Involvement of Right Ventricle in Left Ventricular Hypertrophic Cardiomyopathy: Analysis by Pulsed Doppler Tissue Imaging

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Aims: This study uses pulsed Doppler tissue imaging to analyse right ventricular myocardial function and its interaction with left ventricle in hypertrophic cardiomyopathy involving ventricular septum.

Methods and Results: Thirty-four patients with septal hypertrophic cardiomyopathy and 30 normal subjects, comparable for sex, age, body mass index and heart rate, underwent complete standard Doppler echocardiography and pulsed Doppler tissue imaging of both posterior septum and right ventricular free wall, calculating myocardial velocities and both systolic and diastolic time intervals. Except for peak velocity A, the other Doppler tricuspid inflow measurements were significantly impaired in hypertrophic cardiomyopathy, without changes of tricuspid annular systolic excursion. Right ventricular Doppler tissue imaging showed longer right ventricular myocardial relaxation time in hypertrophic cardiomyopathy than in controls ($P$<$0.00001$), without a significant difference from other myocardial diastolic and systolic measurements. In the overall population, Doppler measurements of right and left ventricular inflow were not significantly associated, while (with the exception of myocardial deceleration time) all the other myocardial systolic and diastolic measurements derived by tissue imaging were directly related to the homologous septal myocardial indexes. In addition, a significant inverse relation was found between septal wall thickness and myocardial relaxation index (right–left myocardial relaxation time/right ventricular relaxation time $\times 100$).

Conclusions: This study shows the usefulness of pulsed Doppler tissue imaging to detect impairment of right ventricular myocardial function and to provide evidence about ventricular interaction in forms of hypertrophic cardiomyopathy which involve interventricular septum.


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Key Words: Doppler tissue imaging; hypertrophic cardiomyopathy; right ventricle; diastole; systolic function.

Introduction

Right ventricular (RV) function is often involved in left ventricular (LV) pathologies as a consequence of a direct injury extension, afterload changes or ventricular interdependence, which is mainly due to the close anatomical association between the two ventricles. This issue is not often explored by non-invasive techniques because of complex RV geometry, which precludes an accurate assessment of RV internal chamber dimensions and their changes during cardiac cycle[1].

Hypertrophic cardiomyopathy (HC) is a primary heart disease usually characterized by increased LV wall thickness and normal or decreased internal cavity dimension[2]. It is reasonable that the right ventricle may participate to the disease due to an extension of myopathic processes or because right and left ventricles share an anatomically hypertrophied interventricular septum. Previous studies showed increased RV wall thickness in a large proportion of patients affected by HC by using magnetic resonance imaging[3] and two-dimensional (2D) echocardiography[4], while RV diastolic dysfunction was observed by Maeda M and co-workers[5] who described impaired RV isovolumic relaxation by biplane RV angiography, and by Suzuki et al.[6] who found

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lower early peak filling rate by magnetic resonance. However, to the best of our knowledge, no information is available about RV myocardial modifications in this pathology.

While standard echocardiography is widely used to assess global LV function in HC, little is known about RV changes under these circumstances. Pulsed wave Doppler tissue imaging (DTI) has been used to analyse myocardial wall motion abnormalities in different cardiac pathologies [7–9] and appears suitable also to assess regional changes associated to HC. On these grounds, the present study was designed to investigate pulsed DTI myocardial properties of RV wall in relation to abnormalities of the interventricular septum and global RV and LV global function.

