ST Segment “Hump” during Exercise Testing and the Risk of Sudden Cardiac Death in Patients with Hypertrophic Cardiomyopathy

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Background: The appearance of a discrete upward deflection of the ST segment termed “the ST hump sign” (STHS) during exercise testing has been associated with resting hypertension and exaggerated blood pressure response to exercise.

Objective: We investigated the prevalence and clinical significance of this sign in a population of patients with hypertrophic cardiomyopathy.

Methods: Eighty-one patients with hypertrophic cardiomyopathy (HCM) who underwent cardiopulmonary exercise testing were followed in a retrospective cohort study for a mean period of 5.3 years.

Results: The appearance of the STHS at the peak of exercise testing was observed in 42 patients (52%), particularly in the inferior and the lateral leads. Patients with the STHS had higher fractional shortening and maximum left ventricular wall thickness and exhibited more frequently outflow tract gradient >30 mmHg at rest. Furthermore, the presence of STHS was a strong independent predictor of the risk of sudden cardiac death (SCD), as the latter occurred in eight of the patients with this sign (8/42, 19%) and in none of the patients without it (0/39, 0%) ($P < 0.001$).

Conclusion: The appearance of a “hump” at the ST segment during exercise testing appears to be a risk factor for SCD in patients with HCM. However, further studies are necessary to validate this finding in larger populations and to elucidate the mechanism of the appearance of the “hump.”

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The standard interpretation of the exercise stress test includes an evaluation of symptoms, exercise capacity, hemodynamics, and changes in the electrocardiogram. Although ST depression and elevation are the most important electrocardiographic findings, a number of other parameters have been shown to be of diagnostic and prognostic value. Among these is a discrete upward deflection of the ST segment termed the ST hump sign (STHS). Previous studies have shown that this sign represents atrial repolarization and is indicative of false positive exercise tests.¹ In addition, the hump sign has been proposed as a predictive sign for normal-

gated exercise thallium testing in a consecutive cohort of 255 patients with abnormal ST segment depression.² Patients with the STHS had better functional capacity and were more likely to have resting hypertension and exaggerated blood pressure responses to exercise. To the best of our knowledge, no data regarding the mechanism of the ST hump have been published.

STHS has been associated with hypertension, a disease characterized by myocardial hypertrophy, diastolic and systolic myocardial dysfunction, fibrosis, and limitation in subendocardial flow reserve.^{3–5} In this study, we investigated

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the prevalence and clinical significance of this sign in a population of patients with hypertrophic cardiomyopathy (HCM), a disease with similar pathologic substrate.

METHODS

Population

One hundred thirty consecutive patients with HCM, who underwent cardiopulmonary exercise testing during the period 1999–2001, were evaluated for inclusion in the study. HCM was defined by standard criteria of left ventricular (LV) hypertrophy of 15 mm or more in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy.⁶ Exclusion criteria included atrial fibrillation or flutter, presence of a permanent pacemaker with intermittent or continuous pacing rhythm, suboptimal electrocardiographic recordings, and early termination (<80% of maximum predicted heart rate for the age of the patient) of the exercise testing due to noncardiopulmonary causes.

Study Protocol

All patients were recruited from the registry of the First Department of Cardiology, Athens University Medical School, in Hippokration Hospital, Greece. The patients underwent upright exercise on a cycle ergometer at room air using a 10 or 15 W/min ramp protocol and simultaneous analysis of respiratory gases. A 12-lead electrocardiographic tracing was recorded every minute and at the peak of the exercise. Blood pressure was measured man-

ually every minute at the brachial artery with the use of a cuff sphygmomanometer. The patients exercised up to volitional exhaustion or the development of symptoms. All patients were instructed to take their medications on the day of the test.

The electrocardiographic recordings at the peak of exercise were evaluated by two independent investigators (M.A. and S.I.), who were unaware of the clinical details of the patients. Averaged beats were not available for any of the exercise testings, therefore optimal electrocardiographic recordings were required for inclusion in the study. A discrete upward deflection of the ST segment was defined as the STHS. This finding had to be apparent in at least three consecutive beats, otherwise it was considered an artifact (Fig. 1). Based on the presence of the STHS, the patients were divided into two groups: group A with the hump sign in at least one lead and group B without the hump sign in any lead. ST segment deviation was defined as (1) horizontal or downsloping ST segment depression of at least 1.0 mm at 60 ms after the J point, (2) upsloping ST segment depression of at least 1.5 mm at 80 ms after the J point, or (3) ST segment elevation of at least 1.0 mm.⁷ When the ST segment was depressed at rest, the additional ST deviation during exercise was taken into account. The value of Kappa measure of agreement between the two investigators for the STHS was 0.80. In case of disagreement between the two investigators, the final decision on the presence of the sign was based on the evaluation of the electrocardiographic recordings by a third observer (T.A.). Intraobserver and interobserver variability for the ST segment changes were 0.08 ± 0.06 mm and 0.09 ± 0.05 mm, respectively.

