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Regression of cardiac hypertrophy in health and disease: mechanisms and therapeutic potential

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Abstract

Left ventricular hypertrophy is a leading risk factor for cardiovascular morbidity and mortality. Although reverse ventricular remodelling was long thought to be irreversible, evidence from the past three decades indicates that this process is possible with many existing heart disease therapies. The regression of pathological hypertrophy is associated with improved cardiac function, quality of life and long-term health outcomes. However, less than 50% of patients respond favourably to most therapies, and the reversibility of remodelling is influenced by many factors, including age, sex, BMI and disease aetiology. Cardiac hypertrophy also occurs in physiological settings, including pregnancy and exercise, although in these cases, hypertrophy is associated with normal or improved ventricular function and is completely reversible postpartum or with cessation of training. Studies over the past decade have identified the molecular features of hypertrophy regression in health and disease settings, which include modulation of protein synthesis, microRNAs, metabolism and protein degradation pathways. In this Review, we summarize the evidence for hypertrophy regression in patients with current first-line pharmacological and surgical interventions. We further discuss the molecular features of reverse remodelling identified in cell and animal models, highlighting remaining knowledge gaps and the essential questions for future investigation towards the goal of designing specific therapies to promote regression of pathological hypertrophy.

Introduction

Despite advances in treatment over the past 50 years, heart disease remains the leading cause of morbidity and mortality in the world[1]. Heart failure onset is typically preceded by cardiac hypertrophy, a compensatory thickening of the muscle in response to elevated left

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ventricular (LV) wall stress. However, the response becomes maladaptive with time, and this pathological hypertrophy is an independent predictor of adverse cardiovascular outcomes including myocardial infarction, arrhythmia and heart failure[2,3]. Although pathological hypertrophy was long thought to be irreversible, partial regression is observed with many existing therapies in a subset of patients and is associated with improved long-term health outcomes[4,5]. Importantly, in almost all cases, the reversal of cardiac hypertrophy leads to improved ventricular function[6]. A similar adaptive response is observed with exercise, in which increased workload precipitates increased cardiac muscle mass[7]. However, this physiological hypertrophy is associated with normal or increased ventricular function and is completely reversible with cessation of training[8]. Physiological hypertrophy also occurs in pregnancy but is rapidly reversible in most cases postpartum[9]. These observations lend strong support for the development of therapies directed at hypertrophy reversal as a treatment for heart disease. Molecular studies over the past decade have begun to shed light on the complexity of hypertrophy and its regression at the level of the cardiomyocyte, and to identify new therapeutic targets for reversal of pathological remodelling.

In this Review, we present an integration of clinical studies and basic science discoveries on cardiac hypertrophy regression. We discuss evidence for the benefits of reverse remodelling from clinical studies with current heart failure therapies. We also examine the molecular features of pathological hypertrophy and regression identified in cell and animal models and human tissue studies, comparing where possible with physiological models. The objective of this Review is to highlight therapies and mechanisms involved in the regression of existing cardiac hypertrophy and, therefore, studies on the prevention of hypertrophy development, although important, are not the focus.

Overview of cardiac hypertrophy

Cardiac hypertrophy is defined as a LV mass increase arising from thickening of the LV wall and/or enlargement of chamber diameter[10]. The structural manifestation of hypertrophy is determined by the type of cardiac insult, broadly categorized as either pressure or volume overload. Examples of pressure overload are aortic stenosis and hypertension, in which increased afterload on the heart triggers ventricular muscle growth. Volume overload underlies hypertrophy in the case of mitral regurgitation and also in physiological growth settings, including postnatal life, exercise and pregnancy[11]. The organ-level structural changes are mediated by distinct responses to increased pressure or volume at the cellular level by cardiomyocytes, the predominant cardiac cell type[12]. Postnatal cardiomyocytes have limited proliferative capacity and consequently, to increase organ size, the individual cells grow larger[13]. An exception in which cardiomyocyte proliferation does have a minor role is in early postnatal development; however, in this setting, cardiomyocyte hypertrophy is also the predominant factor[14]. With sustained pressure, cardiomyocytes undergo concentric hypertrophy, becoming thicker by the parallel addition of sarcomeres — the contractile units of striated muscle cells. Serial addition of sarcomeres occurs with volume overload, extending cardiomyocyte length to drive eccentric growth and leading to increased chamber diameter.

Molecular mechanisms of cardiac hypertrophy

The cellular and molecular mechanisms of physiological and pathological hypertrophy are well established. Although both manifestations of hypertrophy are initially adaptive, pathological hypertrophy becomes maladaptive and can lead to heart failure. The stimuli and mechanisms that regulate these two types of growth are distinct and, in some cases, antagonistic[15] (Fig. 1). In this section, we discuss the factors known to initiate each type of hypertrophy and the downstream cellular signalling cascades.

Physiological hypertrophy

During development, pregnancy or long-term exercise, cardiomyocytes undergo hypertrophy to meet increased volume demands. This adaptation leads to unchanged or improved cardiac function[15,16]. At the cellular level, circulating factors trigger signalling cascades that mediate survival and growth and thereby permit a fully adaptive response[15]. Several factors contribute to physiological hypertrophy and herein we focus primarily on hypertrophy-promoting circulating factors and the organ-level changes and cellular signalling cascades they initiate.

Insulin and insulin-like growth factor 1 (IGF1) regulate a broad range of cellular functions, including growth, survival and metabolism. Their receptors are highly expressed in cardiomyocytes and have a prominent role in regulating cardiac function and mediating physiological growth[17,18]. Both hormones and their respective tyrosine kinase receptors are structurally similar and stimulate shared pathways, including the phosphoinositide 3-kinase (PI3K)–AKT and RAS–MAPK pathways[15,19]. Binding of insulin or IGF1 to their receptors activates the PI3K–AKT pathway by triggering the recruitment of insulin receptor substrate 1 (IRS1) and IRS2 (refs.[20,21]). The p100α isoform of PI3K is the master regulator of exercise-induced hypertrophy and has a crucial protective role for cardiomyocytes in the context of pathological stimuli[21,22]. AKT activation downstream of PI3K leads to the inhibition of several negative regulators of hypertrophy, including glycogen synthase kinase 3β (GSK3β), forkhead box protein O1 (FOXO1), FOXO3 and CCAAT/enhancer-binding protein-β (C/EBPβ)[23–25]. AKT also indirectly activates mechanistic target of rapamycin (mTOR), which contributes to hypertrophy by increasing protein synthesis and inhibiting autophagy[26]. Insulin and IGF1 also activate the RAS–MEK–MAPK pathway by recruiting the growth factor receptor-bound protein 2 (GRB2)[18,21]. When recruited, GRB2 activates RAS–RAF, which in turn activates MEK1 or MEK2 to trigger the MAPK cascade[18]. Stimulation of MEK1 or MEK2 is linked to physiological hypertrophy and cell survival through inhibition of apoptosis[27].

The thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) also mediate physiological growth[28]. These hormones are released after birth and inhibit the expression of fetal-related genes while activating the expression of genes that promote cardiomyocyte maturation[15,28]. T_3 activates the PI3K–AKT pathway after binding to either of its receptors, thereby leading to physiological growth[28,29]. Additionally, in rat and mouse hearts, T_3 and T_4 stimulate the expression of *Myh6* and *Serca2a*[30,31], which encode proteins that are important for maintaining cardiomyocyte contractility. Several studies in animal models have shown that low thyroid hormone levels are associated with heart failure and impaired cardiac function,

but pathological hypertrophy is reversed with increased T_3 levels, resulting in improved cardiac function[32–34]. Other circulating factors, including fatty acids, have also been shown to promote physiological hypertrophy. A study of hypertrophy in the infrequently feeding Burmese python identified three circulating fatty acids (myristic acid, palmitic acid and palmitoleic acid) that regulate hypertrophy in response to a meal[35]. Injection of these fatty acids into fasted pythons and mice led to the recapitulation of cardiac hypertrophy[35].

