

EDITORIAL COMMENT

Left Ventricular Hypertrophy: A “Factor of Risk”

Mass Is Reversible, but Is the Risk?*

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Left ventricular hypertrophy (LVH), specifically as it relates to systemic arterial hypertension, is a major risk factor underlying coronary heart disease (CHD). The reduction of ventricular mass has not yet been demonstrated to ameliorate that risk, even though several reports have attested to the fact that left ventricular (LV) mass is reduced by drugs. This commentary concerns the subject of two papers published in this issue of the *Journal* (1,2) that address this topic.

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The importance of LVH was stimulated by the Framingham Heart Study demonstration, which showed that it was one of three major “factors of risk” underlying CHD (3). Thereafter, investigative effort focused on the pathophysiologic development of LVH. The study (4) soon reported that hypertension was the most common cause of cardiac failure, undoubtedly due to systolic dysfunction because antihypertensive therapy has not been available long enough. However, despite its subsequent use, hypertension has remained the major cause of cardiac failure, although diastolic dysfunction also was postulated to be operative (5).

Soon after the earlier Framingham report, our laboratory, using roentgenographic and electrocardiographic (ECG) criteria of LVH, demonstrated clinical progression from no evidence of hypertensive heart disease (HHD) to its earliest ECG manifestation of left atrial (LA) abnormality and then to clearly identifiable LVH (6). The LA abnormality was highly concordant with the fourth heart sound, higher arterial pressure, and greater prevalence of cardiac dysrhythmias. With the adaptation of echocardiography for HHD, these findings were extended in the first echocardiographic HHD study demonstrating that patients with an LA abnormality already had increased LV mass as well as greater septal and posterior wall thicknesses, although their ECGs did not yet demonstrate LVH (7). Furthermore, LV ejection fraction also was relatively reduced in patients with an LA abnormality, decreasing further in patients with ECG-LVH (7). Soon, clinical interest in hypertensive LVH became stimulated further, and the Framingham

group confirmed their earlier ECG-LVH observation using echocardiography as a means for earlier identification of LVH risk (8). Attention soon focused on the potential of antihypertensive therapy to “reverse” LVH (9).

It is inappropriate to consider herein that the clinical correlates responsible for the development or reversal of LVH are not pathophysiologically homogeneous, involving a spectrum of diseases and an increasing number of humoral, endocrine, growth, and other factors. Because hypertension is the most common disease producing LVH, one may not assume that LVH is only the result of hypertension; it may occur with burned out myocardial infarction, ischemic or valvular heart diseases, aging, and so forth, and may be promoted through similar biological mechanisms. Conversely, LVH may not be diminished pharmacologically through similar mechanisms. Initially, our experimental studies demonstrated that short-term pharmacologic treatment reduced LV mass (10), suggesting that nonhemodynamic as well as hemodynamic factors were important in both LVH development and reversal (11,12). These reports clearly showed that rapid reduction in LV mass was evident with all classes of antihypertensive agents except, perhaps, the smooth muscle vasodilators (10), although when vasodilators were administered for long enough periods of time, LV mass diminished (13,14). Early on, we demonstrated LV mass reduction by using an angiotensin-converting enzyme inhibitor (15). Subsequently, broad interest in this and other classes of antihypertensive drugs focused on LVH reversal.

It is important to emphasize that the clinical reversal (i.e., “regression”) of hypertensive LVH does not necessarily mean reduced risk, *pari passu*. Although the clinical surrogates of LVH represent adaptive functional responses to pressure overload, they do not demonstrate the fundamental risk factors that are associated with LVH. Furthermore, LVH induced by exercise neither impaired systolic function nor diastolic function, although hypertension did (16). Most important, ECG (or echocardiographic) demonstration of therapeutic LV mass reduction provides no information about underlying risk mechanisms. Thus, even if LV mass and risk are diminished pharmacologically, it does not follow that the mass reduction was responsible for reduced risk. Other pharmacological epi-phenomena often co-exist (17), including ischemia (18), ventricular and perivascular fibrosis in extracellular matrix (19), apoptosis (20), and thrombosis.

Ischemia associated with LVH occurs in pure HHD, but it also occurs with co-existing atherosclerotic epicardial coronary arterial disease. Hypertensive heart disease ischemia also results from increased myocardial oxygen demand, coronary arteriolar constriction, and endothelial dysfunction (17).

Reversible fibrosis has been confirmed clinically by septal biopsy of patients with pure HHD relating to alterations in collagen synthesis, metalloproteinases, collagenases, and

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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other mechanisms (21–23). Apoptosis is not produced by myocardial infarction but by programmed cellular death associated with such biological mechanisms as the local renin-angiotensin-aldosterone system in the heart and vessels. In fact, recent studies have demonstrated that more apoptotic cells in the hypertensive heart than the normal heart (18) is reversed by angiotensin II receptor blockade and may explain the greater prevalence of cardiac failure in HHD (24).

