Sudden Cardiac Death: Investigation of the Classical Risk Factors in a Community-Based Hypertrophic Cardiomyopathy Cohort

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Introduction: The identification of high-risk patients in hypertrophic cardiomyopathy (HCM) is still a challenge. The classical clinical risk factors for sudden death have been reported by studies coming from referral HCM cohorts. So far, other studies of community-based HCM populations have not managed to identify risk factors for sudden cardiac death. The aim of the present study was to determine the clinical course of the disease in a community-based HCM population, as well as to identify the clinical factors of sudden death in such a population.

Methods: Three hundred four (304) consecutive HCM patients (202 males, age 48 ± 18.5 years) from 280 different families were assessed. Referral was based on disease diagnosis, irrespective of clinical status or treatment needs. All patients were examined clinically, echocardiographically, by 24h ambulatory electrocardiographic monitoring, and by cardiopulmonary exercise testing at regular intervals, for a period of 56.4 ± 29.9 months.

Results: Most patients (n=264/304, 87.2%) were in New York Heart Association functional class I or II. The disease was familial in 60.5%. At initial examination, maximum left ventricular wall thickness was 19 ± 4.4 mm and a left ventricular outflow gradient >30 mmHg was present in 30.9% patients. The annual sudden death mortality was 1.2%. Familial sudden death, non-sustained ventricular tachycardia, severe left ventricular hypertrophy >30 mm, and young age were predictors of sudden cardiac death.

Conclusions: In this community-based HCM population, the risk factors for sudden death were similar to those found in referral cohorts.
patient populations. Previous studies of non-referral populations have not been focused on clinical risk factors, since there were no available or suitable data concerning SCD during follow up (due to the size of the cohort and the duration of follow up).

The present study aimed to identify the clinical factors that are predictors of SCD in a community-based HCM cohort.

Methods

Population

Over a decade, 304 consecutive patients originating from 280 families were evaluated prospectively. The mean age at presentation was 48.3 years (SD 18.5, range 5.1-81.9 years). Two hundred two patients (66.4%) were male. The mean follow-up time was 56.4 months (SD 29.9, range 4.7-128.3 months). The diagnosis of HCM was based on standard diagnostic criteria.

Patients were evaluated prospectively at our unit. Referral of the patients from other hospitals or primary care health services was based merely on the diagnosis of the disease and was irrelevant to the clinical status and treatment needs of each patient. The studied population could be separated into four groups:

1. Patients referred from regional hospitals based on the diagnosis (52%), either symptomatic (30%) or asymptomatic (22%).
2. Patients diagnosed in our hospital as inpatients or at the outpatients’ clinic (29%), most of them (25%) symptomatic.
3. Patients referred from privately practicing cardiologists (5%).
4. Patients diagnosed during pre-participation screening (5%), pre-surgery cardiovascular evaluation (2%) and family screening (7%). Most of them were asymptomatic (8%).

Asymptomatic referred patients were 108 (35.4%) and the initial diagnosis was based on an echocardiogram performed in a regional hospital or health center, or a private clinic, where they presented because of a cardiac murmur, an abnormal ECG, done before an operation or for pre-participation athletic cardiac screening. Patients whose hypertrophy was “secondary” and associated with other conditions, such as aortic stenosis, hypertension, certain type of athletic activity, clinical peripheral myopathy (Duchenne, Becker), Friedreich ataxia or other syndromes, and causes of “secondary” hypertrophy, including metabolic diseases, were excluded from the study.

Clinical evaluation

Initial assessment comprised clinical evaluation, 12-lead resting ECG, echocardiogram (M-mode, 2-D-Echo, Doppler), and 24-hour Holter monitoring. In a significant proportion of patients the initial assessment also included cardiopulmonary exercise testing. The patients had a regular follow up.

Echocardiographic assessment

The echocardiographic assessment was performed using General Electric ultrasound machines. The wall thickness of the left ventricle was measured from a short axis slice at the level of the mitral valve, the papillary muscles, and the apex. The measurements were performed at 4 points: inferior septum, anterior septum, lateral wall, inferior-posterior wall. The end-diastolic and end-systolic diameters, as well as the dimensions of the rest of the cardiac chambers were also measured, according to the classical criteria.

