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Right ventricular dysfunction in hypertrophic cardiomyopathy as evidenced by the myocardial performance index

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Abstract

Background: Left ventricular function in hypertrophic cardiomyopathy (HCM) has been extensively studied, whereas right ventricular function is much less explored. The myocardial performance index (MPI) has been shown to be useful in functional assessment of both ventricles. Furthermore, right ventricular MPI was found to be of predictive value in heart failure due to dilated cardiomyopathy and ischemic heart disease. The aim of this study was, therefore, to evaluate the right ventricular MPI in patients with HCM.
Methods: Fifty patients with HCM and 250 healthy controls were studied by conventional Doppler echocardiography and Doppler tissue imaging.
Results: Patients showed increased global, 0.48 (0.15) *vs*. 0.21 (0.14), and regional, 0.71 (0.23) *vs*. 0.55 (0.17), right ventricular MPI, as compared to controls, $p<0.001$. Tricuspid annular plane systolic excursion and peak myocardial systolic velocities were also reduced. Patients with dyspnoea had increased global right ventricular MPI (0.53 *vs*. 0.36, $p<0.05$) as compared to those without dyspnoea.
Conclusion: In the present study, patients with HCM showed evidence of both global and regional right ventricular dysfunction. Previous studies of the right ventricle in HCM have only shown evidence of diastolic dysfunction, contrary to our results, showing impairment of both systolic and diastolic function. This study suggests that HCM should not only be regarded as an isolated disease of the left ventricle, but rather as a biventricular disease. The predictive value of our findings in HCM needs to be assessed in a separate study with special reference to those with and without dyspnoea.

Keywords: Hypertrophic cardiomyopathy; Echocardiography; Myocardial performance index; Doppler tissue imaging

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterised by left and/or right ventricular hypertrophy, with predominant involvement of the interventricular septum in the absence of other causes of hypertrophy, such as hypertension or valvular heart disease [1]. The disease is genotypically and phenotypically heterogeneous, with a wide variety of clinical manifestations, ranging from asymptomatic individuals to severe symptoms and early death [1]. The clinical presentation of patients with HCM includes dyspnoea, chest pain, palpitations and sometimes syncope.

The main clinical problem in HCM was originally considered to be the presence of left ventricular outflow tract obstruction. This phenomenon has been much investigated and its importance questioned. Left ventricular systolic function is not a primary problem and left ventricular (LV) diastolic dysfunction seems to be an early phenomenon explaining much of the symptomatology in the disease. Myocardial performance index of the LV has been assessed in one study only, and was found to be abnormal [2]. The patients may also have a reduced capillary density and coronary flow reserve which is associated with a poor outcome [3,4]. More recently, the importance of right

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Table 1
Clinical characteristics of patients and controls

	Controls (n=250)	HCM (n=50)	p-value
Age (years)	52.3 (18.8)	54.2 (17.3)	ns
Gender (male/female)	127/123	36/14	<0.01
Height (cm)	171 (9)	173 (10)	ns
Weight (kg)	72.7 (13.5)	76.8 (12.8)	ns
BMI	24.7 (3.6)	25.6 (3.6)	ns
SBP (mmHg)	128 (15)	132 (16)	ns
DBP (mmHg)	76 (7)	75 (10)	ns
Heart rate (bpm)	65.9 (10.4)	62.6 (8.9)	ns
LA (mm)	34.4 (4.5)	41.8 (6.3)	<0.001
IVSD (mm)	9.6 (1.5)	18.4 (3.9)	<0.001
LVPWD (mm)	8.6 (1.4)	12.2 (2.1)	<0.001
LVEDD (mm)	49.5 (5.3)	45.4 (4.7)	<0.001
LV EF (%)	63 (8)	63 (8)	ns
RVWT (mm)	3.9 (1.4)	5.6 (1.0)	<0.001
TR grad (mmHg)	21.8 (5.5)	23.7 (7.5)	ns
TAPSE (mm)	25.2 (4.5)	20.5 (4.5)	<0.001
Familial/sporadic HCM	–	16/34	–
LVOT-obstruction [a]	–	9 (18%)	–
Exertional dyspnoea [b]	–	27 (52%)	–
Chest pain	–	12 (24%)	–
Beta-blocker treatment	–	20 (40%)	–
Ca-channel inhibitor	–	9 (16%)	–

