Myocardial deformation abnormalities in paediatric hypertrophic cardiomyopathy: are all aetiologies identical?

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Aims Hypertrophic cardiomyopathy (HCM) is a disease with a heterogeneous clinical and morphological presentation. It can be secondary to mutations in genes encoding for sarcomeric and non-sarcomeric proteins. The pattern of ventricular hypertrophy can vary from isolated basal septal to concentric hypertrophy. We investigated if there are differences in regional myocardial function in different forms of HCM.

Methods and results We performed echocardiograms on children with (i) isolated asymmetric septal HCM, (ii) isolated concentric HCM, (iii) Friedreich’s ataxia associated with concentric HCM, and (iv) healthy controls. Wall thickness, left ventricular dimensions, ejection fraction, and mitral inflow were measured. Peak early diastolic myocardial velocities, peak systolic myocardial velocities, peak systolic strain rate (SR), peak systolic strain (e), post-systolic shortening and time to maximal e were measured in the basal and mid-septum and basal lateral wall to evaluate longitudinal myocardial function. Similar data were acquired and analysed in the anterior septum and infero-lateral wall to evaluate the radial myocardial function. All three groups with HCM had had increased wall thickness, reduced left ventricular dimensions, and evidence of impaired diastolic filling compared to controls. All forms of HCM had reduced early diastolic and systolic myocardial velocities and peak systolic SR and peak systolic e compared with controls in all myocardial segments investigated. Children with asymmetric septal HCM had reduced systolic deformation, increased post-systolic shortening, and prolonged time to maximal e in the basal septum compared with the other two groups with HCM. There were no differences in any echocardiographic variable between patients with isolated concentric HCM and Friedreich’s ataxia and resulting HCM.

Conclusion Myocardial deformation is abnormal in all forms of paediatric HCM. Myocardial deformation is more reduced and associated with post-systolic shortening in the more hypertrophied basal septum in patients with asymmetric septal HCM. In contrast, this reduction is uniformly distributed in all myocardial segments in patients with concentric HCM irrespective of whether HCM results from isolated or secondary HCM. Our findings suggest the pattern of hypertrophy influences myocardial deformation more than the underlying cause of HCM.

KEYWORDS
Hypertrophy; Cardiomyopathy; Strain rate; Tissue Doppler; Post-systolic shortening

Introduction
Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium defined as increased wall thickness without an identifiable haemodynamic cause.1 Hypertrophic cardiomyopathy is a genetic disease with a heterogeneous clinical and morphological presentation. Histopathologically, it is associated with myocardial hypertrophy, fibre disarray, increased loose connective tissue, and fibrosis all of which are all thought to interfere with the generation of force and impede relaxation of the cardiac muscle.4 The familial form, also called isolated HCM, is caused in a large majority of affected families by mutations in genes

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encoding for sarcomeric proteins. Secondary forms, also called systemic HCM, are caused by mutations in genes encoding for a diversity of non-sarcomeric proteins and are associated with multi organ involvement as in Friedrich's ataxia and Noonan syndrome. The secondary forms are more common in children than in adults.

The cardiac phenotype and outcome are highly variable in HCM. Especially, the degree and type of hypertrophy can range from isolated asymmetric septal hypertrophy to concentric forms involving the entire left ventricular (LV) mass. Isolated HCM presents more frequently as asymmetric septal hypertrophy, whereas patients with systemic HCM usually develop concentric HCM. It is unknown if the type of hypertrophy influences regional myocardial function. It is also unknown if there are differences in myocardial function between the isolated and systemic forms of HCM.

Hypertrophic cardiomyopathy is considered to be a predominantly diastolic disorder with relaxation abnormalities and preserved systolic function in the early stages. We have recently reported that there is reduced systolic myocardial deformation in paediatric patients with isolated HCM. This reduction is more pronounced in the more hypertrophied myocardial segments and is associated with post-systolic shortening. Post-systolic shortening is a marker of regional myocardial dysfunction and asynchrony. Thus, by measuring post-systolic shortening, one can detect inhomogeneous myocardial deformation.

The aims of our current study were to characterize the regional myocardial deformation in different types of HCM and to determine if either the pattern or the cause of hypertrophy influences the regional myocardial deformation in paediatric patients with HCM.

