CLINICAL RESEARCH

Relation between left ventricular outflow tract obstruction and left ventricular shape in patients with hypertrophic cardiomyopathy: A cardiac magnetic resonance imaging study

Relation entre la géométrie ventriculaire gauche et l’obstruction intraventriculaire gauche dans la cardiomyopathie hypertrophique: une étude par IRM

Romain Martin\textsuperscript{a,b}, Olivier Laires\textsuperscript{a,b,c,d,\ast}, Nicolas Boudou\textsuperscript{a}, Simon Méjean\textsuperscript{a,b}, Thibault Lhermusier\textsuperscript{a,e}, Nicolas Dumontel\textsuperscript{a}, Matthieu Berry\textsuperscript{a,b,d}, Thomas Cognet\textsuperscript{a,b,c}, Pierre Massabau\textsuperscript{a,b}, Meyer Elbaz\textsuperscript{a,d}, Hervé Rousseau\textsuperscript{d,f}, Michel Galinier\textsuperscript{a,b,d}, Didier Carrié\textsuperscript{a,b,e}

\textsuperscript{a} Department of Cardiology, Rangueil University Hospital, 1, avenue Jean-Poulhès, TSA 50032, 31059 Toulouse cedex 9, France
\textsuperscript{b} Cardiac Imaging Center, University Hospital of Toulouse, Toulouse, France
\textsuperscript{c} Department of Nuclear Medicine, University Hospital of Toulouse, Toulouse, France
\textsuperscript{d} Rangueil Medical School, Toulouse, France
\textsuperscript{e} Purpan Medical School, University of Toulouse, Toulouse, France
\textsuperscript{f} Department of Radiology, Rangueil University Hospital, Toulouse, France

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Abbreviations: CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVARa, left ventricular--aortic root angle; LVMa, left ventricular--mitral angle; MPMa, mitral papillary muscles angle; MRI, magnetic resonance imaging; SD, standard deviation.

\ast Corresponding author. Department of Cardiology, Rangueil University Hospital, 1, avenue Jean-Poulhès, TSA 50032, 31059 Toulouse cedex 9, France. Fax: +33 5 61 32 27 54.
E-mail addresses: lairez@gmail.com, olivier.lairez@gmail.com (O. Laires).

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LV outflow tract obstruction and LV shape in hypertrophic cardiomyopathy

Background

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disease with a prevalence of 1/500 [1] and a heterogeneous phenotype. Left ventricular (LV) outflow tract obstruction is of great concern in the exploration and management of HCM because of the association with poor outcome and symptoms [2]. Mechanisms that underlie the obstruction are complex and require special LV hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve. After several years dedicated to the description of abnormal myocardium, including LV hypertrophy and LV outflow tract, the emergence of new imaging techniques now allows the role of the mitral apparatus in the genesis of LV outflow tract obstruction to be highlighted [3–8]. Abnormalities of the mitral valve have previously been described, including increased mitral leaflet areas, decreased mobility of the posterior mitral leaflet, increased numbers and mass of papillary muscles and abnormal positions of papillary muscles [3–8]. Providing a good contrast and a high spatial resolution, cardiac magnetic resonance (CMR) imaging allows a precise assessment of LV geometry and mitral apparatus [9,10]. The purpose of our work was to study the relation between left ventricular shape, mitral valve angle and left ventricular outflow tract obstruction at rest using CMR.
Methods

Sample

We retrospectively studied 44 consecutive patients with HCM who underwent CMR between January 2006 and February 2012 in the Cardiac Imaging Centre at Rangueil University Hospital, Toulouse, France. The clinical diagnosis of HCM was based on the demonstration by bi-dimensional echocardiography of a non-dilated and hypertrophied left ventricle (maximum left wall thickness ≥ 15 mm) in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy [11–13]. During the same period, 15 control subjects without cardiomyopathy were retrospectively recruited from consecutive referrals to our Cardiac Imaging Centre for persantin CMR to detect silent myocardial ischaemia. Any patients with clinical evidence of coronary artery disease were excluded, including patients with a clinical history and typical electrocardiogram associated with biochemical, angiographic or CMR evidence of previous myocardial infarction. Patients with a positive stress magnetic resonance imaging (MRI) test were also excluded. Demographic data, cardiovascular risk factors and medications were extracted from medical records.

