ORIGINAL ARTICLE

Prognostic value of intra-left ventricular electromechanical asynchrony in patients with mild hypertrophic cardiomyopathy compared with power athletes

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Objectives: We sought to assess the indexes of myocardial activation delay, using Doppler myocardial imaging (DMI), as potential diagnostic tools and predictors of cardiac events in patients with hypertrophic cardiomyopathy (HCM) compared with power athletes.

Background: the distribution and magnitude of left ventricular (LV) hypertrophy are not uniform in patients with HCM, which results in heterogeneity of regional LV systolic function.

Methods: The study population comprised 70 young patients with HCM (mean (SD) age 29.4 (5.9) years) with mild septal hypertrophy (15–19 mm) and 85 age and sex matched athletes with septal thickness >12 mm, followed up for 44.4 (10.8) months. Using pulsed DMI, myocardial peak velocities, systolic time intervals, and myocardial intraventricular and interventricular systolic delays were measured in six different basal myocardial segments.

Results: DMI analysis showed in HCM lower myocardial both systolic and early diastolic peak velocities of all the segments. Patients with HCM also showed significant interventricular and intraventricular delay ($p < 0.0001$), whereas athletes showed homogeneous systolic activation of the ventricular walls. During the follow up, seven sudden deaths occurred in the HCM group, while no cardiovascular event was observed in the group of athletes. In patients with HCM, intraventricular delay on DMI was the most powerful independent predictor of sudden cardiac death ($p < 0.0001$). An intraventricular delay >45 ms identified with high sensitivity and specificity patients with HCM at higher risk of ventricular tachycardia and cardiac events (test accuracy 90.6%).

Conclusions: DMI may be a valid supporting tool for the differential diagnosis between HCM and "athlete's heart". In patients with HCM, DMI indexes of intraventricular delay may provide additional information for selecting subgroups of patients with HCM at increased risk of ventricular arrhythmias and sudden cardiac death at follow up. Accordingly, such patients may benefit from early intensive treatment and survey.

Miniabstract: Doppler myocardial imaging may represent a valid supporting tool for the differential diagnosis between mild hypertrophic cardiomyopathy (HCM) and "athlete's heart". In patients with HCM, DMI indexes of intraventricular delay may provide additional information for selecting subgroups of patients with HCM at increased risk of ventricular arrhythmias and sudden cardiac death at follow up.

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Hypertrophic cardiomyopathy (HCM) is a primary heart disease characterised by a disorganised myocardial architecture, chaotic alignment of myofibres, and areas of scarring resulting from myocyte death and repair.^{1–5} It is well known that the distribution and magnitude of left ventricular (LV) hypertrophy are not uniform in patients with HCM, which results in regional heterogeneity of both LV and right ventricular (RV) systolic and diastolic function.^{6–8} As HCM is characterised by markedly variable clinical manifestations and morphological and haemodynamic abnormalities, defining reliable clinical non-invasive markers for the diagnosis and early identification of high risk subgroups, especially in young patients with mild septal hypertrophy, remains a challenge.

Mildly increased LV wall thicknesses due to HCM should be distinguished from certain extreme expressions of the physiologically based "athlete's heart".^{9–12} In particular, strength trained athletes, involved in mainly static exercise, usually show increased LV wall thickness, with a pattern of concentric LV geometry caused by pressure overload typical of this type of effort.

Although standard Doppler echocardiography has been widely used to distinguish athlete's heart from pathological

LV hypertrophy, few reports have described myocardial systolic adaptation to extensive physical exercise.^{13–15} The aims of this study were: (a) to evaluate, using Doppler myocardial imaging (DMI)^{16–17} regional LV and RV systolic peak velocities and activation times in patients with mild HCM compared with power athletes; and (b) to assess the potential prognostic value of DMI indexes in predicting ventricular tachyarrhythmias and cardiovascular events in patients with HCM and athletes during a 4 year follow up.

METHODS

Subjects

Approval for the study was obtained from the ethics committee of Monaldi and Rummo Hospitals. Patients were enrolled after giving their informed consent.

