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FOCUS ISSUE: HYPERTROPHIC CARDIOMYOPATHY

Outcome of Patients With Hypertrophic Cardiomyopathy and a Normal Electrocardiogram

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Objectives This study sought to clarify the frequency, clinical phenotype, and prognosis of those patients with hypertrophic cardiomyopathy (HCM) who present with a normal electrocardiogram (ECG).

Background Hypertrophic cardiomyopathy is the most common cause of sudden death in young people. Screening advocates have recommended a 12-lead ECG for the early detection of HCM in athletes, yet the clinical outcomes of those presenting with a normal ECG remains to be fully delineated.

Methods Baseline characteristic and echocardiographic data were collected on all patients with HCM who initially presented to our institution with a diagnostic echocardiogram but a normal ECG. Follow-up was obtained and compared with the prognosis of HCM patients who presented with abnormal ECGs.

Results We compared 135 HCM patients with a normal ECG with 2,350 HCM patients with an abnormal ECG. The latter group was more likely to have worse symptoms, have higher gradients, and a greater degree of septal wall thickness than the patients with a normal ECG. Severe obstructive symptoms requiring surgical myectomy and implantation of an implantable cardioverter-defibrillator were more common in patients with abnormal ECGs. Cardiac survival was significantly better in the group with a normal ECG at presentation—none of these patients had a cardiac death at follow-up.

Conclusions Almost 6% of patients presenting with demonstrable echocardiographic evidence of HCM had a normal ECG at the time of diagnosis. This subset of patients with normal ECG-HCM appears to exhibit a less severe phenotype with better cardiovascular outcomes. (J Am Coll Cardiol 2009;54:229–33) © 2009 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a disease of the sarcomere characterized by left ventricular hypertrophy. The pattern of hypertrophy is typically asymmetric affecting predominantly the ventricular septum, yet some patients exhibit a disproportionate involvement of the apex or free wall. The electrocardiogram (ECG) is abnormal in most patients with HCM, with electrocardiographic criteria for left ventricular hypertrophy and widespread Q waves (1). Variants such as apical HCM may show a distinctive pattern of diffuse symmetric T-wave inversions across the precordium (2–4). The ECG is often used as a principle screening tool for HCM, particularly in large otherwise healthy populations and pre-participation athletic screening programs (5–8). The purpose of this study was to examine how frequently patients with echocardiographically documented HCM present with a completely normal ECG and to characterize the phenotype and outcomes of patients with a normal ECG-HCM.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. All patients with the diagnosis of HCM and normal 12-lead ECG at the Mayo Clinic, Rochester, in the period from April 1, 1994, to October 30, 2006, were identified. During this period, 2,485 patients with a diagnosis of HCM were seen. Of those, 135 patients were identified as having a normal ECG, and the remaining 2,350 patients exhibited an abnormal ECG. The diagnosis of HCM was based on the presence of a hypertrophied, nondilated left ventricle in the absence of other diseases capable of producing the degree of observed hypertrophy. The primary imaging modality used for diagnosis in all patients was transthoracic 2-dimensional and Doppler echocardiography. Patients found to have outflow tract

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Abbreviations and Acronyms

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

gradients below 40 mm Hg, routinely underwent Valsalva maneuvers. If this provocation did not raise the gradient significantly, then amyl nitrite inhalation was performed in our echocardiographic evaluation. Exercise testing or invasive assessment was obtained in select cases at the discretion of the clinician if the echocardiogram demonstrated no resting or latent obstruction.

Patients with potential confounding coexisting disease(s) were excluded from this analysis, by definition, as were patients with other causes for left ventricular hypertrophy. Follow-up obtained via clinic visit, mailed questionnaire, telephone survey, and Social Security Death Index search was 100% complete for the patients with a normal ECG at 6.6 ± 6.0 years with respect to mortality.

The HCM-related mortality included sudden cardiac death (unexpected within 1 h of a witnessed collapse or nocturnal), heart failure death (in the context of progressive cardiac decompensation), and stroke-related death (9). Appropriate discharges from implantable defibrillators for ventricular fibrillation or sustained ventricular tachycardia were regarded as sudden deaths. Invasive septal therapy was offered to patients with significant outflow tract obstruction who remained symptomatic despite appropriate pharmacologic therapy (10,11). The choice of pursuing implantable cardioverter-defibrillator insertion was made on an individual patient basis, taking into consideration the presence of 1 or more risk factors for sudden cardiac death (12), following a comprehensive discussion of the risks and benefits of this particular risk management strategy. No patients, however, had undergone septal myectomy or septal ablative therapy before the initial visit ECGs. Coronary artery disease was excluded by history of prior infarction or intervention, or the presence of symptoms. Patients with cardiovascular risk factors or over 40 years old routinely underwent coronary angiography before septal reduction surgery.

