Cardiac arrhythmias in hypertrophic cardiomyopathy

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SUMMARY This study was designed to assess the prevalence of cardiac arrhythmias in a group of relatives of patients who had come to necropsy with hypertrophic cardiomyopathy. Another aim of the study was to assess the validity of an interventricular septal thickness of 1.3 cm or more, measured by echocardiography, as a diagnostic criterion of hypertrophic cardiomyopathy among relatives of cases proven at necropsy. Fifty close relatives of eight deceased patients were examined. By the above definition 22 relatives had hypertrophic cardiomyopathy and 28 did not. A comparison of the prevalence and types of cardiac arrhythmias, as shown by 24 hour ambulatory electrocardiographic monitoring, was made between the two groups and a third apparently healthy group of 40 people. The patients with hypertrophic cardiomyopathy showed a significant increase in supraventricular extrasystoles/24 hours, supraventricular arrhythmias, high grade ventricular arrhythmia, and the number of patients with more than 10 ventricular extrasystoles every 24 hours when compared with the other groups. There was no significant difference between normal relatives and controls. The prevalence and types of arrhythmia in these patients were similar to those found by other investigators using different diagnostic criteria. These results support the contention that these patients do indeed have hypertrophic cardiomyopathy and suggest that all close relatives of necropsy proven cases should be examined by echocardiography and subsequently by ambulatory electrocardiographic monitoring if the interventricular septal thickness is 1.3 cm or more.

Patients with hypertrophic cardiomyopathy frequently die suddenly and unexpectedly, presumably from cardiac arrhythmias.1-3 In a recent Icelandic study the inheritance pattern of hypertrophic cardiomyopathy was described.4 The diagnosis was based on inordinate interventricular septal thickening (≥1.3 cm). Most of the patients had no symptoms, and were only identified after necropsy findings suggesting hypertrophic cardiomyopathy in a close relative. No single echocardiographic marker, however, is pathognomonic for hypertrophic cardiomyopathy.5-7 It has been suggested that an interventricular septal thickness cut-off point at 1.3 cm may be both too sensitive and non-specific as a diagnostic criterion.8-10

To study the validity of this echocardiographic criterion we have compared the prevalence and types of cardiac arrhythmias in the group of relatives who had an interventricular septal thickness of 1.3 cm or more in relation to those relatives whose septum was thinner than 1.3 cm.

Patients and methods
Our previous study included 58 close relatives of eight patients (out of a total of 11) who had necropsy criteria of hypertrophic cardiomyopathy in Iceland during the years 1966 to 1977.4 The eight index patients were male patients and all died suddenly from cardiac causes except one who died in an accident.11 Their average age at the time of death was 29 years (3 months to 47 years) and only two had had symptoms previously.

Twenty-three relatives had echocardiographic criteria (≥1.3 cm) of hypertrophic cardiomyopathy. Of these, 22 were investigated by 24 hour electrocardiographic monitoring: 16 men (12 first degree and four second degree relatives of deceased patients) and six women (five first degree and one second degree). Their average age was 50 years (18 to 83 years). Table 1 shows their sex, age, symptomatic status, electrocardiogram, and echocardiographic findings and cardiac arrhythmias. Nineteen were in New York Heart Association12 class I, two were in class III, and one in class IV. A male patient in class III complained of dyspnoea and dizziness on mild exercise. A woman, previously thought to have ischaemic heart disease, complained of angina pectoris and shortness of breath. She had a typical systolic anterior motion of the mitral valve as well as interventricular septal thickening. A woman in class IV had a long history of
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Table 1  Summary of clinical, electrocardiographic, echocardiographic, and 24 hour ambulatory electrocardiographic findings in 22 patients with hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Symptomatic status 12</th>
<th>Electrocardiographic findings†</th>
<th>Echocardiographic findings (cm)</th>
<th>Rhythm disturbances</th>
<th>No. of ventricular extrasystoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>63</td>
<td>I</td>
<td>AF</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>82</td>
<td>I</td>
<td>AVB</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>71</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>M*</td>
<td>70</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>67</td>
<td>III</td>
<td>LVH, Q AVB</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>64</td>
<td>IV</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>63</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>61</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>60</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>58</td>
<td>III</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>M*</td>
<td>55</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>53</td>
<td>I</td>
<td>ICD</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>51</td>
<td>I</td>
<td>AVB</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>47</td>
<td>I</td>
<td>LVH, Q</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>45</td>
<td>I</td>
<td>Left atrial abnormality</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>31</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>26</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>M*</td>
<td>25</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>24</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>23</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>M*</td>
<td>20</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>18</td>
<td>I</td>
<td>LVH</td>
<td>IVS 1.4 LVPW 1.7</td>
<td>SVT</td>
<td>4</td>
</tr>
</tbody>
</table>

1 Second degree relatives of patients who died with hypertrophic cardiomyopathy and came to necropsy, otherwise first degree relatives.