Several non-coding RNAs (ncRNAs) also regulate physiological hypertrophy. MicroRNA-222 (miR-222) and miR-17–3p are each upregulated in exercise-induced hypertrophy in mice[36,37]. Both microRNAs activate pathways that promote cell proliferation, growth and survival[36,37]. The long ncRNA (lncRNA) cardiac physiological hypertrophy-associated regulator (CPhar) was shown in mice to be cardioprotective as well as necessary for exercise-induced hypertrophy in a C/EBPβ-dependent manner[38]. Conversely, the lncRNA lncExACT1 is downregulated in exercise-induced physiological hypertrophy and upregulated in pathological hypertrophy[39]. Furthermore, inhibition of lncExACT1 led to physiological hypertrophy and increased cardiomyocyte proliferation through regulation of miRNA-222 and the Hippo–Yap signalling pathway[39]. Additional involvement of ncRNAs in reverse remodelling has been extensively reviewed previously[6].

One factor that distinguishes physiological hypertrophy from pathological hypertrophy is the degree of angiogenesis. The capacity of the heart to maintain vascularization and perfusion largely depends on increased capillary density mediated by vascular endothelial growth factor[40]. Increased cardiac angiogenesis allows proper supply of nutrients and oxygen, which contributes to the fully adaptive physiological growth[41]. Angiogenesis decreases in pathological hypertrophy, thereby resulting in hypoxia and insufficient nutrients[40,42]. Therefore, angiogenesis is a key process not only for promoting adaptive growth but also for preventing maladaptive responses.

Pathological hypertrophy

Maladaptive cardiac hypertrophy develops in pathological settings, including hypertension, obesity and certain genetic cardiomyopathies. Compared with physiological growth, the stimuli and signalling mechanisms that trigger this maladaptive response promote fibrosis, apoptosis, and other cellular and structural dysfunction, which can ultimately lead to heart failure[15,43]. Circulating factors including catecholamines, natriuretic peptides and peptide hormones contribute to pathological remodelling. In this section, we discuss these factors and the downstream signalling mechanisms (Fig. 1).

Catecholamines are neuroendocrine hormones that are released after activation of the adrenergic nervous system in response to stress[44]. These hormones bind to cardiomyocyte adrenergic receptors, G protein-coupled receptors that subsequently activate adenylyl cyclase[44]. After activation of adenylyl cyclase, cAMP levels increase, which in turn activates protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC). Activation of PKA stimulates the upregulation of the activity of calcium-handling proteins and increases basal cardiac contractility[44]. EPAC, which is independently activated by cAMP, stimulates the phosphatase calcineurin and its downstream effector nuclear factor of activated T cells (NFAT), which regulates pathological growth and gene expression[45].

EPAC also activates calcium/calmodulin-dependent protein kinase II (CaMKII), which stimulates the transcription factor myocyte-specific enhancer factor 2A (MEF2A) to induce pathological hypertrophic gene expression[46,47]. The continual release of catecholamines eventually leads to adrenergic receptor desensitization and heart failure[44,48]. This process is mediated by G protein-coupled receptor kinase 2 (GRK2), GRK5 and β-arrestins[49]. GRK5 also positively regulates MEF2A in a histone deacetylase 5 (HDAC5)-dependent manner, as well as NFAT[50–52]. Additionally, catecholamines activate MAPK proteins and the downstream p38 and JNK pathways, which trigger pathological hypertrophic gene expression[53,54].

The circulating levels of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are elevated in heart failure and are a common indicator of pathological hypertrophy[55]. In healthy physiology, ANP and BNP are antihypertrophic by preventing increases in intracellular calcium levels in cardiomyocytes[56,57]. Circulating ANP and BNP bind to natriuretic peptide receptors, which activate guanylyl cyclase and lead to increases in intracellular cGMP concentration[57,58]. cGMP activates PKG, which inhibits the prohypertrophic molecules calcineurin–NFAT, MEF2A and transient receptor potential canonical channel (TRPC)[55,59]. However, chronically elevated levels of circulating ANP and BNP in heart disease cause natriuretic peptide receptor desensitization, increased intracellular calcium levels in cardiomyocytes and pathological cardiac remodelling[60,61]. Additionally, in pathological hypertrophy, the expression and activity of phosphodiesterases (PDEs), which regulate cGMP homeostasis, are increased[59,62]. Inhibition of PDEs blocks prohypertrophic signalling pathways[59,62,63].

The circulating levels of the peptide hormones angiotensin II and endothelin 1 are upregulated in heart failure[64,65]. These humoral factors are released in response to mechanical stress in the vascular system and promote cardiac structural and functional changes[66–68]. Binding of these hormones to their receptors on cardiomyocytes stimulates G proteins, which activate the phospholipase C–calcineurin–NFAT, MAPK and calmodulin–CaMKII pathways, leading to maladaptive gene expression[69–71]. CaMKII phosphorylates class II HDACs, which repress cardiomyocyte hypertrophy by inhibiting MEF2A expression[72]. After phosphorylation, HDACs are exported from the nucleus, enabling the upregulated expression of prohypertrophic genes[73]. Angiotensin II also regulates hypertrophy through the Toll-like receptor 3 (TLR3)–TIR domain-containing adapter molecule 1 (TRIF) and TLR4–TRIF immune pathways, which are activated by inflammation caused by hypertension[74].

Clinical relevance of hypertrophy regression

Before 1990, pathological hypertrophy was considered to be an irreversible condition. However, it has become clear that modest regression is possible in a subset of patients (Table 1), and this reverse remodelling is associated with improved cardiac function and long-term health[75,76]. In this section, we discuss the data supporting reverse remodelling with existing pharmacological and surgical therapies, as well as with implementation of exercise and dietary changes.

Pharmacological therapies

RAAS blockade.—In heart disease, compromised haemodynamic function triggers sustained renin–angiotensin–aldosterone system (RAAS) activation, leading to fluid retention, high blood pressure and elevated LV preload and afterload[77]. Therefore, several compounds have been developed to antagonize the RAAS. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were among the first identified and remain the most effective monotherapies for reversing cardiac hypertrophy[78–80]. Patients receiving ACE inhibitors show progressive reductions in LV mass index (LVMI; where LVMI = LV mass (grams)/body surface area (square metres)) beginning 3 months after treatment[81–83]. ACE inhibition also prevents the development of LV dilatation, a feature of end-stage heart failure[84]. ARBs have similar effects to those of ACE inhibitors on regression of hypertrophy and the concurrent improvement in LV function and are effective in reversing both eccentric and concentric hypertrophy[80,85–87].

Another approach targeting the RAAS is the use of mineralocorticoid receptor antagonists. Mineralocorticoid receptor antagonists reduce LVMI, restore ventricular compliance and reduce all-cause mortality[88,89]. Mineralocorticoid receptor antagonists are also effective in reducing cardiac hypertrophy and diastolic dysfunction in patients with heart failure with preserved ejection fraction[90]. A newer class of compounds targeting both the angiotensin receptor and the membrane metallopeptidase neprilysin (angiotensin receptor–neprilysin inhibitors (ARNIs)) is the most effective for reversing cardiac remodelling[91,92] (Box 1). More pronounced regression of cardiac hypertrophy with ARNIs is associated with reduction of plasma amino-terminal pro-BNP (NT-proBNP) levels[93–96]. In patients with heart failure with reduced ejection fraction, ARNI therapy increases LV ejection fraction by 5% compared with ACE inhibitors or ARBs alone, suggesting that increased regression of hypertrophy is associated with further functional improvements[97]. Various factors affect the efficacy of RAAS blockade in inducing cardiac hypertrophy regression, and less regression is observed in patients with ischaemic heart disease, older age, longer duration of hypertension, greater degree of pathological remodelling or higher BMI[87,98–100]. Interestingly, reverse remodelling with RAAS blockade can occur even when hypertension is not rectified[89,101,102]. The mechanisms underlying pressure-independent hypertrophy regression are an important topic for future study.

