Risk factors for sudden cardiac death in hypertrophic cardiomyopathy.

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ABSTRACT: Aim of this study was the evaluation of six non invasive clinical indices as risk factors for sudden death (SD) in hypertrophic cardiomyopathy (HCM). Previous syncope, family history of SD, non sustained ventricular tachycardia, abnormal blood pressure response during exercise, excessive hypertrophy ≥3 cm and left ventricular outflow tract obstruction with a peak gradient ≥30 mmHg were evaluated in a cohort of 166 patients(112 males, 51.8 ± 15.6 years), followed up for a median of 32.4 months (range 1 to 209 months). During follow up 13 patients reached study's endpoints: SD, cardiac arrest, documented sustained ventricular tachycardia and/or Implantable Cardioverter Defibrillator (ICD)-discharge. Patients having experienced syncope or presenting with a Maximum Wall Thickness ≥3cm in echocardiography were more sensitive to SD emergence since they had a 13.07 (95%CI: 4.00-46.95, $p < 0.0001$) and a 10.07 (95%CI: 2.92-34.79, $p = 0.003$) greater relative risk respectively. In our cohort of patients only two of the six 'recognised' potential risk factors for SD were found sensitive, a result causing scepticism about the validity of criteria used for ICD implantation in HCM patients for SD prevention.

Key words: Risk factors, Sudden death, Hypertrophic cardiomyopathy.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death (SD) in young people, including trained athletes[1]. Since the major characteristic of HCM is its clinical heterogeneity, risk factors for SD may differ among countries, even among regions of a single country. Aim of our study was the identification of the clinical markers for SD in a cohort of HCM patients coming from Northern Greece.

METHODS

Study population

Two hundred and ninety five consecutive patients with documented HCM have been assessed from February 1992 to December 2007 in AHEPA Hospital, Thessaloniki, Greece, and are currently followed-up in our Institution. The diagnosis of HCM was based on the demonstration by two dimensional echocardiography of left ventricular maximum wall thickness (LVMWT) greater or equal to 15 mm, in the absence of any other cause capable of producing such hypertrophy[2,3]. HCM was also considered present in patients with LVMWT 13 or 14 mm in the presence of a positive family history for HCM and/or electrocardiographic (ECG) changes compatible with the disease.

In this study we included patients who had undertaken all non invasive tests for risk stratification; clinical evaluation; 12-lead ECG; transthoracic echocardiography; 24-h ambulatory ECG monitoring; and symptom-limited upright exercise test. Patients with documented sustained ventricular tachycardia (VT) or out-of-hospital cardiac arrest and those who were on amiodarone at first evaluation were excluded.. The presence or absence of any other medications was not used as a selection criterion. The final study cohort comprised 166 patients from the whole HCM regis-

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try meeting the aforementioned criteria**.** Six non invasive-clinical features were tested as potential risk factors for SD: *1) Syncope*. A history of syncope was defined as one or more episodes of unexplained loss of consciousness preceding patient's first visit to our Hospital. *2) Premature sudden death*. A family history of premature SD was defined as SD in one or more first-degree relatives <50 years old. *3) Non-sustained ventricular tachycardia (NSVT)*. NSVT was defined as a run of three or more consecutive ventricular beats at a rate of ≥120 beats/min, lasting <30 s. *4) Abnormal blood pressure response (ABPR)*. An ABPR was defined as a failure of systolic blood pressure to rise more than 20 mmHg, or a fall of systolic blood pressure >10 mm Hg, during exercise. *5) Excessive hypertrophy*. Excessive hypertrophy was defined if LVMWT was ≥3 cm in any myocardial segment. *6) LV outflow tract obstruction (LVOTO)* with a peak gradient ≥30 mm Hg.

Commencement of patients' follow-up was defined as the time the initial diagnosis was made even if the diagnosis preceded baseline patient evaluation in our clinic. The patients were followed every 12 months, unless an important clinical event-reason urged for more frequent evaluation.

The endpoint of the study was defined as SD, cardiac arrest, documented sustained VT, or Implantable Cardioverter Defibrillator (ICD)-discharge. All patients gave written informed consent and the protocol of the study was reviewed and approved by the institutional ethics committee.