Data given as mean (SD). BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; LA = Left atrium; IVSD = Interventricular septum dimension in end diastole; LVPWD = Left ventricular posterior wall dimension in end diastole; LVEDD = Left ventricular diameter in end diastole; LV = Left ventricular; EF = Ejection fraction; RVWT = Right ventricular wall thickness; Tr grad = Tricuspid regurgitation gradient; TAPSE = Tricuspid annular plane systolic excursion. LVOT = Left ventricular outflow tract.

[a] >30 mmHg at rest or >50 mmHg under stress.

[b] NYHA class II or III, none of the patients was in NYHA class IV.

ventricular (RV) function in heart failure caused by dilated cardiomyopathy and ischemic heart disease has been recognized, its function being correlated with exercise tolerance [5] and prognosis [6]. However, echocardiographic evaluation of the RV function has been limited by the complex geometry of the RV. Therefore, non-geometric echocardiographic methods, such as the myocardial performance index [7], tricuspid annular plane systolic excursion (TAPSE) [8] and tricuspid annular peak systolic velocity [9] have been developed.

The recently described myocardial performance index (MPI) is derived from both systolic and diastolic parameters and is calculated as the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT), divided by ejection time (ET). In the studies of the LV, the MPI has been demonstrated to predict morbidity and mortality in dilated cardiomyopathy and cardiac amyloidosis [10,11]. Furthermore, the MPI of the RV has been shown to be a marker of prognostic importance in patients with heart failure and primary pulmonary hypertension [12,13].

Exertional dyspnoea often occurs in spite of normal systolic LV function and is usually attributed to diastolic dysfunction [14–16]. Much less is known about the RV systolic and diastolic functions in HCM, and their relation to LV function. The main aim of this study was to assess RV myocardial function in order to better understand the pathophysiology and symptomatology of the disease, which might have future therapeutic implications.

2. Material and methods

2.1. Patients

Forty-six patients with HCM were initially included in the study as previously described [17]. The family members were offered examination with ECG and echocardiography. Each patient had at least one living first-degree relative >18 years old. In 12 cases, all first-degree relatives were studied and in another 28 cases, as many as possible, but not all were studied. In six cases, no relatives were studied, mainly because they were asymptomatic and did not wish to participate. By these further investigations, 20 more cases with HCM were found. Both sporadic and hereditary cases were represented. Sixteen cases with atrial fibrillation, left or right bundle branch block in the electrocardiogram (ECG) were excluded, in order to avoid alterations in timings of the cardiac cycle due to conduction disturbances. The clinical characteristics of the remaining 50 patients, (age range 16–82 years, 14 females) are described in Table 1. Twenty-seven patients suffered from exertional dyspnoea, NYHA class II or III, none of the patients were in NYHA class IV. Twenty patients were on regular treatment with beta-blockers and 9 patients were treated with calcium channel inhibitors. The diagnosis of HCM was based on echocardiographic presence of left ventricular hypertrophy (LVH) ≥15 mm, in the absence of other known cardiac and non cardiac causes of LVH [18].

2.2. Controls

Control subjects were recruited from Umeå General Population Heart Study as was previously described [19]. A total of 250 subjects (123 females), age range 22–89 years, constituted the control population. The identity of all patients and controls were coded and analyses were made blindly. All subjects gave informed consent for the study, which was approved by the ethics committee of Umeå University.

