Left Ventricular Hypertrophy
Pathogenesis, Detection, and Prognosis

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When the heart faces a hemodynamic burden, it can do the following to compensate: (1) use the Frank-Starling mechanism to increase crossbridge formation; (2) augment muscle mass to bear the extra load; and (3) recruit neurohormonal mechanisms to increase contractility. The first mechanism is limited in its scope, and the third is deleterious as a chronic adjustment. Thus, increasing mass assumes a key role in the compensation for hemodynamic overload. This increase in mass is due to the hypertrophy of existing myocytes rather than hyperplasia, because cardiomyocytes become terminally differentiated soon after birth. In response to pressure overload in conditions such as aortic stenosis or hypertension, the parallel addition of sarcomeres causes an increase in myocyte width, which in turn increases wall thickness. This remodeling results in concentric hypertrophy (increase in ratio of wall thickness/chamber dimension).

According to LaPlace's Law, the load on any region of the myocardium is given as follows: (pressure×radius)/(2×wall thickness); thus, an increase in pressure can be offset by an increase in wall thickness. Because systolic stress (afterload) is a major determinant of ejection performance, the normalization of systolic stress helps maintain a normal ejection fraction even when needing to generate high levels of systolic pressure.[1] Volume overload in conditions such as chronic aortic regurgitation, mitral regurgitation, or anemia engenders myocyte lengthening by sarcomere replication in series and an increase in ventricular volume. This pattern of eccentric hypertrophy (cavity dilatation with a decrease in ratio of wall thickness/chamber dimension) is also initially compensatory, such that the heart can meet the demand to sustain a high stroke volume. However, chronic hypertrophy may be deleterious because it increases the risk for the development of heart failure and premature death.

This review will focus on the pathogenesis of pressure-versus volume-overload types of left ventricular hypertrophy (LVH), detection, clinical manifestations, and prognosis. Where possible, observations from human studies will be presented that have led to major insights regarding the pathogenesis of hypertrophy and the potential for its reversal.

Pathogenesis of Load-Induced Hypertrophy
Pressure Versus Volume Overload

It is generally believed that a mechanical signal initiates a cascade of biological events leading to coordinated cardiac growth. If this is true, the signals for volume versus pressure overload are either quite different or result in remarkably different patterns and mechanisms of growth. Within hours after a pressure overload occurs in the heart in vivo, myosin heavy chain synthesis increases by ≈35%; this increase is initially mediated by an increase in translational efficiency[2] (Figure 1). In contradistinction, in severe, pure volume overload, as is seen in mitral regurgitation, much of the increase in left ventricular (LV) mass may accrue from a decrease in the myosin heavy chain degradation rate.[3] If hypertrophy were perfectly regulated by the mechanical signal using a typical feedback loop, changes in radius, thickness, and pressure would be orchestrated such that wall stress would be constantly normalized. However, this often does not occur. For example, a large myocardial infarction imposes a volume overload on the remaining myocardium, and cardiac dilatation with an increase in LV mass rapidly occurs.[4] Although the initial dilatation may be compensatory to maintain stroke volume, adverse remodeling often develops whereby the ventricle becomes progressively more spherical and wall stress increases, perpetuating the dilatation. In individuals with aortic stenosis and hypertension, especially older women, exuberant hypertrophy develops, wall stress is subnormal, and ejection performance is normal or supernormal.[5,6]

Both forms of hypertrophy are usually accompanied by complex changes in gene reprogramming.[7] These changes include the re-expression of immature fetal cardiac genes, including the following: (1) genes that modify motor unit composition and regulation, (2) genes that modify energy metabolism, and (3) genes that encode components of hormonal pathways (eg, atrial natriuretic peptide, angiotensin converting enzyme). In addition, variable or later blunted expression occurs in other genes that modify intracellular ion homeostasis (eg, downregulation of sarcoplasmic reticulum calcium ATPase [SERCA-2], with variable upregulation of the Na^+/Ca^{2+} exchanger), and key parasympathetic and sympathetic receptors are downregulated (eg, downregulation of β_1-adrenergic receptors and M2 muscarinic receptors and

(*Circulation*. 2000;102:470-479.)

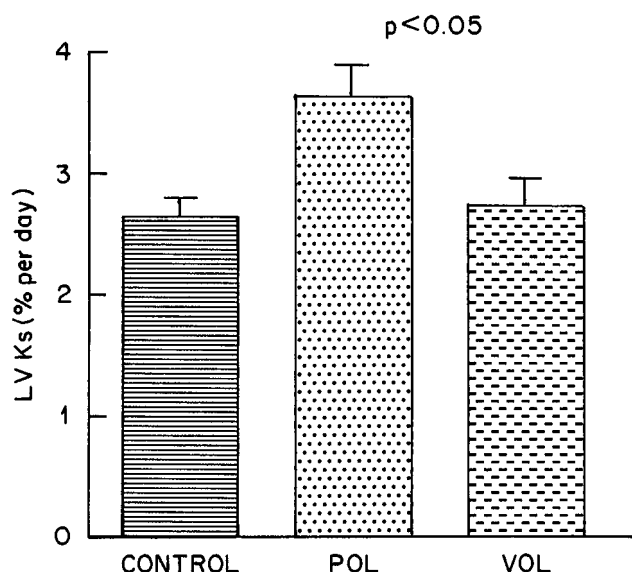*Circulation* is available at http://www.circulationaha.org