Echocardiography

Transthoracic bi-dimensional echocardiography was performed using the commercially available system Philips IE33 (Philips Healthcare, Best, The Netherlands). The peak instantaneous LV outflow tract gradient was measured at rest with continuous-wave Doppler in the apical five-chamber view with the simplified Bernoulli equation. Obstructive HCM was defined by a peak instantaneous LV outflow gradient greater or equal to 30 mmHg at rest [2,14].

Cardiovascular magnetic resonance

CMR (Siemens Avanto 1.5-T, Erlangen, Germany, n = 25 and Philips Intera 1.5-T, Eindhoven, The Netherlands, n = 19) was performed using cine steady-state free precession breath-hold sequences (echo time [TE]/repetition time [TR] = 1.5/25 ms, flip angle 80°, matrix 192 × 156, field of view = 350 × 350 mm, temporal resolution 35 ms for the Siemens scan; and TE/TR = 1.5/3.5 ms, flip angle 60°, matrix 160 × 146, field of view = 350 × 350 mm, temporal resolution 35 ms for the Philips scan) in four-chamber, long-axis and LV outflow track views; and sequential 8-mm short-axis views (no gap) from the atroventricular ring to the apex. The late gadolinium enhancement images were acquired 10 minutes after intravenous gadolinium-diethylenetriamine pentaacetic acid (0.2 mmol/kg) in identical short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320–440 ms). In all patients, imaging was repeated for each short-axis image in two separate phase-encoding directions to exclude artefacts. Late gadolinium enhancement was assessed visually and was only deemed to be present when the area of signal enhancement could be seen in a cross-cut long-axis image by the independent observers.

Ventricular volumes and function were measured using standard techniques and analysed using semi-automated software (Argus software, Siemens, Erlangen, Germany and ViewForum software, Philips, Eindhoven, The Netherlands). LV mass was indexed to body surface area. LV shape and mitral angles were measured in end-diastole at rest using the open source software Osirix (http://www.osirix-viewer.com). The LV-mitral angle (LVMa) was defined as the angle between the LV axis and the mitral annulus in the four-chamber view (Fig. 1A, left panel). The mitral papillary muscles angle (MPMa) was defined as the angle between the middle of the base of both mitral papillary muscles and the centre of the left ventricle in the LV short-axis view (Fig. 1B, left panel). As previously described, the LV-aortic root angle (LVArA) was defined as the angle between the LV inflow and outflow tract by tracing a line between the apex and the middle of the mitral annulus and a line passing through the long axis of the aortic root in the three-chamber view [15] (Fig. 1C, left panel).

Statistical analysis

Baseline characteristics are summarized using means and standard deviations (SDs) for continuous variables, and numbers and percentages for categorical variables. Associations between categorical variables were investigated using the Fisher’s exact test; and the mean values of continuous variables were compared using a Mann-Whitney test. Spearman’s correlation co-efficient was used to assess the association between angles and peak instantaneous LV outflow tract gradients. Reproducibility was assessed in 10 randomly selected patients and expressed as the absolute difference between two paired measurements divided by their average. The statistical difference was considered to be significant when P-values were < 0.05. All analyses were performed using Statview (SAS Institute Inc., Version 5).

Results

Population

Among the 44 patients with HCM explored by CMR imaging between January 2006 and February 2012, 24 (55%) were men and the mean age was 55 ± 15 years. Of these 44 patients, 29 (66%) had LV outflow tract obstruction at rest (mean peak instantaneous LV outflow tract gradient 62 ± 57 mmHg). All of the patients with obstructive HCM had a systolic anterior motion of the mitral valve. Among the 15 patients without LV outflow tract obstruction, two (5%) patients had peak instantaneous LV outflow tract gradients of 12 and 18 mmHg at rest. The other patients without LV outflow tract obstruction had no gradient at rest. The mean indexed LV mass of all 44 patients was 95 ± 27 g/m². Thirty-four patients (77%) with HCM had symptoms: 21 (48%) and 13 (30%) of patients were New York Heart Association (NYHA) stages II and III, respectively. HCM patients and control subject characteristics are shown in Table 1.
LV outflow tract obstruction and LV shape in hypertrophic cardiomyopathy

Figure 1. Right: cardiac magnetic resonance (CMR) images of the (A) angle between the left ventricle and the mitral annulus plane (LVMa), (B) interpapillary muscle angle (MPMa) and (C) angle between the left ventricle and the aortic root (LVARa). Left: box-whisker plots of the (A) angle between the left ventricle and the mitral annulus plane (LVMa), (B) interpapillary muscle angle (MPMa) and (C) angle between the left ventricle and the aortic root (LVARa) in control subjects and patients with non-obstructive hypertrophic cardiomyopathy (NOHCM) and obstructive hypertrophic cardiomyopathy (OHCM). The boxes show the first and third percentiles; the line shows the median; the whiskers show 95 percentiles and the circles are outliers. *P < 0.05 vs NOHCM. **P < 0.01 vs NOHCM; ***P < 0.001 vs non-obstructive HCM; †P < 0.05 vs controls; ††P < 0.01 vs controls; †††P < 0.001 vs controls.

