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STATE-OF-THE-ART PAPER

Left Ventricular Structural Remodeling in Health and Disease

With Special Emphasis on Volume, Mass, and Geometry

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The changes in left ventricular (LV) structure and geometry that evolve after myocardial injury or overload usually involve chamber dilation and/or hypertrophy. Such architectural remodeling can be classified as eccentric or concentric. Consideration of LV volume, mass, and relative wall thickness (or mass/volume) allows classification of LV remodeling that includes virtually all LV remodeling changes that are seen in health and disease. These various architectural changes generally include the development of LV hypertrophy in a pattern that is closely related to the type of injury or overload, and they are accompanied by differences in cardiac function and hemodynamics. Some patterns of remodeling are associated with adverse outcomes whereas others appear to be adaptive and physiologic without adverse consequences. Considering all patients with LV hypertrophy as a homogenous group is inconsistent with our understanding of the various remodeling patterns that are discussed in this review. (J Am Coll Cardiol 2011;58:1733–40) © 2011 by the American College of Cardiology Foundation

Structural remodeling of the left ventricle and a variety of functional changes have long been known to follow injury (e.g., myocardial infarction) or overload (e.g., systemic arterial hypertension), but the relative importance of alterations in structure versus change in function is an ongoing topic of discussion. Over the years clinicians and physiologists have contributed to an evolution and embellishment of the definitions of left ventricular (LV) structural remodeling that were developed by Linzbach (1). However, the lack of a standardized classification of LV remodeling patterns, particularly those with eccentric/dilated geometry contributes to difficulties in our attempts to compare the data among different published studies and limits our efforts to define specific populations for clinical trials. In this article, we will review the alterations in LV structure and geometry that are seen in a variety of physiologic and pathologic conditions. We will consider changes in LV mass and volume, and we will emphasize the ratio of LV wall thickness to chamber radius, which is referred to as relative wall thickness (RWT). The review will include a historical, physiologic, and clinical basis for the application of a structural classification of LV remodeling in the assessment of the LV response to hemodynamic overload. Our goal is to develop a scheme that classifies specific patterns of structural remodeling seen in health and a wide spectrum of disease states.

Background

Fifty years ago, Linzbach opined that the pathologic physiology of the heart can be understood only when we have defined the "quantitative structural relations of the organ in health and disease" (1). Based on an extensive experience at the Pathologic Institute of the University of Marburg, he developed anatomic/structural definitions of several LV remodeling patterns that appeared to be closely related to LV systolic function. He argued that when the pressure demands of the heart are increased, as in aortic stenosis or hypertension, a concentric hypertrophy develops with "no change in the size of the internal cavity." In this pattern of hypertrophy, peak systolic wall stress remains normal, but its time course peaks in late systole. This is a reversal of normal where peak force occurs in early systole. He also defined eccentric hypertrophy in which myocardial mass is increased in the presence of a chamber that is "larger than normal." As in concentric hypertrophy, peak systolic stress occurs in late systole; but in eccentric hypertrophy, systolic wall forces tend to be higher than normal. Linzbach contrasted these 2 abnormal patterns with that seen in human beings with normal hearts and in athletes with "physiologic" hypertrophy. He also described a "dilation without hypertrophy" that he called "plastic dilation." This condition was said to be seen in some patients with chronic coronary heart disease, myocarditis, and in the late stages of aortic or mitral

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Abbreviations and Acronyms

LV = left ventricular

LVH = left ventricular hypertrophy

MR = mitral regurgitation

MRI = magnetic resonance imaging

M/V = mass to volume ratio

RWT = relative wall thickness

regurgitation. It was considered to be irreversible and associated with a very limited cardiac reserve. His estimates of LV systolic wall forces and fiber shortening were later confirmed by direct measurements in patients with and without heart disease (vide infra). Based on this work with pathologic specimens, Linzbach concluded that such structural (and functional) remodeling forms the "morphologic substrate of the decompensated heart" and the clinical syndrome of heart failure.

