin insensitivity – but also has a direct effect on the heart as well as the associated cardiovascular comorbidities.

Effects of exercise on hypertrophy and function—To date, there is very limited research on the effects of AET in DCM. In clinical populations, the evidence is mixed; for example, six months of monitored exercise that met current American College of Sports Medicine prescription guidelines did not alter LV function in humans with T2DM (Sacre et al. 2014), but eight weeks of AET reduced total vascular resistance and improved peak exercise cardiac output in humans with metabolic syndrome (Fournier et al. 2014). Although numerous translational studies have evaluated the effects of exercise on cardiac function in DCM, these conclusions are difficult to synthesize, because pre-clinical studies of DCM have traditionally used highly inconsistent methodology (Cox et al. 2014). In our lab, eight weeks of exercise training did not alter the heart weight:tibia length ratio in *db/db* mice with T2DM (Cox et al. 2013). However, others reported that 10 weeks of treadmill exercise enhanced aortic flow in a rat model of type 1 diabetes (Broderick et al. 2005). There is still very limited evidence regarding the effects of AET in T2DM at this time.

Effect of exercise on molecular characteristics—T2DM has unique effects on cardiac metabolism that may underlie functional changes in the diabetic heart (Stanley et al. 1997). As mentioned above, pathological hypertrophy in response to pressure overload is typically characterized by increased glycolytic metabolism relative to FAO (Stanley et al. 2005, Kolwicz et al. 2011). However, the diabetic heart shows the opposite phenotype in that it is primarily reliant on fatty acid metabolism, and develops lipotoxicity (Stanley et al. 1997, Broderick et al. 2005, Carley et al. 2005, Chess et al. 2008, Pulinilkunnil et al. 2013). While upregulating FAO is probably a compensatory response to insulin resistance and glucose scarcity, the lipotoxic effects of chronically elevated FAO are associated with apoptosis and contractile dysfunction.

Reducing FAO in the diabetic heart improves the phenotype of DCM (Kolwicz et al. 2012), suggesting that exercise interventions that reduce FAO may be therapeutic in DCM. In mice with diet-induced obesity, 8-10 weeks of moderate intensity treadmill training reduces FAO, increases glycolytic flux and mitochondrial function, and increases cardiac output in the hearts of mice with diet-induced obesity (Hafstad et al. 2013). In a rat model of type 1 diabetes, 10 weeks of treadmill exercise increased translocation of GLUT4, permitting glucose entry into cardiomyocytes (Hall et al. 1995). In a similar model, 10 weeks of treadmill exercise enhanced both glycolytic metabolism and cardiac function (Broderick et al. 2005). While these studies support the idea that AET improves cardiac function in T2DM, additional studies are needed to confirm this hypothesis.

CONCLUSION

Current recommendations for exercise in cardiac patients focus on reducing cardiovascular risk factors and accomplishing goals such as blood pressure and glucose management. However, AET induces beneficial, physiological changes in the heart that alter chamber dimensions and function. Therefore, it is possible that different exercise regimens will have

specific rehabilitative effects following different types of cardiac events. For example, the beneficial effect of AET in the diabetic heart may be due to enhanced insulin sensitivity and normalization of myocardial metabolism, suggesting that a long duration and moderate intensity exercise prescription may be best for improving cardiac function in this patient population. Conversely, a heart that is concentrically hypertrophied due to chronically high afterload would benefit primarily from reduction in afterload. Therefore, short and repeated intervals of exercise that repeatedly induce post-exercise hypotension may be the best approach for this patient population. At the present time, however, these speculations are not supported by systematic research, thus preventing more specific guidelines and recommendations for exercise prescription.

It is important to note that a major limitation to such systematic research is patient adherence (Conraads et al. 2012). There is very limited research on this topic, but recent meta-analyses show that adherence can be improved by reducing individual patients' barriers to exercise (Davies et al. 2010), providing extensive personalized follow-up, and providing all-male or all-female exercise groups (Karmali et al. 2014).

In conclusion, this review highlights the need for systematic, controlled research into the effects of exercise mode, intensity, frequency, and duration on the function and morphology of the hypertrophied heart. Because AET is a highly effective and low-cost intervention, has virtually no side effects, and improves almost every comorbidity associated with cardiac hypertrophy, this is a very promising avenue of research for the future of cardiovascular medicine.

ACKNOWLEDGEMENTS

E.J. Johnson is supported by a National Science Foundation Graduate Research Fellowship. This work was supported by the National Institutes of Health (HL-104549), Diabetes Action Research and Education Foundation, and Washington State University College of Pharmacy.

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Figure 1. Phenotypes of physiological and pathological cardiac hypertrophy

(A) Chronic pathological insults such as hypertension, myocardial infarction, and chronic diabetes result in morphologically distinct types of pathological cardiac hypertrophy. (B) Physiological stimuli such as exercise and pregnancy induce physiological cardiac enlargement, or hypertrophy. Tan areas indicate fibrotic lesions. Orange areas indicate fatty streaks.