Echocardiography

Echocardiographic studies were performed using commercially available equipments. Echocardiographic examination included M-mode, two-dimensional, pulsed- and continuous-wave Doppler echocardiography, as well as Tissue Doppler Imaging. Segmental LV hypertrophy was measured by two-dimensional echocardiography in the parasternal short axis plane at the level of mitral valve and the papillary muscles according to previous described methods.[3] Standard M-mode measurements were made according to the recommendations of the American Society of Echocardiography[4]. Basal subaortic gradient was determined using continuous wave Doppler echocardiography and the modified Bernouilli equation from the apical three and five chambers view[5]. LVOTO was considered to be present when the peak instantaneous outflow gradient was estimated to be at least 30 mm Hg with the use of continuous-wave Doppler echocardiography under resting conditions[5].

Stress test

Patients underwent symptom-limited upright treadmill exercise test using the Bruce protocol. Blood pressure was estimated using a mercury sphygmomanometer and auscultation of the Korotkoff sounds over the brachial artery at rest, every minute during exercise and for the first 3 min of recovery.

Holter monitoring

All patients underwent 24-h ambulatory electrocardiography while performing ordinary daily activities.

STATISTICAL ANALYSIS

Continuous data are expressed as mean±SD or median (25th to 75th percentile) based on whether they have a normal distribution or not. Categorical data are presented as absolute values and percentages.

Survival was plotted according to the Kaplan-Meier method. Potential independent predictors of outcome were identified by univariate analyses. All univariate predictors were then entered in a stepwise manner into a multivariable Cox proportional-hazards regression model, with entry and retention set at a significance level of <0.05. 14.0 (SPSS Inc., Chicago, Illinois) was used for all analyses.

RESULTS

The mean age at diagnosis for the cohort of 166 patients (67.4% male) was 47.9 ± 16.3 years (range 5 to 81 years), and the mean age at first evaluation was 51.8 ± 15.6 years (range 16 to 81 years.) The median follow-up duration was 32.4 months (range 1 to 209 months). In 102 patients (61.4%) the diagnosis was made in other hospitals or by out hospital cardiologists. These patients were then referred to our Institution for further evaluation. Fifty one patients (30.7%) had a family history of HCM, 21 patients (12.6%) had paroxysmal or permanent atrial fibrillation, 119 patients (71.6%) were on cardioactive medication, 19 patients (11.4%) were NYHA class III or IV the day of first evaluation. The prevalence of risk factors

Table 1. Demographic and clinical characteristics of 166 patients with HCM.

Variable	Overall Population (n = 166)
Demographics	
Age at initial evaluation, y	51.8±15.6
Age at diagnosis, y	47.9±16.3
Follow up, months	32.4 (1-209)
Male gender	112 (67.4%)
Referrals	102 (61.4%)
Family history of HCM	51 (30.7%)
NYHA class III/ IV	19 (11.4%)
AF	21 (12.6%)
Risk factors	
Syncope	24 (14.4%)
Family history of SD	16 (9.6%)
NSVT	28 (16.8%)
ABPR	44 (26.5%)
LVMWT ≥3 cm	15 (9%)
LVOTO	50 (30.1%)
Medications	119 (71.6%)
Endpoint	13 (7.8%)

Values are expressed as mean ± SD, median (range) or number (percentage). ***HCM*** *= hypertrophic cardiomyopathy,* ***NYHA*** *= New York Heart Association,* ***AF*** *= atrial fibrillation,* ***SD*** *= sudden death,* ***NSVT*** *= nonsustained ventricular tachycardia,* ***ABPR*** *= abnormal blood pressure response,* ***LVMWT*** *= left ventricular maximum wall thickness,* ***LVOTO*** *= left ventricular outflow tract obstruction*

was: syncope in 14.4% of patients; family history of premature SD in 9.6%; NSVT in 16.8%; ABPR in 26.5%; LVMWT ≥3 cm in 9%; and LVOTO with a peak gradient ≥30 mm Hg in 30.1% of patients. The above data are outlined in Table 1.

