JACC: CARDIOVASCULAR IMAGING VOL. 4, NO. 1, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2010.10.008

iREVIEWS

STATE-OF-THE-ART PAPER

Left Ventricular Remodeling in Heart Failure

Current Concepts in Clinical Significance and Assessment

Marvin A. Konstam, MD, Daniel G. Kramer, MD, Ayan R. Patel, MD, Martin S. Maron, MD, James E. Udelson, MD

Boston, Massachusetts

Ventricular remodeling, first described in animal models of left ventricular (LV) stress and injury, occurs progressively in untreated patients after large myocardial infarction and in those with dilated forms of cardiomyopathy. The gross pathologic changes of increased LV volume and perturbation in the normal elliptical LV chamber configuration is driven, on a histologic level, by myocyte hypertrophy and apoptosis and by increased interstitial collagen. Each of the techniques used for tracking this process—echocardiography, radionuclide ventriculography, and cardiac magnetic resonance—carries advantages and disadvantages. Numerous investigations have demonstrated the value of LV volume measurement at a single time-point and over time in predicting clinical outcomes in patients with heart failure and in those after myocardial infarction. The structural pattern of LV remodeling and evidence of scarring on cardiac magnetic resonance have additional prognostic value. Beyond the impact of abnormal cardiac structure on cardiovascular events, the relationship between LV remodeling and clinical outcomes is likely linked through common local and systemic factors driving vascular as well as myocardial pathology. As demonstrated by a recent meta-analysis of heart failure trials, LV volume stands out among surrogate markers as strongly correlating with the impact of a particular drug or device therapy on patient survival. These findings substantiate the importance of ventricular remodeling as central in the pathophysiology of advancing heart failure and support the role of measures of LV remodeling in the clinical investigation of novel heart failure treatments. (J Am Coll Cardiol Img 2011;4:98–108) © 2011 by the American College of Cardiology Foundation

Mechanisms and Characteristics of Ventricular Remodeling

The term *ventricular remodeling* refers to alteration in ventricular architecture, with associated increased volume and altered chamber configuration, driven on a histologic level by a combination of pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis (1–3). Although originally described after myocardial infarction (MI), ventricular remodeling develops in response to a variety of forms of myocardial injury and increased wall stress (4,5).

Early work by Pfeffer and Braunwald (6) in a rodent MI model showed that a greater degree of myocardial injury was associated with a greater degree of chamber remodeling over

From the Cardiovascular Center, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts. Dr. Konstam has received research support and/or is a consultant for Otsuka, Merck, and Pfizer. Dr. Udelson has received research support and/or is a consultant for Otsuka, Merck, Pfizer, and Medtronic. All other authors report that they have no relationships to disclose.

Manuscript received August 6, 2010; revised manuscript received September 24, 2010, accepted October 4, 2010.

time. Since that time, multiple studies have substantiated the relationship between infarct size and the extent of left ventricular (LV) remodeling (3,7,8). Solomon et al. (9) showed that patients with larger MIs, as evidenced by greater elevations in serum creatine kinase concentrations, manifest greater 90-day increases in LV end-diastolic volume (EDV) and greater reductions in left ventricular ejection fraction (LVEF) (Fig. 1).

The initial post-MI phase of LV remodeling results from fibrotic repair of the necrotic area with scar formation, elongation, and thinning of the infarcted zone (Fig. 2). LV volumes increase, a response that is sometimes considered adaptive, associated with stroke volume augmentation and maintenance of normal cardiac output (10). However, beyond this early stage, the remodeling process is driven predominantly by hypertrophic myocyte elongation in the noninfarcted zone, resulting in increased wall mass, chamber enlargement, and a shift from an elliptical to a more spherical chamber configuration (3,11–13). These changes, together with a decline in performance of the pathologically hypertrophied myocyte and interstitial fibrosis within the noninfarcted zone, result in progressive decline in ventricular performance. Left unchecked, LV hypertrophy, dilation, and contractile dysfunction appear to advance indefinitely, regardless of the initial inciting cause, as evidenced by progressive increases in LV volumes (12,14,15).

Pathologic LV remodeling is closely linked to activation of a series of neuroendocrine, paracrine, and autocrine factors, which are up-regulated after myocardial injury and in the setting of increased LV wall stress and hemodynamic derangement. Contributing factors include the renin-angiotensin-aldosterone axis, the adrenergic nervous system, increased oxidative stress, proinflammatory cytokines, and endothelin. Renin-angiotensin system inhibition (14–18) and beta-adrenergic blockade (19–23) have each been shown to markedly attenuate or reverse LV remodeling in patients with heart failure and LV dilation, although aldosterone blockade has yielded mixed results (24,25), and findings with antagonists of endothelin (26) and vasopressin (27) have been disappointing.

With continued application of imaging techniques within populations of patients with MI and/or heart failure, there has been increased understanding of the various macroscopic patterns of LV remodeling and their relationship to underlying etiology and prognosis. Verma et al. (28), examining patients with heart failure and/or LVEF ≤35% after MI, in the VALIANT (VALsartan In Acute myocardial iNfarcTion) echocardiographic study, defined 3 patterns of LV remodeling based on measurement of the LV mass index (LVMi) and relative wall thickness (RWT): concentric remodeling (normal LV mass index LVMi and increased RWT), eccentric hypertrophy (increased LVMi and normal RWT), concentric hypertrophy (increased LVMi and increased RWT) (Fig. 3) (28). Each of these patterns was associated with a higher risk of subsequent cardiovascular events than that of normal LV morphology, with each of these 3 patterns carrying progressively worse prognosis (see the "Relationship between LV remodeling and prognosis in patients with heart failure and decreased LVEF" section).

Techniques for Assessing Ventricular Remodeling

LVEF, the most common metric of cardiac performance in clinical practice, is influenced by the degree of LV remodeling more than by any other factor (29). Other, more precise metrics of remodeling, such as LV volumes and mass, have received greater focus in clinical trials than in clinical practice (30), yet these measurements relate more closely to prognosis and to the impact of therapy than does LVEF. For example, White et al. (31) demonstrated that within groups with various degrees of post-MI LV dysfunction defined by LVEF, analysis of LV end-systolic volume (ESV) further risk-stratified patients, suggesting that it is a more powerful metric for that purpose. At present, echocardiography remains the predominant clinically applicable noninvasive test of choice, based on broader availability, whereas alternative modalities, such as radionuclide imaging and cardiac magnetic resonance (CMR), also play an important role, with each modality offering advantages and disadvantages.

Two-dimensional (2D) and 3-dimensional (3D) echocardiography. 2D echocardiography is a widely available and well-established means of assessing LV remodeling. This technique can be performed in nearly all patients, including those who are critically ill, and is not associated with any radiation exposure. However, estimates of LV volumes derived from 2D images are subject to variability and error imposed by selection of the imaging plane, inaccuracies in identi-

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
3D = 3-dimensional
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
ESV = end-systolic volume
LGE = late gadolinium enhancement
LV = left ventricular
LVEF = left ventricular ejection fraction
LVMi = left ventricular mass index
MI = myocardial infarction
RVG = radionuclide ventriculography
RWT = relative wall thickness