β-Adrenergic receptor blockade.—Chronic sympathetic activity in heart disease leads to downregulation of cardiomyocyte β-adrenergic receptors and reduced contractility[103]. β-Adrenergic receptor antagonists increase receptor expression and membrane density, leading to restoration of cardiomyocyte contractility[104]. β-Blockers lower all-cause mortality and mildly reduce existing hypertrophy in patients with heart failure, while increasing LV ejection fraction in a dose-dependent manner[105]. Compared with other therapies, β-blockers are less effective in reversing hypertrophy, and several studies found no effect on reverse remodelling (Table 1). However, combination therapy with RAAS blockade has additive benefits for ventricular geometry and function[106–108].

Calcium channel blockade.—Calcium channel blockers are antihypertensive medications that act on L-type calcium channels, inhibiting calcium uptake in the

vasculature and stimulating vasodilatation[109]. Several studies suggest that calcium channel blockers are the most effective pharmacological therapy for stimulating reverse remodelling in the short-term, consistently reducing LVMI by ≥10% after 3 months[110–113]. However, unlike RAAS-targeting therapies, calcium channel blockers reverse only concentric hypertrophy and have limited additional benefit on regression with longer duration of treatment[112] (Table 1). As with other treatments, the benefits of calcium channel blockers for hypertrophy regression are limited to non-ischaemic heart disease[114]. Calcium channel blockade increases hypertrophy regression when used as an add-on treatment with RAAS antagonists or thiazide diuretics[115,116]. Calcium channel blockers also induce hypertrophy regression, without affecting blood pressure levels, in patients with LV hypertrophy and normal blood pressure[117].

Other drug therapies.—Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which prevent the reabsorption of glucose in the proximal renal tubules, were developed as a treatment for patients with type 2 diabetes mellitus[118]. However, SGLT2 inhibitors have since proven to be effective for improving outcomes in patients with heart failure regardless of diabetes presence[119]. The mechanisms underlying heart failure reduction with SGLT2 inhibitors are unclear; however, studies have found that SGLT2 inhibition mildly reduces LV mass and ambulatory blood pressure[120,121]. Improved prognosis with SGLT2 inhibitors in patients with heart failure is associated with reverse remodelling and might be blood-pressure independent[120]. In the MET-REMODEL trial[122], another diabetes drug, metformin, reduced LVMI by 5% after 12 months compared with placebo in patients with coronary artery disease without diabetes. Another study found that adding the PDE5 inhibitor sildenafil to a traditional treatment regimen with RAAS inhibition and β-blockade increases hypertrophy regression[123]. Modest reverse remodelling has also been observed with cardiac myosin inhibitors and mTOR inhibitors[124–126].

Surgery and device therapies

Aortic valve replacement.—Pressure overload from aortic valve stenosis or insufficiency leads to pathological hypertrophy. Aortic valve replacement (AVR) reduces ventricular outflow gradient pressure and triggers reverse remodelling[127]. The effects of AVR are immediate, beginning 7 days after surgery with a reduction in LV mass of 10% by 1 month[128,129]. This reduction in LV mass is driven by a decrease in cardiomyocyte volume in the early remodelling phase and later (6–12 months) by fibrosis reduction[130,131]. Greater regression with AVR is associated with lower serum NT-proBNP levels and rehospitalization rates[128,130]. Despite most patients experiencing structural improvements, <20% of patients show a regression to a normal LVMI in the first 18 months[132]. However, longer-term studies identified LVMI normalization in most patients 8–10 years after AVR[4,129]. Stented bioprostheses (compared with stentless bioprostheses), higher BMI and systemic hypertension are associated with less hypertrophy regression after AVR[128,133–135].

Bariatric surgery.—Obesity causes diastolic dysfunction and is a leading risk factor for heart disease[136]. Bariatric surgery reduces long-term cardiovascular morbidity and concentric cardiac hypertrophy[137]. Beneficial cardiac structural remodelling and improved diastolic function are observed within 3 months after surgery, and normal LV geometry is

achieved in ~70% of patients by 3 years[138–140]. LV mass reduction after bariatric surgery occurs regardless of cardiovascular comorbidities or medications used[141]. However, patients receiving β-blockers have the most pronounced hypertrophy regression, compared with patients receiving other compounds[141]. The role of blood pressure reduction in hypertrophy regression after bariatric surgery is unclear[139,141,142].

Cardiac resynchronization therapy.—Optimal ventricular function requires tightly coordinated electrical activation. In many patients with heart disease, dyssynchrony owing to ventricular pacing or left bundle branch block contributes to the pathology. Cardiac resynchronization therapy (CRT) was developed to resynchronize contraction, and multiple clinical trials have indicated its benefits for both long-term health and reverse remodelling[143–145]. Reduced LV dimensions and volume with CRT are associated with a small but significant increase in LV ejection fraction by 3 months that is independent of concurrent pharmacological therapy[146]. The structural effects of CRT peak at 2 years and are sustained until at least 5 years[147–149]. Early intervention is important given that patients with NYHA class IV heart failure have the least reverse remodelling with CRT[150].

Left ventricular assist device therapy.—The number of patients with heart failure who require heart transplantation far exceeds donor heart availability. LV assist devices (LVADs) mechanically pump blood from the left ventricle to the aortic root and have been used as a bridge-to-transplantation for almost three decades in patients with end-stage heart disease[151]. Numerous studies indicate that LVADs restore cardiac output and reverse hypertrophy in these patients[152]. The extent of hypertrophy regression is positively correlated with the duration of LVAD support, although the majority of remodelling occurs in the first 40 days[153,154]. Importantly, the effects of LVAD on hypertrophy are similar in ischaemic and non-ischaemic heart disease[155]. LVADs induce the most pronounced hypertrophy reduction of any existing therapy for heart failure (Table 1), highlighting the pressure-dependent aspect of hypertrophy regression. Interestingly, LVAD therapy does not reduce right ventricular hypertrophy, suggesting that reduced LV preload drives the hypertrophy regression[156].

Lifestyle modifications

Aerobic exercise.—Regular exercise in healthy individuals is associated with physiological hypertrophy. Interestingly, reduced LV volumes and increased LV ejection fraction have been observed when patients with heart disease adopt an aerobic exercise routine[157]. Exercise-induced hypertrophy regression requires months of training, and strength training has no added effects[158,159]. The regression is most pronounced in patients with non-ischaemic heart failure, whereas for patients after myocardial infarction the benefits of exercise are greatest for those who start early and continue for more than 3 months[160,161]. Exercise leads to a reduction in circulating angiotensin II, noradrenaline, BNP and aldosterone levels[158], which mitigates hypertension and might underlie hypertrophy regression in this patient population[159]. Notably, one study found that exercise-induced weight loss did not contribute to the reverse remodelling because BMI was unchanged whereas LV mass decreased by 12% after 4 months of low-intensity exercise[159].

These studies suggest that the effect of exercise on reverse remodelling is similar to that of most drug therapies.

Calorie restriction.—Preclinical models suggest that calorie restriction and intermittent fasting paradigms might be effective for preventing and reversing adverse cardiac remodelling[162,163]. In rodent models of metabolic syndrome-induced and obesity-induced cardiomyopathy, calorie restriction attenuated cardiomyocyte hypertrophy, oxidative stress and fibrosis[162,164]. Starting alternate-day intermittent fasting in rats before or directly after a myocardial infarction reduced cardiomyocyte hypertrophy and LV dilatation 12 weeks after the myocardial infarction[163]. In another study, starting calorie restriction 4 weeks after myocardial infarction also ameliorated cardiac dysfunction, reduced heart mass and restored adrenergic sensitivity[165]. Using calorie restriction and naturally occurring compounds that mimic calorie restriction (such as curcumin and resveratrol) to treat heart failure is an appealing therapeutic strategy that requires further investigation[166].

