Early identification of mutation carriers in familial hypertrophic cardiomyopathy by combined echocardiography and tissue Doppler imaging

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Aims
Preliminary studies suggested that tissue Doppler imaging (TDI) was able to identify mutation carriers in familial hypertrophic cardiomyopathy (HCM) before the development of hypertrophy. However, data are limited. We performed a systematic analysis of echocardiography, TDI, and electrocardiogram (ECG) in familial HCM to identify parameters associated with genetic status.

Methods and results
We analysed 120 adults spread out in three groups: HCM patients with hypertrophy (LVH+, n = 48), mutation carriers without hypertrophy (LVH-/G+, n = 24), and normal control subjects (n = 48). Several parameters were significantly different in LVH-/G+ compared with controls. Multivariate logistic regression identified only three independent echographic/TDI parameters associated with genetic status: the inter-ventricular septum/left posterior wall ratio (P = 0.006), relative wall thickness (P = 0.026), and septal E/Ea ratio (P = 0.008). An echo/TDI score determined after receiver operating characteristic analysis identified mutation carriers with 67% sensitivity and 96% specificity. In comparison, only 29% were identified by the previously proposed TDI criterion (lateral Ea velocity < 14 cm/s) and only 33% by major ECG abnormalities.

Conclusion
Tissue Doppler imaging velocities alone were not reliable enough to identify LVH-free mutation carriers in HCM. In contrast, abnormal LV remodelling was a frequent early manifestation of HCM. We developed a new score, combining echocardiographic and TDI parameters, that identifies mutation carriers before and independently of hypertrophy with high accuracy.

Keywords
Hypertrophic cardiomyopathy • Genetics • Echocardiography • Tissue Doppler imaging • Diagnosis

Introduction
Early diagnosis of hypertrophic cardiomyopathy (HCM) is of paramount importance as this inherited disease, transmitted as an autosomal dominant trait, is considered as one of the most common causes of sudden death in the young.1,2 Clinical diagnosis is based on the presence of unexplained left ventricular hypertrophy (LVH), usually detected by echocardiography.1,3 The clinical spectrum of HCM is broad, as some patients may have mild or no LVH but a high incidence of sudden death, as observed in families with TNNT2 mutations.4,5 Moreover, LVH is not an early marker for HCM because of delayed onset or age-related penetrance, especially in families with MYBPC3 mutations.6,7

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Genetic testing is the optimal strategy for the identification of relatives at risk of developing HCM, but the first condition is to identify the causal mutation in the propositus of the family. This process is long (due to the high genetic heterogeneity of the disease) and uncertain (identification in only 50–70% of propositus).8,9 There is therefore a need for the identification of clinical markers able to diagnose HCM before and independently of LVH.

Experimental data from animal models mimicking the human HCM phenotype suggested that impaired diastolic and systolic myocardial function could precede LVH, which appears as a compensatory process.10–12 Tissue Doppler imaging (TDI) is a validated echocardiographic technique that can appropriately assess systolic and diastolic myocardial function, as well as left ventricle (LV) filling pressures.13 Data from a transgenic rabbit model for HCM, as well as preliminary echocardiographic studies in humans suggested that TDI, through the measurement of systolic (Sa) and early diastolic (Ea) peak myocardial velocities, could be an accurate technique to identify HCM before LVH, with high sensitivity and specificity.14–16 A subsequent study in human observed that only diastolic Ea peak velocities were different in LVH-free mutation carriers compared with controls and that TDI was not sufficiently sensitive as a sole diagnostic criterion but might be helpful in combination with LV ejection fraction.17 Another recent study observed no difference for Sa and Ea peak velocities between LVH-free mutation carriers and controls.18 Owing to these limited and contrasting data, we performed a systematic analysis of echocardiography and TDI in genotyped HCM families to identify diagnostic parameters for genetic status. We included LV morphological or remodelling parameters, such as the interventricular septum/left posterior wall (IVS/LPW) ratio, the relative wall thickness (RWT), and the Maron–Spirito index,19,20 which were not part of TDI studies. We also sought to determine the contribution of the electrocardiogram (ECG) in addition to echocardiography.