Figure 1. Representative recordings showing the appearance of the STHS in lead III at the peak of exercise testing in a patient. (A) Without ST segment deviation. (B) With ST segment depression. Arrows point to the STHS.

A failure of systolic blood pressure to increase by 20 mmHg from rest to peak exercise or a decrease in blood pressure during exercise was regarded as an abnormal response.⁸ Systolic blood pressure equal or greater than 230 mmHg and diastolic blood pressure equal or greater than 100 mmHg were considered as an exaggerated response.

The Sokolow-Lyon index was used for the electrocardiographic diagnosis of LV hypertrophy. The echocardiographic measurements in each of the patients were made with two-dimensional and Doppler echocardiography by a single investigator. Coronary angiography was undertaken when age, gender, atherothrombotic risk factors, and presence of angina raised the suspicion of coronary artery disease.

Follow-Up

The patients were followed in a retrospective cohort study. The follow-up begun at the time of exercise stress test (recruiting period from 1999 to 2001), and was continued for 7 years (ended at 2005–2008). The clinical end points were (1) death related to HCM (i.e., sudden cardiac death (SCD) or aborted SCD or death due to congestive heart failure) and (2) SCD or aborted SCD alone. SCD was defined as a sudden and unexpected collapse in patients who had previously had a relatively uneventful clinical course.⁹ Aborted SCD was defined as potentially lethal arrhythmias in which patients received appropriate shocks by an implantable cardioverter defibrillator. Death related to heart failure was defined as that occurring in the context of cardiac decompensation and a progressive course with limiting symptoms of more than 1-hour duration, particularly when it was complicated by pulmonary edema or required hospitalization for treatment, or both.⁹

Statistical Analysis

All statistical analyses were performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, USA). Categorical data were compared with chi-square analysis. All continuous variables were reported as the mean $\pm$ SEM. Analyses were performed with the Student's *t*-test for continuous data. Non-parametric tests were used if the data were not normally distributed. Normality was assessed with normal probability (Q-Q) plot and with nonparametric Kolmogorov-Smirnov test. Odds ratios and

95% confidence intervals (CI) were calculated with univariate logistic regression. Multivariate analysis was performed with a stepwise logistic regression model. Survival curves were constructed according to the Kaplan-Meier method. The log-rank test was used to test the equality of the survivor function across groups. A value of $P < 0.05$ was accepted as indicative of statistical significance.

RESULTS

The study population consisted of 57 men (70%) and 24 women (30%) with a median age of 42 years (range: 12–77 years). The appearance of the STHS at the peak of exercise testing (arrows in Fig. 1) was observed in 42 patients (52%), most commonly in the inferior (39/42 patients) and the lateral (27/42 patients) leads. In 3 of the 42 patients the STHS was also present at rest. The clinical, echocardiographic, and electrocardiographic characteristics of the two groups of patients are summarized in Table 1.

There were no significant differences between the two groups with respect to gender, age, family history of SCD, history of syncope, and NYHA functional class. LV end-diastolic diameter, left atrium anterior-posterior diameter, and the presence of nonsustained ventricular tachycardia on continuous ambulatory ECG monitoring did not differ significantly between the two groups.

Patients with the STHS had higher fractional shortening, higher LV ejection fraction, and greater maximum LV wall thickness, and more frequently had a LV outflow tract gradient >30 mmHg at rest [16/42 (38.1%) vs 7/39 (17.9%), $P = 0.045$] and ECG findings of LV hypertrophy [33/42 (78.6%) vs 22/39 (56.4%), $P = 0.033$]. The proportion of patients with extreme hypertrophy (>30 mm) did not differ significantly between the two groups (Table 1).

Exercise parameters, including the proportion of patients with an abnormal blood pressure response, were similar in the two groups; patients in group A tended to have significant ST segment deviation more frequently than patients in group B (15/42 vs 7/39, $P = 0.07$) (Table 2).

