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EDITORIAL COMMENT

Hypertrophic Cardiomyopathy Without Hypertrophy

An Emerging Pre-Clinical Subgroup Composed of Genetically Affected Family Members*

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Hypertrophic cardiomyopathy (HCM) is characterized by an exceedingly broad spectrum of phenotypic expression (1–3). This disease, initially regarded as typically associated with diffuse and particularly substantial left ventricular (LV) wall thickening and mass, has now been shown to include morphologic forms demonstrating a wide range in the magnitude of LV hypertrophy (3). Indeed, mild and segmental wall thickening constitutes an important proportion of the HCM morphologic spectrum, as underscored by a recent cardiovascular magnetic resonance imaging study that showed that fully 20% of patients with a clinically expressed HCM phenotype (namely, increased LV wall thickness) paradoxically showed normal overall LV mass (4).

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Furthermore, an intriguing and evolving subset comprising asymptomatic children and adult family members, who inherit a disease-causing mutation encoding proteins of the cardiac sarcomere (but appear clinically unaffected with normal LV wall thickness and mass), is now being identified with greater frequency owing to the expanding availability of diagnostic genetic testing for HCM. By way of definition, such genotype-positive–phenotype-negative family members are encountered within either of 2 clinical scenarios. Most commonly, of these are pre-adolescents before the abrupt onset of LV wall thickening, which usually occurs at ages 13 to 17 years, associated with accelerated growth and maturation (5). Less frequently, a few other HCM family members have been documented with delayed, age-dependent phenotypic penetrance in which evolution to LV hypertrophy occurs much later into midlife and beyond (adult-onset hypertrophy) (6,7).

However, there are many unresolved issues concerning the pathophysiology and natural history of patients with pre-clinical HCM. Do these patients with only sarcomere mutations in fact harbor a pathologic condition (namely, HCM), and what are the potential complications (if any) or clinical course of this subset? Is the LV structurally and functionally abnormal (i.e., "cardiomyopathic") while not obviously hypertrophied? Are these genetically affected individuals all predestined to develop the HCM phenotype with LV wall thickening, or can LV hypertrophy remain absent throughout a life-time in genetically affected persons?

It is the latter question concerning the morphologic and functional condition of the myocardium in apparently healthy at-risk family members that has been addressed by several lines of investigation. A number of years ago, 12-lead electrocardiogram patterns were noted to be distinctly abnormal before the appearance of LV hypertrophy on echocardiogram in HCM family members, with the magnitude of precordial and standard lead voltages predictive for the degree of future LV hypertrophy (8). The underlying cellular abnormalities responsible for such early alterations in electrocardiographic pattern remain unresolved, but could be related to the alternations in diastolic filling discussed in the following text.

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Genetically modified animal models of HCM (heterozygous knock-in mice and transgenic rabbits with the myosin heavy chain missense mutation, Arg403Gln) have provided the initial insight that abnormalities of diastolic function could precede the development of LV hypertrophy (as well as myocyte hypertrophy and disarray, or myocardial replacement fibrosis) (9–12). Subsequently, 3 groups of investigators have used tissue Doppler imaging (TDI) and 2-dimensional echocardiography to study genetically affected but asymptomatic family members without LV hypertrophy, demonstrating that altered functional parameters of LV relaxation and diastolic function can be identified in this pre-hypertrophic phase.

In this regard, Ho et al. (13) studied 18 mutation-positive–phenotype-negative relatives with mutations in the beta-myosin heavy chain gene and found early mitral annular diastolic (Ea) velocity to be significantly lower than in controls, and indicative of impaired relaxation. Nevertheless, Ea velocity was not significantly sensitive as a sole diagnostic criterion to discriminate family members with normal LV wall thickness who carried sarcomere mutations from those who did not. However, when combined with hyperdynamic LV function (ejection fraction ≥68%), low Ea velocity was highly predictive of a genotype in those young persons without overt manifestations of HCM. Somewhat in contrast, Nagueh et al. (14) studied 13 gene-positive–phenotype-negative relatives with beta-myosin heavy chain, myosin-binding protein C (MBPC3), and troponin T mutations and reported Ea velocities to be >40% lower than in normal control subjects, and itself highly specific for pre-clinical HCM. Finally, Cardim et al. (15) reported a family with 5 pre-clinical HCM members in whom markedly reduced Ea velocities were identified.