In 1965, Grant et al. (2) used cardiac catheterization and angiographic methods to measure LV "cavity size and RWT" in patients with valvular heart disease. They defined eccentric hypertrophy as increased LV mass with "cavity enlargement" which differed from concentric hypertrophy in which "cavity size is not increased." Their patients with aortic stenosis exhibited concentric hypertrophy with an increase in both relative and absolute wall thickness. By contrast, patients with aortic or mitral regurgitation exhibited eccentric hypertrophy with a modest increase in absolute wall thickness but a normal or low RWT. They also mentioned a "mixed hypertrophy" as might be seen in combined pressure and volume overload (e.g., aortic stenosis and regurgitation). These early hemodynamic studies in conscious human beings were consonant with Linzbach's original observations that were made in pathologic specimens. Both Linzbach (1) and Grant et al. (2) based their definitions on 2 factors: 1) the presence or absence of LVH; and 2) the presence or absence of LV chamber enlargement. Although Grant et al. (2) measured RWT, neither Linzbach (1) nor Grant et al. (2) defined a specific range of normal for RWT.

Relative Wall Thickness

In an analysis of heart size and hemodynamics, Ford (3) reviewed the factors influencing myocardial work and the LV workload in humans and animals of widely varying body (and heart) size. He noted the nearly constant ratio of stroke volume to end-diastolic volume in normal healthy mammals with widely varying body size and argued that if LV systolic wall stress exhibited a similar "constancy" in ventricles of different size, the RWT should depend solely on LV systolic pressure. We used the slope of the relation between RWT and peak systolic pressure (RWT = 0.003 pressure) from Ford to estimate the normal range for RWT (3). Thus, in normal adults with a systolic arterial pressure ranging from 140 to 110 mm Hg, the RWT ranges from approximately 0.42 to 0.33. A lower pressure, often seen in children, provides a lower limit that could approach 0.30. Recognizing that an exact range of normal has not been precisely defined, we propose a range from 0.42 to 0.32, which is consistent with published data (vide infra).

More than a decade after Ford's observations, others recognized the potential utility of describing differences in RWT in a variety of populations with and without known heart disease. Using M-mode echocardiographic data from 4,975 participants in the Framingham Heart Study, Savage et al. (4) described a spectrum of morphologic types of LV hypertrophy in a "free living population." Three types of hypertrophy were defined simply on the basis of RWT >0.45 or <0.45; concentric hypertrophy was defined by a RWT above this limit whereas eccentric hypertrophy was said to be present if RWT was less than this value. Eccentric hypertrophy was then divided into those with an increased LV end-diastolic diameter and those with a normal LV end-diastolic diameter. These subtypes were referred to as "eccentric dilated" and "eccentric nondilated." They determined the prevalence of each of these patterns of hypertrophy in various age and sex groups. However, the application of their definitions is problematic because LVH with a normal RWT in the presence of a normal end-diastolic size, termed eccentric nondilated, is a conceptual inconsistency.

Huwez et al. (5) noted this conflict in terminology and they concluded that "nondilated eccentric hypertrophy is a dubious entity." They discussed other limitations of the Savage classification that relies primarily on RWT, and they proposed a classification in which the geometry of hypertrophic hearts was described as either concentric (increased mass/normal volume) or eccentric (increased mass/increased volume). They recognized chronic LV volume overload with normal mass (Linzbach's plastic dilation), but they did not include concentric remodeling or physiologic hypertrophy in their classification. Otherwise, their approach was similar to that used by Linzbach (1) and Grant et al. (2).

Koren et al. (6) were among the first to use M-mode echocardiography to study the relationship of RWT to clinical outcomes. They studied LV remodeling in 230 hypertensive patients and reported different morbidity and mortality in those with different patterns of structural remodeling. They used the term "concentric hypertrophy" to describe hearts exhibiting increased LV mass (>125 g/m^2) with a high RWT (≥ 0.45), and they introduced the term "concentric remodeling" to describe those with a normal mass and high RWT. Thus, they were able to include hypertensive patients who had abnormal geometry, but no hypertrophy. The term "eccentric hypertrophy" was applied to those with increased LV mass and a "normal" RWT (i.e., RWT <0.45). Total mortality as well as cardiovascular events were most frequent in patients with concentric hypertrophy, followed by eccentric hypertrophy and concentric remodeling. A most important result of this study was the confirmation that concentric remodeling had an adverse prognostic impact despite the lack of an absolute increase in LV mass. Using similar definitions of these geometric patterns, Ganau et al. (7) studied 165 untreated hypertensive patients and 128 normal adults and found that each of the remodeling patterns exhibited charac-

teristic hemodynamics and different clinical outcomes. The work by Koren et al. (6), Ganau et al. (7), and others (8–10) was followed by several large studies—all of which confirm the importance of distinguishing the various patterns of ventricular remodeling in populations with hypertension. Concentric remodeling generally exhibits a trend toward higher LV mass than is seen with a truly normal geometry; it appears to be an early response to a LV pressure overload. When concentric hypertrophy is fully established in hypertensive patients, it is associated with the most adverse outcomes. Thus, the various geometric patterns of remodeling are related to systemic hemodynamics, traditional cardiovascular risk factors, adverse cardiovascular events, and mortality.