Methods

Study group

In this retrospective study, four groups of paediatric patients were included: (i) patients with isolated asymmetric septal HCM; (ii) patients with isolated concentric HCM; (iii) patients with Friedrich's ataxia with associated concentric HCM; (iv) healthy controls. Hypertrophic cardiomyopathy was defined as an otherwise unexplained increase in end-diastolic wall thickness (Z-score > 2) in at least one myocardial segment or a proven genetic diagnosis in a child with an affected relative. Patients with isolated HCM were considered to have asymmetric septal HCM or concentric HCM depending on whether the septal to infero-lateral wall thickness ratio at end diastole was larger than 1.3 or not. Friedrich's ataxia was diagnosed if patients fulfilled Harding's criteria for typical Friedrich's ataxia and were homozygous for the GAA repeat expansion in the frataxin gene. Patients with ventricular hypertrophy secondary to hypertension, other syndromic disorders (i.e. Noonan's syndrome), and other neuromuscular diseases such as Duchenne muscular dystrophy or inborn errors in metabolism were excluded.

Data acquisition

Standard transthoracic echocardiograms, blood pool Doppler and 2-D tissue Doppler studies were performed using a commercially available echocardiographic system (Vivid 7, GE Vingmed, Horten, Norway) equipped with a 2.5 MHz transducer. In each patient, standard parasternal and apical views were recorded. Real-time tissue Doppler data were recorded to evaluate longitudinal function in the interventricular septum and lateral LV free wall using an apical four-chamber view. To evaluate radial function in the infero-lateral LV wall, tissue Doppler data were recorded from the parasternal short-axis view, as previously described. To obtain high frames rates (180 ± 30 frames/s), each myocardial wall had to be acquired separately.

Standard echocardiographic data analysis

The maximal end-diastolic thickness of the interventricular septum and LV infero-lateral wall as well as the LV end-diastolic and end-systolic diameters was determined by M-mode recordings taken from the parasternal short-axis view. From these measurements, LV fractional shortening was calculated. Ventricular dimensions and wall thickness were expressed as the Z-score relative to the distribution of these measurements vs. body surface area in normal children. The modified Simpson's method was used for the determination of LV ejection fraction. Pulsed Doppler recordings at the tip of the mitral leaflets were used to measure peak early filling (E-wave) velocity, peak atrial filling (A-wave) velocity, E/A ratio, and E-wave deceleration time. The peak systolic gradient within the LV outflow tract was measured at rest using the modified Bernoulli equation.

Tissue Doppler imaging data analysis

All data were digitally transferred from the ultrasound machine and post-processed on an off-line workstation. The tissue Doppler imaging data sets were analysed using dedicated software (Software Package For Echocardiographic Quantification Leuven, Speqle 4©, Catholic University of Leuven, Belgium), allowing the off-line computation of regional myocardial velocities, natural strain rate (SR) and strain (ε) values as previously described.

Longitudinal peak systolic SR and ε were estimated from the apical four-chamber view at the following myocardial segments: (i) basal-mid-segment of the interventricular septum in the region of maximal wall thickness; (ii) mid-apical segment of the interventricular septum, where the hypertrophy was less pronounced; and (iii) basal-mid-LV lateral segment. Radial peak systolic SR and ε were measured at: (i) basal-mid-infero-lateral LV and (ii) basal-mid-antero-septal myocardial segments from a parasternal short-axis view (Figure 1). A computational area of 10 and 5 mm was used for longitudinal and radial SR estimations, respectively. A semi-automatic M-mode-based tracking algorithm was applied to maintain the sample volume within the mid-myocardial region of interest throughout the cardiac cycle. Myocardial velocity and SR data were averaged over three consecutive cycles and then smoothed with a mask of 5 × 1 pixels (axial-lateral) to reduce noise. The regional SR profiles were integrated over time to obtain the natural ε profiles. To determine the duration of systole, the aortic valve opening and closure clicks were introduced from blood pool pulsed or continuous wave Doppler tracings recorded from cycles with comparable R-R interval. The aortic valve closure click was considered the end of systole.