Determinants of reversibility in pathological hypertrophy

One feature that distinguishes pathological from physiological hypertrophy is that pathological hypertrophy is typically only partially reversible. The reasons for the often-incomplete regression remain unclear. However, one possible explanation is the presence of extensive fibrotic remodelling driven by proliferation and activation of cardiac fibroblasts in pathological settings[167]. Indeed, for most therapies, patients with the lowest baseline levels of fibrosis experience greater regression of hypertrophy[168]. Interestingly, one of the factors thought to underlie the more rapid regression observed in female patients after AVR is that they develop less pressure-overload-associated fibrosis than male patients[169]. This observation might also explain why less regression is observed in ischaemic heart disease, which is associated with greater fibrosis than non-ischaemic heart failure[98]. However, longer-term studies of AVR found that fibrosis only slows the rate of reverse remodelling[131,170], and long-term LVAD therapy has also been shown to reduce fibrosis and expression of collagen-encoding genes[153]. Inhibiting the progression of fibrosis with antifibrotic drugs has received interest in the past decade, and a clinical trial of the antifibrotic drug pirfenidone in patients with heart failure with preserved ejection fraction indicated that fibrosis reduction is possible in this patient population[171]. Future research on combination treatments of pirfenidone with existing first-line therapies for heart failure are needed to explore the potential for rapid and complete reversal of pathological hypertrophy.

Like fibroblasts, immune cells also uniquely contribute to the development of pathological cardiac hypertrophy and might have a role in the incomplete reversibility[172]. Although the role of immune cells in reverse remodelling remains to be fully investigated, preclinical studies indicate that modulation of these cells might be efficacious[173,174]. Treating mice with pressure-overload-induced cardiac hypertrophy with an antibody against CD20, which suppresses B cells, reversed hypertrophy and inhibited pathological transforming growth factor-β (TGFβ)–SMAD2/SMAD3 and ERK1/ERK2 signalling[173]. In other studies using the same mouse model, treatment with granulocyte colony-stimulating factor, which caused neutrophil infiltration and increased IL-1β expression, led to regression of fibrosis[174].

Further study is required to clarify the involvement of the immune system in reverse remodelling.

Mechanisms of hypertrophy regression

Regression of physiological hypertrophy

Pregnancy.—Chronic volume overload in pregnancy leads to eccentric cardiac hypertrophy. This physiological growth, which is mediated by the IGF1–PI3K–AKT and ERK pathways[175,176], is associated with normal cardiac function and is completely reversible postpartum. In humans, the timing of cardiac hypertrophy development and regression is temporally coupled to haemodynamic load[177]. Pregnancy-associated changes in contractility, valve area and LV mass are reversed over several months postpartum[178,179]. Similar results have been observed in rodents, but hypertrophy regression is evident after 1–3 days postpartum and is complete at 2–3 weeks[180–182]. In addition to the reduction in heart weight, changes in LV pressure, contractility and angiogenesis are notable at 1 week postpartum[180,182]. The regression might be mediated by the ubiquitin–proteasome system, given that proteasome activity and expression of *Fbxo32*, encoding an E3 ligase, are upregulated immediately postpartum in mice[176]. These findings are further supported by the observation in mice that protein polyubiquitination is reduced in late pregnancy and subsequently increases 1 day postpartum[182]. Micro-array analysis immediately postpartum also identified changes in the expression of genes related to chemokine, glucocorticoid receptor and cytochrome P450 pathways[176]. Non-fibrotic extracellular matrix remodelling is an important feature of hypertrophy regression after pregnancy, and increased expression of genes encoding extracellular matrix-related proteins (*Adam15*, *Mmp2* and *Timp1*) has been identified in multiple studies[176,180,183,184]. Notably, hypertrophy regression does not occur in lactating rats because increased circulating blood volume sustains volume overload on the heart[9,185]. However, stopping lactation by separating newborn pups from the mother induces rapid hypertrophy regression[9,186]. Lactation is associated with increased phosphorylation of ERK1, ERK2, FOXO1 and FOXO3 at 1 week postpartum in mice[186], which might contribute to the extended hypertrophy.

Exercise.—Exercise-induced cardiac hypertrophy is associated with normal or improved cardiac function and reverses rapidly when training is stopped. In one study, rats with 9 weeks of swim training had substantial cardiac hypertrophy that had completely reversed 2 weeks after training cessation[187]. In these rats, reduced heart weight was associated with diminished mRNA content, suggesting that reduced protein synthesis contributes to hypertrophy regression[187]. Given that the serum IGF1 level is known to increase with endurance exercise[188], reduced protein synthesis in sedentary animals might be due to decreased growth pathway activity downstream of IGF1. However, this represents an important area for future research. In humans, complete hypertrophy regression is observed within 1 month of stopping activity and is mediated by a decrease in the intracellular compartment, suggesting reduction of myofibrils[8]. Interestingly, exercise preconditioning ingrains antihypertrophic memory to future pathological insults. In mice that underwent 3 weeks of swim training, complete hypertrophy regression had occurred 1 week after training cessation and was associated with upregulation of lncRNA *Mhrt779* expression[189].

When these mice were later subjected to pathological stimuli, *Mhrt779* conveyed anti-hypertrophic effects through regulation of HDAC2 and the AKT–GSK3β pathway[189]. The calcium-binding proteins S100A8 and S100A9 are also upregulated with exercise and suppress calcineurin–NFAT signalling, which mitigates pressure-overload-induced cardiac hypertrophy[190]. Other mechanisms by which exercise is thought to reverse pathological cardiac hypertrophy include reduction of circulating catecholamines and blood pressure levels[157,191].

Regression of pathological hypertrophy

LVAD mechanical unloading.—Owing to the number of studies using tissue samples obtained before and after LVAD therapy, the molecular mechanisms of cardiac hypertrophy regression after mechanical unloading are the best characterized (Fig. 2). The effects of LVADs are numerous and include changes to myocardial metabolism, contractility, protein synthesis, protein degradation and immune response[152]. The detrimental reversion to fetal-like metabolism, in which glucose is preferentially used over fatty acids, in heart failure is well established[192]. Mechanical unloading induces partial restoration of oxidative phosphorylation, upregulation of fatty acid metabolism, increased expression of genes encoding components of the mitochondrial respiratory chain complex and repression of fetal-like gene expression[193–197]. Additionally, the pentose phosphate pathway and one-carbon metabolism have been implicated in recovery after LVAD therapy, given that NADH — a key by-product of these pathways — is involved in the biosynthesis of other metabolites and helps protect against oxidative damage[198]. Several studies have identified an upregulation of calcium-handling proteins, including sarcoplasmic–endoplasmic reticulum calcium ATPase 2A (SERCA2A), ryanodine receptor 2 and the sodium–calcium exchanger, after LVAD therapy, which is associated with increased cardiomyocyte developed force[199,200]. Furthermore, the β-adrenergic responsiveness that is lost in heart failure is restored after LVAD therapy, permitting increased contractility in response to inotropic stimulation[201]. LVADs are one of few therapies that substantially reduce existing fibrosis, which is reflected at the molecular level by reduced expression of genes encoding collagen and matrix metalloproteinases (MMPs)[194,196,202]. Individuals who respond favourably to LVAD therapy show a reduction in the expression of *Il1B*, *NPPB* and *EPAC2* at the time of LVAD explantation compared with non-responders[203].

Protein degradation pathways have been well characterized after mechanical unloading, with some seemingly conflicting results. The ubiquitin–proteasome system is upregulated after LVAD placement, as indicated by increased proteasome activity and upregulation of the expression of *FBXO32* (encoding F-box only protein 32; also known as atrogin 1) and *TRIM63* (encoding E3 ubiquitin protein ligase TRIM63; also known as MURF1)[204–206]. The involvement of atrogin 1 and TRIM63 in mechanical unloading-induced regression was corroborated in mouse studies showing that these proteins are required for regression of heart mass[206,207]. Expression and activity of the calcium-activated calpain proteases also increase following mechanical unloading in humans and rats[208].