Much of this work was derived from population studies, largely involving patients with hypertension. Different partition values for normal and abnormal RWT were used (4–10). The upper limit of normal for RWT has been redefined and it is now recommended that the partition value should be 0.42 (11). However, there has been no attempt to define a lower limit of normal RWT, and there has been little attempt to include large dilated/failing hearts as was done in the earlier studies discussed previously.

Mass/Volume Ratio

The ratio of LV mass to end-diastolic volume (M/V) is closely related to the RWT. Conceptually, changes in this ratio should carry the same implications as changes in RWT. The relationship of M/V and RWT shown in Figure 1 was developed by specifying thickness, radius, and the corresponding RWT, and then calculating the mass, volume, and the corresponding M/V using standard methods that were published by the American Society of Echocardiography (11). This method assumes a uniform LV wall thickness, which is a limitation in the presence of coronary heart disease with regional disturbances in thickness and shape (vide infra). It can be seen that the normal RWT range of 0.32 to 0.42 corresponds to an M/V range of approximately 1.0 to 1.5. These estimates are consistent with angiographic (12,13), echocardiographic (7), and cardiac magnetic resonance imaging (MRI) (14) data indicating average normal values ranging from 1.1 to 1.3.

In a population-based study of subclinical cardiovascular disease, the Dallas Heart Study, Khouri et al. (15) used cardiac MRI to measure LV mass and volume in 2,803 participants, and they describe 4 "distinct geometric patterns" of LV remodeling. Their 4-tiered classification was based on whether concentricity and end-diastolic volume were increased or not; concentricity was defined as M/V and $M/V^{0.67}$. The vast majority had a normal end-diastolic volume. Of patients with LVH (n = 875), the most common geometric pattern (n = 468) was termed "eccentric and indeterminate" (increased mass with a normal end-diastolic volume, and normal concentricity). This pattern is

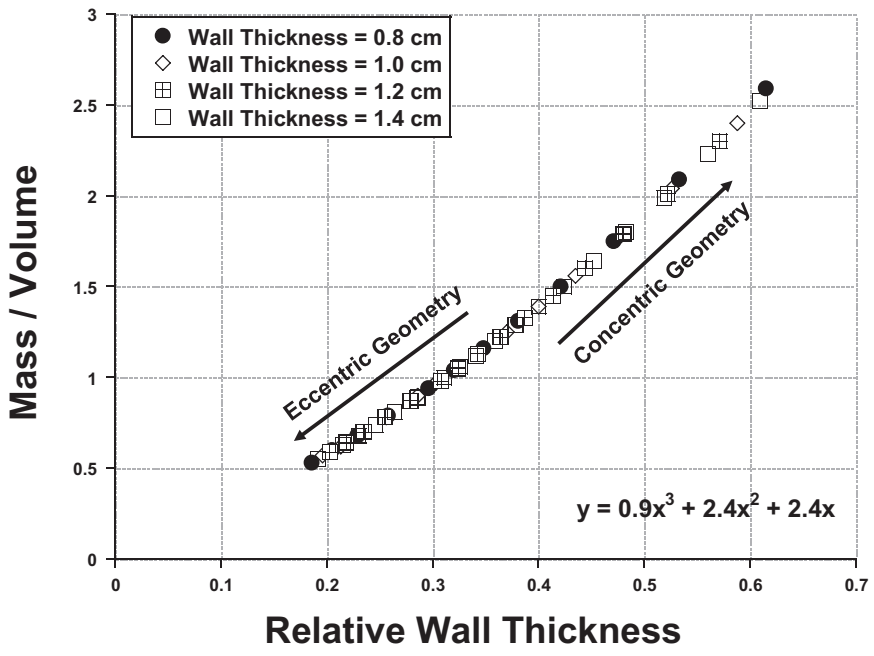

Figure 1 Left Ventricular RWT and M/V

Wall thickness and radius, and relative wall thickness (RWT), were specified, and the corresponding mass and volume and ratio of mass to volume (M/V) were calculated. See text for details. The normal range of RWT (0.32 to 0.42) corresponds to an M/V of 1.0 to 1.5. Low values indicate concentric geometry, and high values indicate eccentric geometry. For wall thickness, **solid circles** = 0.8 cm; **diamonds** = 1.0 cm; **cross boxes** = 1.2 cm; **open boxes** = 1.4 cm.