**Methods**

**Study Population**

Patients with HC considered for the present study were studied between January 1995 and July 1999 at the echocardiographic laboratory of the Cardiology Division of Monaldi Hospital. Diagnosis of HC was confirmed by echocardiographic evidence of hypertrophied interventricular septum without any other disease inducing LV hypertrophy. RV hypertrophy was excluded by 2D measurement of the RV free wall at two different levels (basal, middle and apical) (values at end-diastole < 5 mm). Extent and distribution of hypertrophy was measured in parasternal short-axis view. HC was defined as asymmetric hypertrophy of anterior and posterior septum without involvement of the free lateral wall [10]. Patients taking cardiac drugs (primarily beta-blockers and calcium channel blockers) were withdrawn from therapy at least 48 h before the echocardiogram, according to the rules of our Institutional Committees. Exclusion criteria were: diabetes mellitus, arterial hypertension, coronary artery disease (angina and/or ECG signs of myocardial ischaemia), valvular heart disease, more than second grade of mitral regurgitation, and two because of chronic atrial fibrillation. The final group consisted of 34 patients. Of these, 10 were defined to have obstructive HC based on the evidence of LV outflow tract gradient ≥ 30 mmHg. The control group consisted of 30 healthy volunteers without clinical or echocardiographic evidence of cardiovascular disease.

**Procedures**

Standard Doppler echocardiography and DTI were performed with the subjects in partial left decubitus, by Acuson 128 XP10 ultrasound system (Mountain View, Calif, U.S.A.) equipped with DTI capabilities. A variable frequency phased-array transducer (2.5–3.5–4.0 MHz) was used for 2D, M-mode and Doppler imaging. Doppler echocardiographic and DTI tracings were recorded on VHS videotapes and high fidelity paper strips at a velocity of 150 or 100 mm/s. All the measurements were analysed by two experienced readers, over an average of ≥3 cardiac cycles.

Two-dimensional measurements of septal and lateral wall thickness were obtained at end-diastole in parasternal short-axis view, and integrated by parasternal long-axis and apical views. Endocardial fractional shortening was calculated as LVDD – LVIDs/LVIDd × 100, where LVDd=LV internal end-diastolic diameter and LVIDs=LV internal end-systolic diameter. RV free wall thickness was measured in the apical four-chamber view at basal, middle and apical level. However, we also took into account visual assessment of the sub-costal long-axis view to exclude the hypertrophy of the RV free wall. Tricuspid annular plane systolic excursion (TAPSE) was calculated as index of RV global systolic function by the difference between end-diastolic and end-systolic measurement (in mm) [11]. Pulsed Doppler assessment of LV inflow was performed in the apical four-chamber view, with the sample volume placed at the tips level. The following measurements of global LV diastolic function were determined: peak velocities of E and A wave (m/s) and their ratio, deceleration time of E wave (ms), isovolumic relaxation time (ms), measured as the time interval occurring between the end of systolic output flow and the transtimal E wave onset, by placing pulsed Doppler sample volume between the outflow tract and mitral valve [12]. Transmural inflow was analysed also by Valsalva manoeuvre to detect pseudonormal patterns [13]; during the strain phase of this manoeuvre, according to a lowering preload, both E and A peak velocities decreased in all of the study population, thus showing no evidence of pseudonormalization in patients with HC. Pulsed Doppler RV diastolic indexes were determined in the apical four-chamber view, placing the sample volume at the tips of tricuspid valve; E and A peak velocities (m/s) and their ratio were calculated. Our methods and reproducibility in measuring Doppler indexes have been previously reported [14].

DTI was performed by transducer frequencies of 3.5–4.0 MHz, adjusting the spectral pulsed Doppler signal filters to obtain the Nyquist limit of 15–20 cm/s, and using the minimal optimal gain. In the apical four-chamber view the pulsed Doppler sample volume was subsequently placed in two different regions: the middle interventricular septum and the middle RV free wall. The apical four-chamber view was chosen to obtain quantitative assessment of regional myocardial wall motion almost simultaneously to Doppler RV and LV inflow and to minimize the incidence angle between Doppler beam and longitudinal motion of the left ventricle. Schema of the normal DTI pattern, characterized by a myocardial systolic wave (S_m) and two diastolic waves—early (E_m) and atrial (A_m)—and measurement
methodology are depicted in Figure 1. The following measurements were determined in each region as indexes of regional function: myocardial peak velocity of S_m (m/s), myocardial pre-contraction time (from the onset of electrocardiographic QRS to the beginning of S_m), and contraction time (from the beginning to the end of the S_m wave) (all in ms) as systolic indexes, myocardial early (E_m) and atrial (A_m) peak velocities (m/s), E_m/A_m ratio, deceleration time (DT_m) and relaxation time (RT_m) (ms) – as the time interval occurring between the end of S_m and the onset of E_m – as diastolic measurements. Similar to previously described methods using standard Doppler RV relaxation index, we calculated DTI-derived myocardial relaxation index as RV RT_m = LV RT_m/RV RT_m × 100[15]. Methods and reproducibility of DTI indexes in our laboratory were described in a recent report, the intra- and inter-observer regression coefficients being >0.85 for all the assessed DTI measurements in a population of 16 male subjects[16].