The extent and distribution of the left ventricular hypertrophy were assessed using the two-dimensional ultrasound images. The severity of the subvalvular gradient was estimated using continuous wave Doppler imaging; gradients over 30 mmHg were considered as clinically significant. The diastolic function was assessed using the standard indexes of transmitral and pulmonary vein flow.

Holter ECG

The examination was performed using a Syneflash recorder. Most patients were not receiving any treatment during the initial evaluation. Treatment with medication affecting cardiac function was discontinued for a period as long as 5 half lives before the initial Holter evaluation. In contrast, evaluation during follow up was performed while patients were taking their medication.

Cardiopulmonary exercise testing

One hundred ninety-four (194) of the 304 patients underwent cardiopulmonary exercise testing on a cycle ergometer (Sensormedics ergometrics 800) using a ramp protocol. The work rate was selected according to a subjective assessment of the patient’s
functional capacity. The aim was to achieve an exercise time of around 10-12 minutes by selecting the appropriate exercise ramp rate for each participant. Subjects rode to the limit of volitional exhaustion.\textsuperscript{19,20} Breath-by-breath gas exchange analysis was performed continuously throughout exercise testing using a dedicated metabolic cart (V Max 29, Sensormedics).

**Regular follow up**

The mean follow-up time was 56.4 ± 29.9 months (range 4.7-128.3 months). Regular follow up of the patients was performed every 6-12 months. Each visit consisted of clinical evaluation, 12-lead resting ECG, echocardiographic examination, and 24-hour Holter recording. Most of the patients (194), mainly those aged under 50 years, underwent cardiopulmonary exercise testing at least once during their initial evaluation.

Information concerning patients who died was derived from local forensic offices and from death certificates issued by hospitals or doctors who treated them as inpatients or had them under their care at a primary level. The 2 patients who died suddenly underwent postmortem analysis as required by the law.

**Association of clinical factors with SCD**

The clinical factors that were considered to be potentially correlated with SCD were derived from the literature, which comes mainly from referral centers, and were selected because they are simple to use in everyday medical practice.

**Statistical analysis**

The overall profile of sudden deaths in time is described by a Kaplan–Meier curve, in which the time until the final event is defined as the time from the moment of the initial assessment to the moment sudden death occurred. Patients who died from another cause or who lived without a sudden death event until the final study date were censored (with censoring time the final study date).\textsuperscript{21}

The association between sudden death events and clinical and demographic variables was tested using Cox proportional hazard regression, aiming to verify or not the initial hypothesis, since the necessary requirements for its application were satisfied. More specifically, the method was initially used to construct a multivariate model to examine the influence of five factors (family history of SCD, syncope, maximum left ventricular wall thickness ≥30 mm, abnormal blood pressure response during the exercise test, short-duration episodes of ventricular tachycardia on the Holter recording) on the risk of SCD. Subsequently, the method was used to construct a multivariate model showing the influence of “the number of these five parameters” on the risk of SCD. In both cases, the influence of other factors, such as gender, age at initial assessment, possible cardiac failure, left atrial dimensions, and the presence or absence of a clinically significant pressure gradient (>30 mmHg) at the left ventricular outflow tract, on the multivariate model were studied.

For one of the studied variables (abnormal blood pressure response during exercise testing), some patients (n=110) did not have any data. This problem was tackled using the method of multiple imputation.\textsuperscript{22,23}

**Results**

**Demographic and clinical characteristics**

The patients’ mean age at diagnosis was 41 ± 18.2 years; 64.6% of them were diagnosed due to symptoms, while 35.4% were diagnosed during family screening, preoperative checkup, athlete’s screening, or incidentally. The disease was familial (at least one affected first-degree relative) in 184 of the 304 patients (60.5%).

Most of the patients were male (202/304, 66.4%). From the symptomatic point of view, 264/304 (87.1%) were in New York Heart Association (NYHA) functional stage I or II. The characteristics of the studied patients at initial assessment are summarized in Table 1.