2.3. Echocardiography

Echocardiographic evaluation was performed with the same protocol for patients and controls, using an Acuson xp/10 or Acuson Sequoia ultrasound system (Acuson, Mountain View, CA, USA), equipped with multiple-frequency (2–3.5 MHz) imaging transducer. An ECG and phonocardiogram (PCG) was simultaneously recorded. All echocardiographic examinations were made according to the recommendations of the American Society of Echocardiography [20]. Measurements were made at end expiration, using the mean value from three cardiac cycles. Right ventricular wall thickness was measured in the basal part of

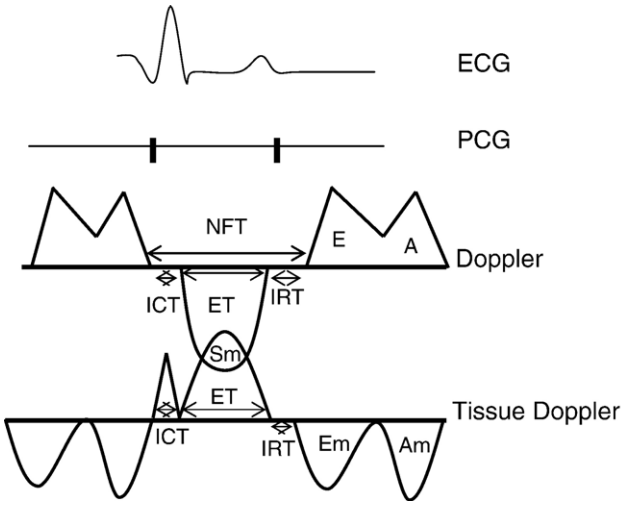

Fig. 1. Measurement of myocardial performance index. Schematic tracing. ECG = Electrocardiogram; PCG = Phonocardiogram; NFT = nonfilling time; ET = ejection time; ICT = Isovolumic contraction time; IRT = Isovolumic relaxation time.

the free RV wall from the apical four-chamber view [21]. M-Mode and Doppler tracings were all recorded at sweep speeds of 50 and 100 mm/s. The data were recorded on videotape and/or magneto optical disks and later analyzed off-line, using the same type of ultrasound machine on which the images were obtained.

The mitral and tricuspid inflow velocity patterns were recorded using pulsed wave Doppler technique with the sample volume positioned at the tip of the mitral and tricuspid valve leaflets in the apical four-chamber view. Pulmonary venous (PV) flow was obtained from the same view with the sample volume placed in the right superior pulmonary vein proximal to the LA guided by colour flow Doppler. The pulmonary flow velocity was recorded from the parasternal short-axis view with the sample volume positioned just below the pulmonary valve. Left ventricular outflow velocity was recorded from the apical five-chamber view with the sample volume positioned just below the aortic valve.

Doppler tissue imaging was performed from the apical four-chamber view, with the sample volume placed at the basal segment of the LV lateral, septal and RV free wall. The wall motion velocity pattern was recorded and expressed as: systolic (S_m), early diastolic (E_m) and late diastolic (A_m) myocardial velocities.

From the same position, systolic atrioventricular plane displacement was measured at the tricuspid free wall annulus (TAPSE), as an index of systolic RV function.

2.4. Measurement of myocardial performance index

Left ventricular MPI was measured from mitral inflow and LV outflow Doppler tracings. In principle, measurements were made as described by Tei et al. [22], except that the PCG was used in the present study for the determination of IRT (Fig. 1). The interval from cessation to onset of mitral inflow was measured, which is equal to the sum of ICT, ET and IRT. Ejection time was derived from the LV outflow Doppler tracing. IRT was measured from the second heart sound on the PCG to onset of the transmitral E-wave. ICT was calculated by subtracting the IRT and ET from the interval between cessation and onset of mitral inflow. The LV MPI was calculated as the sum of ICT and IRT, divided by ET. The corresponding RV MPI was calculated using pulmonary flow velocity and tricuspid inflow velocities instead of LV outflow and mitral inflow.

A regional MPI was measured by using DTI. Unlike the conventional Doppler technique, DTI allows the measurement of ICT, ET and IRT from the same image. The ICT was measured from the end of A_m to onset of S_m. Ejection time was equal to the duration of S_m and IRT was measured from the second heart sound on the PCG to onset of E_m. The regional MPI was then calculated as the sum of ICT and IRT, divided by ET.