During the follow up period 13 patients reached study's end point. More specifically, 1 died suddenly, 2 had resuscitated cardiac arrest, 5 experienced ventricular tachycardia/ventricular fibrillation (VT/VF) and 5 patients experienced an appropriate ICD-intervention. The cumulative event-free survival rate was 92.2% in our study cohort. Using univariate analysis, we showed that patients having experienced syncope or presenting with a LVMWT ≥3cm in echocardiography or manifestating NSVT in Holter ECG were more sensitive to SD emergence since they had a 13.07 (95%CI: 4.00-46.95, $p < 0.0001$), a 10.07 (95%CI: 2.92-34.79, $p = 0.003$) and a 3.53 (95%CI: 1.06-11.75, $p = 0.03$) greater relative risk respectively (Table 2). In a stepwise multivariable regression model including the traditional referred risk factors (syncope, family history of premature SD, LVMWT ≥3 cm, ABPR on exercise, NSVT in 24-h Holter monitoring), and the presence of resting LVOTO, the only independent prognostic indicators were a LVMWT ≥3 cm and the presence of syncope (Table 3).

DISCUSSION

In our cohort of HCM patients a previous unexplained syncope along with a LVMWT ≥3 cm were the most powerful predictors of SD. Risk stratification in HCM patents without a history of sustained VT or documented cardiac arrest is a big clinical challenge and sometimes very difficult.

According to previous studies, 5 non invasive clinical markers were thought to be potential risk factors for SD: Syncope, Family History of SD, NSVT, ABPR during exercise and LVMWT in any myocar-

Table 2. Univariate analysis between risk factors and sudden death/cardiac arrest/ventricular tachycardia/ventricular fibrillation/implantable cardioverter defibrillator-discharge in 166 Patients with HCM.

Variable	RR (95%CI)	Univariate p
FHSCD	1.81 (0.36-8.98)	0.47
Syncope	13.70 (4.00-46.95)	**<0.0001**
LVMWT ≥3 cm	10.07 (2.92-34.79)	**0.0003**
NSVT	3.53 (1.06-11,75)	**0.03**
ABPR	1.26 (0.37-4.30)	0.71
LVOTO≥30 mmHg	1.03 (0.30-3.53)	0.95

***ABPR** = abnormal blood pressure response, **FHSCD**= Family History of Sudden Cardiac Death, **LVMWT** = left ventricular maximum wall thickness, **NSVT** = nonsustained ventricular tachycardia. **LVOTO**,= left ventricular outflow tract obstruction*

Table. Multivariate analysis between risk factors and sudden death/cardiac arrest/ventricular tachycardia/ventricular fibrillation/implantable cardioverter defibrillator-discharge in 166 Patients with HCM

Variable	RR (95%CI)	Univariate p
Syncope	10.40 (2.67-40.56)	**0.0007**
LVMWT ≥3 cm	7.46 (1.83-30.50)	**0.005**
NSVT	1.41 (0.33-6.09)	0.64

***LVMWT** = left ventricular maximum wall thickness, **NSVT** = nonsustained ventricular tachycardia.*

dial segment of ≥3 cm[6-10]. Previous studies have also suggested that HCM patients with LVOTO carry an increased risk of cardiovascular death[11,12]. However, the prognostic value of LVOTO in estimation of SD risk, has been a subject of intense controversy leading to expertise discrepancy[13,14].

In our study we tested the aforementioned 5 non invasive clinical markers along with the presence of LVOTO, as potential risk factors for SD. Among these clinical markers, unexplained syncope and LVMWT ≥3 cm were found as the only independent predictors for SD in patients with HCM. Regarding the role of LVOTO on the incidence of SD, our results are comparable with the results of previous studies.[13,14] On the contrary, no prognostic value was recognised for the rest 3 factors. The recorded disparity regarding the comparison of our results with preceding studies[6-10] may be due to the unique clinical and genetic heterogeneity of the disease, along with the low mortality rates for SD also reported by our study. Both of the fore mentioned factors do not allow addressing clearly the sensitivity of the potential risk factors, a combined sensitivity not exceeding 20%. Furthermore, influence of possible confounding factors, such as age and treatment, is an issue to be kept in mind since their potential impact on SD prevalence is important.

