Is Inhibition of Hypertrophy a Good Therapeutic Strategy in Ventricular Pressure Overload?

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Hypertrophic growth of ventricular myocytes is a hallmark feature of numerous forms of cardiovascular disease.1 The hypertrophic process is complex, involving a vast array of structural, signaling, transcriptional, electrophysiological, metabolic, and functional events within the growing cell.2,3 Other cellular elements within the ventricle, fibroblasts, vascular smooth muscle cells, and endothelium, also manifest intrinsic stress responses, resulting in fibrosis, inflammatory cell infiltration, endothelial dysfunction, and vascular stiffness. Current thinking holds that these events, the reaction of the heart to a host of pathological stresses, provide short-term benefit. However, if disease-related stress remains unchecked, these remodeling events become maladaptive and predispose to cardiovascular morbidity and mortality.

Response by Crozatier and Ventura-Clapier on p 1447

Among the risks conferred by disease-related ventricular hypertrophy are ventricular tachyarrhythmia, predisposing to sudden cardiac death, and transition to heart failure. Ultimately, these events derive from wholesale reprogramming and relative dedifferentiation of the cardiac myocyte, coupled with similar events in other cell types.

Conventional thinking holds that hypertrophic growth of the myocardium is a compensatory response of the heart to increases in workload demand, serving to minimize wall stress and maintain contractile function. However, several lines of evidence, preclinical and epidemiological, highlight the maladaptive features of chronic ventricular hypertrophy. Indeed, in many instances, suppression of load-induced growth is well tolerated.4 Furthermore, left ventricular hypertrophy is among the most robust markers of increased risk for developing chronic heart failure.5 Therefore, we submit that suppression of load-induced ventricular hypertrophy warrants careful consideration as a therapeutic strategy.

Cardiomyocyte Hypertrophy: Comprehensive Reprogramming of the Cell

Although evidence suggests that a small fraction of cells within the ventricle are capable of re-entering the cell cycle,6–8 the majority of cardiomyocytes are postmitotic and, hence, do not retain the ability to divide. Rather, they respond to stress by growing, shrinking, or dying. In the context of many disease-related stresses, cardiac myocytes undergo hypertrophic transformation, which entails significant cellular growth. In the setting of uncontrolled hypertension, for example, cardiomyocytes hypertrophy. Similarly, after myocardial infarction, surviving cardiomyocytes in border and remote zones of tissue increase in size in response to increases in hemodynamic...
demand arising secondary to the loss of ventricular tissue. In both cases, when the pressure overload state is persistent, the hypertrophic phenotype of the myocardium inexorably progresses to a state of decompensation and clinical heart failure. Mechanisms governing this transition from adaptive hypertrophy to maladaptive failure remain poorly understood.

Hypertrophic transformation of the cardiomyocyte involves much more than simple cell growth. Rather, it entails a near-comprehensive retooling of multiple aspects of cellular architecture and machinery. One element of this process is relative dedifferentiation of the cell and reactivation of numerous transcriptional, signaling, electrical, and metabolic events that characterized the cell during development. As part of this, a wide range of transcriptional and posttranslational events occur, including activation of a pattern of gene expression reminiscent of that observed during fetal development (fetal gene program). Indeed, the fetal gene program, which was extinguished shortly after birth, reignites rapidly in the setting of disease.

Based on the pattern of sarcomere reorganization, it is possible to distinguish 2 broad patterns of ventricular hypertrophy.9 Pressure stress provokes concentric hypertrophy, which is characterized by recruitment of sarcomeres laid down in parallel; on the contrary, excess volume elicits eccentric hypertrophy in which cardiomyocytes respond with the addition of new sarcomeres. Rather, this highly dynamic cellular response involves intricate coordination of de novo protein synthesis and organelle biogenesis, sarcomere remodeling, protein degradation, organelle breakdown, transcriptional reprogramming, and metabolic shifts. In many ways, the entire cellular architecture of the myocyte–frame, chassis, drive train, and engine—is retooled.

In contrast to disease-related triggers, physiological stresses, such as endurance exercise and pregnancy, induce a hypertrophic response characterized by normal or enhanced contractile function coupled with normal architecture and organization of cardiac structure.12 Beyond differences in growth triggers, biological phenotypes, and clinical outcomes, pathological and physiological hypertrophy differ in the signaling cascades that drive the process. Some evidence suggests that the distinct phenotypes do not derive simply from differences in the duration of the stimulus, highlighting significant gaps in our understanding of these 2 remodeling responses.13 Other data suggest that cell size is regulated by shared signaling pathways, but cell shape and sarcomeric organization are regulated by distinct pathways.14 Current understanding does not allow us to parse the effects of the myriad genes and pathways involved, but it is thought that some confer benefit, whereas others are maladaptive.