2.5. Reproducibility of measurements

Interobserver variability was assessed in 25 study subjects (17 patients and 7 controls) by a second observer, who performed the measurements without knowledge of the results from the first investigator. Variability was calculated as the mean percentage error, derived as the difference between two sets of measurements, divided by the mean of the observations.

2.6. Statistical analyses

Continuous data are expressed as mean value (SD). Analysis of variance (ANOVA) was used to compare differences in continuous variables between patients and controls. Age, gender, heart rate, LVOT-obstruction and body mass index (BMI) were included as co-variates in the analyses of all the echocardiographic parameters. The effect of pharmacological treatment with a beta-blocker or a

Table 2
Characteristics of left atrial and ventricular filling

	Controls (n=250)	HCM (n=50)	p-value
Transmitral E (cm/s)	62 (16)	77 (18)	<0.001
Transmitral A (cm/s)	53 (18)	64 (25)	<0.01
E/A ratio	1.3 (0.6)	1.4 (0.6)	ns
IRT (ms)	66 (23)	89 (21)	<0.001
E deceleration time (ms)	184 (52)	202 (56)	<0.05
E/E_m	4.4 (1.7)	7.2 (2.5)	<0.001
Pulmonary venous flow			
Peak systolic velocity (cm/s)	55 (13)	58 (15)	ns
Peak diastolic velocity (cm/s)	45 (13)	49 (13)	ns
Peak atrial velocity (cm/s)	29 (10)	30 (13)	ns

Data given as mean (SD). E = Early diastolic filling; A = Late diastolic filling; IRT = Isovolumic relaxation time; E_m = Early diastolic LV lateral myocardial velocity.

Table 3
Measurements from conventional Doppler and tissue Doppler imaging

	Controls ($n=250$)	HCM-patients ($n=50$)	p-value
Conventional Doppler			
Left ventricle			
ICT (ms)	44 (39)	76 (50)	<0.001
ET (ms)	316 (26)	300 (30)	<0.001
IRT (ms)	66 (23)	89 (21)	<0.001
(ICT+IRT)/ET	0.36 (0.13)	0.55 (0.19)	<0.001
Right ventricle			
ICT (ms)	35 (41)	91 (39)	<0.001
ET (ms)	332 (33)	306 (27)	<0.001
IRT (ms)	31 (16)	56 (24)	<0.001
(ICT+IRT)/ET	0.21 (0.14)	0.48 (0.15)	<0.001
Tissue Doppler imaging			
LV lateral			
ICT (ms)	96 (26)	95 (32)	ns
ET (ms)	266 (33)	277 (27)	ns
IRT (ms)	66 (25)	83 (21)	<0.001
(ICT+IRT)/ET	0.61 (0.17)	0.65 (0.19)	ns
Septal			
ICT (ms)	93 (22)	84 (22)	<0.05
ET (ms)	262 (35)	263 (41)	ns
IRT (ms)	77 (28)	104 (26)	<0.001
(ICT+IRT)/ET	0.66 (0.18)	0.73 (0.19)	<0.05
RV free wall			
ICT (ms)	91 (26)	95 (23)	ns
ET (ms)	265 (35)	261 (47)	ns
IRT (ms)	53 (27)	84 (28)	<0.001
(ICT+IRT)/ET	0.55 (0.17)	0.71 (0.23)	<0.001
S_m, (cm/s)	14.8 (6.1)	11.9 (3.7)	<0.01

Data given as mean (SD). ICT = Isovolumic contraction time; ET = Ejection time; IRT = Isovolumic relaxation time; S_m = Systolic myocardial velocity.

calcium channel inhibitor was assessed by ANOVA, comparing the treated and non-treated patient groups. A nonparametric chi-square test was used when appropriate. The level of statistical significance was defined as a two-tailed p value <0.05.