Figure 1. LV myosin synthesis rate (LV Ks) for normal dogs (CONTROL), dogs subjected to pressure overload (POL), and dogs subjected to volume overload (VOL); *$P<0.05$. Myosin heavy chain synthesis rate increases in response to acute pressure overload, but it does not increase in acute experimental volume overload. Adapted with permission from Imamura T, McDermott PJ, Kent RL, et al. Acute changes in myosin heavy chain synthesis rate in pressure versus volume overload. *Circ Res.* 1994;75:418–425.

increase in ratio of angiotensin II AT2 to AT1 receptor subtypes). Some of these switches, such as the increased expression of the slow myosin ATPase isoform β-myosin heavy chain relative to the fast myosin ATPase isoform α-myosin heavy chain, are adaptive and promote a more favorable myoenergetic economy. However, the long-term functional implications of many of the changes in gene expression are still unclear in the context of integrated cardiovascular function in vivo.

How Is Mechanical Information Transduced to Cardiac Growth?

The essence of hypertrophy is an increase in the number of force-generating units (sarcomeres) in the myocyte. How does an increase in force on the myocyte trigger an increase in force-generating units (sarcomeres) in the myocyte? The implication is that mechanical input is transduced into a biochemical event that modifies gene transcription in the nucleus. An excellent candidate for such a transducer is the focal adhesion complex, whereby integrins connect the internal cytoskeleton of the cell (which is connected to the nucleus) to the extracellular matrix (ECM).[8] Multiple tyrosine-phosphorylated kinases and serine-threonine kinases that are implicated in the signaling of hypertrophy can be found in the ECM.[9] Although critical proximal steps in mechanosignal transduction are not yet well understood, there is now evidence that the disruption of cell-cell and cell-ECM contact is sufficient in itself to modulate both cell growth and apoptosis (anoikis).[10] In chronic hypertrophy, there are changes in integrin expression[11] and possible integrin shedding into adjacent ECM,[12] which raises the potential for

disordered biomechanical signal transduction for growth and suboptimal myocyte-ECM coupling for force generation.

Acute biomechanical signal transduction in experimental models is often accompanied by recruitment of the G-protein–coupled neurohormones (such as angiotensin II and endothelin-1), whose activation likely serves to amplify the growth signaling triggered by the mechanical event itself. The current review by Sugden[13] discusses current models of growth-signaling pathways activated by G-protein–coupled neurohormones. In clinical medicine, a critical question is whether a proximal neurohormonal signaling molecule serves as a master switch for load-induced hypertrophy.

Some have postulated that angiotensin II, via the AT1 receptor, plays a mandatory role in the induction of hypertrophy because this hormone can directly induce the molecular events of early cardiac growth,[14–16] its synthetic machinery is upregulated in hypertrophied rat[17] and human[18] myocardium, and it seems to be required for the growth of stretched neonatal myocytes in vitro.[19] However, recent studies in experimental hypertrophy[20] and the observations that pressure overload produces robust hypertrophy in transgenic mice with AT1a receptor knockout[21,22] show that angiotensin II is not mandatory for load-induced hypertrophy.

The avid search for a signaling molecule that serves as a master switch for clinical hypertrophy recently shifted to calcineurin, a calcium calmodulin-dependent phosphatase. Transgenic mice that overexpress components of the calcineurin signaling pathway develop a hypertrophic phenotype that can be suppressed by pharmacological inhibitors of calcineurin.[23] However, calcineurin inhibitors fail to suppress experimental hypertrophy in several animal models[24,25] and in humans with hypertension after cardiac transplantation.[26] Taken together, these experimental animal and human observations suggest that redundant signaling pathways are likely to modulate load-induced hypertrophy, with the potential for recruitment of alternate signaling cascades when a single pathway is suppressed.[27]

Hypertrophy and Connective Tissue

For myocyte growth to support an increased biomechanical load, it must be accompanied by coordinated increases in the surrounding architecture of connective tissue and ground substance, as well as the capillary and nerve networks. The connective tissue itself is primarily composed of collagen with smaller amounts of elastin, laminin, and fibronectin. Although collagen types I, III, and V are found in the myocardium, type I comprises ≈85% of the total collagen in the area. The complex collagen weave provides a mechanism for translating individual myocyte force generation into ventricular contraction, it restrains the development of interstitial edema, and it is responsible for much of the ventricle's passive diastolic stiffness.[28]