Substantial evidence points to alterations in transmembrane Ca2+ fluxes, another central feature of pathological remodeling, as a proximal trigger contributing to the pathogenesis of hypertrophy and failure.15 These alterations perturb excitation-contraction coupling, alter mitochondrial metabolism, and abnormally activate Ca2+-responsive signaling pathways.

Recent evidence indicates that β-myosin heavy chain is induced by pressure overload in rodents in only a minor subpopulation of smaller cardiac myocytes.16 The myocytes that hypertrophied after surgical constriction of the thoracic aorta express α-myosin heavy chain only. Thus, hypertrophic transformation may involve yet another layer of complexity in that it manifests significant heterogeneity among myocytes.

Cardiac Myocyte Death

Cell death within the myocardium is characteristic of a number of cardiac diseases, and it can occur to some extent in cardiac hypertrophy. The major types of cardiomyocyte death are necrosis and apoptosis, with the former occurring to a greater extent. An emerging literature has demonstrated that necrosis can occur as a result of a series of programmed events, not just as simple catastrophic dismantling of the cell. Indeed, programmed necrosis and apoptosis share a number of features and may represent different manifestations of a common mechanism termed necroptosis.17,18

Both dying and hypertrophying cells often harbor signs of activated autophagy, an evolutionarily ancient process of ordered recycling of intracellular contents.19 Whether activation of the autophagic cascade reflects a cellular response to stress, serving to promote cell survival, or is a process contributing to cell death and disease progression, is context dependent.20

Fibrosis

Another hallmark feature of pathological hypertrophic remodeling is accumulation and deposition of excessive extracellular matrix.21 This surplus extracellular matrix, which constitutes tissue scar or fibrosis, perturbs electrical conduction, thereby predisposing to rhythm disturbances. It also promotes dysfunction of both mechanical contraction and relaxation. As a result, cardiac fibrosis contributes importantly to morbidity and mortality in cardiac hypertrophy. Indeed, the amount of fibrotic scar in the myocardium correlates directly with the incidence of arrhythmias and sudden cardiac death.22–24
Extracellular matrix deposition and fibrosis arise through the action of cardiac fibroblasts. These cells, the most abundant cell type in the myocardium, proliferate in response to pathological stress. Furthermore, they differentiate into myofibroblasts, thereby gaining the capacity to contract and secrete collagen I, collagen III, and fibronectin. Fibrosis can be categorized as reactive (perivascular or interstitial) or replacement, occurring at the site of an eliminated myocyte. Myofibroblasts derive from activated, resident fibroblasts, but may also originate from adult epicardial cells and circulating, collagen-secreting, bone marrow–derived cells. Both individual myofibroblasts and collagenous septa within the tissue facilitate and propagate the arrhythmic phenotype of the hypertrophied heart.

Cardiac fibrosis is an independent and predictive risk factor for heart failure development in the setting of ischemic or non-ischemic cardiomyopathy. Importantly, strong evidence indicates that cardiac fibrosis, long held to be irreversible, may regress under certain conditions. However, although several signaling pathways have been implicated in fibrogenesis, tailored therapeutic approaches targeting cardiac fibrosis remain elusive.

Electrical Remodeling

Patients with left ventricular hypertrophy are at increased risk of malignant arrhythmia, which contributes significantly to morbidity and mortality. Indeed, arrhythmia, especially ventricular tachyarrhythmia, is a major cause of death in patients with cardiac hypertrophy or failure. Underlying mechanisms, collectively termed electrical remodeling, encompass alterations in multiple electric transport and signaling processes within the cardiac myocyte. Although numerous insights have emerged in elucidating the molecular pathogenesis of cardiac hypertrophy, our understanding of mechanisms underlying the myriad facets of electrical remodeling remains limited. As a result, pharmacological treatment of hypertrophy-associated arrhythmias lacks efficacy, and device-based therapy has emerged as a widely used surrogate.