Data on the role of autophagy after mechanical unloading are less clear. One study of human tissue samples obtained after LVAD therapy found significant decreases in beclin 1,

autophagy-related gene 5 (ATG5), ATG12 and microtubule-associated protein light chain 3II (LC3II), suggesting reduced autophagy, whereas levels of BNIP3 (an adaptor protein for mitophagy) increased[205]. However, in mouse and cell models of mechanical unloading, increased autophagic activity was required for cardiac hypertrophy regression downstream of FOXO1, which upregulated the expression of the autophagy genes *Bnip3*, *Gabarapl1* and *Ulk2* (ref.[209]). *FOXO1* and *FOXO3A* gene expression was also shown to increase after LVAD therapy in a study of human heart samples[210]. The apparent incongruence between the findings of these studies might be due to timing. In the mouse study, autophagy activity was assessed 1 week after mechanical unloading, whereas the mean duration of unloading in the initial LVAD study was 214 days. Therefore, autophagy might be upregulated in the acute phase of mechanical unloading and then deactivated later to prevent further hypertrophy regression. Another study of mechanical unloading in rats found that the transcriptional factor eyes absent homologue 2 (EYA2) was involved in cardiac hypertrophy regression[211], indicating the importance of its downstream gene targets in this process.

Other surgical and device therapies.—Compared with LVAD, the molecular changes and potential mechanisms underlying cardiac hypertrophy regression with other surgical therapies are poorly characterized. One study in patients receiving CRT suggests that miR-30d is an important determinant of a positive patient response to CRT[212]. Elevated plasma miR-30d levels were associated with reduced myocardial necrosis, and an increase in cardiomyocyte miR-30d levels was protective against detrimental tumour necrosis factor (TNF) signalling[212]. In a dog model, CRT was found to increase mitochondrial ATPase activity through reduction of cysteine disulfide bonds and to upregulate the expression of redox enzymes, leading to improved cardiomyocyte metabolism[213,214]. CRT is also associated with reduced expression and activity of CaMKII, p38 and TNF, and reversal of calcium channel and potassium channel remodelling[215]. Patients who respond favourably to CRT have increased *SERCA2A* and *MYH6* expression and reduced *NPPB* expression[216].

Modest molecular-level data are available for AVR. In a study in patients, multiple microRNAs were dysregulated 1 week after AVR and increased circulating levels of miR-122–5p were associated with LV dysfunction at 7 days and 6 months after AVR[217]. This finding was recapitulated in a mouse model, in which miR-122–5p reduced the expression of *BCL2* (encoding an anti-apoptotic protein) and decreased cardiomyocyte viability[217]. Therefore, in patients who respond poorly to AVR, targeting miR-122–5p might be of therapeutic value.

Pharmacological therapies.—Molecular-level studies with other models of pathological hypertrophy regression are scarce; however, similar pathways to those involved in mechanical unloading are implicated. In rats with hyperthyroidism-induced cardiac hypertrophy, ARNI therapy reduced the levels of cardiac inflammatory markers, increased autophagy and suppressed TGFβ–SMAD signalling compared with the control group[218]. Similar findings were noted for therapy with ARB alone; however, the effects were milder than for treatment with an ARNI[218]. One study used mice treated with angiotensin II or the β-agonist isoprenaline to induce cardiac hypertrophy followed by cessation of treatment (mimicking ARB and β-blocker therapy, respectively) and cardiac hypertrophy

regression was assessed over 1 week[219]. Regression in both cases was associated with increased autophagy, increased or no change in proteasome activity and reduced TGFβ–SMAD signalling, with evident sex-related differences[219], as discussed below. In another study, hypertensive rats treated with a thiazide diuretic had reverse remodelling and reduced fibrosis, which was associated with reduced expression of genes encoding collagens and TGFβ, reduced reactive oxygen species production and suppression of RHO kinase activity[220]. The mechanisms regulating hypertrophy regression with drug therapies remain very poorly defined and further investigation is warranted.

Hypertrophy regression in genetic cardiomyopathy

Monogenic variants are estimated to account for 25–50% of cases of dilated cardiomyopathy (DCM) and 30–60% of hypertrophic cardiomyopathy (HCM)[221]. In a cohort of patients with DCM, hypertrophy regression potential with standard drug therapies varied according to the causative gene variants, with pathogenic variants in genes encoding the sarcomere Z-disc components (*DES*, *DMD* and *FLNC*) inversely correlated with reverse remodelling[222]. Another study in patients with DCM found that reverse remodelling was less frequent in genotype-positive patients with DCM than in patients with idiopathic DCM (39.6% versus 46.2%)[223]. *TTN* pathogenic variants (the leading genetic cause of DCM) are linked to improved reverse remodelling with therapy[223–225], whereas regression is limited in patients with *LMNA* variants, the second leading genetic cause of DCM[224,225].

HCM is predominantly caused by variants in *MYH7* and *MYBPC3* (ref.[221]). Exercise can help promote reverse remodelling in this patient population, as shown by a study in which 4 months of modest exercise in a patient with genetic HCM led to a reduction in LV mass of 12% and improved quality of life[226]. However, the type of exercise is an important consideration, and it is generally agreed that patients with HCM should avoid intense exercise to reduce the risk of arrhythmia[227]. The benefits of exercise in patients with HCM are supported by findings from studies in rodents. Voluntary cage-wheel running in mice with an HCM-causing *MYH* variant reversed cardiac hypertrophy, improved cardiomyocyte array and reduced apoptosis[228]. Hypertrophy reversibility has also been observed in non-sarcomeric genetic HCM, a less common aetiology of HCM. Cardiac remodelling associated with variants in *PTPN11* — which cause Leopard syndrome, an autosomal dominant RASopathy — is completely reversible in animal models by treatment with rapamycin[229].

These studies indicate an important contribution of genetics to reverse remodelling. However, the influence of the genetic background on hypertrophy regression remains poorly understood. Studies of hypertrophy development using the Hybrid Mouse Diversity Panel, a collection of 107 inbred mouse strains, identified key loci for heritability of cardiac mass[230,231]. Hypertrophy regression potential is likely to be similarly affected by genetic background, which represents a fertile area for future research.

Biological sex and hypertrophy regression

Sex has a role in regression of cardiac hypertrophy, with female individuals generally experiencing more favourable outcomes. This sex-related difference might be due to

sex hormones and/or genes encoded on the X and Y chromosomes. Oestrogens, for instance, have been linked to upregulation of genes encoding mitochondrial proteins and lipases, whereas testosterone controls glucose tolerance and reduces fatty acid oxidation[232]. Furthermore, hearts from female individuals have higher levels of AKT signalling, better function after pressure overload and less fibrosis development in response to pathological stimuli than hearts from male individuals, suggesting that these features elicit cardioprotective mechanisms and might aid in the more favourable regression outcomes observed in female patients[233]. Among patients receiving CRT, LVAD therapy or AVR, female patients had more pronounced LV volume reduction, improved LV ejection fraction and lower serum NT-proBNP levels compared with male patients[169,234–237]. However, in female patients undergoing AVR, hypertrophy regression is inversely correlated with serum levels of miR-29b, a microRNA that regulates pathological hypertrophy[238].

Sex-related differences are also observed in hypertrophy regression mediated by pharmacological therapies. ARNI therapy is effective in both male and female patients; however, female sex is associated with more reverse remodelling, higher LV ejection fraction and lower serum NT-proBNP levels[239–241]. Other studies have yielded conflicting results. One study of antihypertensive medications found that the extent of cardiac hypertrophy regression was lower in women than in men[99]. Conversely, another study found that female patients treated with ARBs or β-blockers had more regression of cardiac hypertrophy than male patients[242]. A mechanistic study found that regression of pathological hypertrophy shows stimulus-specific and sex-specific regulation[219]. In mice treated with angiotensin II or isoprenaline, female mice had no cardiac hypertrophy regression 1 week after angiotensin II removal, whereas isoprenaline removal was associated with rapid regression[219]. Hearts from male mice showed hypertrophy regression with removal of either stimulus. Regression from isoprenaline-induced hypertrophy was associated with increased autophagy in both sexes[219]. However, only hearts from male mice had increased proteasome activity after stimulus removal. The sex-related difference in regression of angiotensin II-induced hypertrophy might be due to TGFβ–SMAD signalling, which increased during pathological cardiac hypertrophy in both sexes but was sustained after angiotensin II removal in female mice[219]. In a rat model of mechanical unloading, female rats had a greater reduction in fibrosis and fetal-like gene expression than male rats[243]. These studies highlight the importance of considering sex when choosing a treatment strategy for pathological hypertrophy regression.

