Diagnostic accuracy of a 2D left ventricle hypertrophy score for familial hypertrophic cardiomyopathy

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Aims To study the diagnostic value of a new 2D left ventricle hypertrophy (2D LVH) score in families with hypertrophic cardiomyopathy (HCM) in comparison with the conventional maximal wall thickness (MWT) measurement (>13 mm in adults), which is limited by a low sensitivity in relatives.

Methods and results The study was performed in 237 adults from genotyped families with HCM. Population A (derivation sample) comprised 109 adults and population B (validation sample) comprised 128 adults. MWT and 2D LVH scores (sum of thicknesses of four segments) were determined by echocardiography. Genotyping was the gold standard for diagnosis. In population A, a theoretical value for LVH score was determined in the healthy population by a multiple linear regression model including age, sex, and body surface area. An abnormal cut-off value was defined as an LVH score above a maximum theoretical value according to receiver operating characteristic analysis. Sensitivity and specificity were, respectively, 73 and 96% for 2D LVH score and 62.5 and 100% for MWT. Improvement of sensitivity was particularly important in adults <50 years of age (69 vs. 54%, respectively, P < 0.04). These results were validated in population B: sensitivity and specificity of LVH score were, respectively, 75 and 96% in this sample and 67 and 97%, in the subgroup <50 years. In the latter, sensitivity of LVH score increased when compared with that of MWT (67 vs. 53%, P < 0.03).

Conclusions The LVH score has a higher diagnostic value for HCM than the conventional criterion of MWT, particularly in young adults. This echographic parameter may be proposed as an alternative diagnostic criterion for familial screening.

Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder characterized by hypertrophy of the left ventricle, whose affected wall is usually the interventricular septum. Its diagnosis, based on ECG and/or echocardiographic criteria, is of critical importance because of the risk of sudden death in young adults and especially in young athletes. The major echocardiographic diagnostic criterion remains the maximal wall thickness (MWT) measurement whose diagnostic value in relatives of a proband is limited because of low sensitivity. The use of Devereux’s mass index is probably limited in this disease because of the asymmetrical extent of hypertrophy in HCM. Spirito and Maron described a 2D left ventricular hypertrophy (LVH) score which is the sum of the MWT obtained in four LV segments at basal or midventricular level. It is a quantitative hypertrophy score whose accuracy in HCM was validated in echocardiography vs. MRI. However, its diagnostic value in HCM is still unknown and remains to be studied.

The aims of this study were (i) to compare the diagnostic value of a 2D LVH echo score, using a new cut-off value corrected for age, sex, and body surface area (BSA) in each individual, with the conventional MWT measurement in an adult HCM genotyped population (derivation sample) and (ii) to validate prospectively these results in a second HCM genotyped population (validation sample).

Methods

Patients All first degree relatives from 18 families in which the mutation responsible was previously identified were proposed to be...
included in the study. The population consisted of 237 adults (>18 years) and was divided in two populations based on chronological recruitment.

One-hundred and nine adults constituted the derivation sample (population A, n = 109). All subjects were from seven families affected by HCM with seven distinct mutations concerning three different genes (MYH7, MYBPC3, and MYL2). Each individual was genotyped: 55 individuals were genetically healthy (55 Mu−) and 83 were carriers of a mutation (54 Mu+).

One-hundred and twenty eight adults constituted the validation sample (population B, n = 128). The subjects were from 11 families affected by HCM with nine distinct mutations concerning four different genes (MYBPC3, MYH7, TNNI3, and TNNT2). Forty-five adults were healthy (45 Mu−) and 83 were affected (83 Mu+).

### Echocardiography

Echocardiography was performed at the time of genotyping by the referent cardiologist according to a standardized procedure. M-mode, 2D, and Doppler echocardiographic examinations were performed using a 2.5 or 3.5 MHz transducer in standard parasternal long-axis, short-axis, apical four- and two-chamber views and were recorded on VH5 videotape. Five patients with a poor echogenicity were excluded from the study and represented 2% (5/242) of the total population.

The next time, videotapes were independently and successively read by two experts (from J.F.F., P.C., and O.D.) who were blind to the genotype. Mean values of the three measurements were calculated. In case of discrepancies, echos were reviewed by a third expert and a final agreement was achieved by the three experts.

MWT was measured in 2D echocardiography. To determine the hypertrophy score proposed by Spirito and Maron (2D LVH score), the left ventricle was divided into four segments corresponding to the anterior and posterior ventricular septum and the anterolateral and posterior left ventricular free walls. The 2D LVH score is the sum of the measurements of MWT obtained in each of the four left ventricular segments. MWT for each segment was defined as the greatest thickness identified in the basal (mitral valve) or midventricular (papillary muscles) short-axis planes in any of the four segments (Figure 1).