**Statistical Analysis**

All analyses were performed using a commercially-available statistical package. Variables are presented as mean ± 1 standard deviation. The t-test for unpaired data was used to estimate difference between the two selected groups. Linear regression analyses and partial correlation test by Pearson’s method were used to assess univariate relations. Differences were considered significant at $P<0.05$.

**Results**

**Clinical and Echocardiographic Characteristics of the Study Population**

The two groups were comparable for age (40.7 ± 11.9 years in controls and 39.9 ± 16.5 years in HC), body mass index (24.4 ± 2.3 and 24.8 ± 9.0 kg/m$^2$, respectively) and heart rate (70.2 ± 11 and 69.4 ± 8.9 bpm). Echocardiographic analysis comparison of both left and right ventricle is reported in Table 1. LV endocardial fractional shortening was greater in HC ($P<0.001$), while TAPSE was not significantly different between the two groups. Among LV diastolic indexes, peak velocity E/A ratio was lower

**Table 1. Standard Doppler echocardiographic comparison between the two groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>HC</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal wall thickness (mm)</td>
<td>9.1 ± 1.3</td>
<td>20.9 ± 4.0</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>8.1 ± 0.9</td>
<td>8.5 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>49.5 ± 4.4</td>
<td>45.7 ± 5.7</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>32.8 ± 4.3</td>
<td>27.4 ± 6.0</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Endocardial fractional shortening (%)</td>
<td>34.2 ± 4.7</td>
<td>41.2 ± 8.6</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Peak velocity E (m/s)</td>
<td>0.65 ± 0.1</td>
<td>0.70 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Peak velocity A (m/s)</td>
<td>0.48 ± 0.1</td>
<td>0.68 ± 0.2</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Peak velocity E/A ratio</td>
<td>1.30 ± 0.3</td>
<td>1.03 ± 0.4</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>E wave deceleration time (ms)</td>
<td>127.2 ± 21.7</td>
<td>226.7 ± 84.4</td>
<td>$&lt;0.00001$</td>
</tr>
<tr>
<td>Isovolumic relaxation time (ms)</td>
<td>74.9 ± 14.7</td>
<td>85.9 ± 18.8</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV wall thickness (mm)</td>
<td>4.0 ± 0.6</td>
<td>3.9 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>19.6 ± 3.4</td>
<td>18.9 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Peak velocity E (m/s)</td>
<td>0.62 ± 0.1</td>
<td>0.47 ± 0.1</td>
<td>$&lt;0.02$</td>
</tr>
<tr>
<td>Peak velocity A (m/s)</td>
<td>0.46 ± 0.1</td>
<td>0.47 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Peak velocity E/A ratio</td>
<td>1.38 ± 0.3</td>
<td>1.00 ± 0.4</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>E wave deceleration time (ms)</td>
<td>151.2 ± 79.4</td>
<td>251.6 ± 94.9</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>
and both deceleration time and isovolumic relaxation time significantly longer in HC in comparison with controls. With the exception of peak velocity A, all RV diastolic inflow measurements were significantly impaired in patients with HC. No difference of tricuspid inflow indexes was found between patients with HC having or not having LV obstruction.