The action potential phenotype of ventricular myocyte hypertrophy is characterized by delayed repolarization leading to prolongation of action potential duration (APD). This derives, at least in part, from distorted transmembrane electric currents. Indeed, a wide range of alterations in myocyte ion channels and electrogenic ion transporters contribute to APD prolongation. Delayed recovery of excitability, in turn, predisposes to early and late afterdepolarizations. Hypertrophy is also associated with myocardial fibrosis (vide supra), altered electrotonic coupling among cells, slowed conduction, and dispersion of refractoriness, which together promote re-entrant arrhythmias.

This electrical remodeling response is heterogeneous within the ventricle. In the setting of excessive afterload, such as in severe transverse aortic constriction-induced heart failure, APD is prolonged more in subepicardial ventricular myocytes than in subendocardial myocytes. Additional evidence for heterogeneity of APD prolongation has been reported in a model of pacing-induced heart failure in dogs where APD prolongation in midmyocardial cells was substantially greater than in subepicardial cells.

Alterations in Ca²⁺ handling contribute to both hypertrophic signaling and electrical remodeling. For example, L-type Ca²⁺ current (I_Ca,L) is a major mechanism of Ca²⁺ influx in cardiac myocytes. As a general rule, I_Ca,L density correlates inversely with disease progression; in models of mild-to-moderate hypertrophy, I_Ca,L is often increased, whereas in severe hypertrophy and failure, I_Ca,L often manifests significant declines. Importantly, because membrane impedance is relatively high during phase 2 of the action potential, small changes in I_Ca,L can have significant effects on action potential morphology and duration. Furthermore, entry of small amounts of extracellular Ca²⁺ triggers release of much larger amounts of Ca²⁺ from intracellular stores. As a consequence, modest increases in inward Ca²⁺ flux are amplified within the cell.

Electrical activity within the myocardium hinges critically on electrotonic cell-cell coupling, such that depolarization in one cell is transmitted seamlessly to neighboring cells. This coupling is mediated through gap junctions, such as connexin 43, which can become disorganized in the hypertrophied or failing heart, disrupting normal impulse conduction.

It is worth remembering that the atria are also touched by remodeling events in cardiac hypertrophy and failure. Reduced contractility, development of fibrosis, and chamber enlargement can occur, leading to heterogeneity of conduction velocity and propensity to atrial fibrillation. This arrhythmia, in turn, eliminates the component of ventricular filling provided by atrial contraction. Furthermore, it promotes decreases in the atrial myocyte effective refractory period and shortened APD, which together promote sustained atrial fibrillation.

Metabolic Remodeling

The metabolic demands of the myocardium are exceptionally high. As a continuously working pump, the heart consumes robust quantities of ATP, more than any other organ in the body, and myocardial energy reserves are remarkably low, sufficient for less than 10 contractions. The cardiomyocyte derives ATP largely from fatty acid oxidation. That being said, the heart is a metabolic omnivore that can flexibly burn fuel derived from a wide range of sources. In the end, cardiomyocytes must generate energy continuously, consuming nutrients constantly and without interruption.

Among the characteristic changes occurring with cardiac hypertrophy is a shift in energy substrate use. This metabolic remodeling response entails upregulation of glucose uptake and glycolysis, whereas β-oxidation of fatty acids is reduced. Approximate numbers are that glycolysis accounts for 10% of ATP production in the normal heart and 20% in the hypertrophied heart. Conversely, ATP production from fatty acid metabolism drops from 70% to 50%. These shifts are consistent with the overarching process of cellular dedifferentiation in the pathologically stressed myocardium, because...
the shift in metabolism mimics the metabolic program in fetal myocardium.

The impact of the partial switch to a fetal program of glucose metabolism from preferential use of lipid remains uncertain. Arguably the greatest impact derives from improvements in oxygen efficiency. However, concerns have been raised because of evidence that cardiomyocytes cultured in high-glucose media are dysfunctional.

To accomplish the synthesis of macromolecules and organelles required for cardiomyocyte hypertrophic growth, exogenous nutrients, such as glucose, cannot be metabolized exclusively for ATP production. Rather, metabolic intermediates must be channeled to support anabolic pathways. Here, interplay between the plasticity of metabolic pathways and protein quality control is critical to providing intermediate metabolites that feed into the tricarboxylic acid cycle for ATP production, as well as serving to promote macromolecule synthesis. Overall, currently available information implicates metabolic reprogramming in the hypertrophied heart as an ultimately maladaptive response.