In pressure-overload hypertrophy, the increase in collagen production that occurs as an adaptation to overload must be distinguished from pathological collagen deposition, which is characterized by both perivascular and interstitial fibrosis.[28–31] It is not clear whether the initiation of reactive fibrosis in some models is, in part, triggered by defective cell-ECM contact, myocardial ischemia, or the local activa-

tion of trophic peptides such as angiotensin II, aldosterone, and/or catecholamines, which results in the sequential expression of transforming growth factor-β1, fibronectin, and relative increase in collagen I.[29–31] Autopsy and biopsy studies of patients with severe chronic hypertension or aortic stenosis frequently show changes in collagen architecture, as well as severe increases in the percentage of fibrosis occupying the myocardium; this fibrosis reaches a maximum at $\approx$30%.[31,32]

Role of Metalloproteineases in Volume-Overload Hypertrophy

ECM remodeling seems to be very different in volume-overload hypertrophy, in which cavity dilatation occurs in part due to both myocyte elongation and changes in collagen cross-linking and the collagen weave.[33–36] Dissolution of the collagen weave leads to increased elasticity, muscle fiber slippage, and an increase in chamber size.[37] Such dissolution is predominantly related to the activation of matrix metalloproteineases (MMPs), a family of zinc-containing proteins that includes stromalysins, collagenases, gelatinases, and membrane-type MMPs.[38,39] Observations in animal models[39–41] and humans[42] with end-stage dilated cardiomyopathies show that an increase in MMP activation and a downregulation of localized tissue inhibitors is critical for the changes in the collagen matrix that permit chamber expansion. The role of MMPs is less well understood in concentric hypertrophy; however, preliminary observations from our laboratory show that MMPs are also activated in experimental pressure overload hypertrophy (E. Goldsmith, PhD, et al, written communication, February 2000).

Diagnosis of LVH

Echocardiographic Detection

Pathological hypertrophy may be associated with an absence of symptoms for many years before the development of congestive heart failure or unexpected sudden death. Thus, in contemporary clinical practice and population studies, the diagnosis of LVH depends predominantly on echocardiographic measurements or novel noninvasive imaging techniques. Methods for 2D targeted M-mode echocardiographic measurements of LV dimensions and the calculation of LV mass are standardized and have been reported in detail elsewhere.[43] The detection of pathological LVH requires adjustments for sex, height, and body mass. Although multiple studies have offered echocardiographic criteria for LVH, analyses of the large original cohort and offspring subjects (n=6148) of the Framingham Heart Study have provided criteria that are based on a healthy population distribution of LV mass (Table).[44] Using these mass/height criteria, the prevalence of LVH in the entire Framingham Study population is 16% in women and 19% in men.[44] Echocardiographic LVH is more prevalent than LVH detected by electrocardiography, with overall rates of 17.4% versus 2.4%, respectively.

Normal ranges of LV and right ventricular mass have been described in healthy male and female subjects using cine-MRI as well as ultrafast CT. In a recent study of 75 healthy subjects, the upper limit (95% confidence limit) of LV mass normalized to body surface area was 113 g/m^2 in men and 95

Echocardiographic Criteria for Normal Upper Limits of LV Mass

	Men	Women
n	347	517
Age, y	42±12	43±12
LV mass, absolute, g	259	166
LV mass, corrected for BSA, g/m^2	131	100
LV mass, corrected for height, g/m	143	102

BSA indicates body surface area.

Criteria for upper limit values of LV mass in adult men and women are set at 2 SD above the mean values of healthy population subjects derived from the original cohort and offspring subjects of the Framingham Heart Study. Echocardiographic measurements were performed in accordance with the American Society of Echocardiography, and calculation of LV mass (LVM) was done using the modified formula of

$$LVM = 0.8 \times [1.04 \times (LVID + LVPWT + IVST)^3 - LVID^3]$$

where LVID indicates LV internal diameter; LVPWT, LV posterior wall thickness; and IVST, intraventricular septal thickness.[44]

Adapted with permission from Levy D, Savage DD, Garrison RJ, et al. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol.* 1987;59:956–960 and Heider AW, Larson MG, Benjamin EJ, et al. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol.* 1998;32:1454–1459.

g/m^2 in women.[45] The recent review by Lorenz et al[45] summarizes normative sex-based values of LV mass reported by additional contemporary MRI and CT studies. In comparison with the Framingham Heart Study, which echocardiographically detected LVH, current novel imaging studies are limited by the much smaller size of the study populations and less robust longitudinal outcome data.

Prognostic Implications of LVH

Analyses from the Framingham Heart Study have unequivocally demonstrated the prognostic value of echocardiographically detected LVH. First, echocardiographic LVH identifies a population at high risk for cardiovascular disease. Subjects with LVH are older, more obese, have higher blood pressures, and are more likely to have preexisting coronary disease and depressed LV systolic function (ejection fraction).[46] Second, echocardiographic LVH predicts an increased risk of cardiovascular morbidity and death, even after adjustment for other major risk factors (age, blood pressure, pulse pressure, treatment for hypertension, cigarette use, diabetes, obesity, cholesterol profile, and electrocardiographic evidence of LVH).[47] In otherwise healthy subjects followed for 4 years in whom LVH was defined as an LV mass adjusted for height of >143 g/m in men and >102 g/m in women, the relative risk of developing cardiovascular disease was 1.49 in men and 1.57 in women for each increment of 50 g/m in LV mass. This increment of LV mass was also associated with a relative risk of cardiovascular death of 1.73 in men and 2.12 in women and a relative risk of all-cause death of 1.49 in men and 2.01 in women.