For our analysis, patients with a first- or second-degree relative confirmed to have the diagnosis of HCM were classified as having a positive family history of the disease.

Electrocardiographic measurements. The 12-lead ECGs for each of the eligible patients were obtained from the Mayo Clinic Electrocardiography Database. This database provides electronic copies of all electrocardiographic tracings and includes detailed, prospectively defined and validated computerized interpretations that are over-read and confirmed by technicians and cardiologists. The reference ECG used was a standard 12-lead that was obtained in all study subjects at the time of the initial evaluation for HCM at the Mayo Clinic. An ECG was diagnosed as "normal" on the basis of criteria that were outlined in the initial description of ECG abnormalities in HCM by Savage et al. (13) and were again individually reviewed by 1 author (C.J.M.). It is important to note that these criteria do encompass the definitions set by the European Society of Cardiology (7) and Italian pre-participation screening programs (14). Essentially, the normal ECG group presented no evidence of rate abnormality, P- or QRS-axis deviation, abnormal voltage for age and sex, criteria for left or right atrial enlargement, ST- or T-wave changes (15), P-R (≥200 ms) or QRS prolongation (≥120 ms), or abnormal Q waves (15). One ECG was reclassified during the over-read process as abnormal, based on Cornell, Scott, and Estes criteria, after an initial normal computer-based classification.

Statistical methods. Data are presented as mean ± SD for continuous data and as number and percentage for categorical data. A p value <0.05 was considered significant in all statistical analyses. Pearson likelihood ratio tests were used in the contingency analysis—and these are displayed in the tables—and the *t* test was used in the 1-way analyses. Survival analysis testing between groups was compared using log-rank testing, and the Kaplan-Meier survival curves were constructed using the product-limit method.

Results

Patients with HCM and a normal ECG. A total of 135 patients (6% of total eligible HCM patients) were identified as having a normal ECG. There were 57 (42%) men and 78 (58%) women; the mean ± SD age was 55 ± 18 years (range 8.4 to 91.5 years). Fourteen patients (10.4% of those with a normal ECG and <1% of all studied HCM patients) were individuals under the age of 30 years. In the group of patients who were under the age of 30 years and presenting with a normal ECG, 11 (78.6%) of 14 had a family history of HCM. In the remaining 3 patients, the diagnostic investigation with echocardiography was pursued by the physician because of a murmur (n = 2) or poor effort tolerance (n = 1). Clinical and echocardiographic characteristics of the group are shown in Table 1. The septal thickness averaged 17.3 ± 4 mm, and the mean resting gradient was 29.1 ± 33 mm Hg (range 0 to 154 mm Hg).

Forty-seven (34.8%) patients presented with a history of pre-syncope, and 11 (8.1%) gave a history of syncope. In addition, a large proportion of the patients were asymptomatic from a New York Heart Association functional classification standpoint: 97 (71.9%) were free from anginal symptoms, and 61 (45.2%) were free from dyspnea. Only 2 patients had angina at rest, and a single patient had dyspnea at rest—class IV symptoms. Six patients (4.3%) had a background of a prior stroke. Furthermore, 66 patients (46.8%) were mildly hypertensive and 11 (7.8%) were diabetic.

The most commonly used cardiac medications were beta-adrenergic blockers (43.7%), calcium-channel antagonists (25.2%), disopyramide (1.5%), and amiodarone (n = 1).

Follow-up of this group (after an average of 5.7 ± 6 years) revealed that 30 (22.2%) patients were subsequently referred for septal myectomy to relieve obstructive symptoms refractory to pharmacotherapy, and 6 (4.4%) under-

