Incremental prognostic value of restrictive filling pattern in hypertrophic cardiomyopathy: a Doppler echocardiographic study

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Aim To study frequency and incremental prognostic value of restrictive filling pattern (RFP) in hypertrophic cardiomyopathy (HCM).

Methods and results Eighty-seven consecutive HCM patients (64% men, mean age 45 ± 19 years) underwent physical and Doppler echocardiographic evaluation at our centre from March 1993 to February 2001. Mean length of follow-up was 96 ± 54 months. RFP was found in 14 patients (16%) at index evaluation. Patients with RFP had higher NYHA class, more frequent signs of heart failure and lower left ventricular ejection fraction (P = 0.018, P = 0.002 and P = 0.001, respectively). During follow-up, cardiac death plus heart transplantation was significantly higher in HCM patients with RFP than in those without RFP (P = 0.0001). NYHA class (HR = 5.95, 95% CI: 1.34–26.38, P = 0.019), indexed left atrial diameter (HR = 1.68, 95% CI: 1.01–2.82, P = 0.047) and RFP (HR = 2.94, 95% CI: 1.25–6.88, P = 0.01) were selected as predictors of cardiac death or heart transplantation in a multivariate proportional hazard model. The AUC of ROC curve from multivariate regression models for predicting adverse outcome significantly improved from 0.76 considering only NYHA class to 0.84 after inclusion of RFP and indexed left atrial diameter (P = 0.01).

Conclusions RFP is rare, but not exceptional, in HCM. Echo-Doppler evaluation of filling pattern confers additional prognostic power to clinical stratification.

KEYWORDS
Hypertrophic cardiomyopathy; Diastole; Echocardiography; Prognosis

Introduction
Restrictive filling pattern (RFP)1,2 corresponds to severe diastolic dysfunction and increased LV stiffness3; even if typical of restrictive cardiomyopathy, it has been also recognized in heart failure (HF) and LV systolic dysfunction, being associated with worse clinical status, increased LV filling pressure and worse prognosis.1,2

RFP has never been systematically evaluated in HCM; therefore, aim of our study is to evaluate frequency, clinical significance and prognostic implications of RFP in HCM.

Methods
Selection of patients
We considered all consecutive patients with HCM studied by echo-Doppler at our Department from March 1993 to February 2001.

Diagnosis of HCM was done in accordance to international criteria.4 Patients with severe LV dilatation and/or significant systolic dysfunction (ejection fraction (EF) < 40%) were included if HCM with preserved LVEF was documented in previous echocardiographic examinations.

The study was approved by the Ethical Committee of Azienda Ospedaliero-Universitaria ‘Ospedali Riuniti’ of Trieste, Italy and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Participants gave informed consent for inclusion into the study and for the management of the clinical data.

Clinical and echo-Doppler assessments
All patients underwent clinical, electrocardiographic and echocardiographic examination. Time interval between onset of symptoms and diagnosis was also considered. Patient’s treatment was administered according to clinical judgement and currently available evidence2 and was recorded in a patient’s database.

Echocardiographic study
At M-mode, LV end-diastolic and end-systolic diameters and shortening fraction, end-diastolic thicknesses of interventricular...
quantitatively as the area of the color-Doppler regurgitant jet. MR 50 mmHg as severe. Mitral regurgitation (MR) was assessed semi-
than 30 mmHg were considered as significant, greater than 
continuous-Doppler technique. Systolic peak gradients greater 
view.

Systolic intraventricular gradients were assessed using 
employed.6 Current criteria for transplantation were 
Survival follow-up data were obtained by clinical controls or tele-
Follow-up assessment

Survival follow-up data were obtained by clinical controls or tele-

Filling was assessed by pulsed Doppler at the level of mitral 
tips. E and A wave peak velocities and E/A ratio were measured,
with EDT
EDT/C21
220 ms; normal (or ‘pseudonormal’) filling in presence 
intermediate patterns. In patients with atrial fibrillation, only 
E wave data were considered.

