Left Ventricular Hypertrophy
The Next Treatable, Silent Killer?

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AN INCREASE IN THE MASS OF LEFT VENTRICULAR muscle is intimately associated with most chronic diseases of the heart.[1-6] Classically, left ventricular hypertrophy, which represents an extreme increase in left ventricular mass, has been thought to represent a reaction to pressure or volume overload.[7,8] In the short run, increases in left ventricular mass may be beneficial by allowing the heart to compensate for increased wall stress and potential hemodynamic compromise; in the long run, left ventricular hypertrophy is harmful.[8]

Although the development of left ventricular hypertrophy has been related to a number of conditions,[4] including obesity,[9] diabetes,[10] prior myocardial infarction,[11] aortic stenosis,[12] and regurgitant valvular heart disease,[12] hypertension may well be the condition about which the most is known.[13] Data from the Framingham Heart Study have shown that even mild increases in blood pressure are associated with increased left ventricular mass.[14] Furthermore, left ventricular hypertrophy associated with hypertension appears to be reversible—ie, a long-term reduction of blood pressure has been shown to be associated with reductions in left ventricular mass.[15] Some data have suggested that specific types of drugs, such as angiotensin-converting enzyme receptor blockers or calcium blockers, may be more effective than others in reducing increased left ventricular mass associated with hypertension,[16,17] whereas other reports suggest that the specific drug used to reduce blood pressure may not be that important.[18]

For more than 30 years, it has also been recognized that left ventricular hypertrophy is a risk factor for premature death and cardiovascular events.[19] A landmark article from the Framingham Heart Study published in 1970 reported that left ventricular hypertrophy, as noted on the electrocardiogram, is associated with a mortality rate that is as high as having a Q-wave myocardial infarction.[19] Although subsequent studies have confirmed the strong association between electrocardiographic left ventricular hypertrophy and cardiovascular risk, it has also been recognized that the electrocardiogram may be relatively insensitive for detecting prognostically important increases in left ventricular mass.[20] With the advent of echocardiography, milder increases in left ventricular mass could be easily detected. Additional data from the Framingham Study,[6] as well as data from Cornell University[21] and the Cardiovascular Health Study,[1] among others, have demonstrated that a strong gradient exists between increased echocardiographic left ventricular mass and increased cardiovascular risk.

Despite the wealth of literature linking electrocardiographic and echocardiographic left ventricular mass to increased cardiovascular risk, left ventricular hypertrophy is often not thought of as a "standard" or "classic" risk factor. One explanation is that left ventricular hypertrophy—similar to, for example, increased carotid intimal-medial thickness detected by ultrasound—may be considered in the category of subclinical disease—intermediate on the continuum from standard risk factors to clinically manifest cardiovascular disease. However, another reason may be that relatively little data are available on the impact that reversing left ventricular hypertrophy has on outcomes. In contrast, a wealth of literature now shows that reduction of blood pressure, levels of cholesterol and blood glucose, and use of tobacco are associated with important clinical benefits. Observational data have suggested that a decrease in left ventricular mass with treatment for hypertension is associated with a better outcome.[22] However, prospective and systematic clinical trial data have been meager.

In this issue of *JAMA,* 2 reports systematically document that changes in left ventricular mass in the setting of a trial of hypertension treatment have been correlated with long-term cardiovascular outcome. Okin and colleagues[23] report on more than 9000 patients who were enrolled in the LIFE hypertension trial. This randomized trial involved a comparison of losartan-based therapy with atenolol-based therapy.[24] Although the degree of blood pressure reduction was similar with the 2 drugs, losartan was associated with a greater reduction in left ventricular mass[17] and a variety of cardiovascular outcomes.[24,25] In the current study reported by Okin et al, patients enrolled in the trial had electrocardio-

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grams obtained at baseline and then at yearly intervals thereafter. A clear-cut gradient was noted: the greater the decrease in left ventricular mass as assessed by electrocardiogram, the greater the reduction in major cardiovascular events.

In the accompanying article by Devereux and colleagues,[26] a prospective substudy cohort was assembled in which echocardiography was obtained at baseline with systematic yearly follow-up thereafter. Just as in the electrocardiographic study, increasing reductions in echocardiographic left ventricular mass were associated with greater reductions in cardiovascular event rates. In both studies, the reduction in left ventricular mass was predictive of a lower rate of events independent of the degree of blood pressure reduction, as well as other potential confounders.