Methods

Study population

The study population was composed of adults (≥18 years old), recruited from families with HCM in the Department of Cardiology at Pitie´-Salpeˆtrie`re Hospital, spread out in three groups: the LVH group composed of patients with typical HCM (not necessarily genotyped, maximal LV wall thickness or MWT >13 mm); the LVH−/G+ group composed of genotyped first-degree relatives of HCM patients with a mutation but without echocardiographic hypertrophy (MWT <13 mm); and the control group composed of genetically unaffected adults healthy volunteers with no history of cardiovascular disease and normal echocardiography. Two LVH+ and two control subjects were included for each LVH−/G+ subject, controls being matched for age (±7 years) and sex with LVH−/G+ patients. Individuals with atrial fibrillation, pacemaker or poor echogenicity were excluded to limit echocardiographic measure bias. Affected HCM patients with isolated apical hypertrophy or with previous myomectomy or septal alcohol ablation were also excluded. The genetic study was approved by the Ethics Committee of our Institution and written informed consent was provided from all subjects undergoing genetic testing.

Echocardiographic study

Echocardiographic studies were performed with an Acuson Sequoia C256 system with measures in standard two-dimensional (2D) mode, M-Mode, pulsed Doppler and TDI, according to the ASE guidelines.21 The following data were collected in M-mode in long-axis parasternal view: end-diastolic LV IVS and LPW thickness, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and end-diastolic left atrial (LA) diameter. Left ventricular ejection fraction was calculated according to the Teichholz formula and LV mass according to the ASE guidelines.21 We also calculated the IVS/LPW ratio and the RWT, defined by the ratio of end-diastolic (IVS + LPW)/LVEDD.22 The MWT was defined by the maximal LV thickness in any of the four LV segments (anterior septum, posterior septum, posterolateral wall, and anterolateral wall) measured in short-axis parasternal view (2D-mode). The Maron–Spirito index was defined as the sum of the LV maximal thickness at these four segments.19,20 The early (E) and late (A) transmitral peak velocities (cm/s), E/A ratio, and E deceleration time (EDT in ms) were measured from mitral inflow by pulsed Doppler from apical four-chamber view. Myocardial velocities were recorded by pulse-TDI at lateral and septal mitral annulus: systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities.

All the echocardiographies from the LVH−/G+ and LVH+ groups were performed by a single observer blinded to knowledge of the genetic status (P.C.). All the echocardiographic studies were subsequently analysed offline (with Image Arena software, Tomtec) by a second observer (E.G.).

Electrocardiographic study

A 12-lead surface ECG was performed in all LVH−/G+ individuals and interpreted by a single cardiologist. Electrocardiogram was considered abnormal in the presence of at least one among the following major criteria: abnormal Q-waves ≥0.1 mV in at least two derivations except V1, V2, and aVR; LVH assessed by a Romhilt–Estes score ≥4.13,24 Statistical analysis

First, a multiple group comparison study was performed between the three groups using non-parametric Kruskal–Wallis and Fisher tests, as sample size for some groups was small and normal distribution could not be verified for all variables. Results were therefore displayed as median and inter-quartiles (25–75%). Means and standard deviations are available in Supplementary material online, Table S5. Significant parameters were then analysed by post hoc tests between the control group and the two others (LVH+ and LVH−/G+ groups). Univariate analyses were expressed with corrected P-values (Pc) using Bonferroni correction according to the number of variables analysed in the multiple group comparison study (4 clinical variables, 19 standard echocardiography variables, and 13 TDI variables) and to the number of post hoc tests. A Pc-value <0.05 was considered as statistically significant. Stepwise multivariate logistic regression was performed to identify parameters independently associated with an affected genotype in LVH-free subjects (details see Supplementary material online, Table S6). First, a principal component analysis was performed in the control group using varimax rotation, in order to determine groups of interrelated variables among the large number of variables analysed. Then, logistic regression was performed in each group identified. Finally, all significant variables identified in the previous analysis were included in the final regression model. Age was included in each step and tested in the final model. Receiver operating characteristic (ROC) curves were built to determine the optimal cut-off values for the identification of an affected genotype. The inter- and intra-observer reliability of echo assessments were
determined by measuring the intraclass correlation coefficient (ICC) from a two-way random effects model with analysis of the ‘absolute agreement’ of measurements for the inter- and of the ‘consistency’ for the intra-observer reliability. Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA) and SPSS 15.0 for Windows.