similar to the "eccentric nondilated" geometry described by Savage et al. (4) and criticized by Huwez et al. (5) (vide supra). Only 53 had typical eccentric hypertrophy, while concentric hypertrophy was present in 361. A small group (n = 13) exhibiting an increase in mass, volume, and concentricity was classified as "thick and dilated"; this mixed pattern is similar to the "mixed" geometry described by Grant et al. (2). These 4 geometric patterns were associated with different clinical characteristics, biomarkers, and ejection fractions. The group with eccentric (dilated) or concentric hypertrophy exhibited lower LV ejection fractions than the other 2 groups. The researchers concluded that identification of these "distinct phenotypes" may convey prognostic information.

This study differed from previous publications in that modern cardiac MRI was used to assess LV volume, mass, and geometry (15). The definitions of concentric and eccentric geometry also differed from those previously used. For example, the inclusion of patients with dilated ventricles in the concentric group and patients with normal end-diastolic volume in the eccentric group makes it difficult to compare results of this study with those published by others. It should be recognized that the LV volume and mass, the clinical characteristics, and the biomarkers in the "indeterminate group" were very similar to those without hypertrophy. Despite differences in methods and definitions, the conclusions by Khouri et al. (15) about prognosis and distinct phenotypes are similar to those in the earlier echocardiographic studies discussed herein.

The M/V is a parameter that, like the ejection fraction, does not require consideration of or correction for body size. This can be a major advantage, especially as there is little agreement as to the appropriate allometric scaling and normalization of LV volume or mass (16). The RWT has a similar advantage. The M/V and RWT are not only descriptors of LV geometry, but they are also integral components of parameters and indices that reflect the systolic and diastolic properties of the ventricle (17,18). Large population studies are now in progress (14,15), and we can expect refinement in our definitions of the remodeling patterns shown in Figure 2.

Classification of LV Remodeling

In an attempt to provide an inclusive classification of a wide variety of ventricular remodeling patterns, we developed an amalgam of the information discussed previously with other