Follow-up assessment

Survival follow-up data were obtained by clinical controls or tele-

Table 1 Baseline clinical and echocardiographic characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients with HCM (n = 87)</th>
<th>HCM patients with RFP (n = 14)</th>
<th>HCM patients without RFP (n = 73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45 ± 19</td>
<td>40 ± 18</td>
<td>46 ± 19</td>
<td>ns</td>
</tr>
<tr>
<td>Male sex</td>
<td>56 (64%)</td>
<td>11 (79%)</td>
<td>45 (62%)</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.6 ± 0.6</td>
<td>1.9 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.018</td>
</tr>
<tr>
<td>NYHA class II–III</td>
<td>41 (48%)</td>
<td>11 (79%)</td>
<td>30 (42%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13 (15%)</td>
<td>6 (43%)</td>
<td>7 (10%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>75 (87%)</td>
<td>11 (79%)</td>
<td>64 (89%)</td>
<td>ns</td>
</tr>
<tr>
<td>LV-EDDI (cm/m²)</td>
<td>2.5 ± 0.4</td>
<td>2.7 ± 0.6</td>
<td>2.4 ± 0.4</td>
<td>0.016</td>
</tr>
<tr>
<td>LV-ESDI (cm/m²)</td>
<td>1.5 ± 0.5</td>
<td>1.9 ± 0.8</td>
<td>1.4 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>LV dilatation (LV-EDD &gt; 5.5 cm)</td>
<td>9 (11%)</td>
<td>4 (29%)</td>
<td>5 (7%)</td>
<td>0.017</td>
</tr>
<tr>
<td>LV-EDVI (ml/m²)</td>
<td>45 ± 19</td>
<td>52 ± 29</td>
<td>44 ± 16</td>
<td>ns</td>
</tr>
<tr>
<td>LV-ESVI (ml/m²)</td>
<td>17 ± 13</td>
<td>27 ± 23</td>
<td>15 ± 9</td>
<td>0.003</td>
</tr>
<tr>
<td>LV-EF (%)</td>
<td>66 ± 14</td>
<td>54 ± 20</td>
<td>69 ± 10</td>
<td>0.001</td>
</tr>
<tr>
<td>LV systolic dysfunction (EF &lt; 50%)</td>
<td>7 (8%)</td>
<td>5 (38%)</td>
<td>2 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAAI (cm²/m²)</td>
<td>15.4 ± 5</td>
<td>19.5 ± 7</td>
<td>14.6 ± 4</td>
<td>0.03</td>
</tr>
<tr>
<td>IVS thickness (cm)</td>
<td>2.1 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>2.1 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>PW thickness (cm)</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Prevalent IVS thickness</td>
<td>73 (84%)</td>
<td>12 (86%)</td>
<td>61 (84%)</td>
<td>0.001</td>
</tr>
<tr>
<td>IV systolic gradient</td>
<td>17 (20%)</td>
<td>3 (21%)</td>
<td>14 (19%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximal IV systolic gradient (mmHg)</td>
<td>95 ± 44</td>
<td>104 ± 70</td>
<td>93 ± 41</td>
<td>0.001</td>
</tr>
<tr>
<td>E wave velocity (m/s)</td>
<td>0.61 ± 0.20</td>
<td>0.74 ± 0.22</td>
<td>0.59 ± 0.19</td>
<td>0.011</td>
</tr>
<tr>
<td>A wave velocity (m/s)</td>
<td>0.54 ± 0.25</td>
<td>0.38 ± 0.28</td>
<td>0.56 ± 0.24</td>
<td>0.024</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.40 ± 0.93</td>
<td>2.52 ± 1.39</td>
<td>1.20 ± 0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>195 ± 68</td>
<td>104 ± 26</td>
<td>212 ± 58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean value ± SD or number (percentages in parentheses). EDT: E wave deceleration time; HCM: hypertrophic cardiomyopathy; IV: Intraventricular; IVS: Interventricular septum; LAAI: left atrium area index; LADI: left atrial diameter index; LV: left ventricle; LV-EDDI: left ventricular end-diastolic diameter index; LV-EDVI: left ventricular end-diastolic volume index; LV-ESDI: left ventricular end-systolic diameter index; LV-ESVI: left ventricular end-systolic volume index; RFP: restrictive filling pattern.

Statistical analysis

The SPSS statistical package (SPSS Statistical Software Inc., Chicago, Illinois) was used for all analysis. Data are expressed as mean (± SD), or number of patients (percentage). Means were compared using unpaired Student’s t-test, and frequency of events using chi-square test; P < 0.05 was considered statistically significant.

Probability of event-free survival (cardiac death and heart trans-
plantation) was calculated using Kaplan–Meier method; survival 
curves were compared using log-rank test. To determine whether 
differences in event-free survival between the two groups could 
be explained by disease-related variables, univariate and multi-
variate stepwise Cox proportional hazard regression (retention set 
at a significance level of 0.05) analyses were performed.

Receiver operating characteristic (ROC) curves were used to 
evaluate ability of a model assembled with selected variables to 
predict event-free survival. A simplified scoring system based on 
selected independent variables was then established and presented 
using a nomogram.