Regression versus atrophy

The distinction between hypertrophy regression and cardiac atrophy — the latter of which occurs with cancer, starvation and spaceflight — remains poorly defined[244–246]. The simplest discrimination might be that atrophy is a progressive, active, muscle-wasting condition, whereas regression occurs only to a certain baseline level without continued cardiac mass loss. Additionally, hypertrophy regression is associated with improved structure and function. However, in cardiac atrophy, fibrosis, sarcomere structural disarray and reduced LV performance are observed[245,247]. At the molecular level, several features of cardiac atrophy overlap with hypertrophy regression (Fig. 3). Cancer-associated cachexia, a severe form of muscle wasting that occurs in 30–80% of patients with cancer, is associated

with cardiac dysfunction[248,249]. Mice with colon cancer-induced cachexia have a reduction in heart mass of ~20% compared with healthy controls, which was more pronounced in male mice and was associated with upregulation of gene expression and activity of autophagy proteins[250]. The involvement of *FBXO32*, *TRIM63* and the proteasome in cancer-associated cachexia is unclear, with studies showing either increased activity or no change[250,251]. Other studies in mice with cancer-induced cachexia found inactivation of protein synthesis pathways downstream of AKT and mTOR[252,253]. Chemotherapies are also independent drivers of cardiac atrophy, and their use is associated with exacerbated muscle wasting in cancer-associated cachexia[254]. In mice, cardiac atrophy induced by the chemotherapy drug doxorubicin is dependent on *Trim63* upregulation[255]. Less is known about the mechanisms of starvation-induced cardiac atrophy. However, a study in rabbits found reduced protein synthesis and myofibrillar protein half-life during starvation-induced cardiac atrophy, suggesting that similar mechanisms to those underlying cancer-associated cachexia are involved[246].

Spaceflight causes cardiac atrophy owing to microgravity-induced mechanical unloading of the heart[256]. LVAD therapy also induces mechanical unloading but the acute effect on cardiac mass is more pronounced with spaceflight than with LVAD therapy, with a reduction in LV mass of 12% in astronauts after just 10 days in space[257]. An in vitro study of cardiomyocytes in microgravity found a bias towards mitochondrial protein synthesis at the expense of whole-cell protein production and no change in apoptosis or protein degradation[258]. In a mouse microgravity model, the levels of the proteolytic proteins calpain 1 and calpain 2 were upregulated compared with normal-weight-bearing controls, whereas cardiomyocyte-specific knockout of *Capns1* prevented microgravity-induced cardiac atrophy[259]. Increased expression and activity of ubiquitin–proteasome system components were observed in *Drosophila* flies reared on the International Space Station (microgravity) compared with flies reared on Earth (normal gravity)[260]. In mice, 15 days of spaceflight altered the expression in the heart of genes related to oxidative stress, cell cycle and senescence, suggestive of rapid cardiac ageing[261,262]. Spaceflight is associated with increased cardiac stiffness and risk of arrhythmia[245]. By comparison, with LVAD-induced mechanical unloading, reduced protein synthesis, increased calpain and proteasome activity, and expression changes in genes related to mitochondria and metabolism are observed[193,205,208,263]. In this case, the mechanical unloading is generally beneficial and is associated with improved cardiomyocyte developed force and LV ejection fraction, albeit with an increased risk of arrhythmia[199,264,265].

One commonality of all forms of cardiac atrophy is an increase in the levels of circulating factors that stimulate downstream atrophic remodelling, including myostatin, activin A and inflammatory cytokines[266–269]. Myostatin and activin A trigger signalling cascades that inhibit protein synthesis and activate atrophy-related gene expression[270]. Whereas atrophy is widely agreed to be an active process driven by these factors, whether regression of hypertrophy is an active process or a passive response to the removal or inhibition of a stimulus remains unclear. Further investigation is needed to address this question.

Conclusions

Hundreds of clinical studies in the past almost 40 years indicate that regression of pathological cardiac hypertrophy is unequivocally linked to improved health outcomes. However, many factors have a role in determining whether and to what extent reverse remodelling occurs with existing therapies. These factors include hypertension duration, type of hypertrophy (concentric versus eccentric), age, BMI, sex, physical activity, genetic background, disease aetiology and concurrent medications. The result is that <50% of patients receiving heart failure therapies currently undergo hypertrophy regression, and those without hypertrophy regression have poor quality of life and increased mortality compared with patients who have reverse remodelling[271,272]. However, if regression of cardiac hypertrophy were considered a primary end point in the treatment of heart disease, as many studies suggest it should be, data-informed choice of therapy is possible thanks to the wealth of clinical literature. The use of computational approaches towards this goal might make it possible to predict whether a patient will respond to a given therapy with reverse remodelling and thereby inform clinician decision-making.

In the subset of patients who undergo regression of cardiac hypertrophy with existing therapies, full normalization of LV mass in most patients does not occur even after years of treatment[87]. Therefore, the development of new therapies informed by molecular studies to target LV hypertrophy specifically might prove more effective than current medications in restoring heart health in this patient population and in non-responding patients. However, despite the long-established functional and quality-of-life benefits of reverse remodelling, the molecular characterization of this process remains in its infancy. What is apparent from molecular studies is the involvement of protein degradation pathways (calpains, ubiquitin–proteasome system and autophagy) in hypertrophy regression. This finding might not be surprising, given that regulation of cardiac mass can be fundamentally distilled to a balance between protein synthesis and degradation, in which inhibiting protein synthesis and/or activating protein degradation results in net protein loss and thus tissue mass regression. However, targeting these crucial pathways with broadly acting compounds will have off-target effects on other tissues, and without careful titration might be cardiotoxic. Development of therapies that target specific molecules in these pathways with tissue specificity should permit a wider dose range and limit adverse effects. However, the lead molecular candidates for drug development remain to be elucidated, and future study in this area is paramount to advancing the field. One particularly under-studied area in which such targets might be identified is in the regression from physiological cardiac hypertrophy, in which reverse remodelling is rapid and complete. We hope this Review stimulates discussion and investigation in these areas towards the goal of reducing morbidity and mortality in the millions of people living with heart disease worldwide.

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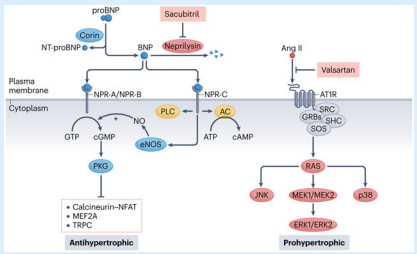
Box 1

Mechanism of action of ARNI therapy

Angiotensin receptor–neprilysin inhibitors (ARNIs) are a promising class of heart failure therapies that target both the renin–angiotensin–aldosterone system (RAAS) and natriuretic peptide system. Data suggest that ARNI therapy with sacubitril–valsartan (Entresto) is the most effective first-line therapy for patients with systolic heart failure[92]. Sacubitril promotes the activation of the antihypertrophic natriuretic peptide system, and valsartan antagonizes the prohypertrophic RAAS. The benefits of sacubitril–valsartan include improved ventricular function, reduced risk of arrhythmia, mitigation of hypertension and stimulation of cardiac hypertrophy regression.