**Cardiopulmonary exercise testing**

One hundred ninety-four HCM patients (mean age 39 ± 17 years) were evaluated (Table 2). Patients exercised up to volitional exhaustion and reached a mean maximum oxygen uptake of 24.2 ± 18.3 mL/kg/min, or 71.6 ± 9.4% of their predicted values. Based on the graph of VCO\(_2\) against VO\(_2\) (V-slope method), the patients’ anaerobic threshold (AT) was recorded at 1.0 ± 0.3 L/min or 39.3 ± 10.6% of the predicted maximum oxygen uptake (%predicted AT). The oxygen uptake divided by the heart rate at
maximum corresponds to oxygen pulse (O₂pulse), which was found to be 12.1 ± 3.8 mL/beat in the present study. All values are presented as mean ± SD (Table 2). Furthermore, it should be mentioned that 35 out of 194 patients (18%) had an abnormal blood pressure response during exercise testing. These results are in agreement with previous studies.

Follow up

Morphologic examination

The echocardiographic findings of the latest evaluation in each patient during the follow up were not significantly different to those of the initial assessment, with the only exception being five patients (1.6%) who developed severe left ventricular systolic dysfunction during the follow up and progressed to congestive heart failure. Two of them had a successful heart transplantation. In addition, 18 adolescents (mean age 16 ± 3.4 years) developed morphologic evolution of the disease during the follow up, which increased the left ventricular wall hypertrophy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCM patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>%predicted oxygen uptake (VO₂)max</td>
<td>71.6 ± 9.4</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>24.2 ± 18.3</td>
</tr>
<tr>
<td>Anaerobic threshold (AT) (L/min)</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>%predicted AT</td>
<td>39.3 ± 10.6</td>
</tr>
<tr>
<td>O₂pulse (mL/beat)</td>
<td>12.1 ± 3.8</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>35/194 (18%)</td>
</tr>
</tbody>
</table>

Arrhythmias during the follow up

Apart from the initial evaluation, the Holter recordings during follow up were performed under treatment (beta-blockers, verapamil, disopyramide, amiodarone). During follow up, the most common arrhythmias detected were atrial fibrillation (chronic or paroxysmal) in 20 patients (6.6%), paroxysmal supraventricular tachycardia in 5 patients (1.6%) and episodes of non-sustained ventricular tachycardia (NSVT) in 15 patients (4.9%).

Treatment

Patients who participated in the study received beta-blockers, calcium channel antagonists, or amio-
rone, as necessary: 70 patients were under verapamil; 57 patients received antiarrhythmic medication (35 amiodarone, 15 disopyramide, 7 sotalol); 15 patients needed a combination of verapamil and beta-blocker to control their symptoms; while 15 required amiodarone in combination with beta-blockers (Figure 1).

All patients who were in atrial fibrillation, chronic or paroxysmal, received anticoagulants. Patients who had signs of congestive heart failure, left ventricular heart failure or a restrictive pattern of left ventricular function received mild doses of diuretics plus angiotensin-converting enzyme (ACE) inhibitors. Anticoagulants were also prescribed to patients with severe left systolic dysfunction or an enlarged left atrium (>50 mm). Until the end of the study, 42 patients had defibrillators (ICD) implanted (Table 3).

Classical clinical risk factors

Fifty two (52) of the HCM patients (17.1%) had a family history of SCD. Syncope was reported by 44/304 (14.5%) patients, while presyncopal episodes were recorded in 100/304 (32.5%). Only 8/304 (2.6%) patients had left ventricular hypertrophy of more than 30 mm. Ventricular tachycardia episodes were recorded on the 24-hour Holter in 45/304 (14.8%) patients, while 35/194 (18%) of the patients presented an abnormal blood pressure response during cardiopulmonary exercise testing (Table 4). Two risk factors were present in 9.2% of the total patients, while only 2.6% had more than two (Table 5).

Mortality

During the follow-up period, 13 patients suffered an episode of SCD. Of these, 2 patients were successfully resuscitated after a cardiac arrest and 9 who had an ICD (as primary prevention in clinically characterized high-risk patients) had an appropriate ICD discharge. The other 2 patients died; one had 1 risk factor (left ventricular hypertrophy) and a high left ventricular outflow tract gradient, while the other was young and appeared to have had no clinical risk factors, although it is possible that he ignored the symptoms (presyncope). A further 2 patients died from heart failure, 1 from cardiovascular accident, and 11 from non-cardiac diseases. Overall, the annual cardiac mortality was 1.4% while the annual mortality from SCD was 1.2%.