†Classifications of Ryan et al. AF, atrial fibrillation; AVB, atrioventricular block; ICD, intraventricular conduction defect; IVS, interventricular septum; LVH, left ventricular hypertrophy; LVPW, left ventricular posterior wall; PAF, paroxysmal atrial fibrillation; Q, abnormal Q waves; SVT, supraventricular tachycardia.

A 12 lead electrocardiogram showed left ventricular hypertrophy in 14 (64%) patients, using Romhilt-Estes' and/or Sokoloff's criteria. Three had abnormal Q waves, three had a long PR interval (>0.20 s), one had an interventricular conduction delay, and one had an enlarged left atrium. Only one patient had a rhythm disturbance on a conventional electrocardiogram (atrial fibrillation). Another patient in sinus rhythm had had atrial fibrillation earlier. He was being treated with quinidine.

Twenty eight close relatives of deceased patients with hypertrophic cardiomyopathy had normal echocardiographic findings (interventricular septal thickness <1.3 cm): nine men (four of them second degree) and 19 women (two second degree). Their average age was 39 years (10 to 82 years). None of these had any signs or symptoms of heart or lung disease, and their electrocardiograms were normal.

A further control group was composed of 20 men and 20 women, all hospital employees. None of them had symptoms suggesting cardiac or pulmonary disease. In all, physical examination was normal and their electrocardiograms and echocardiographic examinations did not disclose any abnormalities. Their interventricular thicknesses were 1-2 cm or less.

In all three groups, ambulatory 24 hour electrocardiographic recordings were performed, using one-channel Oxford Medilog recorders. All subjects were instructed to record their activities and complaints at least hourly during waking hours. A Reynolds High Speed Pathfinder machine was used for arrhythmia analysis. The same physician (IB) analysed and classified all the recordings.

Ventricular arrhythmias were classified according to Ryan et al. (Table 2). Unless otherwise stated, Fisher's exact test for 2×2 tables was used to assess statistical significance.

Results

Fig. 1 shows the total number of supraventricular extrasystoles during 24 hours in patients with hypertrophic cardiomyopathy, in their relatives, and in the control group. Seven patients with hypertrophic car-

Table 2 Grading of ventricular extrasystoles (VE) of Ryan et al. 16

<table>
<thead>
<tr>
<th>Class</th>
<th>Character of ventricular arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No VE/24 h</td>
</tr>
<tr>
<td>I</td>
<td>Occasional &lt;30/h</td>
</tr>
<tr>
<td>II</td>
<td>Frequent &gt;30/h</td>
</tr>
<tr>
<td>III</td>
<td>Multiform</td>
</tr>
<tr>
<td>IV A</td>
<td>Couplets (two consecutive VE)</td>
</tr>
<tr>
<td>IV</td>
<td>Ventricular tachycardia (three or more consecutive VE)</td>
</tr>
</tbody>
</table>
diomyopathy had 50 or more extrasystoles, but only one in the control group and none in the group of relatives. The number of patients with cardiomyopathy who had more than 50 supraventricular extrasystoles was significantly greater than in the other two groups (p<0.02).

Two control subjects and one relative had episodes of supraventricular arrhythmia as compared with eight in the group with hypertrophic cardiomyopathy (p<0.003). Two had paroxysms of atrial fibrillation and five had supraventricular tachycardia, each episode lasting less than 10 seconds. One patient had constant atrial fibrillation. He had several RR intervals lasting up to three seconds (Fig. 2).

Six out of eight patients with supraventricular arrhythmias were over 60 years of age, compared with two out of 14 under 60 years of age (p<0.01).

Fig. 3 shows the classification of ventricular arrhythmias. Fourteen (64%) of the patients with hypertrophic cardiomyopathy were in classes III and IV. Three of them had episodes of ventricular tachycardia (Fig. 4), in each case lasting less than three seconds (nine beats). Six patients were in class I and only two had no ventricular arrhythmias. In the control group, one subject was in class III and one in class IVA. Sixteen were in class I, however, and 22 (55%) had no ventricular arrhythmia. In the group of relatives two subjects were in class II, nine in class I, and 17 (61%) had no ventricular arrhythmias. The occurrence of high grade arrhythmia (III or higher) was significantly more common (p<0.0001) in the group

Fig. 1 Number of supraventricular premature beats during 24 hour ambulatory electrocardiographic monitoring in an apparently healthy control group, in relatives without hypertrophic cardiomyopathy, and in 21 patients with hypertrophic cardiomyopathy.

Open circles indicate second degree relatives of patients who died with hypertrophic cardiomyopathy and came to necropsy, closed circles first degree relatives.

Fig. 2 A strip from an ambulatory electrocardiographic recording of a patient with established atrial fibrillation showing a period of asystole of three seconds duration.
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Fig. 3 Prevalence of ventricular premature depolarisation grade during 24 hour ambulatory electrocardiographic recording in an apparently healthy control group, in relatives without hypertrophic cardiomyopathy, and in 22 patients with hypertrophic cardiomyopathy. Symbols as in Fig. 1.