The study of Michels et al. (16) from the Netherlands in this issue of *iJACC* employs a design similar to that in prior reports to study 27 gene-positive–phenotype-negative relatives who carry 1 of 3 different Dutch MBPC3 founder mutations (17), each predicted to cause truncation of the protein due to small insertion/deletions (c.2373dupG and c.2864-2865delCT) or premature termination (Arg943X). These data contribute to the available experience in characterizing diastolic abnormalities in genetically affected HCM family members without LV hypertrophy. However, in contrast to prior studies, neither global or regional Ea and mitral annular systolic (Sa) velocities in the gene-positive–phenotype-negative relatives differed from controls; these parameters were, nevertheless, reduced compared with those of family members expressing the overt HCM phenotype with LV wall thickening. The sole metric of abnormal diastolic function in the study of Michels et al. (16) was increased late diastolic (Aa) velocity in the pre-clinical subset relative to controls.

It is perhaps surprising that the authors did not find a significant reduction in Ea, as has been consistently identified in the other studies (including that of Nagueh et al. [14]) in which more than one-half of the gene-positive–phenotype-negative cohort bear the same MYBPC3 mutation as 30% of the subjects in the present report (c.2373dupG, also known as InsG791). This discrepancy may be related to the unusually low Ea velocities evident in the control population used. Nevertheless, Michels et al. (16) concluded that while TDI velocities were not sufficiently sensitive to reliably predict genotype status in individual family members, their data are nevertheless consistent with the principle that diastolic function is often altered in pre-clinical HCM before development of LV wall thickening. Therefore, it is important to underscore that TDI abnormalities are not ideal diagnostic markers in this asymptomatic pre-clinical subset and cannot substitute for genetic testing to achieve definitive identification of genetically affected HCM family members. Nevertheless, TDI has proved useful in characterizing early functional LV abnormalities and providing potentially important insights into the disease pathogenesis of HCM.

The mechanisms underlying diastolic dysfunction in pre-clinical HCM are not completely understood, although data from animal models have incriminated altered cross-bridge kinetics, where the presence of a sarcomere mutation slows the rate of dissociation of actin and myosin (10,11). Furthermore, altered intracellular calcium handling with a decreased rate of calcium uptake into sarcoplasmic reticulum may also contribute to the impaired relaxation (18,19).

Major questions remain concerning the management of pre-clinical HCM family members, and are becoming increasingly relevant with the greater penetration of commercially available genetic testing for HCM. At present, treatment strategies including drugs and primary prevention implantable defibrillators are generally not recommended for such genetically affected persons without LV hypertrophy. For example, our HCM center in Minneapolis has prophylactically implanted defi-

brillators in only 2 adults in this subgroup, both with a strong family history of HCM-related sudden cardiac death due to HCM (and to date neither has experienced an appropriate device intervention).

However, a clinical dilemma arising with increasing frequency involves young genotype-positive–phenotype-negative persons who are engaged in competitive athletic programs. The 36th Bethesda Conference recommendations (20) are relatively liberal regarding such athletes with sarcomere mutations, allowing full participation in the absence of the HCM phenotype (i.e., LV hypertrophy). On the other hand, the European Society of Cardiology recommendations (21) are more restrictive in this regard, and have disqualified athletes from competition based solely on the presence of a mutation. Such difficult clinical decisions concerning eligibility for competitive sports are further compounded when HCM-related sudden death is part of the family history.