B-type natriuretic peptide (BNP) is synthesized in cardiomyocytes as an inactive pro-hormone (proBNP), which is released into the bloodstream in response to high pressure or stretch[300]. In the circulation, the biologically active BNP is released from its precursor proBNP by the enzyme corin, which generates the inactive amino-terminal pro-BNP (NT-proBNP) as a by-product[301] (see the figure). In healthy physiology, BNP acts on the natriuretic peptide receptors (NPR-A, NPR-B and NPR-C) expressed on cardiomyocytes and triggers antihypertrophic signalling through endothelial nitric oxide synthase (eNOS) and protein kinase G (PKG)[55]. However, increased activity of neprilysin in heart failure leads to reduced circulating levels of biologically active BNP, mitigating its antihypertrophic effects. Neprilysin is a membrane-spanning, proteolytic enzyme expressed predominantly in kidney cells that actively degrades BNP[302]. Neprilysin does not degrade NT-proBNP, which is why circulating levels of this inactive factor are used as a gold-standard biomarker in heart failure[303]. Sacubitril was the first-developed neprilysin inhibitor and successfully restores natriuresis and vasodilatation in patients with heart failure[304]. However, inhibiting neprilysin alone triggers a compensatory increase in RAAS activity, thereby necessitating dual treatment with an angiotensin receptor blocker[304]. Valsartan is an angiotensin II type 1 receptor (AT1R) antagonist and prevents binding of the receptor to circulating angiotensin II (Ang II), thereby blocking downstream pathways associated with pathological hypertrophy, including JUN N-terminal kinase (JNK), p38, ERK1 and ERK2 signalling. In the PARADIGM-HF trial[94], improved outcomes with sacubitril–valsartan were associated with reduced circulating NT-proBNP levels.

AC, adenylyl cyclase; GRBs, growth factor receptor-bound proteins; MEF2A, myocyte-specific enhancer factor 2A; MEK, MAP/ERK kinase; NFAT, nuclear factor of activated T cells; NO, nitric oxide; PLC, phospholipase C; SHC, SHC-transforming protein; SOS, son-of-sevenless homologue; SRC, proto-oncogene tyrosine protein kinase SRC; TRPC, transient receptor potential canonical channel.



Key points

- Pathological cardiac hypertrophy is a leading risk factor for cardiovascular morbidity and mortality and is associated with increased fibrosis and apoptosis that lead to ventricular stiffness, risk of arrhythmia and impaired cardiac function.
- Partial reversal of cardiac hypertrophy occurs with many existing heart failure therapies, including renin–angiotensin–aldosterone system, β-adrenergic receptor, calcium-channel and SGLT2 antagonists, but is achieved in only a subset of patients.
- The potential for reverse remodelling in heart disease is influenced by many factors, including biological sex, genetics, duration of hypertension, BMI, age and disease aetiology.
- Exercise-induced and pregnancy-induced physiological cardiac hypertrophy is driven by cellular mechanisms distinct from those in pathological hypertrophy, and is completely reversible, whereas moderate exercise in heart failure antagonizes pathological cellular pathways and promotes hypertrophy regression.
- At the molecular level, hypertrophy regression is associated with metabolic shifts, reduced protein synthesis, extracellular matrix remodelling and altered activity of proteolytic pathways.

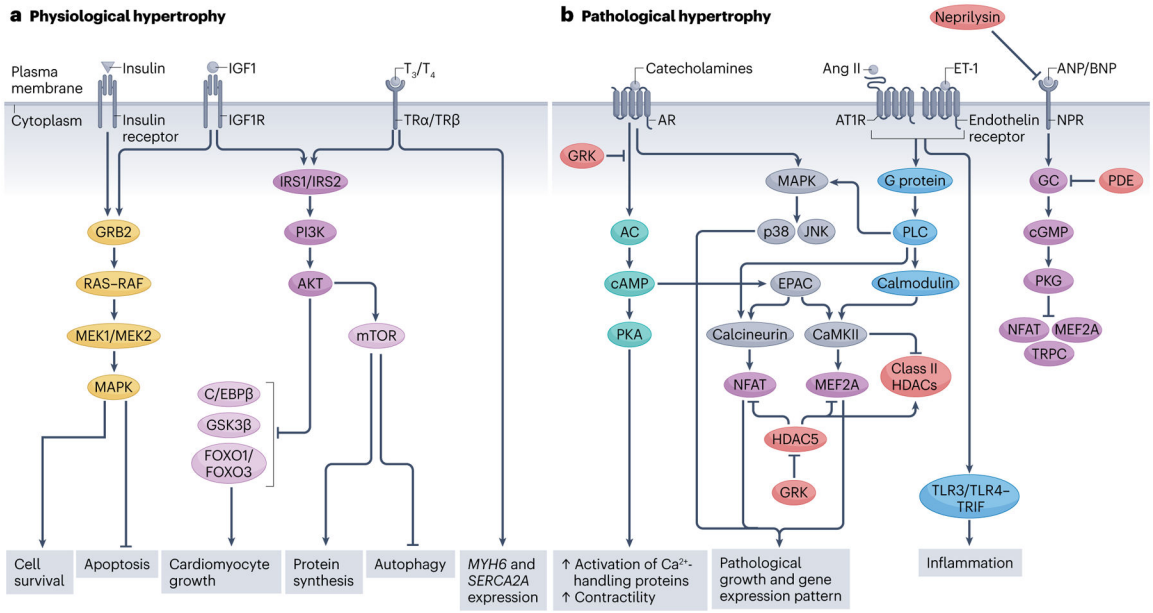


Fig. 1 |. Cellular signalling pathways of physiological and pathological hypertrophy.

a, Cellular pathways of physiological hypertrophy. Insulin or insulin-like growth factor 1 (IGF1) bind to the insulin receptor or IGF1 receptor (IGF1R), respectively, and activate RAS–mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)–AKT pathways, which promote cell survival and growth and protein synthesis. The thyroid hormones triiodothyronine (T_3) or thyroxine (T_4) also trigger the PI3K–AKT pathway and cause increased transcription of *MHY6* and *SERCA2A*. The PI3K–AKT pathway inhibits CCAAT/enhancer-binding protein-β (C/EBPβ), glycogen synthase kinase 3β (GSK3β), forkhead box protein O1 (FOXO1) and FOXO3, all of which are negative regulators of hypertrophy. **b**, Cellular pathways of pathological hypertrophy. Catecholamines, angiotensin II (Ang II) and endothelin 1 (ET-1) trigger pathways that promote maladaptive gene expression and growth. Catecholamines and Ang II–ET-1 activate the downstream effectors calcineurin and calcium–calmodulin-dependent protein kinase II (CaMKII), which stimulate the transcription factors nuclear factor of activated T cells (NFAT) and myocyte-specific enhancer factor 2A (MEF2A), responsible for pathological growth. G protein-coupled receptor kinases (GRKs) mediate adrenergic receptor (AR) desensitization and promote pathological hypertrophy by inhibiting histone deacetylases (HDACs). Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) typically inhibit NFAT, MEF2A and transient receptor potential canonical channel (TRPC) but in heart failure, their receptors become desensitized. Increased neprilysin activity in heart failure triggers degradation of circulating BNP levels, further repressing natriuresis. Additionally, phosphodiesterases (PDEs) inhibit cGMP production resulting in maladaptive gene expression. AC, adenylyl cyclase; AT1R, angiotensin II type 1 receptor; EPAC, exchange protein directly activated by cAMP; GC, guanylate cyclase; GRB2, growth factor receptor-bound protein 2; IRS, insulin receptor substrate; JNK, JUN N-terminal kinase; MEK, MAP/ERK kinase; mTOR, mechanistic target of rapamycin; NPR, natriuretic peptide receptor; PKA, protein kinase A; PKG, protein kinase G; PLC, phospholipase C; TLR, Toll-like receptor; TRIF, TIR domain-containing adapter molecule 1; TR, thyroid hormone receptor.