Table 1 Baseline Characteristics

	Normal ECG (n = 135)	Abnormal ECG (n = 2,350)	p Value
Age, yrs	55 ± 18	47 ± 21	<0.001
Patients <30 yrs	14 (10.4)	453 (19.3)	0.001
Males	57 (42.2)	1,318 (56.1)	0.0002
Myectomy	30 (22.2)	790 (33.6)	0.002
Ablation	6 (4.4)	145 (6.2)	0.37
ICD	4 (3.0)	315 (13.4)	0.0003
Angina			0.18
1	94 (69.6)	1,211 (57.8)	
2	31 (23.0)	532 (25.4)	
3	8 (5.9)	289 (13.8)	
4	2 (1.5)	33 (1.6)	
Dyspnea (NYHA functional class)			0.04
1	58 (43.0)	748 (33.7)	
2	34 (25.2)	510 (23.0)	
3	42 (31.1)	890 (40.1)	
4	1 (0.7)	68 (3.1)	
Family history of HCM	28 (20.7)	572 (24.3)	0.15
Pre-syncope	47 (34.8)	852 (40.4)	0.21
Syncope	11 (8.1)	263 (12.1)	0.12
Sudden cardiac arrest	0 (0.0)	14 (1.3)	0.82
Atrial fibrillation (paroxysmal)	10 (7.4)	374 (17.6)	0.007
Atrial fibrillation (chronic)	1 (0.7)	50 (4.4)	0.08
Stroke	6 (4.4)	102 (4.8)	0.95
Diabetes mellitus	11 (8.1)	98 (4.7)	0.09
Hypertension	66 (48.9)	668 (31.5)	<0.001
Beta-blocker	59 (43.7)	1,301 (70.0)	<0.0001
Calcium blocker	34 (25.2)	729 (41.2)	0.01
Disopyramide	2 (1.5)	161 (8.3)	0.01
Amiodarone	1 (0.7)	116 (5.9)	0.02
Warfarin	3 (2.2)	238 (12.2)	0.001
Resting gradient, mm Hg	29.1 ± 33	42.4 ± 43	<0.001
Septal wall thickness, mm	17.3 ± 4	19.8 ± 6	<0.001
Clinical follow-up	5.7 ± 6	4.5 ± 5	

Values are mean ± SD or n (%).
ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

went septal ablation. Based on perceived increase in risk of sudden cardiac arrest, 4 (3.0%) patients were referred for placement of an implantable defibrillator device for primary prevention only. Atrial fibrillation developed in 11 patients (8.1%). There were no documented episodes of sudden cardiac death or appropriate implantable cardioverter-defibrillator discharges in the follow-up of this group. A total of 58 patients (43%) had a subsequent ECG performed at least 2 months after the initial ECG. Among these patients, 30 (52%) remained normal at a mean follow-up time of 6.0 ± 4.1 years. The remaining 28 (48%) had developed a detectable ECG abnormality.

An increased body surface area may attenuate the increased ECG voltage found in hypertrophy. Patients presenting with a normal ECG but a body surface area >2.4 m^2 were identified (n = 7), and there were no differences in clinical characteristics or outcomes in this group.

Comparison with HCM patients with an abnormal ECG. The normal ECG group was compared subsequently with patients from our HCM database who initially presented with an abnormal ECG (Table 1). The abnormal ECG group was composed of younger patients with more of a male preponderance, and an overall higher New York Heart Association dyspnea class. There was no significant difference in the frequency of a background of family history of the disease. They were also more likely to undergo septal myectomy surgery at a later date for severe intractable symptoms. There was a higher resting gradient and septal wall thickness in this abnormal ECG group. Interestingly, the finding of hypertension was far more common in the patients presenting with a normal ECG (48.9% vs. 28%, $p < 0.001$).

Survival analysis. Overall survival of the normal ECG group at 5 and 10 years was 92% and 81%, respectively, and was not different from age- and sex-matched controls from the general population (chi-square: 0.18) (Fig. 1A). Comparison with the abnormal ECG-HCM group, however, revealed improved cardiac survival in the normal ECG group, as there were no cardiac deaths noted in this group (Fig. 1B) (chi-square: 0.04).

Discussion

The 12-lead ECG is a fundamental initial diagnostic modality for the early evaluation of a patient suspected of having HCM; at times, it is the only sign of the disease in an otherwise asymptomatic individual (16). In prior investigations (17–19) of patients with mutations in cardiac myofilaments, ECG had a similar accuracy (sensitivity: ~60%, specificity: ~98%) in the diagnosis of HCM as echocardiography (left ventricular wall thickness: >13 mm).

The principle findings of the current study are: 1) that a normal ECG can be observed in 5% to 10% of patients with echocardiographic evidence of HCM; and 2) that patients with HCM and a normal ECG have less severe phenotypic expression of HCM as evidenced by lower wall thickness, left ventricular outflow tract gradient, symptom progression, complication rates, and cardiac-related mortality as compared with HCM patients with abnormal ECGs.

Interestingly, ECG has been recommended as the initial screening tool in large healthy populations and preparticipation athletic programs. However, there is a subset of patients with the phenotypic expression of the disease by echocardiography that does not have an abnormal ECG. It is thus necessary to understand the frequency, clinical characteristics, and prognosis of this group.