Increased LV mass is also associated with an increased risk for sudden cardiac death,[48] which is more pronounced in men than in women. Knowledge of geometric remodeling patterns provides little additional prognostic information beyond LV mass and traditional cardiovascular risk factors.[49] A limita-

tion of these data is that the Framingham Heart Study is composed predominantly of white adults. The prevalence of echocardiographic LVH is reported to be higher in black adults, and LVH is associated with a doubling of mortality in both white and black cohorts.[50] Ongoing studies, such as the Jackson Heart Studies, may address unanswered issues regarding the variance and development of hypertrophy in black subjects.

Detection of Physiological Hypertrophy

Measurements of LV mass must be interpreted in the clinical context. In both men and women, age, height, systolic (but not diastolic) blood pressure, and body mass index (a measure of obesity) are highly significant and independent predictors of LV mass.[51] Other demographic studies, corrected for sex and height, have shown that body weight is the most powerful independent predictor of LV mass[52]; in individual patients, increases and reductions in body weight are accompanied by changes in LV mass.[53] It is not yet known if increases in LV mass associated with obesity confer an increased risk for cardiovascular morbidity or mortality.

Cardiac hypertrophy occurs during changes in load and is not deleterious in the following 3 settings: maturation in infancy and childhood, pregnancy, and exercise. It is plausible that a key difference in the biomechanical signals in these states is the intermittence or transient duration of excess load, compared with the sustained load of hypertension or aortic stenosis. In humans, the heart grows in proportion to body growth in a roughly linear relationship, such that the LV weight in grams is 3 to 4 times the body weight in kilograms. Obviously, the 10-fold increase in LV mass that occurs from childhood to adulthood is necessary and not deleterious. During pregnancy, the requirement for an increased stroke volume and cardiac output is accompanied by a substantial increase in LV dimension and mass, which regresses over months in the postpartum period.[54] Finally, both the concentric hypertrophy that occurs in the trained athlete who specializes in sports requiring isometric skeletal muscle contraction (ie, weight lifting, wrestling) or the eccentric hypertrophy that occurs in sports requiring isotonic exercise (ie, long-distance running, cycling) are consistent with normal LV systolic and diastolic function.[55,56] In the Framingham Study, leisure-time physical activity was associated with LV mass in men, but not in women.[51] Thus, an increase in LV mass by itself does not result in muscle dysfunction and must be carefully interpreted in the clinical context.

Clinical Manifestations of Hypertrophy

Patients with LVH due to continuous pressure overload (aortic stenosis) or volume overload (mitral regurgitation) may remain in a compensatory phase with no symptoms and normal or near-normal exercise reserve for years. Others have a transition to heart failure that may be due to diastolic dysfunction, systolic dysfunction, or both.

Diastolic Dysfunction in Hypertrophy: Mechanisms and Detection

In patients with LVH, abnormalities in both myocardial relaxation and passive filling have been detected. Myocardial

relaxation, which reflects the time course and extent of crossbridge dissociation after systolic contraction, is modified by the load imposed on the muscle,[57] the rapid reduction of cytosolic calcium to basal levels, and those factors such as intracellular pH that modify myofilament sensitivity to calcium. The initial rapid fall of cytosolic calcium is achieved by the ATP-dependent sarcoplasmic reticulum pumps (SERCA-2), which move intracellular calcium "uphill" against a concentration gradient into the sarcoplasmic reticulum. The kinetics of these pumps and optimal calcium loading in the sarcoplasmic reticulum are modified both by the ATP-dependent energy charge and the phosphorylation state of the inhibitory regulatory protein phospholamban.[58,59] A slower phase of extrusion of calcium, that entered during depolarization, depends on the low affinity, high-capacity sarcolemmal Na^+/Ca^{2+} exchanger.[60]

The downregulation of SERCA-2 is nearly ubiquitous in animal models of advanced pressure overload hypertrophy, and compelling evidence shows that changes in SERCA-2 levels have the potential to modify the time course of the calcium transient, myocardial relaxation, and the force-frequency response.[61–64] However, the marked reductions in SERCA-2 observed in both models of compensated hypertrophy and end-stage human dilated cardiomyopathy are associated with very divergent degrees of impaired relaxation (as well as systolic performance), which indicate that the reduced expression of this pump cannot be the sole mechanism of impaired function. In humans with dilated cardiomyopathy, reductions in protein levels of SERCA-2 may be partially compensated for by increases in levels of the Na^+/Ca^{2+} exchanger.[65] In humans with load-induced hypertrophy, potential coordinated changes in SERCA-2 and the Na^+/Ca^{2+} exchanger have not yet been well characterized, distinct from end-stage heart failure. In addition to these changes, other molecular adaptations have the potential to modify crossbridge attachment and perturb myocardial relaxation; these adaptations include increased β-myosin ATPase activity, changes in troponin subunit isoform expression and phosphorylation, and blunted cAMP-mediated phosphorylation of regulatory proteins such as phospholamban.[66,67]