Relation between LV shape and LV outflow tract obstruction

LVMa, MPMa and LVARa for control subjects, non-obstructive and obstructive HCM are shown in Table 2 and Fig. 1. LVMa was significantly smaller in patients with obstructive HCM than in patients with non-obstructive HCM or the control subjects (80 ± 5° vs 87 ± 7° [P = 0.0002] and 89 ± 2° [P < 0.0001], respectively). There was no significant difference for LVMa between patients with non-obstructive HCM and the control subjects (P = 0.33). Patients with non-obstructive HCM had greater LVARa than patients with obstructive HCM or control subjects (139 ± 6° vs 135 ± 7° [P = 0.04] and 133 ± 7° [P = 0.03], respectively). There was no significant difference for LVARa between patients with obstructive HCM and control subjects (P = 0.6).

Considering the overall population of patients with HCM, there were significant inverse correlations between the peak instantaneous LV outflow tract gradient at rest and LVMa and MPMa, but not with LVARa (Fig. 2).

The intra- and inter-observer variabilities of the angle measurements, as shown in Table 3, were good.
Table 1  Healthy control subjects’ and hypertrophic cardiomyopathy (HCM) patients’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 15)</th>
<th>Non-obstructive HCM (n = 15)</th>
<th>Obstructive HCM (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 14</td>
<td>50 ± 17</td>
<td>57 ± 14</td>
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<tr>
<td>Men</td>
<td>13 (87)</td>
<td>9 (60)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26 ± 3</td>
<td>26 ± 4</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.1 ± 0.4</td>
<td>1.8 ± 1.0</td>
<td>2.2 ± 0.6†††</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (87)</td>
<td>7 (47)†</td>
<td>3 (10)†††,***</td>
</tr>
<tr>
<td>II</td>
<td>2 (13)</td>
<td>3 (20)</td>
<td>18 (62)†</td>
</tr>
<tr>
<td>III/IV</td>
<td>0</td>
<td>5 (33)††</td>
<td>8 (28)†</td>
</tr>
<tr>
<td>Family history of HCM</td>
<td>0</td>
<td>5 (33)††</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Maximum LV thickness (mm)</td>
<td>10 ± 2</td>
<td>21 ± 7†††</td>
<td>21 ± 4††</td>
</tr>
<tr>
<td>Indexed LV mass (g/m²)</td>
<td>62 ± 17</td>
<td>92 ± 18†††</td>
<td>97 ± 31†††</td>
</tr>
<tr>
<td>Late gadolinium enhancement</td>
<td>0</td>
<td>14 (93)†††</td>
<td>12 (41)†††,***</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>62 ± 10</td>
<td>63 ± 7</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking habit</td>
<td>1 (7)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (40)</td>
<td>3 (20)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (7)</td>
<td>3 (20)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>3 (20)</td>
<td>4 (27)</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diuretic</td>
<td>3 (20)</td>
<td>6 (40)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>5 (67)</td>
<td>4 (27)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3 (20)</td>
<td>11 (73)†††</td>
<td>28 (97)†††,***</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1 (7)</td>
<td>2 (13)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) or mean ± standard deviation. ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; HCM: hypertrophic cardiomyopathy; LV: left ventricular; LV EF: left ventricular ejection fraction; NYHA: New York Heart Association.
† P < 0.05 vs non-obstructive HCM.
** P < 0.01.
*** P < 0.001 vs non-obstructive HCM.
†† P < 0.05 vs controls.
††† P < 0.01 vs controls.
†††† P < 0.001 vs controls.