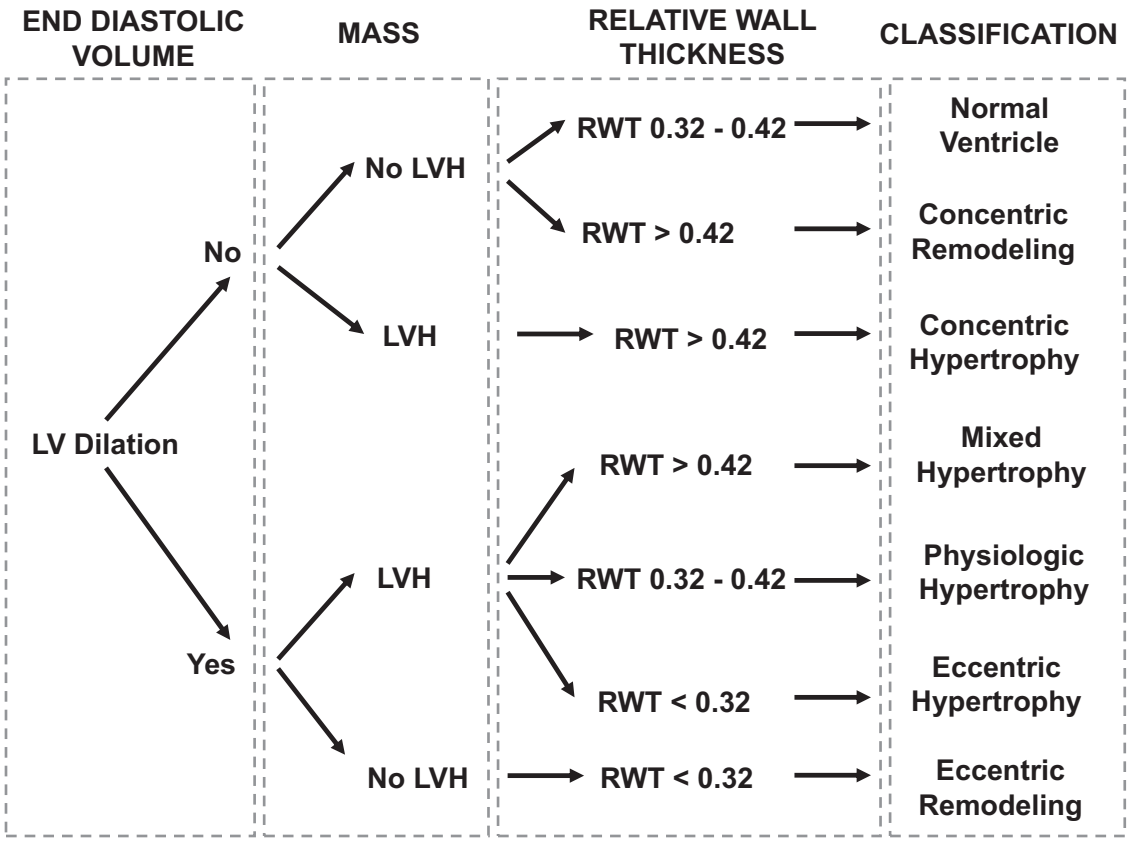

Figure 2 Patterns of LV Remodeling Based on EDV, Wall Mass, and RWT

A normal left ventricular (LV) chamber size (end-diastolic volume [EDV]) indicates a concentric or normal geometry; differences in relative wall thickness (RWT) distinguish concentric from normal remodeling. A dilated chamber dictates an eccentric geometry; those with left ventricular hypertrophy (LVH) are distinguished by differences in RWT.

published data and created the scheme shown in Figure 2. To be inclusive of a wide variety of physiologic and pathologic conditions, a classification of remodeling must consider LV volume, mass, and RWT (or M/V) in concert. Our classification relies on and extends the concepts initially developed by Linzbach (1), Grant et al. (2), and Huwez et al. (5), and it limits the term "concentric" to those without chamber dilation. Therefore, a normal end-diastolic volume and an increased RWT (or M/V) pattern would be classified as concentric hypertrophy if LV mass is increased, and as concentric remodeling if LV mass is normal. These terms are currently used by the American Society of Echocardiography (11). The term "eccentric" is applied exclusively to patterns with enlarged (dilated) ventricles. Thus, eccentric geometry includes those with physiologic hypertrophy, eccentric hypertrophy, and eccentric remodeling. These eccentric patterns are distinguished by differences in LV mass and RWT (or M/V). Mixed hypertrophy exhibits increased volume, mass, and RWT as defined by Grant et al. (2). Eccentric remodeling is used when the LV chamber is dilated, but the LV mass is not increased (1). As will be seen, there are distinct differences in cardiac function, hemodynamics, and clinical outcomes in the different patterns of hypertrophic remodeling. Thus, it can be misleading to consider all increases in LV mass to be homogenous or similar.

The scheme shown in Figure 2 does not include some clinically significant but less common disorders. One such condition is the "disproportionate septal thickening" described by Savage et al. (4). This finding is typically present in hypertrophic cardiomyopathy, as well as apical hypertrophy, proximal septal thickening of the elderly, and ventricular noncompaction. It may also be seen in right ventricular overloads. For example, patients with chronic thromboembolic pulmonary hypertension with right ventricular dilation and dysfunction are said to show a decrease in the mass of the LV free wall with an increase in the interventricular septal mass (19). A second example of LV remodeling that is not included in Figure 2 is the cardiac atrophy that is seen after prolonged bed rest or space flight (20). Under these conditions, LV volume tends to decline more than mass, and there is a trend toward a small increase in M/V. Similar results have been reported in anorexia nervosa (21). These reductions in LV mass and volume are the opposite of those seen in physiologic hypertrophy, but in both LV atrophy and physiologic hypertrophy there appears to be preservation of normal geometry and function.