In humans, myocardial relaxation properties are often estimated by surrogate measurements of the first derivative of LV pressure decay ($-dp/dt$) and by modeling the time course of LV pressure decay between aortic valve closure and mitral valve opening to an exponential function to obtain a time constant (τ) of LV pressure decline. These techniques provide clues to the presence of impaired relaxation but have serious limitations in diseased hearts because isovolumic pressure decay is often not exponential, and the active process of relaxation may be prolonged and dyssynchronous, extending well beyond mitral valve opening.

Diastolic Filling

The dynamics of passive LV filling and the relationship between diastolic volume and pressure are influenced by the time course of active relaxation and the passive deformation properties of the myocardium, including the thickness of the wall and its composition, particularly collagen deposition and its architecture. The hypertrophied myocyte in isolation has

only a limited role in increasing chamber stiffness.[68] Doppler echocardiographic techniques are widely used to assess transmitral valve flow velocity curves, which characterize left atrial emptying and ventricular diastolic filling.[69,70] Alternatively, radionuclide ventriculography is sometimes used in clinical research to estimate the rates of early and peak ventricular filling.[69] The rate and magnitude of diastolic ventricular filling just after mitral valve opening is directly related to the pressure gradient across the mitral valve, which is determined by both left atrial pressure and the active fall of LV pressure to its nadir during this relaxation filling period.

Three patterns of LV filling as assessed by Doppler flow velocity curves are helpful in identifying progressively worse diastolic function.[69,70] These patterns are (1) "slowed relaxation," which is characterized by reduced early diastolic inflow velocity with a compensatory increase in filling due to left atrial contraction (decreased E/A ratio); (2) "pseudonormalization," which has a preserved ratio of the contributions of early diastolic filling and atrial contraction (normal E/A ratio) but a rapid deceleration of early mitral inflow; and (3) a "restrictive pattern," in which almost all filling occurs explosively in early diastole in association with a very short deceleration time, which is suggestive of a high left atrial pressure driving filling into a "stiff" LV. This latter pattern of severe diastolic dysfunction is characterized by an S3 gallop as the auscultatory marker of abrupt cessation of ventricular filling in early diastole and, frequently, increased left atrial regurgitant flow into the pulmonary veins. These patterns must always be interpreted in the context of other clinical features, and they can change abruptly in response to volume overload and exercise, and long-term during normal pregnancy[54] and childhood development.[71] Controversy and conflicting observations still exist regarding the depression of isovolumic relaxation and filling indices during aging in normal humans in the absence of hypertension and hypertrophy.[72–75]

In athletes with moderate hypertrophy, there is usually no evidence of altered systolic contractile indices or indices of diastolic filling.[55,56] In contrast, in patients with LVH due to sustained pressure overload (hypertension and aortic stenosis), a hemodynamic hallmark is the elevation of LV end-diastolic pressure relative to a normal or small LV diastolic cavity volume. This decrease in diastolic chamber distensibility is predominantly related to altered passive properties causing an increase in myocardial stiffness, which is described formally by the mechanical stress/strain relationship. Dynamic abnormalities of slowed isovolumic LV pressure decay, as well as slowed early diastolic mitral inflow velocity and ventricular filling with enhanced reliance on atrial transport (decreased E/A ratio), have been described in multiple studies using both invasive and noninvasive technologies; in some patients with advanced hypertrophy, this pattern may evolve to the more severe abnormality of a restrictive pattern of diastolic filling.[76–80]

In patients with aortic stenosis and regurgitation, combined hemodynamic and biopsy studies suggest that the prolongation of relaxation is closely related to the magnitude of hypertrophy, whereas abnormal increases in myocardial stiffness are more closely related to changes in collagen architecture.[32] Abnormalities of relaxation and passive myocardial stiffness usually precede alterations in systolic ejection indices (end-systolic volume and ejection fraction) and are present in ≈50% of patients with pressure overload and normal systolic ejection indices,[76,77] although more subtle abnormalities, including depressed midwall shortening, may be present.[81,82]

Effects of Aging and Sex on Diastolic Function in LVH

In older patients with isolated systolic hypertension, concentric LVH is common.[83] Diastolic dysfunction, including the presence of a Doppler filling pattern of impaired relaxation, has been observed in >80% of older hypertensives.[84] In patients with aortic stenosis, senescence profoundly influences the pattern of hypertrophic growth and diastolic function. Using hemodynamic studies complemented by morphometric analyses of ventricular biopsies, Villari et al[85] compared younger (<60 years) and elderly (>65 years) patients with comparable severities of aortic stenosis and showed that elderly patients with pressure overload were characterized by more severe hypertrophy and interstitial fibrosis, as well as more severe impairment of relaxation, myocardial stiffness, and filling indices. Ejection fraction and midwall shortening were similar in the 2 groups (younger and elderly patients).

