EDITORIAL COMMENT

Left Ventricular Hypertrophy in Hypertrophic Cardiomyopathy

What’s in a Phenotype?*

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Left ventricular myocardial hypertrophy (LVH) occurs in many conditions, usually, it is thought, as a secondary or “compensatory” response to abnormal pressure or volume loading and to stimuli, as yet incompletely understood, resulting from deficiencies in cardiac performance (1). These responses may be modulated by genetic predispositions, a relationship also not well understood. “Compensatory” hypertrophy may prolong the time to symptom development in patients with hypertension and valvular heart diseases and may forestall development of congestive heart failure in patients with coronary artery disease. Conversely, however, the presence of LVH generally is evidence of an underlying problem requiring compensation. Left ventricular myocardial hypertrophy almost invariably involves not only the cardiomyocytes that generate contractile force but also the cardiac fibroblasts that produce the extracellular matrix, the scaffold on which the myocytes are organized and that transmits contractile force, a key link in the genesis of cardiac mechanical performance. Alterations in the relationship of these myocardial components during LVH may have an adverse effect on cardiac function. Nutrition and maintenance of the hypertrophied myocardium impose burdens that, ultimately, also may add to clinical debility. Indeed, it is well demonstrated that electrocardiographic or echocardiographic LVH is directly related to clinical outcome among individuals unscreened for disease (2,3) and is a particularly potent risk factor for patients with hypertension, coronary artery disease, or diabetes mellitus (4). Thus, in a recent comprehensive metaanalysis involving almost 50,000 persons, Vakili et al. found that adjusted all-cause mortality risk averaged 2.3:1 when individuals with LVH at baseline were compared with those lacking LVH (2), whereas an assessment of more than 3,000 persons in the Framingham Heart Study, initially free of clinically apparent cardiovascular disease, indicated an incremental risk of developing disease of approximately 50% for each left ventricular (LV) mass increment of 50 g/m height (3); again, all-cause mortality also was associated with LVH.

Though LVH may occur most commonly as a response to exogenous loads and other diseases (perhaps modulated by genetic predisposition), hypertrophy may also occur as a primary process. Several specific gene mutations now have been associated with regional or global alterations in myocyte size, physical orientation, and contractile protein metabolism and function (5). The resulting hypertrophic cardiomyopathy (HCM) probably is the most common genetically determined cardiomyopathic condition among humans, occurring in approximately 0.2% of the general population (6). When the hypertrophy is particularly marked in the region of the anterior papillary muscle and superior septum, abnormal systolic anterior motion of the anterior mitral valve leaflet can result in LV outflow obstruction, a dynamic process known as hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subaortic stenosis. The dynamic obstruction can, in turn, potentiate hypertrophy by imposing afterload stress on relatively less affected myocardium, most commonly in the LV free wall. (Indeed, it has been theorized that hypertrophy in this disease is entirely secondary, in response to genetically determined regional dysfunction of a sarcomeric protein, perhaps potentiated by abnormal mechanical stresses imposed on adjacent regions of normal myocardium [6].) In part because of varying degrees of such compensatory hypertrophy together with the variable phenotypic expression of the underlying gene mutations, HOCM commonly, but not always, is associated with hyperdynamic LV contractile performance and supernormal LV ejection fraction, together with subnormal compliance and diastolic dysfunction. Non-obstructive HCM also can manifest as hyperdynamic performance, but normal or even subnormal performance commonly is apparent. The natural history of both forms also is highly variable, though progression to contractile deficiency, LV dilatation, and a picture reminiscent of congestive cardiomyopathy have been described.

The highly variable phenotypic expression of HCM, and the development over the past decade of evidence of many different gene mutations that lead to similar phenotypic manifestations, render overarching generalizations about the implications of any single phenotypic finding to be tenuous. Nonetheless, one thing, at least, seemed relatively certain, specifically, that HCM shared with other diseases characterized by hypertrophy the association of particularly marked LVH (defined for this disease as a maximal left ventricular wall thickness [MLVWT] ≥30 mm by echocardiography) with particularly untoward prognosis (7). Though reasonable, this view is based in part on inference and assumption. The largest and most compelling relevant study involved 480 patients with HCM, 43 of whom had marked LVH. Age ranged from 1 to 89 years (median, 47 years). Mortality was 18.2% in the marked LVH cohort during an average 6.5-year follow-up and was substantially

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lower among those with less LVH. Those with marked LVH were considerably younger (median age, 28 years) than the remainder of the study cohort. The relatively high mortality in the group with marked LVH, plus the relative paucity of marked LVH in the older subgroups, supported the conclusion that marked LVH is ominous in patients with HCM. However, the implicit assumption underlying interpretation of these data is that the patients without marked LVH, a relatively older population, never had manifested MLVWT ≥30 mm. The study of Thaman et al. (8) in this issue of the Journal refutes this assumption with serial echocardiographic observations in well-characterized, carefully studied patients.