The results of both studies are impressive in that substantial reductions of left ventricular mass were obtained using clinically available antihypertensive drugs, and a clear dose-response relationship was observed between greater reductions of left ventricular mass and reductions in risk. Nonetheless, it is important to recognize that the LIFE trial was not a randomized trial of therapy for left ventricular hypertrophy. That is, patients were not randomly assigned to a group in which treatment was based on blood pressure and left ventricular mass (as assessed by either electrocardiography or echocardiography) or to a second group in which treatment was managed based on blood pressure only. Still, these results, in concert with other published studies,[22] strongly suggest that a strategy in which an active effort is made to reduce left ventricular mass may have important clinical benefits.

Based on current developing understanding, left ventricular hypertrophy appears to fit the paradigm of previous risk and treatment models of traditional risk factors. For example, observational studies dating back many decades have shown that increasing levels of cholesterol are associated with an increased risk of cardiovascular events. The first trials demonstrating a clinical benefit of treating hypercholesterolemia primarily focused on very high levels of cholesterol, typically 240 mg/dL (6.2 mmol/L) or higher.[27] As time went on, it was found that treatment of lower levels of cholesterol with lipid-lowering drugs resulted in an improved outcome, almost irrespective of the initial cholesterol level.[28] A similar pattern has been observed with high blood pressure. Whereas early trials focused on marked blood pressure elevations and demonstrated that blood pressure treatment can reduce the risk of stroke and other cardiovascular events,[29] more recent trials have shown a benefit of blood pressure reduction starting at "normal" levels of baseline blood pressure.[30]

Understanding the potential benefits of treating left ventricular hypertrophy may follow a similar path as for cholesterol and blood pressure. The LIFE trial enrolled patients who had electrocardiographic evidence of left ventricular hypertrophy.[24] Given the relatively low sensitivity of the electrocardiogram for detecting left ventricular hypertrophy,[20] these patients must be considered among the "sicker" patients with hypertension. Consequently, the results of the reports of Okin et al and Devereux et al cannot be extrapolated to patients with hypertension and milder increases in left ventricular mass. Although it is reasonable to postulate that benefits will also be present in these milder cases, future trials will be needed to test this hypothesis.

What should clinicians do now, given the results of these 2 investigations? The acquisition of an electrocardiogram in patients with newly diagnosed hypertension is already considered part of the standard initial evaluation.[31] Left ventricular hypertrophy is a marker of more severe disease and its presence provides both clinicians and patients with a greater incentive for aggressive management. Furthermore, it may be reasonable to obtain serial electrocardiograms in patients treated for hypertension to see if left ventricular mass appears to be decreasing. Failure of left ventricular mass to decrease might be an impetus for more aggressive—ie, different—therapy, particularly in patients whose treated blood pressure levels are in the borderline high range with respect to current guidelines.

Traditional electrocardiographic interpretation has been qualitative, identifying certain patterns of left ventricular hypertrophy, such as that associated with ST-segment changes, bundle-branch block, and other abnormalities. The study by Okin et al suggests that a quantitative measure of electrocardiographic voltage may be of value, particularly when obtained sequentially over time. Most currently available electrocardiographic reporting packages do not routinely provide quantitative measures of left ventricular mass. This deficiency could be easily corrected.

Although echocardiography is more sensitive than electrocardiography for detecting left ventricular hypertrophy, it is probably premature to recommend routine serial echocardiograms in patients with hypertensive heart disease. Nonetheless, serial, low-cost echocardiograms limited to evaluating the left ventricle may prove to be cost-effective.[32] Additional studies of such a strategy would be welcome.

Finally, an argument certainly could be made for a large-scale prospective randomized trial in which a strategy of therapy for left ventricular hypertrophy along with blood pressure is compared with a strategy of blood pressure therapy alone. This might provide definitive evidence that left ventricular hypertrophy should be considered a wholly treatable silent killer. While this kind of evidence is currently lacking, the intriguing reports of Okin et al and Devereux et al, combined with the extensive previous literature on left ventricular mass in hypertension, do support a role for evaluating for left ventricular hypertrophy at the time of hypertension diagnosis and, at the very least, for considering changes in left ventricular mass when tailoring long-term antihypertensive therapy.

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