3. Results

The clinical and basic echocardiographic characteristics of patients and controls are summarized in Tables 1 and 2. Compared to controls, the patients showed significantly increased LV and RV wall thicknesses. Left ventricular ejection fraction and mitral E/A ratio were similar in patients and controls, while early mitral deceleration time and IRT were significantly prolonged in patients. A significantly elevated ratio between the Doppler transmitral E velocity and E_m (E/E_m) was found in patients, as well as a reduced TAPSE. Four patients had a TAPSE of 12–14 mm, 12 patients had 15–19 mm, 22 patients had 20–24 mm and 12 patients had a TAPSE ≥ 25 mm.

From conventional Doppler measurements, global RV and LV myocardial performance indices were found to be significantly higher in the patient group as compared to controls (Table 3). In both ventricles, ICT and IRT were significantly prolonged in the patient group, whereas ET was decreased. Patients being symptomatic with dyspnoea (NYHA class II or III) showed an increase in global RV MPI compared to those without dyspnoea (MPI 0.53 *vs.* 0.36, $p<0.05$), but there was no such correlation between dyspnoea and TAPSE, the tricuspid regurgitation gradient, E/E_m, global or regional LV MPI (p-values; 0.28–0.98, data not shown). A tricuspid regurgitation gradient was measurable in 29 patients, but was not significantly elevated compared to the controls (Table 1). Treatment of HCM patients with a beta-blocker ($n=20$) was associated with a significantly lower heart rate (58 vs. 65 beats/min, $p>0.05$). To evaluate the effects of pharmacological treatment, patients treated with a beta-blocker or a calcium channel inhibitor were compared to non treated patients and there were no significant differences between the groups for the following parameters; global LV MPI, regional LV MPI, global RV MPI, regional RV MPI, TAPSE, E/E_m, S_m (p-values; 0.32–0.94, data not shown).

3.1. Tissue Doppler measurements

Regional MPI was elevated in the patients at the septal and RV free wall sites, compared to controls (Table 3). At the LV lateral site, there was also a tendency towards an elevated MPI in patients, although not statistically significant. The tricuspid annular peak systolic velocity was significantly reduced in patients, compared to controls. Patients with dyspnoea did not have a significantly different regional MPI compared to patients without dyspnoea.

3.2. Reproducibility and statistics

Interobserver variability for measurements from conventional Doppler (ET, IRT and the interval from cessation to onset of mitral/tricuspid inflow) and Doppler tissue imaging (ICT, ET and IRT) ranged from 0.8% to 12.6%.

4. Discussion

Right ventricular function has gained increasing attention in evaluating patients with heart failure and has been shown to be of clinical importance both in terms of morbidity and mortality. Right ventricular function is difficult to assess due to complex RV anatomy and geometry. By the advent of non-geometric indices of cardiac function, this is now feasible. Such indices can assess both LV and RV function where a high MPI indicates decreased myocardial function. MPI has been shown to be a useful prognostic marker in other cardiac diseases [10,11,13].

4.1. Right ventricular dysfunction

This study demonstrates the presence of both global and regional RV dysfunction in HCM. Estimation of global RV function showed a reduced TAPSE of <20 mm in 16 patients, of which 4 were <15 mm, but none of the subjects

had severe RV dysfunction (TAPSE < 12 mm). Examination with conventional Doppler showed evidence of altered systolic and diastolic global function, resulting in an increased MPI. Several studies have reported that systolic and diastolic time intervals are closely related to LV systolic and diastolic function [23–25]. Indeed, it has been shown that a high MPI is an early sign of RV dysfunction in cardiac amyloidosis [26].

Interestingly, patients with exertional dyspnoea showed an increased global RV MPI compared to patients without dyspnoea. There was, however, no correlation between dyspnoea and some other markers of RV or LV function (TAPSE, E/E_m, global LV MPI or regional TDI derived MPI), which emphasizes the importance of functional studies of both ventricles in patients with HCM. The present study did not include a longitudinal follow-up in order to assess the possible long-term clinical consequences associated with an increased RV MPI. This issue has been addressed in patients with heart failure caused by dilated cardiomyopathy or ischemic heart disease, where it was found that RV MPI was an independent predictor of event-free survival and could be used as a tool for risk stratification [12]. The findings of the present study suggest that the RV function should be studied further in patients with HCM, in order to elucidate the potential prognostic and therapeutic implications of an impaired RV function.