Inflammation

Activation of immune mechanisms participates in ventricular remodeling, contributing to long-term cardiac injury in certain contexts. In the case of heart failure, a variety of inflammatory molecules and pathways are activated. In preclinical models, pressure overload triggers myocardial inflammation, as demonstrated by increased expression of several proinflammatory cytokines and leukocyte infiltration within the myocardium. This and other evidence, both in animals and patients, highlights the role of inflammation as an important component of pathological hypertrophy and points to the relationship between a proinflammatory state and load-induced ventricular remodeling. Interestingly, myocardial cytokine levels, a surrogate marker of inflammation, are often higher in patients with elevated afterload and preserved left ventricular function compared with those patients with reduced ejection fraction. These data challenge the concept that cytokine activity and an inflammatory response are necessarily detrimental in chronic pressure overload.

A crucial element within the inflammatory response observed in models of pressure overload involves macrophages that infiltrate ventricular tissue, triggering myocardial expression of nuclear factor-κB and inflammatory cytokines. One of the mechanisms whereby macrophages are involved includes actions of macrophage-derived microRNA-155, which functions as a modulator of cardiomyocyte hypertrophy via paracrine mechanisms.

These observations, coupled with the effects of anti-inflammatory therapies in animals, have prompted efforts to translate these insights into patients through clinical trials. However, to date, anti-inflammatory therapies for heart failure in humans have disappointed. Looking to the future, the possible role of novel anti-inflammatory therapies using selective approaches targeting specific cellular and molecular elements of pathological cardiac remodeling and heart failure could be elucidated. Recently, a novel connection among autophagy, afterload stress, and inflammation was reported, where a lack of autophagy-mediated removal of mitochondrial DNA promoted an inflammatory response contributing to depressed cardiac contractile performance.

Vascular Remodeling

The vasculature that supplies the ventricle itself remodels in both physiological and pathological hypertrophy. Hypertrophic growth of the heart involves parallel increases in myocardial mass and vascular supply, the latter occurring through proliferation of endothelium, smooth muscle cells, and blood vessels. Indeed, it is possible to distinguish 2 interdependent phenomena involving heart vessels. The first is remodeling of pre-existing vasculature with modifications of endothelium, smooth muscle cells, and interstitial matrix, and the second is de novo myocardial angiogenesis involving an intricate network of molecules secreted from cardiomyocytes, leukocytes, and fibroblasts (reviewed in References 73 and 74). Paracrine signaling through mediators released by endothelial cells may modify vascular smooth muscle cell function and extracellular matrix components. Also, in the setting of hypertension, vascular smooth muscle proliferates and hypertrophies, culminating in vascular wall thickening. In some settings, flow reserve is compromised.

Dysfunction of vascular endothelial cells occurring in pressure overload–induced heart failure may represent a crucial node in vascular remodeling occurring in pathological hypertrophy. Indeed, one model holds that capillary growth in pathological hypertrophy does not keep up with myocyte growth, leading to inadequate oxygen diffusion capacity. Along those lines, it has also been postulated that an imbalance in the capillary:cardiomyocyte ratio contributes to the transition from compensatory hypertrophy to decompensated heart failure. Consistent with this notion, enhancing angiogenesis in a model of afterload stress can be protective. In fact, therapeutic strategies aimed to restore the capillary network in heart failure have been evaluated in both preclinical models and in humans. Despite some favorable findings, therapeutic myocardial angiogenesis has failed to achieve clinical significance, at least partly because these approaches typically involve the delivery of genetic material or growth factors with attendant complications.

Functional Role of Pathological Hypertrophy

Three stages of hypertrophic transformation of the heart were initially proposed by Meerson. This model emphasizes that the duration of pressure overload dictates the progression of events, including hypertrophic growth and ultimately ventricular systolic function. In this model, short-term hypertrophy represents a beneficial event that serves to normalize wall
stress, whereas prolonged hypertrophy is detrimental, provoking increased oxygen consumption and cardiomyocyte death (Figure 1).

Considerable evidence, from both preclinical and clinical contexts, indicates that chronic, unremitting stress, as occurs in hypertension or valvular heart disease, leads inevitably to systolic dysfunction.85–89 Moreover, the Framingham Heart Study established an association between ventricular hypertrophy and increased cardiac mortality.5 However, the inevitability of the transition from hypertrophy to failure has been questioned. Drazner and colleagues90,91 have identified 3 challenges to this point of view: 1) in animal models of pressure overload, hypertrophy can be blocked without development of heart failure92–94; 2) in humans, concentric hypertrophy does not uniformly progress to failure in the absence of myocardial infarction95–97; and 3) some hypertensive subjects develop dilated cardiomyopathy apparently without antecedent concentric hypertrophy and without clinical evidence of myocardial infarction.98 These important caveats are based on the notion that the time course of transition to heart failure in patients, if it occurs, is relatively uniform and can be captured within the time span of epidemiological studies.