Gender also influences function in pressure-overload hypertrophy in humans.[5,6] In men and women with aortic stenosis and similar aortic valve areas and gradients, men are more likely to have cavity enlargement, a lower ejection fraction, and increased diastolic myocardial stiffness associated with more severe changes in collagen architecture.[86] Sex-based differences in diastolic function are recapitulated in rodent aortic stenosis models in which female animals demonstrate more favorable changes in cardiac geometry,[87,88] as well as better preservation of normal adult cardiac gene expression.[89]

Prevalence and Prognosis of Heart Failure due to Diastolic Dysfunction

In severe cases of chronic LVH associated with diastolic dysfunction and preserved ejection fraction, both male and female patients may experience episodic severe congestive heart failure and hospitalization. Even in patients with milder degrees of hypertrophy and diastolic dysfunction, an inability to augment LV volume during exercise may severely limit exercise cardiac output and exercise reserve. In a case-control study from the Framingham Heart Study,[90] 51% of the subjects with congestive heart failure had a normal LV ejection fraction (≥50%). In these patients, diastolic dysfunction may be inferred, but it was not characterized by quantitative echocardiographic-Doppler indices. Women predominated in this group with normal ejection fractions (65%), whereas men predominated (75%) in the cohort with low ejection fractions.

Although heart failure patients with normal LV ejection fractions had a lower mortality risk than those with reduced ejection fractions, heart failure patients with normal ejection fractions had an annual mortality of 18.9% versus 4.1% for matched control subjects during the 6-year study period,

indicating a >4-fold mortality risk.[90] Atrial fibrillation also modifies diastolic dysfunction in patients with LVH. The increased reliance on atrial contraction to fill the stiff left ventricle means that atrial fibrillation is usually very poorly tolerated. In addition, pressure overload from hypertension is responsible for more atrial fibrillation in the population (≈14% of cases) than any other risk factor, and atrial fibrillation confers a 4- to 5-fold increase in the risk of stroke.[91]

Management of Heart Failure With LVH and Diastolic Dysfunction

No randomized clinical trials or evidence-based consensus guidelines exist regarding end points of survival, hospitalization, or quality-of-life to firmly guide the management of patients with LVH and heart failure due to diastolic dysfunction. On the basis of the above experimental insights, clinical observations, and consensus of expert opinion, current therapy is aimed at the following: (1) preserving sinus rhythm and suppressing tachycardia, (2) reducing elevated left atrial and diastolic ventricular pressures without excessively reducing preload and depressing stroke volume and cardiac output, and (3) preventing or treating the confounding condition of myocardial ischemia due to coronary artery disease.[92–94] These treatment goals are usually achieved by the cautious and combined use of several agents, including β-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, low-dose diuretics, long-acting calcium-channel blockers, and long-acting nitrates.

Although nonhydropyridine calcium-channel blockers have therapeutic roles in limiting tachycardia and reducing filling pressures via vasodilation, no evidence exists regarding benefit via the direct modulation of intracellular diastolic calcium. Digoxin usually has no role in this condition, except as adjunctive therapy to slow rapid ventricular response in atrial fibrillation. Invasive clinical studies suggest that ACE inhibition may directly, albeit modestly, enhance impaired myocardial relaxation via intracardiac effects.[80] Randomized clinical trials are now in progress to examine the use of angiotensin AT1 receptor antagonists in diastolic heart failure. The cornerstone of treatment of hypertrophic heart disease with diastolic dysfunction, progressive systolic dysfunction, or both is complete and continuous reduction of load to promote near-normalization of LV mass. This concept is addressed in detail later in this discussion.

Systolic Dysfunction: Mechanisms and Detection

The changes in cellular biology leading to the transition to systolic dysfunction are complex and almost certainly not due to a single change in gene expression. In chronic pressure overload and extreme volume overload, subendocardial ischemia due to reduced coronary flow reserve probably plays a role in limiting exercise reserve and promoting myocardial fibrosis.[95] Afterload excess due to inadequate hypertrophy to normalize wall stress itself reduces systolic ejection performance, independent of intrinsic changes in contractility,[1,96–98] and it accounts for the extremely rapid improvement in ejection fraction after valve replacement in some patients with aortic stenosis and aortic regurgitation. Implicit in this concept is the conundrum that an assessment of ejection indices (eg, ejection fraction) alone is often inadequate to distinguish afterload excess versus impaired contractile properties in patients with hemodynamic load. Although this can be achieved by meticulous assessment of the relationship between ejection indices and wall stress or by the estimation of Emax during volume unloading (transient caval occlusion), these approaches are research tools that are not practical for usual clinical practice. Meticulous assessment of LV midwall shortening using echocardiography permits the identification of impaired contractile function in some patients in whom the geometric changes of concentric remodeling promote a normal ejection fraction.[81,82]