We selected a study population consisting of 70 relatively young patients with HCM (mean (SD) age 29.4 (6.9) years)

Abbreviations: DMI, Doppler myocardial imaging; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association; Q-Ao, onset of aortic flow; Q-Pulm, onset of pulmonary flow; Q-Sm, precontraction time; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion

with mild septal hypertrophy (interventricular septum thickness 15–19 mm) and 85 age and sex matched athletes (40 short distance competitive swimmers and 45 top level weightlifters) with echocardiographic evidence of LV hypertrophy and interventricular septum thickness >12 mm. All the patients were referred to our echocardiographic laboratories during the period 1998–2001.

Exclusion criteria were: diabetes mellitus, arterial hypertension, coronary artery disease, valvular heart disease, New York Heart Association (NYHA) functional classes III–IV, sinus tachycardia, atrial fibrillation, lung disease, pulmonary hypertension, and inadequate echocardiograms. In particular, all patients with HCM underwent stress 99-technetium sestamibi single photon emission computed tomography at least 3 months before enrolment in our study protocol, in order to exclude underlying coronary artery disease.

HCM group

Diagnosis of HCM was confirmed by echocardiographic evidence of asymmetric hypertrophy of the interventricular septum (15–19 mm) without any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.

Of the patients with HCM, 11 (8.3%) were in NYHA class II. Ten patients (14.3%) had a history of unexplained syncope, and eight (11.4%) of chest pain. Fourteen patients (20%) had a family history of a premature sudden cardiac death related to HCM. Sixteen patients (22.8%) were diagnosed with obstructive HCM based on an LV outflow tract gradient ≥ 30 mm Hg. Patients taking cardiac drugs (primarily beta-blockers and calcium channel blockers) had therapy withdrawn at least 1 week before the echocardiogram.

Athletes group

All the athletes had trained intensively, 15–20 hours/week for >5 years, and were undergoing anaerobic isometric static exercise at incremental workloads of at 40–60% of maximal heart rate. In particular, the training protocol for swimmers included both 3 hours/day of short distance swimming (3000 m/day divided into series of 25, 50, and 100 metres) and 1 hour/day of weightlifting at high workload. The weightlifters spent 4 hours/day weightlifting at high workload.

Procedures

Standard Doppler echocardiography and DMI were performed with the subjects in partial left decubitus (Acuson Sequoia ultrasound system; Mountain View, CA, USA) equipped with DMI capabilities. A variable frequency phased array transducer (2.5–3.5–4.0 MHz) was used for two dimensional, M-mode, and Doppler imaging. Doppler echocardiographic and DMI tracings were recorded on magneto-optical disk. All the measurements were analysed by two experienced readers, using an average of ≥ 3 cardiac cycles.

M-mode and B-mode

LV mass was calculated according to the Penn convention by the following formula: LV mass (g) = $1.04 [(LVEDD + IVST + PWT)^3 - (LVEDD)^3] - 13.6$ where VST is ventricular septal thickness, PWT is posterior wall thickness, and LVEDD is LV internal end diastolic diameter. LV mass was indexed for height^{2.7} (Cornell adjustment).¹⁸

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).^{19–20}

Standard Doppler

Pulsed Doppler assessment of LV inflow was performed in apical four chamber view, with the sample volume placed at the level of valve tips. The following measurements of global LV diastolic function were determined: peak velocities of E and A wave (m/sec) and their ratio, deceleration time of E wave (ms), and isovolumic relaxation time (ms).²¹

The time for global LV activation was evaluated from the onset of QRS to the onset of aortic flow (Q-Ao). The time for global RV activation was determined from the onset of QRS to the onset of pulmonary flow (Q-Pulm). The difference between Q-Ao and Q-Pulm determined Doppler interventricular delay.²²

Pulsed DMI

Pulsed DMI was performed by spectral pulsed Doppler signal with bypassing high pass filter, adjusting the Nyquist limit to 150–200 mm/s (close to myocardial velocities). In apical four chamber and two chamber views, a 5 mm pulsed Doppler sample volume was subsequently placed at the level of five different basal myocardial segments: LV posterior septum, LV inferior wall, LV anterior wall, LV lateral wall (at the level of the mitral annulus), and RV lateral wall (at the level of the tricuspid annulus). In parasternal short axis view, the sample volume was placed at the level of basal LV posterior wall, in order to assess regional circumferential motion. Using DMI, systolic (Sm), early diastolic (Em), and late diastolic (Am) peak velocities were evaluated in six different basal myocardial segments. Index of myocardial systolic activation was calculated as precontraction time (Q-Sm) (from the beginning of Q wave of ECG to the onset of Sm). Intraventricular systolic delay was measured as the difference of Q-Sm in five different LV myocardial segments (difference between the longest and the shortest time interval). Interventricular activation delay was calculated by difference of Q-Sm between the most delayed LV segment and RV lateral wall.²³

ECG Holter monitoring

Two lead (D2 and V5) ECG Holter monitoring (CardioData Inc, Marlborough, MA, USA) was performed for 24 hours. The analysis of the ECG layout was performed using a CardioData Mk4 system.