In an effort to address these issues, magnetic resonance imaging data from the Dallas Heart Study have been used to propose a 4-tiered classification of left ventricular hypertrophy.99 This scheme seeks to overcome the limitations of the concentric versus eccentric hypertrophy model by incorporating left ventricle end-diastolic volume as a categorical variable. Future work will determine whether this 4-tiered classification conveys independent information regarding prognosis or therapy.

Despite these caveats, the presence of left ventricular hypertrophy, per se, is unequivocally associated with adverse cardiovascular outcomes independent of the underlying disease-related cause.5 As noted earlier, whereas ventricular hypertrophy may be beneficial in the short term to minimize wall stress, in the long term it promotes progression to heart failure and other cardiovascular disorders. Numerous epidemiological studies have clearly demonstrated that left ventricular hypertrophy is not benign but rather represents a major risk factor for cardiovascular morbidity and mortality, more robust than other conventional risk factors.5,100–103 Substudies from the Framingham Heart Study have demonstrated marked increases in coronary heart disease, heart failure, and sudden cardiac death associated with left ventricular hypertrophy, revealed by electrocardiographic and echocardiographic approaches.104–106

Together these data clearly identify left ventricular hypertrophy as an important risk factor of cardiovascular disease. However, it is important to highlight that these observations are strictly correlative, and no mechanism(s) of hypertrophy-dependent increase in risk can be inferred. Our knowledge of potential mechanism(s) by which ventricular hypertrophy confers increased cardiovascular risk is limited by the fact that transition from the early, compensatory stage of hypertrophy to the maladaptive phase is poorly characterized.

**Is Load-Induced Hypertrophy Ever Truly Compensatory?**

Traditionally, ventricular hypertrophy has been viewed as an obligatory initial response to pathological stress; only with time does it transition to a disease-promoting event. Consistent with this view, the term compensatory connotes an adaptive role of hypertrophy as a consequence of pressure stress based on the premise that it helps normalize ventricular wall stress and myocardial oxygen demand. However, evidence from genetic and pharmacological studies in mouse models of pressure overload have demonstrated that hypertrophic growth is not universally required to preserve cardiac function.92,94

Shortly after the report107 that calcineurin is capable of triggering a robust cardiac growth response, we set out to determine whether calcineurin signaling is required for afterload-induced growth of the heart. Mice were exposed to thoracic aortic constriction and injected daily with cyclosporine or vehicle, delivered in an investigator-blinded manner. After 3 weeks, hearts were evaluated by echocardiography and by postmortem gravimetric analyses. In the animals exposed to cyclosporine, the load-induced growth response was abolished, leading us to conclude that calcineurin activation was, in fact, required for load-induced cardiac hypertrophy in this context. Very surprising to us,
however, was the fact that ventricular size and function by echo were normal in the cyclosporine-treated animals. This was true despite the imposition of 70 to 80 mm Hg of afterload stress, which was persistently present until the end of the entire study; ventricular volumes and contractile parameters were normal, and the animals behaved normally. This astonishing finding was published, and we estimate that this observation, which often goes unnoticed in the reporting of studies, has been replicated independently at least 100 times since then.

These findings, demonstrating that load-induced hypertrophy is not always required to maintain ventricular size and performance, raise the prospect that the hypertrophic growth response may be a relevant target for therapeutic targeting. It is important, however, to recognize that these observations derive largely from genetically engineered mice and, therefore, are based on models with important limitations. Heart rate in humans is substantially slower than that in mice, and left ventricular ejection fraction is lower. In addition, surgical banding of the aorta triggers an acute increase in pressure stress on the left ventricle and therefore does not mimic conditions of chronic, progressively increasing hemodynamic load as occurs in humans. Most preclinical studies in mice were conducted over a 3- to 4-week period, which amounts to ~3 years in humans; perhaps blocking hypertrophy for a longer period of time would be harmful. Unfortunately, the critical study in large animals has not been performed to date.