The impact of race, sex, and aging on LV geometry was not considered in this article, but there is evidence suggesting that such factors affect LV remodeling. For example, blood pressure is reportedly "more strongly associated with eccentric and concentric hypertrophy in blacks than in whites" (22). Remodeling patterns also appear to be different in Hispanic subgroups and whites (23). Sex likewise is known to affect LV mass and geometry (22,24). The impact of antihypertensive and other medications that potentially affect remodeling should also be considered. Certainly cardiac resynchronization therapy, beta-adrenergic receptor blockade, and inhibition of the renin-angiotensin-aldosterone system have the potential to reverse or attenuate the deleterious remodeling imposed by injury or overload (25).

Other limitations of the concepts presented herein include the limited accuracy and reproducibility of all imaging modalities. Modest measurement errors can have a significant impact on RWT (or M/V). Another potential problem relates to the specific method used to determine LV mass and volume. For example, using cardiac MRI, some investigators exclude the papillary muscles from the LV mass (14), whereas others report that the papillary muscles are included in the mass and excluded from the chamber volume (15). That could result in relatively small, but significant differences in the M/V. Even within the same study there may be discrepancies between RWT and M/V if the LV volume is derived according to the modified biplane Simpson's rule and the LV mass and RWT are derived from linear measurements (26). For example, in a study of LV geometry after myocardial infarction, patients with eccentric hypertrophy exhibited LV enlargement and a normal RWT (0.35 ± 0.05), but the M/V was significantly higher (1.9 ± 0.4) than normal (26). These and other methodological issues limit our ability to compare and contrast information from different publications when different methods are used.

Finally, it should be emphasized that nonuniform wall thickness and regional shape deformation can limit determination of RWT, particularly if the LV wall is assumed to be of uniform thickness. Ventricular remodeling after infarction is a common process that contributes to disability and death (27,28). In such cases, measurement of RWT in a region of thinned scar is obviously inappropriate. The limitation imposed by nonuniform wall thickness may also be seen in hypertensive heart disease where regional differences in thickness, radius of curvature, and deformation have been described (29). Advanced imaging techniques such as 3-dimensional echocardiography or cardiac MRI should provide more accurate measures of LV wall mass and average wall thickness. Cardiac MRI with late-gadolinium enhancement might be useful to separate noncontractile scar from functional myocardium, and thereby differentiate total wall mass from true myocardial mass (30). Such techniques should provide more accurate definition of LV architecture in the presence of nonuniform geometry.

Clinical Applications

The information and concepts discussed previously were applied largely in clinical studies of patients with hypertension, but other applications have been suggested (31). For example, in dilated cardiomyopathy, alterations in LV geometry have prognostic value that may add to the value of the ejection fraction (32). Considerable attention has been directed at the LV remodeling that is seen in patients with heart failure, particularly those with coronary heart disease

(26–28). These and other examples will be used to illustrate the classification of LV structural and geometric remodeling that is shown in Figure 2.

Concentric hypertrophy and remodeling. Pressure overload of the left ventricle results in an increment in ventricular mass with a high RWT; the earliest change appears to be an increase in RWT before there is a detectable increase in LV mass. These architectural changes seen in concentric hypertrophy and concentric remodeling provide a mechanism for maintenance of normal LV systolic wall stress in the presence of a high systolic pressure. Such preservation of systolic wall stress allows a maintenance of normal or near-normal LV systolic function and performance. These current concepts are supported by the work of Grossman et al. (33) who studied patients with valvular heart disease. In aortic stenosis with pressure overload hypertrophy, RWT (0.58 ± 0.05) greatly exceeded that seen in normal hearts (0.34 ± 0.02); systolic wall stresses were similar to those seen in normal hearts. These findings, later confirmed by others (34,35), indicate that hypertrophy "develops in a pattern that is unique to the inciting overload" (33). Such a compensatory increment in LV mass, also seen in hypertensive heart disease, eventually yields a substrate for LV diastolic dysfunction and diastolic heart failure.