End points and assessment

Patient outcome and clinical status were assessed in all patients with HCM and in 83 athletes, for a mean period of 44.4 (10.8) months (range 16–50; median 50). Follow up data were obtained through review of patient's hospital records, by periodical follow up visit in our institution, or by phone interview with the patient. In cases where the patient had died, data were collected by phone contact with a family member. Two athletes were lost to follow up (2.1%).

Primary endpoint was cardiovascular mortality. The definition of cardiac related death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in absence of any other precipitating factors. Sudden death was defined as death occurring within 1 hour without previous worsening of cardiac symptoms. We also took unexpected deaths occurring during sleep to be sudden when patients were found dead by family members sharing the same room. We recorded non-cardiovascular death if cardiovascular events were excluded as cause of death.

Statistical methods

The analyses were performed by SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA). Variables are presented as mean (SD). The *t* test for unpaired data estimated differences

between the two groups. Linear regression analyses and partial correlation test by Pearson's method were performed to assess univariable relations. Receiver operating characteristic (ROC) curve analysis was performed to select optimal cutoff values of echo measurements. Independent predictors of late cardiac events were identified through multivariable Cox proportional hazard regression models. Probability level of 0.05 was used as the significance of the association between predictive variables and events. The risk associated with a given variable was expressed by a hazard ratio (HR) with corresponding 95% confidence intervals (CI). In the multivariable analysis, an interactive stepwise procedure was adopted. The cumulative probability of freedom from cardiac events was calculated by Kaplan-Meier life table analysis and compared between groups using the log rank test.

Reproducibility of measuring the DMI parameters was determined in 55 subjects (30 patients with HCM and 25 athletes), according to previously reported methods. Interobserver and intraobserver variability was examined using Bland-Altman analysis. The 95% confidence limits of a single estimate of the measurements were calculated as $2 \times \text{SD}/\sqrt{2}$, and reported as a percentage of the mean value.

RESULTS

Clinical characteristics of the study population

The two groups were matched for age (29.4 (5.9) years in patients with HCM *v* 28.9 (5.5) years in athletes), male prevalence (82.1% *v* 85.3%) and mean blood pressure (83.5 (4.5) mm Hg *v* 85.2 (3.3) mm Hg), while body surface area was increased in athletes (1.79 (0.08) m² *v* 1.88 (0.11), *p*<0.01).

ECG 24-hour Holter monitoring

Athletes showed lower 24 hour mean heart rate (72.9 (10.2) beats/min in patients with HCM *v* 59.1 (6.6) beats/min in athletes, *p*<0.0001). QRS duration was comparable between the two groups (110.3 (10) ms *v* 109.3 (7) ms) and no intraventricular conduction defect was detected by surface ECG. In 22 patients with patients with HCM (31.4%) non-sustained episodes of ventricular tachycardia (of $\geq$ three beats and of at least 120 beats/min, stopping spontaneously in less than 30 seconds) were documented, while no significant ventricular arrhythmias were evidenced in athletes, in accordance with previous reports.²⁴