Fig. 4 A strip from an ambulatory electrocardiographic recording from an asymptomatic patient. A short burst of ventricular tachycardia (3 s) is shown.

Fig. 5 Relation between the number of ventricular extrasystoles in 24 hours and the grade of arrhythmia in the control group, in relatives without hypertrophic cardiomyopathy, and in patients with hypertrophic cardiomyopathy. Symbols as in Fig. 1.

with hypertrophic cardiomyopathy compared with normal relatives or control subjects. There was no significant difference between normal relatives and control subjects.

Multiple regression techniques did not show a statistically significant relation between the grade of arrhythmia and age or interventricular septal thickness.

Fig. 5 shows the relation between the ventricular arrhythmia classification and the total number of ventricular extrasystoles during 24 hours. Twelve (55%) patients with hypertrophic cardiomyopathy had more than 10 ventricular extrasystoles in 24 hours but only four (10%) out of the control group and two (7%) in the group of relatives. The cardiomyopathy group differed significantly from the others in this respect (p<0.001) while there was no difference between normal relatives and control subjects. The number of subjects with 100 or more ventricular extrasystoles every 24 hours, however, did not differ significantly between the groups. All the most serious ventricular arrhythmias occurred during waking hours. Four patients complained of dizziness and palpitation during the recording. The timing of such complaints, however, did not coincide with the occurrence of serious arrhythmias.

Discussion

This study showed a high incidence of cardiac arrhythmias among symptom-free patients or those with mild symptoms with a thick ventricular septum and close familial links with deceased patients with hypertrophic cardiomyopathy compared with their normal relatives and a normal group. The arrhythmias were always unexpected and not felt by the patients, even in three people with ventricular tachycardia. The common occurrence of arrhythmias in this group supports our previous contention that most of them do indeed suffer from cardiomyopathy.
Table 3 shows our results in comparison with those of other authors. McKenna et al.\textsuperscript{17} studied 30 consecutive patients. The patients of Canedo et al.\textsuperscript{18} had significant symptoms. One third of the patients reported by Savage et al.\textsuperscript{19} had no symptoms and two thirds had symptoms consistent with hypertrophic cardiomyopathy. They found little difference in arrhythmias between the two groups and, on the whole, the four studies show an interesting conformity, though the selection of patients varied. Our results support those of Savage et al.\textsuperscript{19} who found that the correlation between symptoms and cardiac arrhythmias in hypertrophic cardiomyopathy is poor.

The annual attrition rate in hypertrophic cardiomyopathy is 3 to 4%,\textsuperscript{2,20} Maron et al.,\textsuperscript{3} in their study of 26 patients who had died suddenly and unexpectedly, could not identify any physical signs or haemodynamic variables of prognostic importance. All of their patients, however, had an abnormal electrocardiogram, and an unusually thick interventricular septum (mean 25 mm, range 17 to 55 mm). One third of their patients had a family history of sudden death. Another study\textsuperscript{21} illustrated, similarly, that electrocardiographic and haemodynamic findings offered no predictive value, but youth combined with a family history of hypertrophic cardiomyopathy and/or sudden death was a poor prognostic feature. Despite different patient selection and the moderate increase in interventricular septal thickness (mean 17 mm) of our patients it is possible that they form an unfavourable prognostic group because of their family history.

Our study does not show the extent to which cardiac arrhythmias discovered by 24 hour electrocardiographic monitoring may influence the future course of patients with hypertrophic cardiomyopathy. McKenna et al.\textsuperscript{22} have recently reported ventricular tachycardia with multiform and paired ventricular extrasystoles in five patients who died subsequently. In addition, a follow-up study on the patients of Savage et al.\textsuperscript{19} showed that there was a significant increase in sudden deaths among patients with asymptomatic ventricular tachycardia.\textsuperscript{23} The microscopical disorganisation of muscle cells in hypertrophic cardiomyopathy\textsuperscript{24} may conceivably offer a fertile medium for the initiation and maintenance of re-entry mechanisms leading to ventricular tachycardia or fibrillation. It is also possible that pre-excitation may be of importance in this context, as suggested by Krikler et al.\textsuperscript{25} and Bouhour et al.\textsuperscript{26} It therefore seems justifiable to hope that vigorous antiarrhythmic treatment under these circumstances may prevent sudden death in some cases. Recent trials using amiodarone appear particularly promising.\textsuperscript{27} The results of this study also suggest that relatives of patients with hypertrophic cardiomyopathy should be investigated with echocardiograms and then ambulatory 24 hour electrocardiographic recording, if there is a thickened interventricular septum. Finally, our study shows that many patients with hypertrophic cardiomyopathy will remain undiagnosed unless effective objective screening methods are applied to individuals judged to be particularly at risk.

We acknowledge Dr I D Hill for his assistance in the statistical analysis.

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*Br Heart J* 1982 48: 198-203
doi: 10.1136/hrt.48.3.198

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