Clinical factors and risk of SCD

Based on this prospective study, it is estimated that patients who present NSVT on Holter recordings have a 3.4-fold higher risk than those who do not

Table 3. Patients and ICD’s

<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>Indication for ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>36/304 (12%)</td>
<td>≥2 risk factors</td>
</tr>
<tr>
<td>1/304 (0.3%)</td>
<td>Syncope unexplained and mutation in troponin-T gene</td>
</tr>
<tr>
<td>1/304 (0.3%)</td>
<td>Left ventricular hypertrophy &gt;30 mm</td>
</tr>
<tr>
<td>2/304 (0.6%)</td>
<td>Aborted sudden cardiac death</td>
</tr>
<tr>
<td>2/304 (0.6%)</td>
<td>Heart failure (ejection fraction &lt;30%) and apical aneurysm</td>
</tr>
</tbody>
</table>

Table 4. Clinical risk factors in patients with hypertrophic cardiomyopathy.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Data available</th>
<th>Data unavailable</th>
<th>Yes</th>
<th>No</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of sudden cardiac death</td>
<td>304</td>
<td>0</td>
<td>52</td>
<td>252</td>
<td>17.1</td>
</tr>
<tr>
<td>Syncope</td>
<td>304</td>
<td>0</td>
<td>44</td>
<td>260</td>
<td>14.5</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>194</td>
<td>110</td>
<td>35</td>
<td>159</td>
<td>11.5</td>
</tr>
<tr>
<td>Max left ventricular wall thickness</td>
<td>304</td>
<td>0</td>
<td>8</td>
<td>296</td>
<td>2.6</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia on Holter</td>
<td>304</td>
<td>0</td>
<td>45</td>
<td>259</td>
<td>14.8</td>
</tr>
</tbody>
</table>
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Table 5. Number of clinical risk factors in patients with hypertrophic cardiomyopathy.

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>No. of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>164</td>
<td>53.9</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>34.2</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>9.2</td>
</tr>
<tr>
<td>3 or more</td>
<td>8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Table 6. Clinical risk factors for sudden cardiac death.

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>3.4</td>
<td>1.1-10.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Family history</td>
<td>7.0</td>
<td>1.5-31.8</td>
<td>0.020</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.9</td>
<td>0.4-8.0</td>
<td>0.363</td>
</tr>
<tr>
<td>Wall thickness &gt;30 mm</td>
<td>5.2</td>
<td>0.7-37.0</td>
<td>0.095</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>2.2</td>
<td>0.6-9.1</td>
<td>0.260</td>
</tr>
</tbody>
</table>

have this risk factor (95% confidence interval, CI: 1.1-10.4, p=0.036) (Table 6). For HCM patients who have a family history of SCD, the risk seems to increase 7-fold compared to those who do not. The risk seems to increase 5-fold for patients who have left ventricular wall thickness >30 mm (95%CI: 0.7-37, p=0.095) (Table 6).

Number of risk factors and risk of SCD

A second analysis estimated the risk of SCD in relation to the total number of risk factors present in an individual patient (Table 7). This analysis demonstrated that, compared to patients who had no risk factors at all:

1. Patients with three risk factors had a 25-fold risk of SCD.
2. Patients with two risk factors had a 6-fold risk of SCD.
3. Patients with one risk factor had a risk comparable with that of those who had no risk factors at all.

Discussion

Population sample

In the present study, the large number of patients studied and the adequate duration of follow up made possible the investigation of the clinical risk factors for SCD in a community-based HCM population. The studied cohort has characteristics that differentiate it from the studies of Elliott et al.6,7 where the population consisted of consecutive patients from a referral center with an international reputation. In our study, approximately half of the patients were referred by the primary health care services and outpatient clinics and around 36% of the patients were asymptomatic. In comparison to the study of Elliott et al.7 the patients in our investigation were older at the initial evaluation and at diagnosis, while more patients in the present study had no risk factors. However, our population sample is very similar to cohorts in other studies 8-12 that were also community-based. In addition, the referral criterion for all the patients in this study was simply the diagnosis of HCM, and not the severity of the disease. All the above made our cohort representative of a community-based HCM population.