In each myocardial segment, the peak systolic and peak early diastolic (E') myocardial velocities were measured. The mitral E-wave to basal septal E' and mitral E' wave to basal lateral E ratio were calculated. The high temporal resolution of the technique allows identification of abnormal timing of myocardial events, including post-systolic shortening. Post-systolic shortening has been shown to be an important clinical marker of regional myocardial dysfunction, especially when associated with reduced peak systolic strain (εc). Post-systolic thickening index (in the radial direction) or shortening index (in the longitudinal direction) was also calculated. Post-systolic thickening/shortening index was calculated as follows: [maximal ε after aortic valve closure − end systolic εc]/end systolic εc] × 100. As a marker of mechanical dyssynchrony, the time from the beginning of the heart cycle (beginning of the QRS complex) to maximal ε was measured in each myocardial segment.
Statistical analysis

Normally distributed continuous variables are reported as mean value ± standard deviation (SD). Data that are not normally distributed are reported as median and range. If data were normally distributed, different groups were compared with one-way analysis of variance (ANOVA) test followed by Bonferroni’s test for multiple comparisons. Kruskal–Wallis test followed by Dunn’s multiple comparisons were used if data were not normally distributed. An exponential model was used to examine the relation between septal to infero-lateral wall thickness ratio and \( E/E_0 \) ratio with post-systolic shortening. \( P < 0.05 \) was considered statistically significant for all comparisons.

Results

Patient characteristics

A total of 85 subjects were included. Twenty-seven had asymmetric septal HCM (Group 1), 14 had concentric HCM (Group 2), 15 had Friedreich’s ataxia and concentric HCM (Group 3), and 29 were healthy controls (Group 4). Thirteen patients in Group 1 and six in Group 2 had a history of familial HCM. Seven of those patients in Group 1 and two in Group 2 had a mutation known to cause HCM. Eight patients in Group 1, one patient in Group 2, and no patients in Groups 3 and 4 had LV outflow tract obstruction at rest with a peak systolic gradient > 30 mmHg (median peak gradient 8 mmHg, range 4–121 mmHg).

Standard echocardiographic indices

Table 1 summarizes the standard echocardiographic data in the four groups. Patients with Friedreich’s ataxia were older than the patients in the other groups. The three groups with HCM had smaller LV end-diastolic dimension, increased wall thickness, reduced mitral \( E/A \) ratio, and larger \( E/E_0 \) ratio than the normal controls. In patients with asymmetric septal HCM, the interventricular septum was thicker than in the other two groups with HCM.

Tissue Doppler imaging indices of myocardial function

Indices of radial myocardial function from the antero-septal and infero-lateral LV myocardial segments are shown in Figure 2. Peak early diastolic and systolic myocardial velocities were significantly higher in normal controls than in each group with HCM in both the antero-septal and infero-lateral walls. Peak early diastolic and systolic myocardial velocities were also significantly lower in patients with asymmetric septal HCM compared with patients with concentric HCM and Friedreich’s ataxia in the antero-septal wall. Peak systolic SR and peak systolic \( e' \) were significantly higher in normal controls than in any group with HCM in the antero-septal and infero-lateral walls. Peak systolic SR and peak systolic \( e' \) were also significantly lower in patients with asymmetric septal HCM compared with the other two groups of patients with HCM in the antero-septal wall. These variables were, however, significantly higher in the infero-lateral wall in patients with asymmetric septal HCM compared with the other two groups of patients with HCM. The incidence of post-systolic thickening was significantly higher in patients with asymmetric septal HCM than in the other three groups in the antero-septal wall. Time to maximal \( e' \) was longer in patients with asymmetric septal HCM than in the other three groups in the antero-septal wall.

Longitudinal myocardial function is shown in Table 2. Peak early diastolic myocardial velocity, peak systolic myocardial velocity, peak systolic SR, and peak systolic \( e' \) were all significantly higher in controls than in any group with HCM in the three myocardial segments investigated. Peak early diastolic myocardial velocity, peak systolic myocardial velocity, peak systolic SR, and peak systolic \( e' \) were significantly lower in
the basal septum in patients with asymmetric septal HCM compared with patients with concentric HCM and Friedreich’s ataxia. The incidence of post-systolic shortening was significantly higher in patients with asymmetric septal HCM than in the other three groups in the basal and mid-septum. Time to maximal $e$ was significantly longer in patients with asymmetric septal HCM in the basal septum than the other three groups. Figure 3 shows the representative examples of myocardial deformation in the basal septum in the four groups.
Table 2 Longitudinal Left Ventricular Myocardial Function in the Four Different Groups

