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ORIGINAL ARTICLE

The Natural History of Nonobstructive Hypertrophic Cardiomyopathy

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Abstract

Objective: To describe the survival of a large nonobstructive hypertrophic cardiomyopathy (NO-HCM) cohort and to identify risk factors for increased mortality in this population.

Patients and Methods: Patients were identified from the Mayo Clinic HCM database from January 1, 1975, through November 30, 2006, for this retrospective observational study. Patients with resting or provocable left ventricular outflow tract gradients were excluded. Echocardiographic, clinical, and genetic data were compared between subgroups, and survival data were compared with expected population rates.

Results: A total of 706 patients with NO-HCM were identified. During median follow-up of 5 years (mean, 7 years), there were 208 deaths. Overall survival was no different than expected compared with age- and sex-matched white US population mortality rates (P=.77). Independent predictors of death were age at diagnosis, "burned out" HCM, and history of transient ischemic attack or stroke; use of an implantable cardioverter defibrillator (ICD) was inversely related to death. After exclusion of patients with an ICD, there was no difference in survival compared with age- and sex- matched individuals (P=.39); age, previous transient ischemic attack/stroke, and burned out HCM were predictors of death.

Conclusion: In this cohort, patients with NO-HCM had similar survival rates as age- and sex-matched white US population mortality rates. Although use of an ICD was inversely related to death, no differences in overall survival were seen after those patients were excluded. Burned out HCM was independently associated with an increased risk of death, identifying a subset of patients who may benefit from more aggressive therapies.

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Nonobstructive hypertrophic cardiomyopathy (NO-HCM) has been a well-recognized subtype of HCM for more than 50 years.[1] It refers to patients with HCM with a left ventricular outflow tract (LVOT) peak gradient of less than 30 mm Hg at rest and with provocative maneuvers.[2] Contemporary natural history studies of HCM have compared patients who were nonobstructive at rest, approximately 75% of HCM cohorts,[3,4] with those who had LVOT obstruction at rest. Patients with HCM without rest obstruction have demonstrated better outcomes, including less progression to severe heart failure symptoms, less atrial fibrillation, and fewer sudden cardiac and HCM-related deaths.[3,4] However, approximately two-thirds of patients who are nonobstructive at rest reveal latent obstruction with provocative maneuvers such as exercise,[5,6] making the true prevalence of NO-HCM approximately 24% to 30% in referral populations. The only previously published account of prognosis in a small population of proven NO-HCM described no progression to obstruction, no development of congestive heart failure, and no deaths in 25 men (mean age, 52 years; 26% of patients with HCM evaluated) followed for an average of 9 years.[7] Given the paucity of published data regarding the natural history of NO-HCM, we sought to describe the survival of a large NO-HCM

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cohort and to identify risk factors for increased mortality in this population.

METHODS

Approval from the Mayo Clinic Institutional Review Board was granted for this study. All the patients provided informed consent to use clinical data for research purposes. The investigation conforms to the principles outlined in the Declaration of Helsinki. A total of 2763 patients were identified retrospectively from the Mayo Clinic HCM and echocardiography databases, which captured nearly all the consecutive cases of HCM between January 1, 1975, and November 30, 2006. The index date was defined as the first clinical encounter for the evaluation/diagnosis of HCM occurring at Mayo Clinic. A diagnosis of NO-HCM was assigned by a clinician with expertise in HCM based on hemodynamic data ascertained by physical examination, echocardiography, or cardiac catheterization. HCM was defined as left ventricular hypertrophy in the absence of a cardiac or systemic explanation for the magnitude of hypertrophy observed. NO-HCM was defined as HCM in the absence of a significant gradient (<30 mm Hg) across the LVOT at rest and with provocation.[2] Provocative maneuvers are routinely used at Mayo Clinic to exclude latent obstruction, and these maneuvers include Valsalva, squat-to-stand, amyl nitrite, isoproterenol, and exercise. Special consideration was made to avoid the diagnosis of HCM if other physiologic explanations for hypertrophy existed, such as significant hypertension, aortic stenosis, elite endurance athletics, or infiltrative disease. Patients with a history of septal myectomy or alcohol septal ablation were excluded because their underlying disease process is that of obstructive HCM. The 6 patients with NO-HCM who underwent cardiac transplant were excluded because they were too few for subgroup analysis. All the morphologic features of HCM without LVOT obstruction, including patients with apical HCM (ie, hypertrophy primarily localized to the apex of the left ventricle),[8] were included.

Baseline characteristics ascertained at the index clinic visit included patient demographics, family history of HCM and sudden cardiac death in first-degree relatives, symptoms, medications, comorbidities (based on patient report and corroborated by internal or outside medical records when possible), and implantable cardioverter defibrillator (ICD) implantation. Echocardiographic measurements of septal and posterior wall thickness were recorded, and Doppler-derived indices of early mitral inflow velocity and medial mitral annular tissue velocity were available in more recent studies.[9] All-cause mortality was ascertained by clinic visit, survey, or social security death index.

Genetic test results were available for 191 patients who had enrolled in an Institutional Review Board–approved research cohort intended to test genotype-phenotype relationships in HCM that began in 1999. There were 515 patients who were not enrolled in genetic testing for reasons that are unknown but could have included death before 1999, declined enrollment, and pursuit of commercial genetic testing rather than research-based genetic testing. For enrolled patients, genomic DNA was interrogated for mutations in the 8 sarcomeric genes in which mutations that cause HCM most commonly occur (alpha actin, myosin binding protein C, myosin heavy chain, myosin light chain 2, myosin light chain 3, troponin I, troponin T, and alpha tropomyosin), as previously described.[10]

Continuous variables are expressed as mean ± SD when normally distributed and as median (interquartile range) when nonnormally distributed. Categorical variables are expressed as number and percentage. Survival was compared with that expected from the US total population with the same age and sex distribution (based on US census data)[11] using a one-sample log-rank test. Continuous variables were compared between 2 groups using the *t* test, or a nonparametric test (Wilcoxon test) when data were nonnormally distributed. Categorical variables were compared between 2 groups using the Fisher exact test. Univariate Cox proportional hazards regression was performed to assess the association between patient characteristics and mortality. Clinical features that demonstrated a $P<.1$ by univariate Cox proportional hazards analysis were included in a multivariate model to identify independent predictors of mortality. Missing data for each specific variable are indicated in Table 1, where the total number with data for each variable is indicated. A $P<.05$ was

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