Table 1 Standard Doppler echocardiographic comparison between the 2 groups

Variable	Patients with HCM	Athletes	p
LV septal wall thickness (mm)	16.6 (2.1)	12.9 (0.9)	<0.01
LV posterior wall thickness (mm)	8.4 (1.1)	9.6 (1.0)	<0.05
LV end diastolic diameter (mm)	46.4 (3.7)	51.4 (3.2)	<0.01
LV end systolic diameter (mm)	27.0 (4.7)	30.8 (1.9)	NS
LV ejection fraction (%)	62.7 (4.7)	64.2 (6.2)	NS
LV mass index (g/m ^{2.7})	64.4 (9.7)	60.6 (5.5)	NS
Mitral peak E velocity (m/s)	0.68 (0.09)	0.77 (0.2)	<0.001
Mitral peak A velocity (m/s)	0.66 (0.06)	0.36 (0.1)	<0.005
Mitral peak E/A ratio	1.04 (0.4)	2.44 (0.8)	<0.0001
Mitral deceleration time (ms)	206.4 (30.9)	172.1 (14.8)	<0.001
Mitral IVRT (ms)	87.0 (10.5)	78.5 (9.7)	<0.001
RV outflow tract (mm)	20.4 (2.2)	26.2 (3.8)	<0.01
TAPSE (mm)	19.1 (3.5)	20.1 (2.6)	NS
Q-Ao-Q-Pulm (ms)	42.0 (9.5)	14.5 (9.7)	<0.001

IVRT, isovolumic relaxation time; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; Ao, aortic flow; Pulm, pulmonary flow.

Standard Doppler echocardiographic analysis

LV mass index and ejection fraction were comparable between the two groups (table 1). However, septal thickness was higher in HCM, while both LV and RV end diastolic diameters were increased in athletes. All transmitral Doppler indexes were higher in athletes, with increased E/A ratio. In contrast, Q-Ao-Q-Pulm was increased in patients with HCM, showing a significant global Doppler interventricular delay.

Pulsed DMI analysis

DMI analysis detected lower *S_m*, *E_m* and *E_m/A_m* ratio at the level of all the analysed myocardial segments in patients with HCM (table 2). As for time intervals, the athletes group showed homogeneous systolic activation of ventricular walls, while there was significant interventricular and intraventricular delay in patients with HCM (table 3, fig 1). These differences remained significant even after correction for age, sex, heart rate, body surface area, and LV mass index.

Events during the follow up

During the follow up period, there were eight deaths (11.1%) in the HCM group, including seven sudden deaths and one heart failure death (1.4%). No cardiovascular event was observed in the athletes.

Multivariable relations of DMI indexes

In patients with HCM, intraventricular delay was positively associated with both LV outflow gradient (β coefficient = 0.48, *p*<0.001) and septal wall thickness (β coefficient = 0.58, *p*<0.0001). An intraventricular delay >30 ms differentiated between athletes and patients with HCM, with 91.2% sensitivity and 98% specificity. Furthermore, cutoff value >45 ms for intraventricular delay identified patients with HCM with non-sustained episodes of ventricular tachycardia during Holter monitoring (90.9% sensitivity; 95.8% specificity; positive likelihood ratio 21.82, negative likelihood ratio 0.09).

Using Cox proportional hazards regression analysis, family history of sudden cardiac death (HR = 1.28; 95% CI 1.09 to

Table 2 Pulsed DMI peak velocities of different basal myocardial segments in the two groups

Variable	Patients with HCM	Athletes	p
Left ventricular posterior septum			
<i>S_m</i> peak (m/s)	0.07 (0.02)	0.10 (0.03)	<0.001
<i>E_m</i> peak (m/s)	0.06 (0.04)	0.12 (0.04)	<0.0001
<i>E_m/A_m</i> ratio	0.7 (0.6)	1.3 (0.5)	<0.0001
Left ventricular lateral wall			
<i>S_m</i> peak (m/s)	0.08 (0.02)	0.12 (0.03)	<0.001
<i>E_m</i> peak (m/s)	0.09 (0.04)	0.17 (0.04)	<0.0001
<i>E_m/A_m</i> ratio	0.74 (0.6)	1.14 (0.5)	<0.0001
Left ventricular inferior wall			
<i>S_m</i> peak (m/s)	0.08 (0.02)	0.11 (0.03)	<0.01
<i>E_m</i> peak (m/s)	0.09 (0.04)	0.16 (0.04)	<0.0001
<i>E_m/A_m</i> ratio	0.8 (0.6)	2 (0.5)	<0.0001
Left ventricular anterior wall			
<i>S_m</i> peak (m/s)	0.08 (0.02)	0.12 (0.03)	<0.001
<i>E_m</i> peak (m/s)	0.09 (0.04)	0.17 (0.04)	<0.0001
<i>E_m/A_m</i> ratio	0.67 (0.6)	1.6 (0.5)	<0.0001
Left ventricular posterior wall			
<i>S_m</i> peak (m/s)	0.06 (0.02)	0.09 (0.03)	<0.01
<i>E_m</i> peak (m/s)	0.06 (0.04)	0.11 (0.04)	<0.0001
<i>E_m/A_m</i> ratio	0.7 (0.6)	1.1 (0.5)	<0.001
Right ventricular lateral wall			
<i>S_m</i> peak (m/s)	0.10 (0.03)	0.13 (0.03)	<0.05
<i>E_m</i> peak (m/s)	0.11 (0.04)	0.15 (0.04)	<0.01
<i>E_m/A_m</i> ratio	1.26 (0.6)	1.6 (0.5)	<0.01