<table>
<thead>
<tr>
<th></th>
<th>Asymmetric HCM (n = 27)</th>
<th>Concentric HCM (n = 14)</th>
<th>Friedreich’s (n = 15)</th>
<th>Controls (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E’ (cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>−3.7 ± 2.1*</td>
<td>−5.7 ± 2.4</td>
<td>−5.8 ± 1.8</td>
<td>−9.7 ± 1.7**</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>−4.1 ± 2.0</td>
<td>−4.7 ± 2.3</td>
<td>−4.8 ± 1.4</td>
<td>−8.3 ± 1.7**</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>−7.1 ± 3.9</td>
<td>−7.4 ± 3.7</td>
<td>−7.5 ± 2.1</td>
<td>−11.7 ± 3.2**</td>
</tr>
<tr>
<td>Vel sys (cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>3.4 ± 1.1*</td>
<td>4.0 ± 1.2</td>
<td>4.1 ± 1.0</td>
<td>4.9 ± 0.7**</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>2.7 ± 1.0</td>
<td>3.0 ± 1.8</td>
<td>3.0 ± 0.6</td>
<td>3.7 ± 0.9**</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>5.0 ± 3.3</td>
<td>5.1 ± 2.1</td>
<td>5.8 ± 1.5</td>
<td>7.1 ± 1.8**</td>
</tr>
<tr>
<td>SR sys (s⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>−0.7 ± 0.5*</td>
<td>−1.2 ± 0.6</td>
<td>−1.2 ± 0.3</td>
<td>−2.0 ± 0.6**</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>−1.3 ± 0.8</td>
<td>−1.5 ± 0.5</td>
<td>−1.4 ± 0.7</td>
<td>−2.0 ± 0.6**</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>−1.6 ± 0.8</td>
<td>−1.5 ± 0.6</td>
<td>−1.4 ± 0.6</td>
<td>−2.3 ± 0.8**</td>
</tr>
<tr>
<td>ε sys (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>−7.5 ± 7.3*</td>
<td>−16.8 ± 7.8</td>
<td>−15.6 ± 4.9</td>
<td>−24.2 ± 6.1**</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>−15.1 ± 11.1</td>
<td>−17.6 ± 6.9</td>
<td>−15.1 ± 5.8</td>
<td>−26.6 ± 5.9**</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>−16.6 ± 11.2</td>
<td>−16.0 ± 7.4</td>
<td>−14.4 ± 3.2</td>
<td>−26.4 ± 5.9**</td>
</tr>
<tr>
<td>PST (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>84.3 ± 130.3***</td>
<td>3.2 ± 4.1</td>
<td>3.5 ± 5.6</td>
<td>4.2 ± 5.8</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>42.8 ± 77.4***</td>
<td>6.1 ± 11.5</td>
<td>2.3 ± 4.6</td>
<td>2.2 ± 3.3</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>12.5 ± 16.3</td>
<td>8.4 ± 10.2</td>
<td>8.1 ± 8.4</td>
<td>4.5 ± 4.2</td>
</tr>
<tr>
<td>Time to max ε (ms)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal septal</td>
<td>476.5 ± 96.7***</td>
<td>425.7 ± 77.3</td>
<td>407.1 ± 72.3</td>
<td>380.4 ± 76.4</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>418.9 ± 64.4</td>
<td>418.1 ± 58.6</td>
<td>409.9 ± 77.1</td>
<td>387.8 ± 45.4***</td>
</tr>
<tr>
<td>Basal lateral</td>
<td>407.4 ± 84.5</td>
<td>403.6 ± 56.4</td>
<td>405.3 ± 59.7</td>
<td>393.7 ± 39.3</td>
</tr>
</tbody>
</table>

sys, peak systolic myocardial velocity; SR sys, peak systolic strain rate; ε sys, peak systolic strain; E’, peak early diastolic myocardial velocity; PST, post-systolic thickening; Time to max ε, time to maximal ε in the hypertrophied basal septum.

**P < 0.01 asymmetric vs. concentric and Friedreich’s ataxia groups.
***P < 0.001 controls vs. other three groups.
****P < 0.01 asymmetric vs. other three groups.
*****P < 0.01 controls vs. asymmetric.

Relationship between type of hypertrophy and post-systolic shortening

A strong correlation was found between the septal to infero-lateral wall thickness ratio and the magnitude of post-systolic shortening in the basal septum \( r = 0.68; \ P < 0.01 \). Only one patient with concentric HCM and a septal to infero-lateral wall thickness = 1.25 had post-systolic shortening index ≥30%. A higher \( E’/E \) had a significant correlation with an increased post-systolic shortening index \( r = 0.59, \ P < 0.01 \). All patients \( n = 13 \) with post-systolic shortening index >30% had an \( E’/E \) ratio >15. In 12 patients (44%) with asymmetric septal HCM, there was systolic lengthening. Only one patient with concentric HCM and no patients in the other two groups had systolic lengthening.