In our study, a normal ECG was found in 6% of a large, diverse population of patients with documented HCM, which remains in concordance with previous literature (1,13). Compared with HCM patients with an abnormal ECG, those with a normal ECG presented at an older age and with less severe disease expression. This was character-

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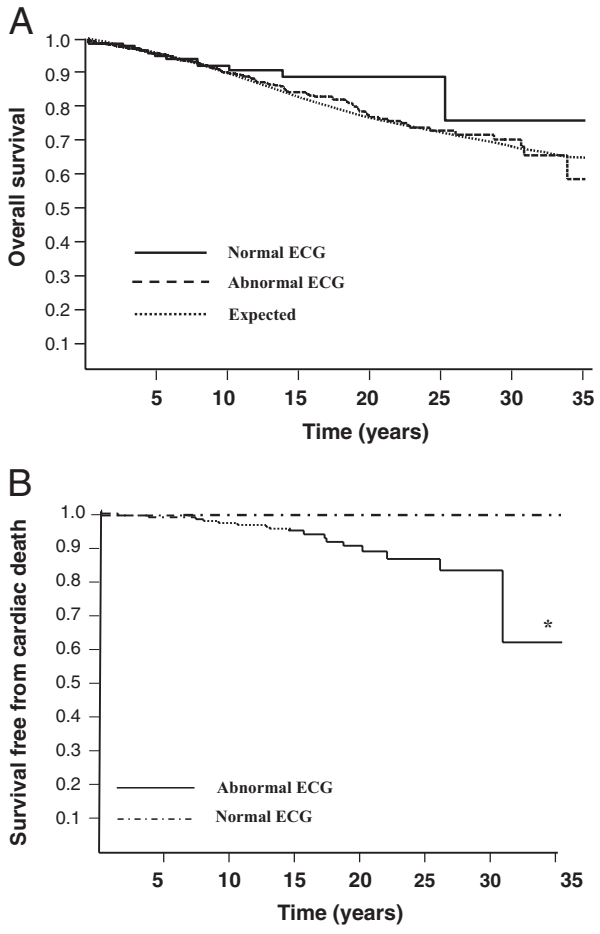

Figure 1 **Clinical Outcomes**

No difference in overall survival was found between the 2 patient groups—stratified according to a normal or abnormal ECG (chi-square: 0.27)—comparing similarly with age- and sex-matched controls (chi-square: 0.18) **(A)**. Cardiac survival, however, was found to be more disparate with no cardiac deaths identified in the normal ECG group (chi-square: 0.04) **(B)**. *p = 0.04. ECG = electrocardiogram.

ized clinically by fewer dyspneic symptoms, less myocardial hypertrophy, and a lower gradient at echocardiography. A normal ECG appears to predict a more benign course with a reduced need for myectomy or an implantable cardioverter-defibrillator, and no patient had sudden cardiac death at intermediate term follow-up. Similarly, extensive experience with ECG screening in Italy has suggested that the identification of athletes without significant repolarization abnormalities (representing 95% of athletes screened) appears to predict a very low risk of subsequent cardiovascular disease or complications thereof (8).

These findings will be of interest to the ongoing international discussions on the appropriate screening for HCM among the general population and competitive athletes (20–24). Although sudden death in young competitive athletes may be due to a variety of cardiovascular diseases, the most common single disease entity in North America is HCM, which occurs in up to one-third of all sudden deaths during athletics (25,26).

Importantly, although only 1 ECG was over-read as abnormal after the initial normal computer-based classification, this misclassified patient subsequently sustained a sudden cardiac death at 41 years of age during exercise, underscoring the importance that physicians not rely solely on the computer-based algorithms for diagnosis and screening.

The 6% incidence of normal ECGs among HCM patients needs to be considered from the other viewpoint. Given that HCM has an overall prevalence of 0.2% in the general screening population and that only 6% of those HCM patients will have a normal ECG, in any general screening, there may be 1 normal ECG-HCM patient for every 10,000 patients screened.

Study limitations. The study is limited by its retrospective nature with a relatively restricted length of follow-up. Furthermore, in lieu of the relatively small sample size and the well-recognized heterogeneity of clinical course in HCM, the absence of cardiac death is not guaranteed by a normal ECG, but rather our data, taken together with the Italian experience, suggest that patients with a normal ECG may have a better cardiac prognosis.

In light of the vast differences in cardiovascular hemodynamics and electrophysiology with exercise and training, these outcomes may not be applicable to the subgroup of highly trained athletes. In addition, no analysis of gene mutation status was performed to offer further insight into genotype-phenotype relationships. Interestingly, as this complex relationship continues to be characterized by newer sophisticated techniques and a heterogeneous entity emerges—initially thought to be hallmarked by increased left ventricular mass (27)—the basic ECG appears to remain a vital screening tool.

Conclusions

Almost 6% of patients presenting with demonstrable echocardiographic evidence of HCM had a normal ECG at the time of diagnosis. This subset of patients with a normal ECG-HCM appears to exhibit a less severe phenotype with better cardiovascular outcomes.

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