The results of our study show that:

1. As far as the risk factors for SCD are concerned, it is verified that in a community-based population the correlations of the classical clinical risk factors with SCD that were reported by studies of populations in large referral centers3,6,7,24 also apply. We believe that this observation is quite significant, since other studies 8,9,11,12 of community-based HCM populations have not managed to identify risk factors for SCD. In particular, only the study by Koflart et al.10 has managed to point out risk factors for SCD, and the only risk factor that was identified was syncope. In the studies of Cecchi et al9 and Kyriakidis et al,11 the identified risk factors were related to total cardiac deaths, including SCD, but also death from congestive cardiac failure provoked by the disease. It is evident, though, that the process leading patients to death from congestive cardiac failure differs from the mechanism of SCD in HCM patients.
2. There is a subgroup of patients (at least 12%) of the HCM cohort with two or more clinical risk factors that is at high risk for SCD. This percentage (12%) is smaller than that found in populations in referral centers.3,6,7,24

3. In a community-based HCM population, the disease has a relatively benign course and low mortality. These findings are in accordance with other studies of non-selected populations.5

**Risk factors**

The risk factor analysis in this study clarifies the risk factors in a community-based HCM population compared to studies from referral centers.3,6,7,24 Our study showed that a family history of SCD, NSVT, or severe left ventricular hypertrophy was related to SCD in the multivariate analysis, i.e. these were independent risk factors for SCD. According to the multivariate analysis, there was no statistically significant correlation between the degree of left ventricular outflow tract obstruction and SCD, a finding that is in accordance with the international literature.

In our sample there was no statistically significant correlation between syncope of undetermined origin or abnormal blood pressure response during stress test and SCD. This result is in accordance with the studies of Elliott et al,7,25 which showed that syncope of unknown origin is not strongly associated with SCD as an independent risk factor.

**Number of risk factors and risk of SCD**

Patients with two or more clinical risk factors are at significantly greater risk of SCD as compared to patients with one or no clinical risk factors. It is interesting that the groups with one risk factor or no risk factor at all showed no significant difference with regard to the risk of SCD. The results of our study clearly demonstrate the HCM patients that are at risk and the ones we may reassure. In contrast, large studies from Europe and the USA reported that patients with one risk factor also run a moderate risk for SCD. At this point, the different results of our study may be explained by the qualitative difference in the composition of the subgroup with one risk factor: it is clearly different if the group consists mainly of young patients with a strong history of SCD or severe hypertrophy, or of middle-aged patients with rare episodes of ventricular tachycardia on 24-hour Holter monitoring.24,26,27

**Geography and genetic pool**

It is well known that HCM displays heterogeneity as far as the morphology and the clinical expression of the genetic background are concerned.13,14,28,29,30 This heterogeneity seems to be influenced by geographic region and by population. In Japan, for example,28 the disease is often expressed by apical hypertrophy with a benign course. The genetic substrate of our population seems to be similar to that of Western countries in general.14

**Study limitations**

**Patient population**

Concerning the cohort’s composition, the only criterion for referral to our institution and enrolment in our study was the diagnosis of HCM, regardless of the severity of the disease. It is therefore evident that our population is very much like other non-selected patient populations, at least as far as the categories of the patients referred are concerned. Nevertheless, we cannot specify the exact percentage of each patient subgroup in the total of the population and compare them with other studies, especially since in most international studies this has not been clearly stated. This may have been one reason for the deviation of our results when compared with those of similar populations. It is important though, that the makeup of our population is clearly different from the high-risk populations of the tertiary centers that reported their studies in the years prior to the last decade as well as recently.

**Arterial blood pressure response during exercise**

A significant number of patients were not checked during the initial assessment, as regards their blood pressure response during exercise. In order to deal with this problem, we used a specific statistical methodology that has been bibliographically validated.22,23

**Conclusions**

The results of the present study show that a family history of SCD, NSVT on Holter recordings, severe hypertrophy of the left ventricular wall, and young age are the risk factors related to SCD in a community-based HCM population. This, according to our data, establishes and reconfirms that classical risk factors are clinically significant for every HCM patient.
References