Survival Analysis

The mean ($\pm$ SD) duration of follow-up, from the initial cardiopulmonary exercise testing to the most recent evaluation or the occurrence of an endpoint

Table 1. The Clinical, Echocardiographic, and Electocardiographic Characteristics in the Two Groups of Patients

	Group A	Group B	P Value
No. of patients	42	39	NA
Female/male, n	12/30	12/27	0.83
Age (y)	41.5 ± 3.1	42.1 ± 2.9	0.88
Family history of HCM with SCD, n (%)	8 (19.0)	4 (10.3)	0.27
History of syncope, n (%)	3 (7.1)	5 (12.8)	0.39
NYHA class			
Mean	1.2 ± 0.6	1.3 ± 0.9	0.61
I, n (%)	33 (78.6)	29 (78.4)	NA
II, n (%)	9 (21.4)	6 (16.2)	NA
III-IV, n (%)	0 (0)	2 (5.4)	NA
Coronary artery disease- n (%)	0 (0)	1 (2.6)	0.48
Drugs-n (%)			
Beta-blockers	12 (28.6)	15 (38.5)	0.35
Verapamil	9 (21.4)	5 (12.8)	0.31
Amiodarone	4 (9.5)	3 (7.7)	1.00
Disopyramide	2 (4.8)	0 (0)	0.49
Echocardiographic measurements			
Maximal LV thickness (mm)	20.6 ± 0.9	18.1 ± 0.7	0.04
Maximal LV thickness >30 mm, n (%)	3 (7.1%)	2 (5.3%)	0.73
LV end-diastolic diameter (mm)	45.5 ± 1.0	46.0 ± 0.9	0.73
LV fractional shortening (%)	41.2 ± 1.0	37.4 ± 0.8	0.005
LV ejection fraction (%)	53.56 ± 1.3	47.7 ± 1.0	0.005
Left atrial diameter (mm)	43.3 ± 1.0	41.4 ± 1.0	0.21
LV outflow tract gradient >30 mmHg at rest	16 (38.1%)	7 (17.9%)	0.045
Electocardiographic findings			
LVH in ECG	33 (78.6%)	22 (56.4%)	0.033
Nonsustained ventricular tachycardia	11 (26.2%)	8 (20.5%)	0.700
Implantable defibrillator present	11 (26.2%)	10 (25.6%)	0.911

Group A = group of patients with the hump sign in at least one lead; Group B = group of patients without the hump sign in any lead; LVH = left ventricular hypertrophy; NA = not applicable.

was 5.3 ± 1.6 years. During the follow-up period, no patient died of heart failure. SCD or aborted SCD occurred in eight of the patients of group A (6 aborted SCD and 2 deaths) and in none of the pa-

tients of group B ($P = 0.004$) (Fig. 2). The six aborted deaths were defined as discharge of defibrillator accompanied by presyncope. In more details, the six aborted deaths were: one discharge due

Table 2. The Exercise Parameters of the Two Groups of Patients

	Group A	Group B	P Value
Duration (min)	10.1 ± 1.6	9.0 ± 0.4	0.50
Maximal heart rate (beats/min)	152 ± 4	153 ± 5	0.76
Percentage of age-predicted maximal heart rate (%)	85.2 ± 1.7	85.4 ± 1.9	0.95
Maximal systolic blood pressure (mmHg)	166 ± 5	170 ± 5	0.62
Maximal diastolic blood pressure (mmHg)	82.6 ± 2	84 ± 2	0.51
Abnormal blood pressure response	12 (28.6%)	8 (20.5%)	0.40
Exaggerated blood pressure response	5 (11.9%)	4 (10.3%)	0.81
Angina	5 (11.9%)	3 (7.7%)	0.52
Dyspnea	6 (14.3%)	2 (5.1%)	0.17
ST displacement	15 (35.7%)	7 (17.9%)	0.07
VO ₂ max (mL/kg per min)	24.3 ± 1.5	23.0 ± 1.4	0.53
AFC (%)	75.0 ± 3.3	77.7 ± 2.8	0.54
AT (mL/kg per min)	13.6 ± 0.8	12.4 ± 1.0	0.42

VO₂max = maximal oxygen consumption; AFC = aerobic functional capacity i.e., VO₂max expressed as a percentage of the theoretical maximal value according to age, sex, and body surface area; AT = anaerobic threshold.

Figure 2. Kaplan-Meier estimates of the proportions of patients without SCD (true or aborted due to successful discharge of implantable defibrillator) among 81 patients with hypertrophic cardiomyopathy, according to the appearance of the STHS at the peak of exercise testing.

to ventricular tachycardia at rate 180–220 bpm in three patients, multiple discharges due to ventricular tachycardia at rate 180–220 bpm in two patients, and one discharge due to ventricular fibrillation in one patient. All the events occurred during the first 3 years of follow-up. Briefly, 21 out of 81 patients had implantable defibrillator, while 60 were without defibrillator. Six out of 21 patients with defibrillator reported at least one successful discharge of their defibrillator and despite their survival they were classified as “patients with events” for the study (named as “aborted death”). Fifteen out of 21 patients with defibrillator survived without any discharge. Two out of 60 patients without implantable defibrillator died, while 78 survived during follow-up.