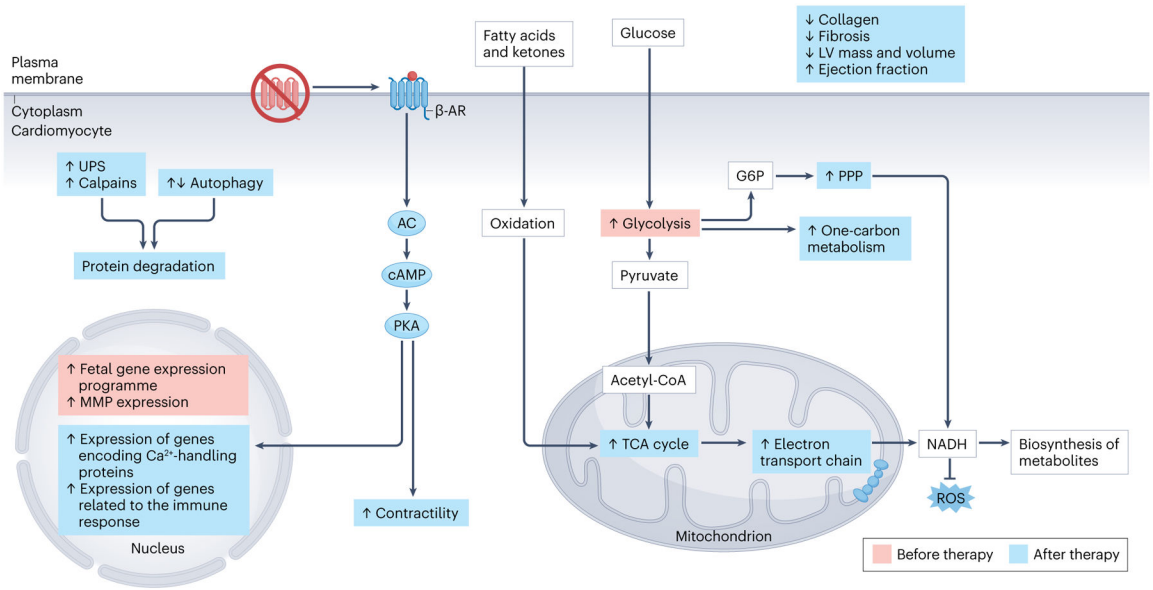


Fig. 2 |. Molecular features of hypertrophy regression with mechanical unloading.

Mechanical unloading induced by left ventricular (LV) assist device (LVAD) therapy alters cardiomyocyte metabolism, protein turnover, gene expression and contractility as well as immune responses. Before LVAD therapy (red boxes), hypertrophic cardiomyocytes have immature phenotypes, such as increased glucose metabolism and a fetal gene expression pattern. Heart failure also causes desensitization of β-adrenergic receptors (β-AR) in cardiomyocytes. After LVAD therapy (blue boxes), β-AR responsiveness is restored, resulting in increased contractility and transcription of genes encoding calcium-handling proteins. The pentose phosphate pathway (PPP), oxidative phosphorylation through the electron transport chain, and one-carbon metabolism increase with LVAD treatment, resulting in the generation of nicotinamide adenine dinucleotide (NADH), a by-product that participates in other metabolic pathways and protects against oxidative damage. The ubiquitin–proteasome system (UPS) as well as the calpain protein degradation pathways become upregulated after LVAD treatment; however, autophagy activation and gene expression have been observed either to increase or to decrease. Altogether, these molecular changes result in decreased fibrosis and LV mass and volume as well as increased ejection fraction and contractility. AC, adenylyl cyclase; G6P, glucose-6-phosphate; MMP, matrix metalloproteinase; PKA, protein kinase A; ROS, reactive oxygen species; TCA, tricarboxylic acid.

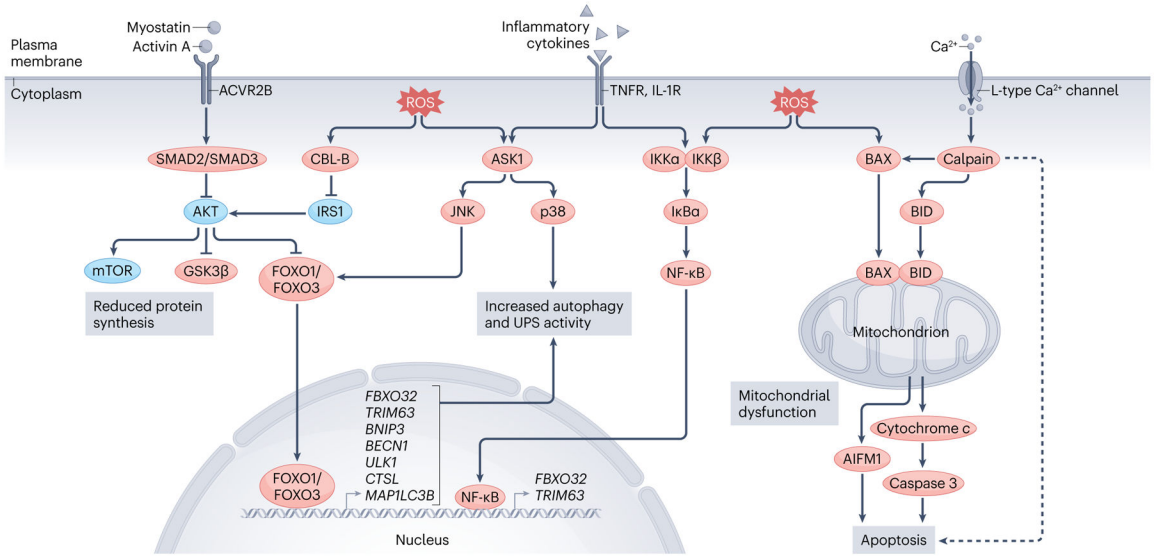


Fig. 3 |. Molecular features of cardiac atrophy.

Atrophy can be initiated by an increase in the circulating levels of certain factors (such as myostatin, activin A and inflammatory cytokines) and/or increased cellular oxidative stress. Myostatin and activin A bind to the activin receptor type 2B (ACVR2B), which stimulates downstream SMAD2 and SMAD3 signalling. SMAD2 and SMAD3 inhibit pro-growth pathways (AKT and mechanistic target of rapamycin (mTOR) pathways) and activate FOXO transcription factors, which translocate to the nucleus and increase the expression of genes related to autophagy and the ubiquitin–proteasome system (UPS). Inflammatory cytokines (such as tumour necrosis factor) activate the p38 and JUN N-terminal kinase (JNK) MAP kinase pathways and nuclear factor-κB (NF-κB), which stimulate atrophic-related gene expression patterns and protein degradation. Increased intracellular levels of reactive oxygen species (ROS) act on similar pathways, while also causing the translocation of apoptosis regulator BAX and BH3-interacting domain death agonist (BID) to the mitochondria, leading to mitochondrial dysfunction and triggering apoptosis through apoptosis-inducing factor mitochondria associated 1 (AIFM1; also known as AIF) and cytochrome *c*–caspase 3 signalling. ROS also inhibit growth pathways and promote FOXO-dependent degradation by activating the E3 ubiquitin protein ligase CBL-B, which mediates insulin receptor substrate 1 (IRS1) degradation and thus represses downstream AKT signalling. Calpain activation owing to increased intracellular calcium levels in cardiac atrophy also triggers proteolysis, mitochondrial dysfunction and (in some instances; dashed line) apoptosis. ASK1, apoptosis signal-regulating kinase 1; GSK3β, glycogen synthase kinase 3β; IL-1R, IL-1 receptor; IκBα, NF-κB inhibitor-α; IKK, inhibitor of nuclear factor-κB kinase; TNFR, tumour necrosis factor receptor.

Table 1 |

Reverse left ventricular structural remodelling with heart failure therapies

Therapy	Regression (%)			Patients responding (%)	Refs.
	≤3 months	6–8 months	≥12 months		
ACE inhibitors	4–12	1–21	10–26	36–46	75,80–84,102,273–276
Angiotensin receptor blockers	2–11	12–20	9–22	21–47	75,80,85,87,277–279
ARNIs	8–12	15	26–27	52–58	92,94,241,275,280,281
Aortic valve replacement	10	17	15–44	90–100	128–130,132,133,135,282
Bariatric surgery	7–22	9–18	19–32	70	137,139–142,283,284
β-Blockers	0–4	0–7	6–10	30	75,106,278,285–287
Calcium channel blockers	10–14	2–18	3–14	40–60	75,78,110–113,273,285,288,289
CRT	3	4–5	10–16	46–72	146,149,290–294
LVAD	20–40	20–40	40–50	70–90	153–155,295,296
Mineralocorticoid receptor antagonists	10–16	10–20	8–18	40	89,90,297,298
SGLT2 inhibitors	Not reported	4	5–9	Not reported	120,121,299

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; SGLT2, sodium–glucose cotransporter 2.