Isovolumic contraction time being prolonged in global Doppler measurements, but normal in DTI is explained by DTI being more load independent, whereas the transmitral and transtricuspid flows are affected by the loading conditions. In an invasive study, it was shown that the transmitral A wave duration was shortened in the presence of significantly elevated end diastolic LV pressures [27]. Increased filling pressures in HCM [28–30], might well explain a shortened transmitral A wave duration and contribute to a prolongation of ICT.

4.2. Comparison with previous studies

In the present study we show both systolic and diastolic RV dysfunction in HCM. Previous echocardiographic studies have not demonstrated systolic RV dysfunction [31,32]. Those investigators measured RV systolic function by the use of TAPSE, but the normal values for TAPSE reported were considerably lower (≈19 mm) than in other studies (≈25 mm) [33–35] and the numbers of controls were smaller than in the present study. Right ventricular diastolic abnormalities in our study are in concordance with other studies [31,36].

Right ventricular hypertrophy in HCM has previously been demonstrated by echocardiography [21] and is in concordance with a study of microanatomy that showed presence of myocardial disarray in all parts of the LV, as well as in the RV [37]. Interdependence of the two chambers has been extensively discussed. As left and right ventricular dysfunction in most cases of HCM are of the same order of magnitude, RV dysfunction is suggested mainly to be a primary phenomenon. Thus, RV dysfunction may be caused by the direct involvement of the myopathic process in the RV wall. Furthermore, the fact that the HCM group did not have elevated tricuspid regurgitation gradients compared to controls could also support the hypothesis of a significant primary RV pathology, instead of RV dysfunction being mainly a secondary phenomenon to elevated LV filling pressures. However, in cases of severe LV dysfunction, RV function might be affected by an interdependence of the hypertrophied LV, in particular the interventricular septum, which is shared by both ventricles [38]. In the present study, an elevated ratio between the Doppler transmitral E velocity and E_m was found, which has been shown to correlate with an increase in LV end diastolic pressure [39]. The finding indicates slightly increased LV filling pressures in HCM, which might in some cases contribute to the RV dysfunction.

In the present study, a phonocardiogram (PCG) was used to determine the timings in the cardiac cycle. This method has usually not been applied in other echocardiographic studies, but it is easy to use and allows us to accurately define systole and diastole, thus both systolic and diastolic time intervals can be calculated.

4.3. Left ventricular dysfunction

Hypertrophic cardiomyopathy has mainly been regarded as a disease of the LV. It was therefore not surprising to find signs of impaired LV function in this study. This was evidenced by an elevation of the global LV MPI. The regional LV function showed a significant elevation of MPI in the septum, which is usually the most hypertrophied part of the LV in HCM.

4.4. Limitations

Patients were investigated under basal conditions, at rest, while symptoms of exertional dyspnoea are present during physical activity. It may therefore be difficult to correlate echocardiographic findings at rest to symptoms that appear during physical activity. It is possible that echocardiographic examination during exercise would be more informative. The RV free wall thickness can be assessed from the apical, parasternal long-axis and subcostal views. In our experience, the rate of acquiring good quality images of the RV is higher from the apical view, compared to the subcostal view. Therefore, the apical four chamber view was used in this study, as described by McKenna et al. [21], although recent guidelines from the American Society of Echocardiography suggest that measurements from the subcostal view will result in less variation [40].

5. Conclusion

In the present study, patients with HCM showed evidence of both global and regional right ventricular dysfunction.

Both systolic and diastolic RV functions were impaired, contrary to previous studies, that have only shown evidence of diastolic RV dysfunction in HCM. This study suggests that HCM should not only be regarded as an isolated disease of the left ventricle, but rather as a biventricular disease. However, this observation needs to be confirmed by further studies. The predictive clinical value of our findings in HCM needs to be assessed in a separate study with special reference to those with and without dyspnoea.

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