Discussion

Our study shows that radial and longitudinal systolic myocardial deformations are reduced in the three forms of paediatric HCM studied. This reduction is uniformly distributed in all myocardial segments in patients with concentric HCM irrespective of whether HCM results from isolated (sarcomeric) or secondary (non-sarcomeric) HCM. On the other hand, patients with asymmetric septal HCM show an inhomogeneous reduction in deformation in the radial and longitudinal directions with predominant involvement of the more hypertrophied basal septum. Patients with asymmetric septal HCM also demonstrate increased post-systolic shortening persisting after aortic valve closure and prolonged time to maximal ε in the hypertrophied basal septum. This indicates the presence of inhomogeneities in regional myocardial function.

Previous studies with tissue Doppler imaging have shown abnormal diastolic function in patients with HCM both in the hypertrophied and non-hypertrophied myocardial segments.\(^{19,20}\) However, as HCM is a disease with marked regional differences in myocardial thickness and function, the use of parameters that reflect regional myocardial function may give additional information. Regional myocardial function can be quantified with several imaging techniques, including radionuclide imaging, magnetic resonance tagging, and tissue Doppler imaging. Experimental and magnetic resonance tagging studies have shown myocardial deformation is also reduced in patients with HCM mainly in the interventricular septum.\(^{21,22}\) Our study confirms these data and shows that systolic radial and longitudinal myocardial deformations are reduced in all myocardial segments investigated, in both isolated and secondary HCM regardless of whether HCM is caused by mutations in genes encoding for sarcomeric or non-sarcomeric proteins. This reduction is more prominent in myocardial segments with the greatest degree of hypertrophy as seen in the basal septum in patients with asymmetric septal HCM. This suggests that mutations in genes encoding for sarcomeric proteins (isolated HCM) or for proteins involved in mitochondrial...
metabolism (Freidreich’s ataxia) lead to cardiac myocyte dysfunction which prompts secondary hypertrophy.

Post-systolic shortening has been used as a marker for regional dysfunction in myocardial ischaemia. Post-systolic shortening has also been found in patients with asymmetric HCM. In our study, post-systolic shortening was significantly more pronounced and associated with reduced systolic deformation in patients with asymmetric HCM mainly in the basal (hypertrophied) septum. This indicates that there is regional non-uniformity in myocardial function in patients with asymmetric HCM with the more hypertrophied myocardial segments exhibiting the most delayed shortening. In contrast, the patients with both forms of concentric HCM as well as the control subjects did not have a significant increase in post-systolic shortening in any of the myocardial segments investigated. This also suggests that inhomogeneities in myocardial thickness and deformation are needed to result in increased post-systolic shortening. This suggests that increased post-systolic shortening is secondary to tethering effects from adjacent more normally contracting myocardial segments that start to lengthen after aortic valve closure, whereas the abnormally thickened and dysfunctional myocardial segments are still shortening after aortic valve closure. We also found a correlation between post-systolic shortening and a higher $E/E'$ ratio which is a parameter for increased LV filling pressures. This suggests that post-systolic shortening is associated with delayed myocardial relaxation and impaired LV diastolic filling. This relationship needs to be further investigated.

**Study limitations**

We were not able to enrol patients with other forms of HCM such as mitochondrial disease or Noonan syndrome due to the rarity of these disorders. Therefore, our findings cannot be extrapolated to these conditions. Second, the cross-sectional nature of our study prevents us from drawing any conclusions on the prognostic significance of our findings. Third, we studied myocardial deformation only in the radial and longitudinal directions. The analysis of circumferential myocardial deformation would have provided additional information on the third component of myocardial deformation.
Conclusions

Myocardial deformation is abnormal in all forms of paediatric HCM. This reduction is uniformly distributed in all myocardial segments in patients with concentric HCM irrespective of whether HCM results from isolated (sarcomeric) or secondary (non-sarcomeric) HCM. Myocardial deformation is more reduced and associated with post-systolic shortening in the more hypertrophied basal septum in patients with asymmetric septal HCM. Our findings suggest the pattern of hypertrophy influences myocardial deformation more than the cause of HCM.

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Conflict of interest: none declared.

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