Table 2  LVM-mitral angle, mitral papillary muscles angle and LV-aortic root angle for healthy control subjects and non-obstructive and obstructive hypertrophic cardiomyopathy (HCM) patients.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 15)</th>
<th>Non-obstructive HCM (n = 15)</th>
<th>Obstructive HCM (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMa (°)</td>
<td>89 ± 2</td>
<td>87 ± 7</td>
<td>80 ± 5†††,***</td>
</tr>
<tr>
<td>MPMa (°)</td>
<td>118 ± 10</td>
<td>136 ± 17†</td>
<td>123 ± 16**</td>
</tr>
<tr>
<td>LVARa (°)</td>
<td>133 ± 7</td>
<td>139 ± 6†</td>
<td>135 ± 7</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; HCM: hypertrophic cardiomyopathy; LV: left ventricular; LVARa: LV-aortic root angle; LVEF: left ventricular ejection fraction; LVMa: LV-mitral angle; MPMa: mitral papillary muscles angle; NYHA: New York Heart Association.
† P < 0.05 vs non-obstructive HCM.
** P < 0.01 vs non-obstructive HCM.
*** P < 0.001 vs non-obstructive HCM.
†† P < 0.05 vs controls.
††† P < 0.01 vs controls.
†††† P < 0.001 vs controls.
relation between LV shape and late gadolinium enhancement

Considering patients with HCM, there was no difference in LV shape according to the presence or absence of late gadolinium enhancement, with respective values of $84^\circ$ and $80^\circ$ ($P = 0.24$) for LVMa, $128^\circ$ and $126^\circ$ ($P = 0.75$) for MPMa, and $136^\circ$ and $136^\circ$ ($P = 0.91$) for LVARa.

Discussion

Our study shows that the angle between the mitral annulus plane and the left ventricle is significantly smaller in patients with obstructive HCM than in those with non-obstructive HCM. Furthermore, for the first time, we have shown that there is an inverse correlation between the angle of the mitral annulus plane with the left ventricle and the peak instantaneous LV outflow tract gradient at rest. We have also shown that the presence of late gadolinium enhancement does not impact the LV shape in patients with HCM. This is the first study to prove the existence of a different angle of the mitral annulus plane with the left ventricle between obstructive and non-obstructive HCM. Previous echocardiographic studies have shown abnormalities of anatomy and motion of the mitral valve in obstructive HCM, especially by elongation of mitral leaflets and increased leaflet areas \[3,16-19\]. These results suggest the association of a defect in the coaptation of mitral leaflets and an excess of valvular tissue to generate a systolic anterior motion of the mitral valve and then LV outflow tract obstruction. Recently, Maron et al. confirmed these findings with an MRI study in a large cohort of patients and showed that the elongation of mitral leaflets is the primary phenotypic expression of HCM \[4\]. Their results suggest that mitral valve abnormalities could be the first step of LV outflow tract obstruction in HCM. In our study, we have confirmed the relation between mitral apparatus and LV outflow tract obstruction in showing that the angle between the mitral annulus plane and left ventricle in patients with non-obstructive HCM is the same as for healthy control subjects. In light of previous results from Maron et al. \[4\], our results suggest that LV outflow tract obstruction in patients with HCM is linked with mitral apparatus geometry but not with LV hypertrophy.

The question of the role of papillary muscles in LV outflow tract obstruction in HCM remains unresolved. Several studies have shown that mitral subvalvular structures and particularly papillary muscles are structurally different in patients with obstructive HCM than in healthy controls. An MRI study has described an increase in the number and mass of papillary muscles in HCM patients \[7\]. Previous two- and three-dimensional echocardiography studies showed abnormalities of papillary muscle insertions and mobility in patients with obstructive HCM. These studies showed an anterior displacement of both papillary muscles \[5,19\] with direct insertion of the anteromedial papillary muscle on the anterior mitral leaflet \[3\] compared with patients with non-obstructive HCM. In our study, we have demonstrated that the anatomic insertion of papillary muscles is different in patients with HCM according to the presence of LV outflow obstruction.
tract obstruction at rest. We have also shown that non-obstructive HCM patients have a higher interpapillary angle than obstructive HCM patients and control subjects. Moreover, we found an inverse correlation between MPMa and peak instantaneous LV outflow tract gradient at rest. These results show that increased outflow tract gradient in HCM is accompanied by decreases in MPMa, to values similar to control subjects.