Two different echo criteria were analyzed as diagnostic tools: the conventional one, where MWT > 13 mm; and the 2D LVH score using an adjusted cut-off value determined by multiple linear regression analysis. The fit of the regression models was evaluated by testing the residuals for normality and by inspecting the residual plots.

### Statistical analysis

Mean values for continuous parameters were compared using Student’s t-test. Categorial parameters were compared using the χ² test. Sensitivities were compared using exact McNemar’s test. A comparison of sensitivities in the subgroup of youngest subjects (<50 years) was planned. The penetrance of the disease is age-related and the subgroup of young subjects is characterized by the lowest sensitivity. Thus, the need for new diagnostic parameters is particularly important in this specific subgroup.

Tests were two-sided and a P value < 0.05 was considered as significant.

The adjustment of the LVH score in the derivation population was performed by multiple linear regression analysis, including age, sex, and BSA as covariables. These parameters were chosen because they are involved in the variability of LV mass. We confirmed the involvement of these parameters in the variability of the 2D score and included them in the definition of the theoretical 2D score.

A cut-off value for the LVH score was subsequently determined according to a receiver operating characteristic (ROC) curve analysis, with a specificity set at 95% and to maximize sensitivity.

### Results

Clinical features of the two populations are summarized in Table 1. In the derivation population (population A), we observed that the 2D LVH score was significantly different between the mutation carriers group and the non-carriers group (51.7 ± 15.9 vs. 36.3 ± 4.5 mm, P < 0.0001).

### Definition of the adjusted LVH score

**Definition of a theoretical LVH score in controls of the derivation sample**

In the healthy derivation sample (Mu−), 2D LVH score was significantly influenced in linear logistic regression analysis by age (P = 0.002), sex (P = 0.04), and BSA (P = 0.05). After multiple linear regression analysis, a new theoretical score was defined in each individual as follows (standard error of the mean predict: 0.84): theoretical LVH score (in mm) = 18.95 + (0.12 × age) + (2.64 × sex) + (6.41 × BSA) with sex (=1 in men and 0 in women), age in years, and BSA in kg/m².
Diagnostic value of hypertrophy scores

The diagnostic value of MWT and 2D L VH score was studied in the derivation population (population A), according to ROC analysis. The cut-off value to maximize the sensitivity at a specificity near 95% was found to be the theoretical score. The cut-off value to maximize the sensitivity at a specificity near 95% was found to be the theoretical score. The cut-off value to maximize the sensitivity at a specificity near 95% was found to be the theoretical score.

Figure 2. Definition of an adjusted 2D L VH score for HCM by comparing observed and theoretical scores in the derivation population (population A), according to ROC analysis. The cut-off value to maximize the sensitivity at a specificity near 95% was found to be the theoretical score. The cut-off value to maximize the sensitivity at a specificity near 95% was found to be the theoretical score.

Table 1. Clinical and echocardiographic features of the populations: derivation sample (population A) and validation sample (population B)

<table>
<thead>
<tr>
<th></th>
<th>Pop. A Mu− (n = 55)</th>
<th>Pop. A Mu+ (n = 54)</th>
<th>Pop. B Mu− (n = 45)</th>
<th>Pop. B Mu+ (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Sex (male/female)</td>
<td>37.4 ± 14.7 30/25</td>
<td>37.7 ± 17.9 27/27</td>
<td>37.4 ± 15.1 22/23</td>
<td>39.1 ± 16.8 43/40</td>
</tr>
<tr>
<td>BSA (kg/m²)</td>
<td>1.78 ± 0.2</td>
<td>1.72 ± 0.17</td>
<td>1.72 ± 0.26</td>
<td>1.73 ± 0.23</td>
</tr>
<tr>
<td>Posterior IVS (mm)</td>
<td>8.8 ± 1.3</td>
<td>13.0 ± 4.6</td>
<td>8.2 ± 1.8</td>
<td>12.1 ± 4.4</td>
</tr>
<tr>
<td>Anterior IVS (mm)</td>
<td>9.5 ± 1.4</td>
<td>16.7 ± 7.2</td>
<td>8.6 ± 2.1</td>
<td>15.0 ± 5.9</td>
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<tr>
<td>Lateral wall (mm)</td>
<td>9 ± 1.2</td>
<td>12.6 ± 3.8</td>
<td>8.3 ± 1.9</td>
<td>11.8 ± 4.2</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>9 ± 1.4</td>
<td>10.1 ± 2.6</td>
<td>8.2 ± 1.7</td>
<td>9.7 ± 2.7</td>
</tr>
<tr>
<td>L VH score (mm)</td>
<td>36.3 ± 4.5</td>
<td>51.7 ± 15.9</td>
<td>33.3 ± 7.2</td>
<td>48.4 ± 15.5</td>
</tr>
<tr>
<td>IVS (TM) (mm)</td>
<td>9.5 ± 1.5</td>
<td>16.1 ± 6.2</td>
<td>9.2 ± 3.4</td>
<td>15.1 ± 6.2</td>
</tr>
</tbody>
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IVS, Interventricular septum; L VH, left ventricular hypertrophy.