S_m, myocardial systolic peak velocity; *E_m*, myocardial early diastolic wave; *A_m*, myocardial atrial diastolic wave.

Table 3 Pulsed DMI systolic time intervals in different myocardial regions between the two groups

Variable	Patients with HCM	Athletes	p
IVS Q-Sm (ms)	169.6 (11.6)	114.6 (12.8)	<0.0001
LV lateral Q-Sm (ms)	149.3 (10.3)	121.6 (10.6)	<0.01
LV inferior Q-Sm (ms)	138.7 (14.5)	117.3 (10.1)	<0.01
LV anterior Q-Sm (ms)	138.5 (13.9)	113.6 (5.3)	<0.01
RV lateral Q-Sm (ms)	128.6 (14.7)	113.5 (14.1)	NS
LV posterior Q-Sm (ms)	131.7 (7.5)	117.3 (8.1)	<0.01
Intraventricular delay (ms)	36.6 (13.2)	9.5 (8.8)	<0.0001
Interventricular delay (ms)	39.5 (10.3)	10.6 (9.6)	<0.0001

Q-Sm, myocardial pre-contraction time; IVS, interventricular septum; LV, left ventricle; RV; right ventricle.

1.32; $p<0.001$), non-sustained episodes of ventricular tachycardia (2.68; 1.2 to 4.32; $p<0.0001$), and DMI intraventricular delay (3.3; 1.3 to 4.4; $p<0.0001$) were the only independent predictors of sudden cardiac death (table 4). The global χ^2 of this combined clinical, ECG Holter, and DMI test model was 66.3 ($p<0.00001$) (fig 2).

In particular, an intraventricular delay cutoff value >45 ms identified patients with HCM at higher risk of sudden cardiac death (89.6% sensitivity, 90.5% specificity, positive predictive value 70.9%, negative predictive value 98.2%, test accuracy 90.6%) (fig 3). The cumulative 4 year mean (SD) survival time free of sudden death was 48.7 (2.5) months in the group with intraventricular delay <45 ms and 36.8 (7.3) months in the group with delay >45 ms (log rank 46.7; $p<0.00001$) (fig 4).

Reproducibility of DMI measurements

Interobserver variability was $\pm 2.6\%$ for Em peak velocity, $\pm 3.2\%$ for Sm peak velocity, and $\pm 4.2\%$ for Q-Sm. Intraobserver variability was similar: $\pm 2.2\%$ for Em peak velocity, $\pm 3.0\%$ for Sm peak velocity, and $\pm 3.8\%$ for Q-Sm.

DISCUSSION

The present study confirms the usefulness of pulsed DMI for analysis of myocardial patterns of both left and right ventricles in either physiological or pathological LV hypertrophy.

In our previous reports we compared LV and RV myocardial diastolic indexes of both patients with HCM^{5 7 25} and athletes^{13 14 17} with those obtained in normal sedentary subjects. However, the present study highlights the existence of extreme myocardial systolic non-uniformity and asynchrony in patients with HCM, even in presence of mild septal hypertrophy, in contrast to the homogeneous myocardial systolic activation assessed in athletes. Furthermore, in patients with HCM, DMI parameters of intra-LV electromechanical asynchrony were the most powerful predictors of sudden cardiac death in the subsequent 4 years, and provided

Figure 2 Incremental value of DMI indexes of intraventricular delay in predicting sudden cardiac death.