Results

Study group characteristics at presentation

Table 1 shows the clinical and echocardiographic characteristics of study population. HCM was diagnosed in 87 patients; 64% were males, mean age was 45 ± 19 years. Mean time from symptom onset to diagnosis was 93 ± 105 months. Mean length of follow-up (available in all patients) was 96 ± 54 months.

At Doppler study, abnormal relaxation pattern was present in 18 (21% of cases) and RFP in 14 (16%) (Figure 1);
Figure 1  Example of restrictive filling pattern with preserved left ventricular systolic function in a patient with hypertrophic cardiomyopathy. (A) Two-dimensional echocardiographic end-diastolic and end-systolic frames from apical four chamber view. Severe left ventricular hypertrophy is present (septum thickness 2.4 cm); left ventricular volumes and ejection fraction were normal (end-diastolic volume 80 ml, end-systolic volume: 36 ml, ejection fraction 55%). (B) Transmitral Doppler curve in the same patient. Restrictive filling pattern is present with predominant E wave (E/A ratio: 7) and shortened E deceleration time (90 ms).

Table 2  Therapeutic management and clinical events observed during follow-up period

<table>
<thead>
<tr>
<th>Event</th>
<th>Total patients with HCM (n = 87)</th>
<th>HCM patients with RFP (n = 14)</th>
<th>HCM patients without RFP (n = 73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period (months)</td>
<td>96 ± 54</td>
<td>87</td>
<td>101 ± 54</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>29 (36%)</td>
<td>80</td>
<td>25 (38%)</td>
<td>ns</td>
</tr>
<tr>
<td>Verapamil therapy</td>
<td>22 (28%)</td>
<td>80</td>
<td>19 (29%)</td>
<td>ns</td>
</tr>
<tr>
<td>Amiodarone therapy</td>
<td>16 (20%)</td>
<td>80</td>
<td>12 (18%)</td>
<td>ns</td>
</tr>
<tr>
<td>ACE-inhibitors therapy</td>
<td>10 (13%)</td>
<td>80</td>
<td>6 (9%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diuretics therapy</td>
<td>11 (14%)</td>
<td>80</td>
<td>6 (9%)</td>
<td>ns</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>7 (9%)</td>
<td>74</td>
<td>6 (10%)</td>
<td>ns</td>
</tr>
<tr>
<td>Septal myectomy surgery</td>
<td>3 (4%)</td>
<td>80</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Heart failure episodes</td>
<td>27 (31%)</td>
<td>87</td>
<td>18 (25%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>21 (24%)</td>
<td>87</td>
<td>13 (18%)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>6 (7%)</td>
<td>87</td>
<td>5 (7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Event-free survivors (cardiac death/heart transplantation)</td>
<td>60 (69%)</td>
<td>87</td>
<td>55 (75%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are presented as mean value ± SD or number (percentages in parentheses).
ACE: angiotensin-converting enzyme.
LV filling pattern was within normal limits (normal or pseudonormal pattern) in remaining patients.

As shown in Table 1, HCM patients with RFP were in more advanced NYHA functional class (P = 0.018). Signs of HF were more frequently found in this patient group (P = 0.002). At echocardiographic study, patients with RFP had more frequently depressed LV-EF (P = 0.01), LV dilatation (P = 0.017), and larger indexed left atrial area (P = 0.03).

Therapeutic management and follow-up data

Table 2 shows patients’ treatments and follow-up events. A major clinical event occurred in 27 patients (31%); 21 died of cardiac cause (11 for sudden death and 10 for refractory HF) and 6 underwent heart transplantation.

Figure 2 shows the actuarial event-free Kaplan–Meier survival curves for HCM patients with RFP (n = 14) compared to remaining patients (n = 73). Patients with HCM and RFP had a poorer event-free survival after 60, 90 and 120 months (71%, 64%, and 43%, vs. 93%, 88%, and 78%, respectively; P = 0.0001).

On univariate Cox analysis, several variables significantly correlated with event-free survival (Table 3). On multivariate model (Cox proportional hazards model), NYHA class II or III vs. I (HR = 5.95, 95% CI: 1.34–26.38, P = 0.019), indexed left atrial diameter (HR = 1.68, 95% CI: 1.01–2.82, P = 0.047) and RFP (HR = 2.94, 95% CI: 1.25–6.88, P = 0.01) were selected as independent predictors of cardiac death or heart transplantation (Table 4).