Over the course of 15 years, these authors prospectively identified 106 patients with HCM and MLVWT ≥30 mm and followed them for an average of almost 8 years. During this interval, 17% died; 5-year survival from sudden death was 90.1% and from heart failure death or transplantation, 97.7%. Almost 80% of patients were alive 10 years after follow-up began. Because more than 70% of patients were younger than age 40 at study initiation, this survival rate is considerably less than might be expected in an unselected age-matched ambient population. Nonetheless, this survival pattern suggests that causes other than death at a young age must account for the paucity of severe LVH among patients with HCM as they age. The authors’ serial echocardiographic substudy, performed in 71 of their 106 patients and covering a follow-up interval of almost 7 years, provides the answer: the LV remodels spontaneously over time, and the walls thin. Indeed, wall thinning of at least 5 mm occurred in more than half the patients; this phenomenon also occurred predominantly among patients less than 40 years of age. Thus, the loss of severe LVH occurred while these people still were relatively young. The biology underlying this change is not known: is it a genetic program that, if discovered, could modify prognostic inferences and, more importantly, could be applied therapeutically to treat patients with HCM, as well as patients with other conditions involving pathologic hypertrophy? Is it an adaptive change resulting secondarily from the effects of abnormal loading, neurohumoral/hormonal or other exogenous factors caused by the primary pathophysiology? Answers to these questions are not known, and should occupy the time of researchers in the future.

Another noteworthy secondary finding was that marked LVH, by itself, was not the predominant risk factor in this group: 5-year freedom from sudden death was 96.5% among people who manifested only MLVWT ≥30 mm, but trended downward (87.4%) if the marked LVH was associated with non–sustained ventricular tachycardia, subnormal blood pressure response to upright exercise testing, family history of sudden cardiac death, or unexplained syncope, factors previously identified as prognostically important for patients with HCM. Thus, the present study does not negate concern about young patients with HCM who manifest marked LVH, but suggests that strategies to maximize their survival must be modified with reference to associated risk factors and to the variable natural history of the condition, which can include spontaneous wall thinning.

To be sure, the present study must be understood in the context of its limitations, most of them very difficult to avoid. First are the twin problems of referral bias and selection bias. The study site is a specialized center for HCM management and research within a major tertiary referral hospital. The majority of patients were referred from elsewhere for opinions about management or risk stratification, suggesting a potential bias toward relatively severely afflicted individuals. Other patients were seen as part of family surveys and, presumably, were asymptomatic and discovered serendipitously. Such a convenience sample may not faithfully represent the full range and course of HCM with severe LVH. However, the study cohort is sufficiently large and sufficiently diverse so that the primary finding, that wall thinning occurs spontaneously, not only can be accepted but plausibly can be considered relevant to a substantial portion of the HCM/severe LVH subpopulation. Another potentially important limitation is the inability of the study design to account for the possible interaction of drugs and/or devices with the disease in affecting MLVWT or outcome. Although it is unlikely that treatment could have affected the primary conclusion, other interesting aspects of the findings may well have been confounded quantitatively if not qualitatively by uncontrolled use of drugs and devices.

Limitations notwithstanding, this is an important study. The overarching conclusion is that it is necessary to associate phenotypic expressions of disease, such as LVH, with the underlying biology to define prognosis and to plan management optimally. In an era characterized by an explosion of knowledge at the molecular level, this message is being heard ever more frequently and more clearly in cardiology. The findings of Thaman et al. (8) strongly suggest that an intrinsic genetic program is activated by as yet unknown factors to modify hypertrophy in patients with HCM. Understanding and harnessing this program may provide substantial benefit in areas unrelated to HCM. Finally, these data indicate that risk stratification in patients with HCM, and preventive strategies that may be undertaken on the basis of hypotheses or incomplete knowledge, now must be modified to account for the relative prognostic importance of risk factors other than marked LVH alone.

References