**DTI Evaluation of Septal and RV Free Wall**

DTI analysis of interventricular septum and RV free wall is summarized in Table 2. At the septal level, myocardial systolic indexes (S, peak, PCT, CT) were not significantly different between the two groups, whereas the majority of myocardial diastolic parameters were impaired in HC. Figure 2 shows normal and prolonged DTI-derived RTm of septal wall in a healthy subject and in a patient with HC, respectively. At the level of RV free wall, again without evidence of changes in myocardial systolic indexes, only RTm was highly significantly longer in HC (P<0.0001), while the other diastolic measurements were similar in the two groups. Figure 3 shows normal and prolonged RTm of the RV free wall in a healthy subject and in a patient with HC, respectively. RV myocardial relaxation index was significantly lower in HC (34.9 ± 21.7%) than in the normal control group (82.6 ± 20.9%) (P<0.0001) (data not shown in table). Note that no difference in DTI RV measurements was found between patients with HC having or not having LV obstruction.

**Relationships between LV and RV Measurements**

The relations between Doppler standard measurements of LV and RV inflow were not significant (r=0.22 for peak E, r=0.20 for peak A, r=-0.10 for peak velocity E/A ratio, r=-0.08 for E-wave deceleration time.

As reported in Table 3, except for myocardial deceleration time, all the other systolic and diastolic myocardial indexes measured by DTI were significantly related one each other. In addition, a significant inverse relation was observed between septal wall thickness and RV myocardial relaxation index in the overall population (Figure 4).

**Discussion**

The present study indicates that in forms of HC which involve interventricular septum: (i) in the absence of RV global systolic dysfunction, the majority of Doppler standard measurements of RV diastolic inflow are impaired showing a pattern of abnormal RV filling; (ii) among DTI diastolic indexes, only RV RTm is largely modified in HC, without evidence of significant changes of myocardial systolic indexes; and (iii) DTI myocardial indexes of the RV free wall are significantly associated with the homologous indexes of interventricular septum, while similar correlations between LV and RV Doppler inflow parameters are not observed.

**RV Inflow in HC**

Despite previous observation about abnormalities of RV filling in HC by using magnetic resonance and invasive RV angiography, little is known about RV tricuspid diastolic inflow by standard Doppler in HC. In a previous report analysing Doppler standard RV inflow of patients with HC, Okamoto et al. described slow deceleration of rapid filling wave, increase in lengthening of atrial contraction and reduction of tricuspid E/A ratio. Similar findings were observed also in the present study, where patients with HC presented with lower tricuspid E/A ratio and longer E-wave deceleration time in comparison to the control group. These data underscore a pattern of RV impaired filling in the forms of HC involving interventricular septum.

**RV DTI Analysis**

To the best of our knowledge, this is the first study to assess RV pulsed DTI patterns in patients affected by HC involving an asymmetrically interventricular septum. In a recent study we had already underscored an impairment of both LV passive diastolic properties and relaxation of hypertrophied septal myocardium, independent of changes of Doppler standard transmitral inflow. The present study confirms septal diastolic dysfunction in HC, since Em/Am ratio, DTm and RTm were significantly impaired at this level. In contrast, among DTI diastolic variables of the RV wall, only RTm was altered (it being significantly longer in comparison with the control group). This result highlights a diastolic asynchronicity involving the RV wall in HC. Why RTm was the only myocardial diastolic parameter to be impaired at the level of the RV free wall needs further investigation. However, it is noteworthy that we found similar alterations in patients with septal HC at the level of LV lateral thin wall where DTm and RTm were longer than in controls, without a significant difference in myocardial diastolic velocities. Interestingly, other reports underlined that RV isovolumic relaxation time measured by standard Doppler is very short or even absent in normal subjects, showing an increasing length in several pathologies involving right ventricle. Similarly, the delay of RV myocardial relaxation in our patients with HC might be explained on the grounds of a direct involvement of RV wall by myopathic process. In the present study we tried to select a homogeneous population by excluding patients with RV hypertrophy but, according to McKenna et al., minor involvement of the RV walls may be definitely ascertained by standard echocardiography only by multiple RV
Figure 2. Normal and prolonged DTI-derived myocardial relaxation time of septal wall in a healthy subject and in a patient with HC (upper and lower panel, respectively). $RT_m =$myocardial relaxation time.
Figure 3. Normal and prolonged DTI-derived myocardial relaxation time of RV free wall in a healthy subject and in a patient with HC (upper and lower panel, respectively). $RT_m =$ myocardial relaxation time.
thickness measurements, since HC is a genetic disorder where the mutations are generally expressed in both ventricles[19]. On the other hand, the lower RV myocardial relaxation index found in HC than that found in the control group suggests that ventricular interaction may be an alternative explanation for the delay in RV myocardial relaxation. Standard Doppler-derived RV relaxation index has been previously used by Larrazet et al.[15] to distinguish the different degree of RV involvement in LV pathologies, showing lower mean values and thus more overt ventricular interaction in patients affected by HC than in those having hypertensive-determined LV hypertrophy.