How Can All This Be?
Increases in afterload elicit early changes in myocyte biology across a wide range of mechanisms. Frank-Starling–related adaptations ensue, triggered by stretch. In addition, contractility continues to increase for >10 to 15 minutes after the initial stretch, a response initially described more than 100 years ago by Gleb von Anrep and now termed the Anrep effect. Initially attributed to increases in circulating catecholamines released by the adrenal gland, the Anrep effect was later demonstrated in isolated ventricular myofilaments and was attributed to increases in myofilament calcium sensitivity. Thus, the Anrep effect, a response that remains poorly characterized, is a rapid, procontractile response that occurs in the setting of abrupt increases in afterload. It is possible that this response, coupled with hypertrophic growth, represents a load adaptation intrinsic to cardiac muscle.

Initial, rapid mechanisms whereby cardiac muscle responds to increased load are, however, insufficient to maintain cardiac contractility for an extended period if the inciting stress is not eliminated. Therefore, increases in cardiac mass ensue but ultimately lead to untoward consequences. Indeed, with persistent pressure stress, the heart undergoes apparently irreversible decompensation, resulting in chamber dilatation and reduced systolic function. This maladaptive hypertrophy, as emerges when the inciting stress is not abated, represents a common feature in virtually all forms of heart failure. Therefore, the concept of transition from a short-term compensatory response to maladaptation points to cardiac hypertrophy as a novel therapeutic target.

Translational Studies in Large Animals
Our understanding of mechanisms that govern the transition between compensated ventricular hypertrophy and heart failure remains incomplete. This stems partly from a lack of longitudinal analyses of ventricular structure and function in patients with increased afterload (eg, aortic stenosis and arterial hypertension). To date, most evidence that provides insight into the effects of suppressing cardiac hypertrophy on cardiac function derives from studies in rodents. However, because of intrinsic differences in contractile performance, Ca$^{2+}$ handling, myosin isoform distributions, heart rate, and life span between rodents and humans, these models do not faithfully recapitulate human disease. In this regard, large animal models could be more informative.

Pressure overload–induced cardiac hypertrophy has been studied in nonhuman primates, where left ventricular hypertrophy and myocardial fibrosis comparable to that seen in patients with aortic stenosis are found. Studies to evaluate molecular mechanisms and pathophysiological adaptations in pressure overload–induced heart failure have been conducted primarily in dogs. In view of the considerable remaining gaps in our understanding of this biology, additional exploration of the role of compensatory hypertrophy in large animal models is warranted.

How Might Hypertrophy Be Targeted?
Clinical management of pathological left ventricular hypertrophy currently focuses on the underlying growth cues (eg, hypertension and valve disease) and typically involves a wide spectrum of pharmacological agents that have shown safety and efficacy in reducing hypertrophy. These pharmacological agents are mostly directed against the crucial neurohormonal axes activated in response to stress. Adrenergic and renin-angiotensin-aldosterone system (RAAS) pathways represent 2 mechanisms recruited to increase contractility in the early phases of stress, becoming deleterious in the chronic context. β-Adrenergic receptor blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are effective in reducing left ventricular mass and are associated with a favorable clinical outcome in clinical settings.

Pharmacotherapy to reduce blood pressure can lead to regression of ventricular hypertrophy. Although all antihypertensive drugs promote hypertrophy regression to some extent, current evidence suggests that the RAAS-targeting drugs are the most efficacious at regressing ventricular hypertrophy. Based on robust evidence that regression of hypertrophy is independently associated with improved cardiovascular outcome, numerous clinical trials have documented the favorable impact of antihypertensive drug therapy. For
Table. Novel Compounds and Targets With Confirmed or Potential Antihypertrophic Activity

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AT1 indicates angiotensin II receptor type 1; DRP1, dynamin-related protein 1; Dynk1A, dual specificity tyrosine-phosphorylation-regulated 1A; E2F2, E2F transcription factor 2; FoxO3, forkhead box O3; HDAC, histone deacetylase; Hif1α, hypoxia inducible factor 1α; HMGA1, high mobility group A1; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; MuRF1, muscle RING-finger protein 1; NFAT, nuclear factor of activated T cells; PDE5, phosphodiesterase type 5; PKCβ, protein kinase Cβ; PPAR, peroxisome proliferator–activated receptor; ROCK, rho-associated protein kinase; SERCA2a, sarcolemmal reticulum Ca2+ ATPase; Socs1, suppressor of cytokine signaling 1; THRAP1, thyroid hormone receptor–associated protein 1; TLR9, toll-like receptor 9; and sGC, soluble guanylyl cyclase.