ROC curve analysis was performed to compare ability of clinical (NYHA class II or III vs. I) and clinical plus echocardiographic (NYHA class II or III vs. I, indexed left atrial diameter, RFP) models to predict event-free survival (Figure 3). Area under the ROC curve (AUC) was 0.76 (SE 0.044, 95% CI 0.67–0.85) for the clinical model and 0.84 (SE 0.047, 95% CI 0.75–0.93) for the clinical plus echocardiographic model; addition of echocardiographic variables to clinical variables conferred a significant incremental value (P = 0.01). The clinical and echocardiographic model had higher sensitivity and specificity (67% and 88%, respectively) in identification of patients at risk for an unfavourable outcome at indexed left atrial diameter cut-off value 3.36 cm/m².

Figure 4 shows a nomogram derived from this clinical-echocardiographic model to quantify risk for cardiac death or heart transplantation at 2, 5, and 10 years of follow-up.

Discussion

Typical hemodynamic abnormality of HCM is diastolic dysfunction, characterized by abnormal relaxation and increased LV filling pressure and chamber stiffness, mainly due to interstitial fibrosis, hypertrophy, and fiber disarray.7,8 LV filling abnormalities were indeed frequent in our series; abnormal relaxation pattern was found in 18 cases and RFP in 14 cases.

Previous Doppler studies on LV filling in HCM evaluated only abnormal relaxation pattern compared to ‘normal’ patternn–12 and no correlation was found between LV filling...
and hemodynamic abnormalities, clinical symptoms, NYHA functional class, degree of hypertrophy, exercise tolerance, and intraventricular pressure gradient. In the present study, the first systematically describing RFP in HCM, the clinical significance of RFP seems to be similar to that described among patients with dilated cardiomyopathy; patients with RFP had higher NYHA functional class, more frequently clinical signs of HF and also more severe echocardiographic abnormalities (lower LV-EF, higher LV and left atrial dimensions) suggesting a more advanced disease. Indeed, presumed disease duration was significantly longer in patients with RFP. While in some cases RFP is expression of LV dysfunction, compatible with evolution to end-stage dilatation and systolic dysfunction of HCM, in others it is associated with normal LV-EF, corresponding to isolated LV diastolic dysfunction (Figure 1).

**Prognostic factors in HCM**

Prognosis of HCM is not well known, since it varies among patient series, presumably due to genotypic and phenotypic heterogeneity and patient selections from different populations. Although most studies were focused on sudden death, our study, similarly to others indicates HF leading to cardiac death or heart transplantation as a relevant problem. Few studies considered echo-Doppler prognostic factors. Severity of LV hypertrophy and presence of LV systolic gradient at Doppler significantly correlated to risk of cardiac death in some studies. Evolution toward wall thinning, LV cavity dilatation and depressed LV-EF seems to confer adverse prognosis and is associated with high risk of HF development.

Previous studies showed that RFP (particularly if persistent despite optimized treatment) is associated with increased risk of death in patients with dilated cardiomyopathy and with HF and depressed LV systolic function. This study is the first demonstrating that RFP is an adverse prognostic factor also in HCM, with incremental value with respect to clinical data. Another useful prognostic echocardiographic parameter is left atrial enlargement. It is a non-specific finding, depending on multiple interrelated factors, such as LV filling pressure and/or duration of disease and MR. Its adverse prognostic significance was demonstrated in elderly patients with dilated cardiomyopathy and also in HCM.

**Study limitations**

Our study has some limitations. A selection bias with over-representation of more advanced patients with HCM could...
have occurred, since ours is a referral centre for study of cardiomyopathies and HF. Our cases were probably studied at different stages of disease, since time interval between symptoms onset and diagnosis varied greatly among patients. Moreover, LV diastolic function was studied only by transmitral flow Doppler parameters; pulmonary venous flow and tissue Doppler data allow a more precise evaluation of LV filling pressure and correlate with exercise capacity and MVO\(^2\) in HCM,\(^10,12\) but were available only in few patients. Finally, only first examination data were analyzed; additive potential prognostic power may be derived from follow-up data.

Clinical implications

Our study shows that RFP is present in some HCM patients. It can occur both in association with systolic dysfunction (presumed end-stage disease, evolution in dilation and hypokinesis), and in preserved systolic function, corresponding to isolated LV diastolic dysfunction. Its clinical significance is similar to that observed in patients with other diseases, like dilated cardiomyopathy, being associated to more advanced functional status and HF. In our series RFP and increased left atrial dimension demonstrated an incremental prognostic value over clinical evaluation in predicting cardiac death plus heart transplantation.

References