Results

Study population

Overall, 120 subjects were included in the study: 24 in the LVH−/G+ group, 48 in the control group, and 48 in the LVH+ affected group. The mean age in the LVH−/G+ group was 38.4 ± 13.8 years old and did not differ from the other two groups; neither did the sex ratio and the body surface area. In comparison with controls, the heart rate was not different in the LVH−/G+ group but significantly lower in the LVH+ group (Table 1). The LVH−/G+ subjects came from 14 different families, and 12 different mutations had been identified in this group. Twelve individuals (50%) from nine families carried seven different c-MycBP-C (MYBPC3) mutations: two mutations leading to an aberrant splicing, c.1928-2A>G (two independent subjects) and c.2308+1G>A (five subjects from two families), one frame shift mutation (p.Asp1220ValfsX20), one stop mutation (p.Gln1233X), and three missense mutations (p.Arg495Gln, p.Leu532Pro, and p.Leu1831Le). Nine individuals (38%) from four families carried four different β-MHC (MYH7) mutations: p.Arg204His, p.Arg403Leu (three subjects), p.Met852Thr (three subjects), and p.Asp896Gly (two subjects). Two related individuals (8%) carried a cardiac troponin T (TNNT2) stop mutation (p.Trp287X). One subject was considered as an obligate carrier since both her sister and her son were affected.

Standard echocardiography and Doppler

In HCM patients with LVH (LVH+ group), all the parameters were significantly different in comparison with controls, except LVED diameter, and E, A, and E/A transmitral velocities (Table 1). The statistical multiple group comparison study was not affected by the exclusion of HCM patients with apical hypertrophy.

In mutation carriers without LVH (LVH−/G+ group), in comparison with controls, we observed that IVS (M-mode) and MWT (2D-mode) were significantly higher (Pc = 0.002 and 0.004, respectively), and the thickness increase was exclusively related to the anterior septum (Pc = 0.004), the IVS/LPW ratio (Pc < 0.001), and the remodelling index RWT (Pc = 0.006) were significantly higher, as well as the LV mass (Pc = 0.028) and the LA diameter (Pc = 0.004) (Table 1). The LVESD, LVEDD, and the ejection fraction were not different. The EDT was significantly increased in the LVH−/G+ group (Pc = 0.006), but E and A transmitral peak velocities and E/A ratio were not different (Table 1).

Within the LVH−/G+ group, no significant difference was observed between MYH7 and MYBPC3 mutation carriers (data not shown).

Tissue Doppler imaging study

In the LVH+ group, Sa and Ea velocities at mitral annulus were significantly decreased compared with controls, but not the lateral Aa velocity or tricuspid Sa and Ea peak velocities (Table 2).

In LVH-free mutation carriers (LVH−/G+ group), in comparison with controls, we observed that only the septal Ea peak velocity was significantly lower (Pc = 0.0034), whereas mitral Sa, Aa, and lateral Ea peak velocities were not different (Table 2). There was a substantial overlap of the individual septal and lateral Ea velocities between groups (Figure 1). In contrast, septal and lateral E/A ratios were less overlapping and significantly increased in LVH−/G+ subjects in comparison with controls (Pc < 0.001 and Pc = 0.004, respectively). Analysis of right ventricular myocardial velocities showed that tricuspid annulus Aa velocity was significantly increased in the LVH−/G+ group (Pc = 0.002), whereas Sa and Ea velocities were not different.

Identification of left ventricular hypertrophy-free mutation carriers

After multivariate logistic regression analysis, only three parameters were independently associated with a positive genetic status in LVH-free subjects: the IVS/LPW ratio [odds ratio (95% confidence interval) = 1.77 per 0.1 U increase (1.18–2.67), Pc = 0.006], the RWT [OR = 7.64 per 0.1 U increase (OR 95% CI: 1.27–46.05), Pc = 0.026], and the septal E/Ea ratio [OR = 1.72 per unit increase (OR 95% CI: 1.15–2.57), Pc = 0.008] (see Supplementary material online, Table S6). Results were not influenced by age. Using an ROC analysis, and fixing specificity at 95%, we identified the following optimal cut-off values: IVS/LPW ratio > 1.43 (sensitivity: 37.5%; RWT > 0.37 (sensitivity: 42%); and septal E/Ea ratio > 7.9 (sensitivity: 37.5%) (Figure 2). The combination of these three factors improved the identification of a positive genetic status in LVH-free subjects, as the presence of only one positive parameter out of the three was associated with 83.3% sensitivity and 87.5% specificity. On the basis of the logistic regression coefficients, an echo/TDI score combining those three parameters was defined as the probability to be affected: $P = -19.1861 + 6.195 \times \text{IVS/LPW} + 22.538 \times \text{RWT} + 0.5613 \times \text{septal E/Ea}$. Receiver operating characteristic analysis for this score indicated an optimal cut-off value > 0.45, associated with 66.7% sensitivity and 95.8% specificity for the diagnosis of mutation carriers. In addition, this combined score identified all affected LVH+ subjects with 100% sensitivity. The combined echo/TDI score was not significantly different between MYH7 and MYBPC3 mutation carriers (data not shown).