For example, the Losartan Intervention for Endpoint Reduction in a Hypertension study reported a greater reduction in left ventricular mass index in the losartan-treated cohort compared with an atenolol-based regimen.17 Several other trials reached a similar conclusion, pointing to a class effect of RAAS-targeting anti hypertensive agents at promoting hypertrophy regression.118–121 Together, these data highlight the role of current therapies targeting chronic neurohormonal activation in the prevention of heart failure and limiting progression of ventricular hypertrophy, lending further support to the notion that inhibiting ventricular hypertrophy is an attractive therapeutic option in patients.

All of these trials were conducted using compounds targeting cardiomyocyte cell-surface receptors. More recently, efforts have focused on antihypertrophic effects of molecules that act inside the cardiomyocyte, targeting crucial signaling cascades that alter gene expression and protein function. These agents include histone deacetylase (HDAC) inhibitors, a wide spectrum of prohypertrophic microRNAs (reviewed in Reference 122), and several other small molecules (reviewed in Reference [12] and Table).

Our group has focused on reversible protein acetylation as a tractable means of governing cardiomyocyte growth,124–127 autophagy,126 and disease responsiveness.128 Among those studies, we have noted that inhibition of HDACs is capable of blunting load-induced growth.127 Beyond that, HDAC inhibitors can promote regression of ventricular hypertrophy despite the persistent presence of afterload stress126 (and with preservation—even improvement—in contractile performance.) HDAC inhibitors, 4 of which are US Food and Drug Administration approved as third-line therapy for Sézary syndrome, may emerge as a novel means of targeting ventricular hypertrophy. Indeed, we have speculated that it might be possible to use HDAC inhibitors to sculpt the hypertrophied ventricle in patients with heart failure with preserved ejection fraction, trimming left ventricular wall thickness progressively, to afford clinical benefit.

Comprehensive understanding of molecular events involved in maladaptive cardiac hypertrophy and the remodeling that culminates in decompensated heart failure is the first step toward developing novel treatments with clinical potential. This is especially true for patients with heart failure with preserved ejection fraction, most of whom harbor ventricular hypertrophy, which contributes to symptoms and clinical outcomes,129 and for which evidence-based therapy is lacking. Although these pathways manifest redundancy in their effects, hypertrophy often remains present in models in which 1 pathway is suppressed, suggesting that serial pharmacological brakes may be required for clinical gain.

A Note of Caution

Considerable evidence points to a progression of remodeling events in which stress elicits the following: 1) a hypertrophic growth response which has beneficial features; 2)
maladaptive hypertrophy, which is a clear-cut marker for untoward events; and 3) the clinical syndrome of heart failure. However, assuming this model has validity, little is known regarding specific markers of these different phases of disease pathogenesis or transition points separating them.

A large number of preclinical studies have demonstrated that it is possible to blunt load-induced hypertrophy, even in the setting of persistent afterload stress, without affecting contractile function. These studies, then, have delineated a strategy wherein one might target maladaptive hypertrophy and thus obviate the untoward consequences of continued progression of this process. Consistently, in both preclinical studies and clinical trials, inhibition of cardiac hypertrophic growth usually results in the amelioration of left ventricular dysfunction. Caution is warranted. Not all forms of pathological cardiac hypertrophy can be blocked without provoking ventricular dysfunction. Although the great majority of studies (again, exclusively in rodents to date) demonstrate that the load-induced growth response can be inhibited without untoward effects, there are examples where hypertrophy elicited by a specific signaling cascade appears to be required. Also, ventricular mass alone may not provide the full picture of the myriad remodeling events involved in heart growth. Therefore, further work is required to determine whether accompanying alterations (eg, contractile function and coronary hemodynamics) associated with ventricular hypertrophy can be reversed by treatment and in which category of patients.

We wish to highlight that, whereas cardiac hypertrophy in response to pathological stimuli manifests common characteristics irrespective of the triggering stress, it is likely that several subtypes of pathological hypertrophy exist. Thus, whereas efforts to block the inciting stimuli are warranted, we do not know whether all forms of maladaptive hypertrophy should be prevented.