Interest in demonstrating a “reversal of LVH” risk stems from obvious reasons. If decreasing elevated arterial pressure or serum cholesterol levels reduce associated cardiovascular risk, then the demonstration of reduced risk might be expected with LVH “reversal.” To be sure, reduction in LV mass echocardiographically correlates with reduced cardiac mass by postmortem examination (25), but reversed myocytic hypertrophy was not demonstrated. Moreover, just because ECG or echocardiographic evidence of LVH is diminished, the reduction of associated LVH risk does not follow. The U.S. Food and Drug Administration followed the same line of thinking: the demonstration of LVH reversal is not accepted as an indication of drug efficacy. Indeed, in 1991, I cautioned that even if ECG or echocardiographic LVH was reduced, it did not follow that actual risk of LVH was similarly diminished (24). One must establish that the reduced LVH risk is independent of the contemporaneous fall in arterial pressure, antiarrhythmic drug effects, improved ischemia, or other epi-phenomena associated with treatment(s) (26). Thus, the challenge of demonstrating reduced CHD risk by decreasing LVH is far more complex.

Several attempts to demonstrate the value of different classes of antihypertensive agents to reduce LV mass involved meta-analysis, but, to my way of thinking, this technique is fraught with problems. For example, some studies that were used included patients of one gender, all ages or only the elderly or young, or one racial or ethnic group. Finally, most patients who had been included were treated with a variety of drugs over varying time periods even though they may have been discontinued before the cited studies (27). Recent work suggests that previous therapy may promote myocytic “memory” from previous cellular stimulation (28). Hence, these efforts provided little to satisfy the need for new knowledge acquisition other than to add further confusion to an already extremely complex problem.

But what about previous large clinical trials that might have added to our understanding concerning whether LVH reduction reduced risk? One very early trial was conducted during the initial years of antihypertensive therapy by the Veterans Administration Cooperative Study Group. It demonstrated a significant reduction in cardiac failure in the patients who received active drug treatment in contrast to placebo (29). A very recent trial that was designed to determine the reduction of LVH risk demonstrated that LVH and arterial pressure were reduced by both study drugs

(atenolol and losartan) (30), but only the angiotensin II (type 1) receptor antagonist demonstrated reduced risk from stroke and end-stage renal disease; however, risk reduction from LVH was not demonstrated. During the intervening four decades, little was gleaned from the numerous trials involving many other antihypertensive agents to demonstrate LVH risk reduction, although all of the trials confirmed the absolute necessity for reduction and control of pressure. However, these studies were neither designed to demonstrate LVH risk reduction nor were their primary (or secondary) end points.

This brings us to the two important reports published in this issue of the *Journal* (1,2). The first, by Drazner et al. (1), is a prospective multicenter trial from the Cardiovascular Health Study, demonstrating that increased LV mass was a risk factor for the subsequent development of depressed LV ejection fraction within five years. The second, by Lonn et al. (2), is a substudy from the Heart Outcomes Prevention Evaluation study, demonstrating that the angiotensin-converting enzyme inhibitor ramipril was effective (10-mg dose) in preserving LV ejection fraction associated with reduced LV mass and function in normotensive high-risk cardiovascular patients.

The Cardiovascular Health Study is a prospective population-based longitudinal study in which 3,042 participants were enrolled and followed for 4.9 years (1). All patients had normal baseline LV ejection fraction and mass followed with two-dimensional echocardiography. All patients were older than 65 years and were followed with a variety of cardiovascular measurements to determine development of LVH and various other cardiovascular diseases. Those patients with baseline echocardiograms having LV mass greater than the median were no different from those with lesser measurements with respect to age, race, baseline fasting blood sugars, and history of diabetes. However, they included more male patients who were hypertensive and who received antihypertensive therapy. They weighed more, had a greater body mass index, had higher serum insulin concentrations, and had a greater amount of subsequent atrial fibrillation, Q waves, LVH, LV mass, and other LV dimensions within the five-year period. Moreover, in their overall follow-up, there were more cardiovascular events (including myocardial infarction, heart failure) and, as emphasized in the overall message of the report, developed impaired depressed LV function. The second report, a substudy of the Heart Outcomes Prevention Evaluation study, demonstrated that high-dose ramipril provided significantly more beneficial effects on LV structure and function with preserved LV ejection fraction in these placebo-controlled high-risk vascular patients (2).

In summary, the prognosis with these two groups of older patients at higher risk of subsequent cardiovascular events, provide encouraging findings that leave open the question of the specific risk of LVH and the issue of LVH risk reversal. We know that patients who were included with controlled hypertension were treated with agents that inhibited the

local cardiac renin-angiotensin system, diminished LV mass, improved LV systolic function, and prevented remodeling and other adverse events. However, there were no positive therapeutic controls. Moreover, little is known about the underlying pathophysiologic events and the various diseases associated with LVH that predispose the patients to increased risk. We must conclude that control of arterial pressure in the hypertensive patients, preferably with an angiotensin-converting enzyme inhibitor, should result in improved cardiovascular outcomes. However, until patients with hypertension are prospectively followed with appropriately positive controls that exclude other potential confounding effects cited previously, the true natural history compared with other therapy must remain a subject of conjecture.

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