Electrocardiogram in left ventricular hypertrophy-free mutation carriers

In the LVH−/G+ group, only eight subjects (33%) displayed an abnormal ECG. The other subjects had either a normal ECG or minor changes considered as non-clinically significant (Table 3). The most common abnormal feature was the presence of abnormal Q-waves (6 of 8), mostly localized in inferior and/or lateral leads, and TWI (4 of 8). Within the LVH−/G+ group, the echo/TDI score was not different between individuals with or without major ECG abnormalities (data not shown). Nine of the 16 LVH−/G+ subjects (56%) with abnormal echo/TDI score
Table 1  Clinical and echocardiographic characteristics in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 48), median [25–75%]</th>
<th>LVH –/G+ (n = 24), median [25–75%]</th>
<th>LVH+ (n = 48), median [25–75%]</th>
<th>Multi-group comparison study (Pc-values)</th>
<th>LVH–/G+ vs. controls (Pc-values)</th>
<th>LVH+ vs. controls (Pc-values)</th>
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<tbody>
<tr>
<td><strong>Clinical data</strong></td>
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<tr>
<td>Age (years)</td>
<td>34 [24–47]</td>
<td>35 [30–48]</td>
<td>34 [22–52]</td>
<td>&gt;0.5</td>
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<tr>
<td>Gender (male)</td>
<td>46%</td>
<td>42%</td>
<td>67%</td>
<td>0.224</td>
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<tr>
<td>BSA (m²)</td>
<td>1.8 [1.6–2.0]</td>
<td>1.8 [1.6–2.0]</td>
<td>1.8 [1.7–2.0]</td>
<td>&gt;0.5</td>
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<td>HR (b.p.m.)</td>
<td>67 [60–76]</td>
<td>66 [59–72]</td>
<td>57 [53–66]</td>
<td>&lt;0.001</td>
<td>&gt;0.5</td>
<td>&lt;0.001</td>
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<td><strong>2D/TM data</strong></td>
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<tr>
<td>IVS (mm)</td>
<td>8.3 [7.1–8.9]</td>
<td>9.5 [8.1–11.0]</td>
<td>18.7 [15.0–23.8]</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
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<tr>
<td>LPW (mm)</td>
<td>7.1 [6.3–7.8]</td>
<td>7.3 [6.4–7.8]</td>
<td>8.1 [7.1–10.2]</td>
<td>&lt;0.001</td>
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<tr>
<td>IVS/LPW</td>
<td>1.1 [1.0–1.2]</td>
<td>1.4 [1.2–1.5]</td>
<td>2.4 [1.7–2.8]</td>
<td>&lt;0.001</td>
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<tr>
<td>RWT</td>
<td>0.32 [0.28–0.34]</td>
<td>0.34 [0.32–0.39]</td>
<td>0.64 [0.50–0.74]</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
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<tr>
<td>LVEDD (mm)</td>
<td>49 [46–53]</td>
<td>47 [44–49]</td>
<td>47 [43–50]</td>
<td>&gt;0.5</td>
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<tr>
<td>LVESD (mm)</td>
<td>30 [28–34]</td>
<td>28 [25–32]</td>
<td>26 [22–30]</td>
<td>&lt;0.001</td>
<td>0.074</td>
<td>&lt;0.001</td>
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<tr>
<td>LA diameter (mm)</td>
<td>33 [30–36]</td>
<td>37 [33–40]</td>
<td>43 [38–47]</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 [62–73]</td>