**Stress-Induced Cardiac Growth: A Model**

How is it that hypertrophy can be both beneficial and detrimental? We propose a model in which hypertrophic transformation of the heart under conditions of disease-related stress is similar to many other processes in biology. There has been significant evolutionary pressure to promote organismal survival until procreation can occur and young can be fostered to independence. However, our species did not evolve to live 9 decades! In the settings of life-threatening stress, activation of both the β-adrenergic cascade and the RAAS axis occurs, and the end result is enhanced cardiac performance and improved survival. These pathways allow for survival in the setting of sublethal injury, for example. However, chronic activation of these processes, life saving in the short term, clearly conveys markedly enhanced risk in the long term. Indeed, chronic suppression of those evolutionarily ancient neurohumoral responses is fundamental to present day, evidence-based therapy for heart failure. Again, a large number of studies have demonstrated robust benefits from therapeutic strategies in which evolutionary adaptations to stress are blocked.

We suggest that ventricular hypertrophy is the same. It provides short-term benefit and long-term harm (Figure 2). If this model holds true, then suppression of ventricular hypertrophy, a therapeutic target currently not under widespread consideration, emerges as a novel and potentially important target for consideration of drug development going forward.

**Summary and Perspective**

Heart failure is defined as a syndrome in which cardiac output is unable to meet the metabolic needs of peripheral tissues. In this setting, when cardiac output is depressed, the myocardium has a limited repertoire of responses, and, as a result, so does the treating physician. The heart is capable of responding in 4 ways: increases in 1) heart rate, 2) ventricular filling, 3) contractility, and 4) mass. Clinically, we have a full spectrum of means to regulate heart rate and optimize ventricular filling pressures. Contractility is a mechanism that we target routinely in the acute setting, but no safe and effective therapies are available that promote contractility chronically. This leaves ventricular hypertrophy as the final frontier of heart failure therapy, a target that has never been developed and that, in fact, seems counterintuitive on initial consideration.
That said, it is critical to recognize that hypertrophic transformation of the ventricle is just that, a transformation involving cellular dedifferentiation and comprehensive reprogramming of the cardiac myocyte and other cellular elements within the ventricle. Although increases in myocyte size and consequent increases in ventricular mass are hallmark features, a wide range of additional events occur in these stressed cells. Here, we present an overview of the large body of robust epidemiological and preclinical data pointing to the untoward consequences of hypertrophic transformation of the myocardium. These data, at the very least, raise the prospect of targeting hypertrophy therapeutically.

In recent years, significant strides have been achieved in our understanding of, and therapeutic targeting of, pathological hypertrophic remodeling. We view hypertrophic transformation as a fundamental, potentially indispensable step in the myocardial response to pressure overload, which is coupled with significant detrimental consequences. This response may be beneficial in the short term, but when maintained chronically it becomes significantly detrimental. It is analogous to the responses of β-adrenergic and RAAS activation, which we now go to great lengths to block and for which suppression seemed counterintuitive at first. We argue that hypertrophy is comparable, and patients may benefit from judicious attenuation of this chronic, long-term hypertrophic response.

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Disclosures

None.

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We agree with many points presented in the review of Sciattarella and Hill, particularly with their description of the abnormalities present in the hypertrophied myocardium. We also acknowledge that ventricular hypertrophy has been identified as a cardiovascular risk factor. However, this does not imply that hypertrophy, per se, has to be blocked. This management of the hypertrophy process has proved to be beneficial in a number of studies, but we also presented examples of detrimental effects of this procedure. Sciattarella and Hill were cautious to say that it cannot be applied to all forms of hypertrophy. We could thus agree with them, but we fully disagree when they state that chronically maintaining hypertrophy is analogous to an activation of β-adrenergic and renin-angiotensin-aldosterone systems. We specifically believe the opposite. As shown in our review, an increased contractility is present in the ventricle that is not allowed to increase its wall thickness. Hypercontractility is necessary for maintaining a normal ventricular function when wall stress is increased. It is likely that, in patients with pre-existing pathologies such as coronaropathies, a prolonged increased contractility will induce a myocardial ischemia and will be detrimental. Alternative strategies directed toward the cause of hypertrophy, such as ventricular assistance devices or renin-angiotensin-aldosterone system and β-adrenergic inhibition, indirectly lead to a regression of hypertrophy. New therapeutic approaches such as those presented in our article that would reorchestrate the different constitutive elements of the ventricles could be promising approaches. They would better protect cardiomyocytes than a direct blockade of hypertrophy.
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