The early and valid recognition of HCM patients being prone to SD, is of major importance since implantation of ICD may be in fact life saving. Unfortunately, the existing clinical indices fail to lead to an ultimate patient selection, i.e. to select patients being most appropriate for CD implantation. Our study results endorse only 2 of the 5 potential clinical risk factors for SD in HCM, previously introduced, addressing for one more time the need to clarify the existing risk factors or even recognize new more sensitive and accurate.

SD among HC patients is mainly connected to the occurrence of VT/VF[15]. There are many studies suggesting that the extent of myocardial disarray-fibrosis, predisposing to re-entry phenomena as part of general arrhythmogenic tendency, constitutes the main stimu-

lus for VT/VF incidence and the appearance of SD consecutively[16]. Maybe, the extent of myocardial disarray-fibrosis in hypertrophic myocardium as this is assessed by newer techniques such as Delayed Hyper Enhancement Magnetic Resonance Imaging could be a creditable risk factor for SD, something that should be examined in future prospective studies[17,18].

Παράγοντες κινδύνου για αιφνίδιο θάνατο σε ασθενείς με υπερτροφική μυοκαρδιοπάθεια.

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ΠΕΡΙΛΗΨΗ: Σκοπός της παρούσας μελέτης είναι η αξιολόγηση έξι μη επεμβατικών κλινικών δεικτών ως παραγόντων κινδύνου για αιφνίδιο θάνατο σε ασθενείς με υπερτροφική μυοκαρδιοπάθεια. Προηγηθείσα συγκοπή, οικογενειακό ιστορικό αιφνιδίου θανάτου, μη εμμένουσα κοιλιακή ταχυκαρδία, μη φυσιολογική απάντηση της αρτηριακής πίεσης κατά τη διάρκεια άσκησης, υπερτροφία που υπερβαίνει τα 3 cm, και απόφραξη του χώρου εκροής της αριστεράς κοιλίας με κλίση πιέσεως ≥30mm Hg ήταν οι παράγοντες που αξιολογήθηκαν σε μια κοόρτη 166 ασθενών (112 άρρενες, 51.8 ± 15.6 ετών), οι οποίοι παρακολουθήθηκαν για ένα διάστημα 32,4 μηνών (από 1 έως και 290 μήνες). Κατά τη διάρκεια της παρακολούθησης τα τελικά σημεία της μελέτης παρατηρήθηκαν σε 13 ασθενείς: αιφνίδιος θάνατος, καρδιακή ανακοπή, διαπιστωμένη εμμένουσα κοιλιακή ταχυκαρδία και/ή εκφόρτιση εμφυτευμένου απινιδωτή. Οι ασθενείς με ιστορικό συγκοπικού επεισοδίου ή αυτοί που παρουσίασαν υπερτροφία οποιουδήποτε καρδιακού τοιχώματος ≥3 cm στο υπέρηχο-καρδιογράφημα ήταν πιο ευαίσθητοι στην εμφάνιση αιφνιδίου θανάτου από τη στιγμή που παρουσίασαν 13,07 (95%CI: 4,00-46,95, p < 0,0001) και 10,07 (95%CI: 2,92-34,79, p = 0,003) μεγαλύτερο κίνδυνο αντίστοιχα. Στην κοόρτη των ασθενών μας μόνο 2 από τους 6 «αναγνωρισμένους» πιθανούς παράγοντες για αιφνίδιο θάνατο βρέθηκαν ευαίσθητοι στην πρόβλεψη μελλοντικών συμβαμάτων, ένα αποτέλεσμα που προκαλεί σκεπτικισμό σχετικά με την εγκυρότητα των κριτηρίων που χρησιμοποιούνται για εμφύτευση απινιδωτή προς αποτροπή αιφνιδίου θανάτου στην υπερτροφική μυοκαρδιοπάθεια.

Λέξεις Κλειδιά: Παράγοντες κινδύνου, Αιφνίδιος θάνατος, Υπερτροφική μυοκαρδιοπάθεια.

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