Additional mechanisms for reduced contractility at the level of the myocyte include impaired calcium homeostasis, which contributes to the depression of the force-frequency relationship,[64] changes in the composition of the motor unit, including a relative increase in β-myosin heavy chain that occurs in both small mammals and humans,[99] and densification of the microtubules within the myocyte, which places an internal viscous load on sarcomere shortening.[100] In volume overload, loss of myofibrils also occurs.[101] Complex changes in energy metabolism may impair the capacity to maintain levels of free energy at ATP hydrolysis (ΔG) where needed for optimal function of both the motor unit and the membrane pumps required for ion homeostasis.[102–104]

Apoptosis may cause a repetitious, albeit very low frequency, loss of myocytes in the hypertrophied heart that would invariably augment the biomechanical load on the remaining myocytes. A low frequency of apoptotic cardiac myocytes has been identified in early pressure overload before the development of adaptive hypertrophy,[105] in experimental models of hypertension,[106,107] and by our laboratory in mice with aortic stenosis during the transition to failure but not in early adaptive LVH.[12] The prevalence of apoptotic myocytes has been wildly variable in studies of end-stage human dilated cardiomyopathy, but it is not yet characterized in human pressure- or volume-overload LVH. Regardless of disputes relating to its frequency, we do not yet know if myocyte apoptosis contributes to the progression of failure and merits suppression, or if it is a homeostatic process that serves to dismantle dysfunctional myocytes in an orderly manner.

Management of Heart Failure With LVH and Systolic Dysfunction

Evidence-based trials have led to the development of consensus guidelines for the management of heart failure associated with LV systolic dysfunction (ejection fraction ≤40%).[93,94] The management of heart failure patients with LVH and systolic dysfunction should follow these guidelines, which include the use of ACE inhibitors, β-adrenergic blockers, diuretics to relieve fluid overload, and digoxin to relieve persistent symptoms. Spironolactone can be considered in advanced heart failure.[94]

Regression of LVH: A Feasible Goal

The population-based evidence discussed above suggests that therapies to limit and reverse LVH in patients are desirable,
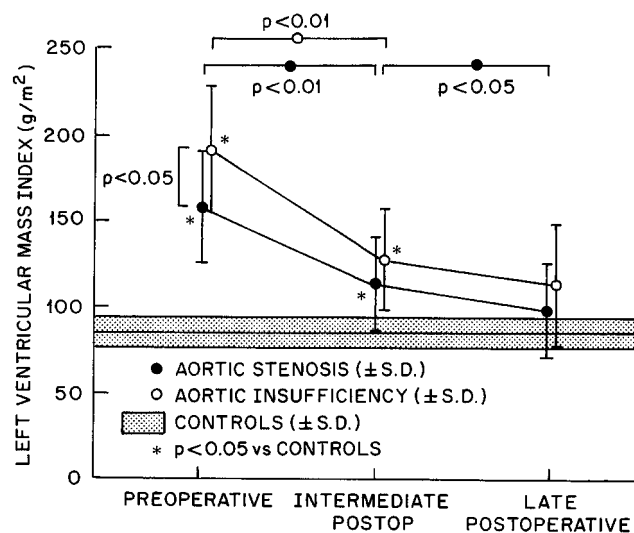
Figure 2. Measurements of LV mass index in patients with hypertrophy due to aortic stenosis (●) or aortic insufficiency (○) preoperatively, in intermediate postoperative period (≈1.5 years), and late postoperatively (≈8 years). The LV mass index in normal adults is shown in the bar. LVH regresses rapidly during the first year after reduction of load via valve replacement and continues to regress further to near-normal levels. Adapted with permission from Monrad ES, Hess OM, Murakami T, et al. Time course of regression of left ventricular hypertrophy after aortic valve replacement. *Circulation*. 1988;77:1345–1355.

Figure 3. The diastolic stress-midwall circumference (top) and stress-strain relations (bottom) are shown before (●) and after (○) aortic valve replacement in a patient with aortic stenosis. The leftward shift in these relationships suggests an increase in myocardial stiffness. In this patient, hemodynamic measurements were correlated with biopsy measurements of fiber diameter and myocardial fibrosis. Parallel to this increase in diastolic myocardial stiffness after aortic valve replacement, LV fiber diameter decreased, whereas the fraction of myocardium composed of fibrous tissue increased. Thus, early after valve replacement, the rapid regression of hypertrophy in the presence of much slower remodeling of fibrous tissue can result in a transient increase of diastolic myocardial stiffness. EF indicates ejection fraction; MFD, myocardial fiber diameter; and IF, volume fraction of interstitial fibrosis. Adapted with permission from Hess OM, Ritter M, Schneider J, et al. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation*. 1984;69:855–865.

