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Obesity and its Association to Phenotype and Clinical Course in Hypertrophic Cardiomyopathy

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Objectives This study sought to assess the impact of body mass index (BMI) on cardiac phenotypic and clinical course in a multicenter hypertrophic cardiomyopathy (HCM) cohort.

Background It is unresolved whether clinical variables promoting left ventricular (LV) hypertrophy in the general population, such as obesity, may influence cardiac phenotypic and clinical course in patients with HCM.

Methods In 275 adult HCM patients (age 48 ± 14 years; 70% male), we assessed the relation of BMI to LV mass, determined by cardiovascular magnetic resonance (CMR) and heart failure progression.

Results At multivariate analysis, BMI proved independently associated with the magnitude of hypertrophy: pre-obese and obese HCM patients (BMI 25 to 30 kg/m^2 and >30 kg/m^2, respectively) showed a 65% and 310% increased likelihood of an LV mass in the highest quartile (>120 g/m^2), compared with normal weight patients (BMI <25 kg/m^2; hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 0.73 to 3.74, p = 0.22 and 3.1; 95% CI: 1.42 to 6.86, p = 0.004, respectively). Other features associated with LV mass >120 g/m^2 were LV outflow obstruction (HR: 4.9; 95% CI: 2.4 to 9.8; p < 0.001), systemic hypertension (HR: 2.2; 95% CI: 1.1 to 4.5; p = 0.026), and male sex (HR: 2.1; 95% CI: 0.9 to 4.7; p = 0.083). During a median follow-up of 3.7 years (interquartile range: 2.5 to 5.3), obese patients showed an HR of 3.6 (95% CI: 1.2 to 10.7, p = 0.02) for developing New York Heart Association (NYHA) functional class III to IV symptoms compared to nonobese patients, independent of outflow obstruction. Noticeably, the proportion of patients in NYHA functional class III at the end of follow-up was 13% among obese patients, compared with 6% among those of normal weight (p = 0.03).

Conclusions In HCM patients, extrinsic factors such as obesity are independently associated with increase in LV mass and may dictate progression of heart failure symptoms. (J Am Coll Cardiol 2013;62:449–57) © 2013 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, characterized by heterogeneous phenotypic expression with extreme diversity in the pattern and extent of left ventricular hypertrophy (LVH), due to molecular pathways and triggers that remain largely unexplained (1–5). In the vast majority of genotype-positive patients, HCM is associated with mutations in genes encoding proteins of the cardiac sarcomere, most commonly beta-myosin heavy chain and myosin-binding protein C (1–3). While these molecular defects are considered responsible for the development of LVH, there is currently no conclusive evidence to explain the variability in phenotypic expression of HCM, ranging from massive degrees to absence of LVH even within the same family (1,4–6).

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Among several hypotheses, the interplay of modifier genes and environmental factors has been commonly offered as a potential explanation for phenotypic diversity (7,8). To date, however, the possibility of an environmental modulation of the HCM phenotype remains speculative, and even the impact

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Abbreviations and Acronyms

BMI = body mass index
CMR = cardiovascular magnetic resonance
HCM = hypertrophic cardiomyopathy
HR = hazard ratio
LGE = late gadolinium enhancement
LV = left ventricular
LVH = left ventricular hypertrophy
NYHA = New York Heart Association

of an obvious candidate variable such as obesity, known to promote LVH in the general population, is unresolved (9–15). In addition, it is unknown whether the adverse metabolic and hemodynamic effects of obesity, to which HCM patients may be exposed during the long-term course of their disease, ultimately affect symptomatic status and prognosis (11,12,16–18). Therefore, the present study was designed, in a consecutive multicenter cohort studied with cardiac magnetic resonance (CMR), to assess the impact of body mass index (BMI) on the phenotype, as well as clinical course, of HCM.