Physiologic hypertrophy. The change in LV architecture seen in physiologic hypertrophy might be considered a form of eccentric remodeling/hypertrophy in that both chamber size and LV mass are increased. However, in physiologic hypertrophy, a normal RWT is maintained. That is in distinct contrast to the low RWT seen in the eccentric remodeling that is present in the dilated hearts of some patients with heart failure (vide infra). Linzbach (1) noted that the myocardial fibers in physiologic hypertrophy became thicker and longer "as if the normal myocardium was viewed through a magnifying glass." He referred to this condition as "magnification hypertrophy," and he considered it to be an extension of normal physiologic growth of the heart. A most common example of physiologic hypertrophy is seen in the normal pregnant female who has LV enlargement with preservation of a normal RWT (0.32 ± 0.01); in this study, the ejection fraction remained in the normal range (36). Such structural remodeling appears to be a normal adaptation to the volume load imposed by the normal pregnant state. The finding of a normal B-type natriuretic peptide during uncomplicated pregnancy is consistent with the concept of a normal or physiologic adaptation (37). Another example of physiologic hypertrophy might be the athlete who also exhibits modest LV chamber enlargement and increased LV mass with a normal RWT (0.36 ± 0.04) and normal LV function (38). Even athletes with substantial LV enlargement exhibit an average RWT (approximately 0.33) that is within the range of normal (39). In athletes with physiologic hypertrophy, LV pump performance (i.e., stroke volume) is increased, while LV contractile function (ejection fraction and mean circumferential fiber shortening velocity) is normal (40).

Eccentric hypertrophy and remodeling. A typical example of eccentric (volume-overload) geometry is that of mitral regurgitation (MR). The LV response to this volume overload consists of a progressive chamber enlargement with characteristic changes in LV mass and RWT that depend, in part, on the severity and duration of the overload (41). In acute MR, the earliest change is an increase in LV volume that is out of proportion to the LV mass. This early transient stage is followed by the development of "volume overload hypertrophy," the RWT returns toward normal, and normal systolic function is maintained. Thus, in compensated MR, the LV remodeling resembles the adaptive changes seen in physiologic hypertrophy. In both, the enhanced stroke volume is "mediated through a normal performance of each unit of an enlarged circumference" (42). In the late stage of MR, the progressive LV enlargement is well out of proportion to the myocardial mass, RWT declines, and systolic function deteriorates. Thus, in chronic MR, LV mass may be increased by twofold or threefold while the RWT ranges from normal to low (0.37 to 0.23); some might be classified as physiologic hypertrophy, but most have eccentric hypertrophy with a RWT <0.32, which is below the lower limit of normal (33,35). Available data suggest that the modest structural remodeling seen in compensated MR is an appropriate and physiologic adaptation (42), but such overlap of the physiologic and eccentric categories is a limitation of the classification scheme. In cases of chronic aortic regurgitation, the RWT tends to be higher than that seen in MR, probably because LV systolic pressure and systolic loads are higher; this results in a pattern of mixed hypertrophy (Fig. 2). Mitral and aortic regurgitation illustrate the idea that hypertrophy "develops in a pattern that is unique to the inciting overload" (33).

Patients with systolic heart failure generally exhibit LV enlargement, usually with eccentric hypertrophy. The eccentric geometry imposes a distinct mechanical disadvantage that is associated with reduced LV systolic function and performance. Some, however, show little or no LV enlargement despite a depressed ejection fraction whereas others show substantial LV enlargement (43,44). In dilated cardiomyopathy, RWT is virtually always low, but in coronary heart disease, the remodeling patterns vary widely. For example, in a study of coronary heart disease with depressed LV ejection fraction, some ventricles exhibited concentric (RWT = 0.48 ± 0.05) hypertrophy or remodeling whereas others showed eccentric (RWT = 0.35 ± 0.05) hypertrophy (26). This variability in geometry is likely related, at least in part, to the nonuniform LV wall thickness that is seen in patients with coronary heart disease, especially those with depressed systolic function.

Conclusions

Chronic heart failure is said to be a progressive process with "a change in the geometry and structure of the ventricle,

such that the chamber dilates and/or hypertrophies and becomes more spherical—a process referred to as cardiac remodeling" (45). The information reviewed in this article is in keeping with this definition of remodeling and lends support to the concept that the pattern of LV remodeling is determined by the type of overload. Thus, with few exceptions, concentric geometry/hypertrophy is a result of systolic pressure overload whereas eccentric geometry/hypertrophy is a consequence of volume overload. The biology and basic science underlying such LV remodeling and the differential effects of pressure and volume overload are currently being explored (46–48). Such information will improve our understanding of the mechanisms that control the unique relation between the inciting stimulus or overload and the pattern of hypertrophy.

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