In conclusion, there are accumulating data obtained largely with TDI in asymptomatic HCM family members (who have inherited the genetic substrate) that underscore the principle that functionally abnormal LV myocardium may be present before the development of hypertrophy. Indeed, subtle but demonstrable cardiomyopathic changes usually consisting of diastolic dysfunction can be a primary component of pre-clinical HCM. Furthermore, these abnormalities in diastolic function appear to be early and fundamental manifestations of sarcomere mutations. However, the clinical significance of such TDI imaging findings remains unresolved—in other words, whether evidence of diastolic dysfunction represents a marker for the future evolution of LV hypertrophy, cardiac symptoms, or major cardiac events, and whether it should be the basis for restricting a physically active life-style. As is often the case in HCM, answers to these important questions regarding this novel patient subgroup will require longitudinal clinical studies carried out over substantial periods of time.

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REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.
2. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology task force on clinical expert consensus documents and the European Society of Cardiology committee for practice guidelines committee to develop an expert consensus document on hypertrophic cardiomyopathy. J Am Coll Cardiol 2003;42:1687–713.
3. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995;26:1699–708.
4. Olivotto I, Maron MS, Autore C, et al. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008;52:559–66.
5. Maron BJ, Spirito P, Wesley YE, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med 1986;315:610–4.
6. Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol 2001;38:315–21.
7. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998;338:1248–57.
8. Panza JA, Maron BJ. Relation of electrocardiographic abnormalities to evolving left ventricular hypertrophy in hypertrophic cardiomyopathy during childhood. Am J Cardiol 1980;63:1258–65.
9. Georgakopoulos D, Christe ME, Giewat M, Seidman CM, Seidman JG, Kass DA. The pathogenesis of familial hypertrophic cardiomyopathy: early and evolving effects from an alpha-cardiac myosin heavy chain missense mutation. Nat Med 1999;5:327–30.
10. Spindler M, Saupe KW, Christe ME, et al. Diastolic dysfunction and altered energetics in the alphaMHC403/+ mouse model of familial hypertrophic cardiomyopathy. J Clin Invest 1998;101:1775–83.
11. Blanchard E, Seidman C, Seidman JG, LeWinter M, Maughan D. Altered crossbridge kinetics in the alpha-MHC403/+ mouse model of familial hypertrophic cardiomyopathy. Circ Res 1999;84:475–83.
12. Nagueh SF, Kopelen HA, Lim DS, et al. Tissue Doppler imaging consistently detects myocardial contraction and relaxation abnormalities, irrespective of cardiac hypertrophy, in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circulation 2000;102:1346–50.
13. Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. Circulation 2002;105:2992–7.
14. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation 2001;104:128–30.
15. Cardim N, Perrot A, Ferreira T, et al. Usefulness of Doppler myocardial imaging for identification of mutation carriers of familial hypertrophic cardiomyopathy. Am J Cardiol 2002;90:128–32.

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JANUARY 2009:65–8

16. Michels M, Soliman OII, Kofflard MJ, et al. Diastolic abnormalities as the first feature of hypertrophic cardiomyopathy in Dutch myosin-binding protein C founder mutations. J Am Coll Cardiol Img 2009;2:58–64.
17. Alders M, Jongbloed R, Deelen W, et al. The 2373insG mutation in the MYBPC3 gene is a founder mutation, which accounts for nearly one-fourth of the HCM cases in the Netherlands. Eur Heart J 2003;24:1848–53.
18. Fatkin D, McConnell BK, Mudd JO, et al. An abnormal Ca(2+) response in mutant sarcomere protein-mediated familial hypertrophic cardiomyopathy. J Clin Invest 2000;106:1351–9.
19. Semsarian C, Ahmad I, Geiwat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. J Clin Invest 2002;109:1013–20.
20. Maron BJ, Zipes DP. 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol 2005;45:1312–75.
21. Pelliccia A, Fagard R, Björnstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the European Society of Cardiology. Eur Heart J 2005;26:1422–45.

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