Methods

Study population. The study cohort comprised 275 adult patients with HCM (age >18 years, mean 48 ± 14 years at study entry; 70% male, maximum left ventricular (LV) wall thickness 21 ± 5 mm) consecutively referred for CMR studies between January 2005 and June 2008 at 3 participating referral centers in the United States and Italy: Minneapolis Heart Institute Foundation (Minneapolis, Minnesota; n = 168); Tufts Medical Center (Boston, Massachusetts; n = 45); and Careggi University Hospital (Florence, Italy; n = 62). Diagnosis of HCM was based on 2-dimensional echocardiographic evidence of a hypertrophied, nondilated LV (maximal wall thickness ≥15 mm), in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident (1,3). We excluded significant atherosclerotic coronary artery disease (>50% stenosis in a major artery) by virtue of 2 specific clinical or CMR criteria: 1) no study patient experienced an acute coronary event associated with increased cardiac enzymes or Q waves on electrocardiogram; and 2) in all patients with late gadolinium enhancement (LGE) distributed in a single coronary vascular territory, hemodynamically significant coronary artery disease was excluded by arteriography or computed tomography angiogram. Furthermore, patients with prior cardiac surgery (including septal myectomy), alcohol septal ablation, and chronic renal failure were excluded (3). The study protocol was approved by the respective Internal Review Boards or research ethics committees of each institution, and written inform consent was obtained from each subject.

Definitions. Body mass index was calculated as weight/(height · height) and expressed in kg/m^2. Patients were classified as normal weight (BMI range <25 kg/m^2), pre-obese (25 to 30 kg/m^2), and obese (>30 kg/m^2), according to existing guidelines (14). Type 2 diabetes was defined (and treated) according to standard guidelines (12,18).

Systemic hypertension was diagnosed based on resting blood pressure values >140/90 mm Hg on ≥3 different examinations and treated medically to optimize blood pressure control, as per standard international guidelines (18). All patients with hypertension had a diagnosis of HCM based on 1 or more of the following criteria: 1) HCM-causing sarcomere gene mutation or family history of HCM; 2) onset of hypertension occurring years after the diagnosis of HCM; 3) maximum LV wall thickness exceeding that expected by hypertension alone (i.e., >20 mm); 4) presence of marked mitral leaflet elongation (19); 5) dynamic LV outflow obstruction (≥30 mm Hg) under resting conditions (20); and 6) distribution of LGE by contrast CMR consistent with HCM (i.e., preferentially mid-wall or transmural, and not confined to a single coronary vascular territory) (3,5,21).

Echocardiography. Echocardiographic studies were performed with commercially available instruments. Left ventricular hypertrophy was assessed with 2-dimensional echocardiography, and the site and extent of maximal wall thickness were identified. Maximal end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the chamber. Left ventricular outflow obstruction, due to mitral valve systolic anterior motion and mitral-septal contact, was identified by a peak instantaneous outflow gradient ≥30 mm Hg occurring under basal conditions (n = 57) (20). Two hundred and eighteen patients were nonobstructive at rest (basal gradient <30 mm Hg), of whom 105 (age 43 ± 13 years, 72% males) underwent maximal symptom-limited exercise echocardiography, as previously described (18); 50 developed dynamic gradients ≥30 mm Hg during effort or recovery (range 48 to 155 mm Hg), and were considered to have provokable outflow obstruction (20).

CMR. All CMR examinations were performed using commercially available scanners (Philips ACS-NT 1.5-T Gyroscan-Intera, Best, the Netherlands) and a commercial cardiac coil. Electrocardiographic gated, steady-state, free precession breath-hold cines in sequential 10-mm short-axis slices (no gap) were acquired starting parallel to the atrioventricular ring and covering the entire ventricle. Left ventricular end-diastolic and end-systolic volumes, left ventricular mass and wall thickness were calculated with commercially available work stations (View Forum, Philips Medical System, Best, the Netherlands) (19,21).

For calculation of LV mass, the endocardial and epicardial borders of the left ventricle were manually planimetered on successive short-axis cine images at end-diastole. The most basal slice at end-diastole was visually inspected and, if ventricular myocardium was present, it was planimetered and included in the mass calculation. If myocardium but no intracavitary blood pool was present on the most apical slice, it was included in the mass calculation by planimetering only the epicardial border. Particular care was taken to avoid including papillary muscles in the LV mass calculation. Left ventricular mass was derived by the summation of