even in the absence of symptoms of heart failure. We already know that a regression of severe LVH can be achieved in some patients. Major insights (Figure 2) regarding the regression of hypertrophy in patients with hemodynamic overload can be drawn from the extraordinary collection of studies from one team in Zurich.[32,76,77,85,86] This team performed serial LV hemodynamic and biopsy analyses before and after valve replacement in patients with valvular aortic stenosis and aortic insufficiency. These patients were characterized by massive LVH, severe collagen deposition, diastolic dysfunction and, in some instances, depression of systolic ejection indices. In brief, these observations demonstrated that near-normalization of systolic load causes a rapid reduction in myocyte hypertrophy and LV mass (≈35% reduction) within a few weeks after valve replacement.[108]

In this early phase of the rapid regression of myocyte hypertrophy but little change in collagen and matrix, myocardial relaxation improves; however, the fraction of collagen in the myocardium actually increases. This increase is accompanied by a worsening of diastolic indices of myocardial stiffness (Figure 3). Astonishingly, during continued reduction of load many months to a few years after valve replacement, regression of interstitial fibrosis and further regression of LVH occurs, resulting in near-normalization of both muscle mass and fibrous tissue content.[108] This initial rapid regression of hypertrophy and later regression of fibrosis is accompanied by a reversal of diastolic dysfunction, an improvement in systolic dysfunction (when present), and an improvement in exercise reserve.

In these studies, the increased biomechanical loads were abruptly reduced by mechanical valve replacement in the absence of pharmacological interventions. These human ob-
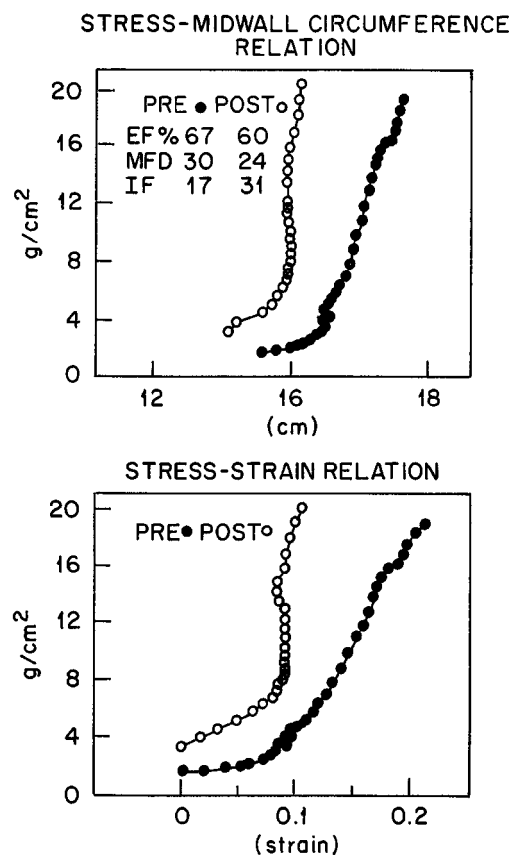
servations speak to the primacy of normalizing the signal of excess systolic load in the regulation of human hypertrophy, rather than modulating secondary neurohormonal and growth-factor signaling independent of load correction. What magnitude of regression is achieved with pharmacological therapy in hypertensive patients? Dahlof et al[109] performed a meta-analysis of 109 studies involving 2357 hypertensive patients; in this analysis, ACE inhibitors reduced LV mass by ≈15%. Lesser reduction was achieved with diuretics (11%), β-blockers (8%), and calcium-channel blockers (8.5%). Overall, LV mass was reduced by only 11.9%, which is far less than the magnitude of early regression and the late near-normalization of mass observed after valve replacement.

The relatively disappointing magnitude of regression observed in pharmacological trials in hypertensive patients is

likely related to an incomplete reduction of hypertension itself rather than to inadequate targeting of downstream signal cascades. In addition to a more effective implementation of available antihypertensive agents to achieve current consensus treatment guidelines,[110] new antihypertensive agents with potent effects on systolic hypertension raise the potential for more complete long-term regression of hypertrophy in hypertensive patients, similar to that which can be achieved with valve replacement in aortic stenosis and regurgitation.

Should Hypertrophy Be Stimulated?

In some pathological conditions, the development of moderate concentric hypertrophy might be beneficial if it could be enhanced. In myocardial infarction, the presence of increased LV mass worsens prognosis. Yet paradoxically, it is the lack of an increase in wall thickness to compensate for the increase in chamber radius which leads to the progressively increased diastolic stress that begets the remodeling that is accompanied by LV systolic dysfunction and increased morbidity and mortality. If one could engineer an increase in wall thickness and limit cavity dilatation after infarction, experimental evidence suggests that this strategy would restrain remodeling and be beneficial.[111] In addition, novel experimental models, such as severe hypertension induced by the inhibition of nitric oxide synthesis,[112] provide proof of the concept that the heart can successfully adapt to severe pressure overload by concentric remodeling and enhanced myocardial contractile function without a significant increase in LV mass. The molecular mechanisms of these adaptations, which enhance cardiac performance during hemodynamic load in the absence of pathological changes in LV mass, await gene discovery for development as pharmacological targets.

Acknowledgments

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