Regarding established risk factors, the occurrence of SCD was associated with age <30 years (odds ratio = 4.7, 95% CI:1.03–21.7, $P = 0.045$) and family history of SCD (odds ratio = 15.2, 95% CI:3.0–77.8, $P = 0.001$), while it tended to be associated with nonsustained spontaneous ventricular tachycardia (odds ratio = 3.7, 95% CI:0.8–16.4, $P = 0.089$) and abnormal blood pressure response to exercise (odds ratio = 3.6, 95% CI:0.8–15.6, $P = 0.095$). No association was found between SCD and history of syncope ($P = 0.794$), extreme hypertrophy (>30 mm) ($P = 0.455$), and LV outflow obstruction ($P = 0.55$). Multivariate analysis controlling for

the aforementioned risk factors revealed that the presence of the STHS was a strong independent predictor of the risk of SCD ($P < 0.001$). Among the established risk factors, only family history of SCD was also found to be independently associated with increased risk of SCD (odds ratio = 13, 95% CI:1.3–105.1, $P = 0.026$).

DISCUSSION

In this article, we evaluate the appearance of a discrete upward deflection of the ST segment termed the STHS in a population of patients with HCM undergoing cardiopulmonary exercise testing. Although this sign was neither associated with exercise performance nor with established risk factors, it was found to be associated with higher fractional shortening and maximal wall thickness of the LV, LV outflow tract obstruction at rest, and most importantly, a higher incidence of SCD.

The findings of our study in conjunction with the reported association of the STHS with resting hypertension and exaggerated blood pressure responses during exercise may link the appearance of this sign with high left intraventricular pressure during systole. It is known that increased LV afterload can lead through myocardial stretch receptors to the increase of cytosolic sodium and calcium.^{10,11} This effect, termed the Anrep effect or

homeometric autoregulation, may offer a possible explanation for the appearance of this wave in the ST segment. Alternatively, since atrial repolarization waves can produce ST depression during exercise,^{1,12} it may be that abnormal atrial repolarization can lead to the appearance of the hump sign in the ST segment.

The tendency of patients with the STHS to have more dramatic ST segment deviation is difficult to explain, since the significance of the latter in HCM has not been clearly elucidated. Several studies have failed to demonstrate any relation between exercise-induced ST depression and evidence of ischemia with myocardial scintigraphy and lactate measurements^{13,14} or coronary artery disease.¹⁵ In contrast, other studies have reported an association of ST depression with metabolic evidence of ischemia during rapid atrial pacing¹⁶ as well as with lower coronary flow reserve¹⁷ and systolic dysfunction during exercise.¹⁸

Another question raised was the mechanism, by which the appearance of this sign could be associated with occurrence of SCD. It has been suggested that greatly elevated LV pressures lead to increased wall stress, myocardial ischemia, and eventually cell death and fibrosis.^{19,20} Also, surgical relief of LV outflow obstruction results in normalization or improvement of myocardial perfusion in the majority of patients with obstructive form of hypertrophic cardiomyopathy.²¹ This cellular remodeling probably increases susceptibility to electrical instability and SCD.²² Furthermore, while myocyte disarray and myocardial fibrosis provide the anatomical substrate for ventricular arrhythmias, periods of increased wall stress, and ischemia, as in the cases of resting or exercise-induced outflow tract obstruction²³ and of hypertrophy,²⁴ have been proposed as the precipitating factors leading to arrhythmogenesis. Consistent with this hypothesis is the adverse prognostic effect of impaired coronary vasodilator reserve, which limits the ability of coronary microcirculation to cope with triggers that abruptly increase oxygen consumption.²⁵ Consequently, the association of the STHS with elevated LV afterload may explain the higher occurrence of SCD in patients with HCM and may offer an easily detectable means of identification of patients, in whom functional triggers of arrhythmogenesis²⁶ arise and therefore more aggressive preventive measures may be justified. Moreover, possible association of the STHS with intracellular calcium overload could implicate de-

layed afterdepolarizations in the genesis of ventricular arrhythmias.²⁷

Although the results of the present study are significant, it is still premature to support that the ST segment hump at the peak of exercise is a risk factor for SCD in patients with HCM. The study population is small therefore the results of this study can only be considered as preliminary. More studies are required to prove this hypothesis at a population basis.

CONCLUSION

The appearance of a "hump" at the ST segment during exercise testing in patients with HCM is associated with higher fractional shortening and maximal wall thickness of the LV, more frequent occurrence of LV outflow tract obstruction at rest, and a higher incidence of SCD. Therefore, its identification may be useful for stratification of these patients and may provide an additional indication for the implantation of cardioverter-defibrillator.

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