Table 3. Univariate relations between DTI LV and RV measurements.

<table>
<thead>
<tr>
<th>DTI LV measurement</th>
<th>DTI RV measurement</th>
<th>R Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal S_m peak</td>
<td>RV S_m peak</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal E_m peak</td>
<td>RV E_m peak</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal A_m peak</td>
<td>RV A_m peak</td>
<td>0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal E_m/A_m</td>
<td>RV E_m/A_m</td>
<td>0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal RT_m</td>
<td>RV RT_m</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Septal RT_m</td>
<td>RV RT_m</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 4. Inverse relation between interventricular septal wall thickness (IVST) and myocardial relaxation index in the overall population.

Relationships Between RV and LV Functional Indexes

In our population sample we did not find any relation between RV and LV Doppler diastolic inflow measurements. Previous experiences had reported significant associations between RV and LV inflow diastolic measurements in normal subjects compared to patients affected by arterial hypertension and heart failure[20]. The absence of similar relations in HC of the present study is not completely unexpected, in view of the selection of our population where we excluded higher degree NYHA class patients, who are probably more prone to haemodynamic overloading of right ventricle. These results are consistent with the findings of Maeda et al., who found no relation between RV and LV isovolumic pressure decay measured by catheterization[5].

On the other hand, among DTI RV diastolic parameters, E_m, A_m and the E_m/A_m peak velocity ratio, as well as RT_m were all related to homologous indexes measured at the septal level. In addition, S_m peak velocity of RV wall was also directly associated with septal S_m. All together, these relations support the hypothesis that a ventricular interaction may occurs in this pathology. This assumption is strengthened further by the direct relation we found between septal wall
thickness and RV myocardial relaxation index in the overall population; the higher the septal hypertrophy, the lower the RV relaxation index. Ventricular interdependence has been described in several diseases, appearing to be mainly determined by septal interaction and, to a lesser extent, by pericardial constraint[11] and may be supposed by the same grounds to occur also in HC.

Study Limitations

The main study limitation is the lack of haemodynamic data. An assessment by RV heart catheterization might have provided more accurate information about RV and right atrial pressures. Furthermore, the data of the present study may not be extrapolated to the overall population of HC because of the exclusion of severe heart failure classes, which may have eliminated patients with advanced systolic impairment from statistical analyses. Likewise, the inclusion of more advanced heart failure grades and/or major involvement of RV wall might have underscored an impairment also of other DTI myocardial measurements. However, we intentionally selected relatively asymptomatic patients to examine early changes of DTI regional diastolic properties in HC.

Conclusions

This study confirms the usefulness of standard Doppler to detect the impairment of RV myocardial diastolic function in HC. Although our findings cannot be extended to the whole HC population, the present study also shows the potential role of pulsed DTI in this disease, and suggests the possible occurrence of diastolic ventricular interaction in the early stages of HC. To take into account regional myocardial diastolic involvement of RV free wall, it might be useful to identify subsets of patients with very delayed RV myocardial relaxation, probably more prone to the development of subsequent RV heart failure. Additional longitudinal studies by DTI analyses will be needed to follow the progression from RV myocardial involvement to the impairment of RV chamber indexes in HC.

References