IVS, Interventricular septum; L VH, left ventricular hypertrophy.
segments of the LV and a better visualization of the anterolateral wall. The second reason may be related to the true absence of hypertrophy in a subset of patients because of the age-related penetrance of the mutations. Indeed, the diagnostic accuracy of echo was shown to increase with age; in this study, sensitivity of the conventional echo criterion was 43% in a first age group between 18 and 29, 68% in a second age group between 30 and 49, and finally increased to 83% in a third age group >50. In our work, sensitivity of MWT in the subgroup <50 years was only 54% and reinforces the previous results. The reasons for the influence of age on the penetrance of mutations remain unclear.

We hypothesized that a 2D LV hypertrophy score could be useful and more accurate than a single wall thickness measurement for the diagnosis of HCM, because it evaluates the extent of hypertrophy at eight different segments of the myocardium. In accordance with previously established variables influencing LV mass, we demonstrated that the 2D LV score was significantly influenced by age, sex, and BSA in the control population. We then defined for each individual an adjusted value for the score using a multiple linear regression model and a theoretical cut-off value using ROC analysis. We found that sensitivity of this 2D LV score was better than that of the conventional criterion, whereas the specificity remained very good. Moreover, in the young population where sensitivity of MWT is low (54%), when we used the 2D LV score, sensitivity significantly increased by 15% (P < 0.04) in the derivation sample and this was confirmed in the validation sample (+14%, P < 0.03). In our model, the adjusted 2D LV score incorporated age, sex, and BSA which are modifying factors of LV mass. This may also explain why a theoretical cut-off value, which incorporates those parameters, is more accurate than a single wall measurement.

It is of critical importance to increase the sensitivity of diagnostic criteria for HCM. First, the molecular process of identification of the mutation responsible in a family is long, expensive, and uncertain and is available in only few institutions. Because of a wide genetic heterogeneity of the disease (11 different genes and more than 220 causal mutations), at least several months are required to identify the responsible mutation. This is why the improvement of HCM clinical diagnostic criteria is crucial in order to improve the assessment of phenotypic status in relatives. Secondly, this improvement of cardiological tools would allow the detection of ‘healthy carriers’, who are genetically affected but are not detected by conventional ECG and echo criteria (30% of genetically affected individuals). This would therefore lead to the early identification of subjects at high risk of developing the disease later. Such ‘borderline’ subjects, with normal conventional criteria but with an abnormal 2D LV score, have a pre-clinical HCM, which is an intermediate step between totally healthy carriers and HCM patients. These subjects should benefit from a medical follow-up, with regular clinical assessment, possibly less frequently than patients with obvious HCM but more frequently than subjects carrying a mutation without any cardiac abnormalities.

The diagnosis of HCM is usually based on the morphologic abnormalities and this is the reason why we focused our work on the expression of hypertrophy. However, the phenotypic expression of HCM is a very complex process including ventricular functional abnormalities (diastolic abnormalities), morphologic abnormalities (LV hypertrophy with or without obstruction, mitral valve abnormalities), and electrogeneis (fibrosis, atrial, and ventricular arrhythmias). It is possible that the early diagnosis of HCM may benefit from the analysis of the functional or electrophysiological aspects of the disease. This may depend on the frequency.
of these abnormalities and, above all, the chronological sequence of those ones. In a mouse model of FHC, cardiac histopathology and dysfunction of the mutated heterozygous mice recapitulated human HCM. Cardiac dysfunction including abnormal relaxation and reduced cardiac output preceded morphologic (left atrial enlargement) and histopathologic changes. The hypothesis was that altered mechanical properties in the mutant sarcomere directly caused cardiac dysfunction, before the occurrence of myocyte disarray, myocyte hypertrophy, and later fibrosis. Whether these findings do apply to human HCM or not remain unknown. Very few studies analysed the chronological sequence of abnormalities in families with HCM. Some data performed in small populations with TDI echocardiography suggested that functional abnormalities precede morphological abnormalities, but areas of uncertainty persist and other studies found that sensitivity was in fact relatively low. Additional studies are required to answer this question.

Conclusion

A 2D LVH score, using a new adjusted cut-off value, appears to be of great value for the diagnosis of HCM, especially in young adults and should therefore be proposed as an alternative diagnostic criterion to conventional ECG and echo criteria.

References