

EDITORIAL COMMENT

Patterns of Ventricular Remodeling After Myocardial Infarction

Clues Toward Linkage Between Mechanism and Morbidity*

Marvin A. Konstam, MD, FACC

Bethesda, Maryland; and Boston, Massachusetts

Since the early 1980s, we have learned much about left ventricular (LV) morphologic change in patients after myocardial infarction (MI) and the relationship of such findings to subsequent clinical course (1–5). Left ventricular end-systolic and end-diastolic volumes are effective metrics for the severity of post-MI remodeling, and their changes are closely linked with clinical outcomes. Within broader populations, LV mass predicts cardiovascular (CV) events, independent of blood pressure (6,7), although the mechanisms for this linkage are uncertain.

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In this issue of *JACC* (*JACC: Cardiovascular Imaging*), Verma et al. (8) relate echocardiographic patterns of LV remodeling an average of 5 days after MI associated with heart failure (HF), left ventricular ejection fraction $\leq 35\%$, or both, to the incidence of subsequent CV events. The authors find that patients with concentric hypertrophy (increased left ventricular mass index [LVMI] and relative wall thickness [RWT]) are at greatest risk for the combined end point of CV death, recurrent MI, HF, stroke, or resuscitation after cardiac arrest, as well as for each individual component. Those patients with eccentric hypertrophy (increased LVMI and normal RWT) and concentric remodeling (normal LVMI and increased RWT) had lesser increases in risk. This work goes beyond

simple measures of LV volume and mass; it defines the patterns of remodeling that carry the greatest risk. More importantly, it bridges a gap between the hypertension and HF research arenas and provides clues to the mechanisms through which LV remodeling is linked to adverse clinical outcomes.

After a large MI, LV remodeling is associated with progressive dilation, initially through infarct zone expansion (1). Subsequent dilation and shape change occur through myocyte hypertrophy within noninfarcted zones and are associated with increased fibrosis and apoptosis. Patients with a greater degree of remodeling manifest worse outcomes, with increased rates of death and the development of HF (3,4). Classes of drugs that attenuate this process generally are associated with reduced incidence of CV events (5). It is reasonable to presume that these sets of events—structural and clinical—are mechanistically linked.

Despite the role of hypertension as both a risk factor for MI and a cause of pathologic myocardial hypertrophy, little attention has been paid to the interplay among hypertension, LV remodeling, and subsequent CV events after MI. The study by Verma et al. (8) represents an important window into understanding the role of antecedent hypertension and its structural consequences on the clinical course after MI. In this study, the relative prevalence of hypertension follows the same pattern as the relative incidence of subsequent CV events: concentric hypertrophy > eccentric hypertrophy > concentric remodeling > normal. By 5 days, some modest structural change may be expected from large MIs, but such change would be characterized by early dilation and eccentric hypertrophy. In this study, the greatest degree of pathologic hypertrophy, particularly in the pattern of concentric hypertrophy, is linked to hypertension, and

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From the Division of Cardiovascular Diseases, National Heart, Lung and Blood Institute, Bethesda Maryland; and the Division of Cardiology, Tufts Medical Center and Tufts University, Boston, Massachusetts.

patients manifesting these findings carry the greatest subsequent clinical risk. This pattern is not particularly associated with LV dilation, although progressive dilation over time, with a shift toward the pattern of eccentric hypertrophy, would imply a major impact of the infarct on LV structure and portend a poor CV prognosis. However, the study by Verma et al. (8) shows that, at the time of MI, antecedent structural consequences of hypertension carry high risk.

A key question remains: why do patients with greater LV mass, and particularly concentric hypertrophy, carry an increased risk for CV events? One possibility is that LV hypertrophy directly predisposes to all of the observed CV clinical consequences. Certainly, it may lead to HF through myocardial functional abnormalities and increased diastolic stiffness. It is also possible that the hypertrophied myocardium is predisposed to ischemic events, although the mechanism of this linkage is uncertain. More challenging is explaining the association between concentric hypertrophy and stroke. Although the overall incidence of stroke after MI is small relative to other types of events, stroke is one of the CV events that occurs with the greatest frequency among patients with concentric hypertrophy. This association could be routed through a predisposition to atrial fibrillation. But this finding, along with the greater incidence of MI, raises the possibility that myocardial structural change represents a marker for the systemic consequences of hypertension, including vascular remodeling, resulting in both cerebral and myocardial ischemic events.

Another clue that linkage between myocardial changes and CV events results partly through association between myocardial and vascular pathology comes from studies relating circulating levels of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide to CV prognosis. In a broad array of populations, including those with chronic HF, acute coronary syndromes, previous MI, established vascular disease, and increased coronary risk and in community-based samples, natriuretic peptide levels correlate with risk for a diverse set of CV events beyond development of HF, including MI and stroke (9). It is unlikely that these events are mediated solely through LV stretch. Rather, it seems likely that natriuretic peptide levels reflect a constellation of factors that contribute to pathologic myocardial hypertrophy and that these factors similarly contribute to vascular pathology predisposing to MI and stroke. A variety of factors stimulate or enhance natriuretic peptide secretion in vitro, including endothelin A, angiotensin II, and

tumor necrosis factor- α (10,11), and these same factors, up-regulated both systemically and locally, drive inflammation, fibrosis, and hypertrophy within the vasculature and the heart.

Myocardial hypertrophy, particularly the pattern of concentric hypertrophy, is driven by factors beyond blood pressure alone. The predictive value of LV mass, independent of blood pressure, may reflect neurohormonal, paracrine, and autocrine factors, including oxidative stress, which influence vascular, as well as myocardial pathology, driving processes of atherosclerosis, vascular remodeling, plaque instability, and susceptibility to thrombosis.

The findings of Verma et al. (8) also illustrate the need to abandon the designations of "systolic" and "diastolic" dysfunction (12). All patients in this study have suffered myocardial ischemic injury, typically considered a cause of "systolic dysfunction," yet some have predominant concentric hypertrophy, characteristic of patients typically designated as having "diastolic dysfunction." Although Verma et al. (8) do not describe functional parameters in the present report, and indeed it is difficult to sort out myocardial inotropic and lusitropic properties from echocardiography, it is likely that the myocardium of all patients with LV remodeling functions abnormally during both systole and diastole. We should move toward characterizing patients and seeking treatments based on underlying disease mechanism and on the pattern of LV remodeling, rather than imagining that EF neatly categorizes a patient as having a singular underlying functional abnormality.

Although LV volumes remain powerful individual metrics for assessing prognosis and treatment effect following MI, the work of Verma et al. (8) further clarifies the patterns of association between myocardial structure and CV outcomes. Their findings, as well as clues from other imaging and biomarker-related association studies, help guide us through the maze of interdependent factors leading to cardiac, vascular, and renal pathology and ultimately to CV morbidity and mortality. In so doing, these findings will help to identify novel treatment targets and potentially more powerful efficacy markers in our efforts to reduce the incidence of both primary and secondary CV events.

Reprint requests and correspondence: Dr. Marvin A. Konstam, Division of Cardiovascular Diseases, National Heart, Lung, and Blood Institute, MSC 7940, 6701 Rockledge Drive, Bethesda, Maryland 20892-7940. E-mail: konstamm@nhlbi.nih.gov.

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