<td>71 [64–76]</td>
<td>75 [70–81]</td>
<td>&lt;0.001</td>
<td>0.488</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MWT (mm)</td>
<td>8.0 [7.6–8.8]</td>
<td>9.1 [8.3–10.4]</td>
<td>21.2 [16.7–26.6]</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
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<tr>
<td>Anterior septum (mm)</td>
<td>7.9 [7.0–8.4]</td>
<td>8.9 [8.0–10.4]</td>
<td>20.6 [15.4–25.3]</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
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<tr>
<td>Posterior septum (mm)</td>
<td>7.6 [7.1–8.4]</td>
<td>7.7 [7.2–9.3]</td>
<td>17.6 [12.8–23.7]</td>
<td>&lt;0.001</td>
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<tr>
<td>Postero inferior wall (mm)</td>
<td>7.3 [6.7–7.7]</td>
<td>7.2 [6.3–7.7]</td>
<td>8.7 [7.7–9.8]</td>
<td>&lt;0.001</td>
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<tr>
<td>Antero lateral wall (mm)</td>
<td>7.3 [6.7–8.0]</td>
<td>7.6 [6.6–8.5]</td>
<td>10.6 [8.7–13.6]</td>
<td>&lt;0.001</td>
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<tr>
<td>Spinto index (mm)</td>
<td>30 [28–32]</td>
<td>32 [29–36]</td>
<td>58 [48–70]</td>
<td>&lt;0.001</td>
<td>0.206</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>131 [100–159]</td>
<td>162 [126–185]</td>
<td>301 [247–431]</td>
<td>&lt;0.001</td>
<td>0.028</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Transmitral pulsed Doppler</strong></td>
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<tr>
<td>Peak E velocity (cm/s)</td>
<td>71 [63–81]</td>
<td>86 [73–98]</td>
<td>79 [60–101]</td>
<td>&gt;0.5</td>
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<tr>
<td>Peak A velocity (cm/s)</td>
<td>51 [43–58]</td>
<td>55 [48–70]</td>
<td>54 [41–70]</td>
<td>&gt;0.5</td>
<td></td>
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<tr>
<td>E/A ratio</td>
<td>1.4 [1.2–1.7]</td>
<td>1.4 [1.1–1.9]</td>
<td>1.5 [1.1–1.9]</td>
<td>&gt;0.5</td>
<td></td>
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<tr>
<td>E deceleration time (ms)</td>
<td>140 [127–155]</td>
<td>165 [145–174]</td>
<td>183 [156–239]</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Results of univariate analysis of control group vs. LVH–/G+ and LVH+ groups. Multi-group comparisons were performed first and, in case of statistical difference for a given parameter, subsequent comparisons between two groups were performed. Pc-values mean corrected P-values after Bonferroni correction. LVH–/G+: LVH-free mutation carriers; LVH+: patients with LVH and typical echocardiographic HCM; BSA, body surface area; HR, heart rate. Intraclass correlation coefficients [ICC (95% confidence interval)] for inter- (ICCinter) and intra-observer (ICCintra) measurements are the followings: IVS: ICCinter = 0.98 (0.96–0.99), ICCintra = 0.96 (0.92–0.98); LVEDD: ICCinter = 0.94 (0.88–0.96), ICCintra = 0.93 (0.88–0.96); PP: ICCinter = 0.88 (0.81–0.93), ICCintra = 0.86 (0.81–0.93); E-peak velocity: ICCinter = 0.98 (0.97–0.99), ICCintra = 0.96 (0.93–0.98).
Mutation carries in HCM by echocardiography and TDI