Our results show that, despite the considerable heterogeneity in morphology and genetic substrates that characterize inherited HCM [20], there is a continuous relation between LV shape and LV outflow tract obstruction. We hypothesize that part of non-obstructive HCM is a myocardial disease with LV hypertrophy leading to the modification of papillary muscle insertions with an increase in MPMa, whereas part of obstructive HCM initially includes a mitral valve abnormality with a decrease in LVMa. This hypothesis could explain the high prevalence of late gadolinium enhancement in patients with non-obstructive HCM, whereas apparition of late gadolinium enhancement in patients with obstructive HCM would occur later with myocardial remodelling. Our results did not allow us to definitely find out if the different angulations of mitral valve apparatus contributed to LV outflow obstruction, nor whether LV remodelling induced by increased intraventricular pressure modified the geometry of mitral annulus in obstructive HCM. However, it was reported that part of LV hypertrophy observed in HCM is after-load dependent and reversible after decrease of LV outflow obstruction by alcohol septal ablation [21]. Moreover, the malposition of the papillary muscles and the mitral apparatus has previously been suspected to play a fundamental role in systolic anterior motion of the anterior leaflet of the mitral valve by increasing the leaflet and chordal slack [16,19]. We can hypothesize that geometric changes in mitral apparatus, including mitral annulus orientation, could alter the distribution of tension on mitral leaflets and lead to outflow obstruction.

Finally, we found that LVARa was larger in patients with non-obstructive HCM than in patients with obstructive HCM and control subjects, but no significant correlation between LVARa and peak instantaneous LV outflow tract gradient at rest was found. These findings are different to those previously reported by Kwon et al., who described a smaller LVARa in patients with HCM or hypertensive heart disease than in healthy control subjects [15]. However, as in our study, they reported that LVARa was larger in non-obstructive than obstructive HCM [15]. They also reported inverse correlations between LVARa and maximal LV outflow tract obstruction at rest; age; basal end-diastolic interventricular septal thickness and body surface area [15]. These results show that LVARa is dependent on parameters other than just intramyocardial haemodynamics; and the small size of our population could explain the lack of a correlation between intraventricular obstruction and LVARa. In our sample, there were no differences between obstructive and non-obstructive HCM patients in terms of clinical characteristics, maximum LV thickness and indexed myocardial mass, suggesting that the observed difference probably depends on LV outflow tract obstruction.

Study limitations

It is now well established that exercise echocardiography in hypertrophic cardiomyopathy is an important part of the accurate evaluation of symptomatic patients without LV outflow tract obstruction at rest [13,14]. The effect of exercise on LV outflow obstruction and angles was not tested in our patients and we can suppose that we have underestimated the real impact of LV outflow tract obstruction on LV geometry, which introduces a bias into our classification of HCM. Some patients characterized as non-obstructive HCM on the basis of the absence of obstruction at rest might have an exercise-induced obstruction. This and the small size of our sample have probably increased the variability in our measurements and could explain the overlap in the groups and the lack of a correlation between LVARa and LV outflow tract obstruction. Furthermore, the dynamic nature of LV obstruction, depending on charge conditions and inotropism, could explain the moderated strength of the correlation between angles and peak instantaneous LV outflow gradient. However, despite these limitations, our results clearly demonstrate a difference in LV shape between both entities of HCM. Lastly, we decided to measure angles in end-diastole and we did not study the dynamic changes of mitral apparatus during the cardiac cycle. However, this has recently been claimed, in a three-dimensional echocardiographic study, to have an impact on LV outflow tract obstruction [22].

Potential clinical implications

Better understanding of the pathophysiogenesis of HCM is the first step to improving the care strategy. The anatomy of the mitral apparatus should be integrated into the global comprehension of the complex and probably multifactorial pathophysiogenesis of the systolic anterior motion of the mitral valve and LV outflow tract obstruction in patients with obstructive HCM. The incomplete resolution of LV outflow tract obstruction after surgical myectomy or alcohol septal ablation [23,24], as well as the high incidence of persistent systolic anterior motion of the mitral valve after septal ablation [25], should lead us to reconsider other targets in the therapeutic management of obstructive HCM, especially in the surgical field. Recent descriptions of new surgical techniques and concepts, such as papillary muscle realignment [26], are likely to be very promising axes of research.

Conclusions

Patients with obstructive HCM display smaller LV to mitral plane angles than non-obstructive HCM and healthy control subjects, whereas the insertion angle between the papillary muscles and the LV to aortic root angle are greater in non-obstructive HCM than obstructive HCM and healthy control subjects. These findings highlight the relation between morphological and functional parameters in HCM, within which the mitral valve is probably part of pathophysiogenesis.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References