We therefore tried to identify new diagnostic parameters and showed that IVS/LPW ratio, RWT and septal Ea/Ea ratio were independently associated with a positive genotype in LVH-free patients. In our population, an echo/TDI score combining these three criteria identifies mutation carriers with a sensitivity of 67% and a specificity of 96%. In addition, the presence of at least one abnormal parameter

Discussion

We performed a systematic analysis of echocardiography, TDI, and ECG in genotyped adults from families with HCM to identify which parameters could identify mutation-positive relatives independently of LVH. This is one of the largest studies in that setting, considering both the size of the population and the broad spectrum of parameters analysed.

Tissue Doppler imaging for the identification of left ventricular hypertrophy-free mutation carriers

We observed that TDI myocardial velocities were not significantly different between LVH-free mutation carriers and controls, except for the septal Ea myocardial peak velocity. Because of a large overlap of the corresponding values between groups, including Ea peak velocity, the analysis of the diagnostic value of previously proposed TDI diagnostic criteria resulted in low sensitivity and/or specificity in our population without clinical application (Table 4 and Figure 1). These results are in contrast with those from previous studies, suggesting that low systolic and diastolic myocardial peak velocities (lateral or septal Sa and Ea peak velocities) displayed high sensitivities and specificities (>90% each) for the identification of LVH-free mutation carriers. The results were, however, subsequently challenged by two studies suggesting that Sa and Ea peak velocities were not accurate enough to be used as a sole diagnostic criterion. The comparative analysis of the different studies available indicates that observed velocities were quite different for the group of patients that is considered (see Supplementary material online, Table S7). As an example, in LVH-free mutation carriers, mean Ea velocity at the lateral mitral annulus was 2.0 cm/s in one study, 4.8 cm/s in our study, and similar to or greater than that observed in previous studies (see Supplementary material online, Table S7). Therefore, age alone cannot explain our results. Overall, myocardial velocities measured at mitral annulus seem highly heterogeneous in distinct populations and therefore not reliable enough alone to achieve preclinical diagnosis in HCM.

Integrated evaluation of echocardiography and tissue Doppler imaging

We therefore tried to identify new diagnostic parameters and showed that IVS/LPW ratio, RWT and septal Ea/Ea ratio were independently associated with a positive genotype in LVH-free patients. In our population, an echo/TDI score combining these three criteria identifies mutation carriers with a sensitivity of 67% and a specificity of 96%. In addition, the presence of at least one abnormal parameter
out of the three is of high diagnostic value, with a sensitivity of 83% and a specificity of 87%. This latter diagnostic strategy is simpler and might be proposed first in clinical practice, but the use of the echo/TDI score is more precise with a better specificity and should probably be preferred. Taken together, our results suggest that these parameters are accurate for preclinical diagnosis of human HCM. The new integrated echocardiographic score may have important implications in clinical practice. The identification of relatives at high risk of developing hypertrophy later and who would benefit from a regular medical follow-up would result in early therapeutic management, as well as physical activity restriction, which may prevent the complications of HCM.

**Electrocardiogram and echocardiography**

In our population, significant ECG changes were present in 33% of LVH-free mutation carriers, in accordance with previous studies. Electrocardiogram changes were preferentially localized in the inferior or lateral leads and pathological Q-waves were the most common feature observed, as previously shown. Interestingly, all but one individual with significant Q-waves in ECG had an abnormal IVS/LPW ratio (>1.43). This is consistent with the hypothesis according to which pathological Q-waves in the infero-lateral leads reflect histological changes (cellular hypertrophy and/or myocyte disarray) appearing in the antero-septal wall in early stages of HCM, before the onset of significant hypertrophy. However, ECG displayed a lower sensitivity than the echo/TDI score within the LVH+/G+ group (33 vs. 67%) and more than 50% of the LVH-free mutation carriers with a positive echo/TDI score had a normal ECG. This suggests that echocardiography is more sensitive than ECG for the detection of early pathological changes in HCM.

**Insight into the natural history and pathophysiology of hypertrophic cardiomyopathy**

Experimental animal studies suggested that impaired sarcomeric dysfunction secondary to sarcomere protein mutations was the stimulus for hypertrophy and that global diastolic or systolic dysfunction were the key steps in the early pathogenesis of HCM. We observed in the present human study that three echographic parameters were associated with a positive genetic status and these abnormalities were present before and
independently of LVH. Increased $E/E_{a}$ ratio at mitral annulus is consistent with an elevation of LV filling pressures as an early marker of the disease in humans. Increased IVS/LPW ratio in LVH-free mutation carriers suggests a local remodelling that is consistent with studies that have documented histological abnormalities, 29–31 and acoustic tissue structural changes 32 in the absence of a significant LVH. Increased RWT observed in mutation carriers indicates a global concentric remodelling of the LV. Interestingly, the three parameters related to regional and global remodelling and the elevation of filling pressures were independently associated with an affected genotype. This suggests that distinct mechanisms may be observed early in HCM and do not necessarily occur at the same stage for all patients. In our study, several LVH-free mutation carriers show a regional and/or global remodelling of the LV cavity, but display normal myocardial $E_{a}$ peak velocities at mitral annulus. This finding suggests that hypertrophic remodelling is not necessarily secondary to myocardial dysfunction or that the latter is not appropriately evaluated by TDI. Prospective studies are needed to better understand the chronology of these different abnormalities in human, and their possible links.

Limitations

Although limited, the size of the population is one of the largest to date. Because of the possible role of the underlying genes and mutations, we cannot exclude bias linked to the genetic background of the population under study, nor to the interdependence of some individuals from the same family. However, since no gene/
Supplementary material

Supplementary material is available at European Heart Journal online.

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