Table 4 Comparison between patients with HCM with or without cardiovascular events (sudden death) during follow up

Variable	SD HCM	No SD HCM	p
Family history for SD (%)	70.5	14.5	<0.0001
NYHA class II (%)	14.2	15.8	NS
Syncope (%)	11.5	16.3	NS
Chest pain (%)	11.1	10.3	NS
Non-sustained VT (%)	57.1	28.5	<0.0001
Interventricular septum (mm)	16.8 (2.1)	15.6 (5.1)	NS
Obstructive HCM (%)	17.3	20.2	NS
Intraventricular delay (ms)	54.4 (5.5)	28.4 (5.8)	<0.0001

SD, sudden death; VT, ventricular tachycardia.

significant incremental prognostic value compared with clinical information and other instrumental data.

To our knowledge, such association between delayed intramyocardial activation and increased risk of sudden cardiac death has not been previously described in HCM.

Myocardial systolic peak velocities in either pathological or physiological LV hypertrophy

In the present study, despite normal indexes of global ventricular systolic function (LV ejection fraction, TAPSE), lower myocardial systolic and early diastolic velocities were observed in patients with HCM in both hypertrophied and non-hypertrophied ventricular walls. As previous reports demonstrated that both systolic and early diastolic regional velocities are directly dependent on myocardial structure, characterised by the percentage of interstitial fibrosis, the impairment of myocardial indexes in our patients with HCM can be easily explained as a consequence of a direct involvement of ventricular walls by the myopathic process, which is characterised by extensive areas of interstitial and perivascular fibrosis, particularly involving the LV subendocardium.^{5 7 15 23 25-28}

Figure 1 DMI pattern of interventricular septum in (A) a patient with HCM and (B) an athlete.

Figure 3 ROC curve analyses and plots of intraventricular delay in patients with HCM. A cutoff point of intraventricular delay >45 ms showed 89.6% sensitivity and 90.5% specificity to detect increased risk of sudden cardiac death during a 4 year follow up.

In contrast, and in agreement with our recent reports on myocardial performance in competitive athletes,^{13 14 17 25} the higher values of myocardial systolic and early diastolic peak velocities and the homogeneous systolic activation in short distance swimmers in all myocardial segments confirm that in the athlete's heart, the increase in LV mass occurs with absolute normality of the functional indexes of both global and regional systolic function.

Prognostic value of intraventricular myocardial activation delay in HCM

In our study protocol, we evaluated three useful measurements of systolic activation delay in patients with mild LV hypertrophy and normal global systolic function: (a) QRS width by surface ECG; (b) Q-Ao-Q-Pulm by standard echo-Doppler; and (c) intraventricular and interventricular delay by DMI.^{22 23} Despite the absence of intraventricular conduction defects on surface ECG, DMI measurements of myocardial systolic dysynchrony were all prolonged in patients with HCM, and associations of these parameters with both septal wall thickness and LV outflow gradient were observed. Furthermore, an intraventricular delay >45 ms (a cutoff value selected by ROC curve analysis) identified with high sensitivity and specificity patients with HCM at higher risk of both ventricular tachyarrhythmias and sudden cardiac death at follow up (fig 3), with incremental value for risk stratification (fig 2). This findings are in accordance with a recent paper by Bader *et al*, which confirmed the role of DMI electromechanical parameters as significant predictors of

cardiac events in heart failure patients, independent of QRS width and LV ejection fraction.²⁹

Previous invasive angiocardiographic and electrophysiological studies have suggested that complex ventricular tachyarrhythmias, emanating from an electrically unstable myocardial substrate and resulting from re-entry, are the most common mechanism by which sudden cardiac death occurs in HCM.^{30 31}

Several hypotheses have been considered regarding the mechanism of LV arrhythmias in HCM, such as myocardial disarray and fibrosis,³² temporal non-uniformity of relaxation and contraction at the respective walls caused by regional differences in the distribution of LV hypertrophy,³³ and myocardial replacement scarring as a repair process following cell death due to intramural small vessel disease or muscle mass to coronary flow mismatch.^{4 34} Our findings indicate that impairment of intraventricular systolic synchronicity in patients with HCM is strongly associated on the one hand with degree of LV hypertrophy, and on the other hand with increased risk of non-sustained ventricular tachycardia on ambulatory Holter ECG recording.³ In addition, recent reports observed a close relationship between myocardial systolic activation delay and increased risk of ventricular arrhythmias in patients with HCM, dilated cardiomyopathy, and after late repair of tetralogy of Fallot.^{23 35 36}

Therefore, myocardial heterogeneity results in HCM against an anatomical and electrical background that may on the one hand determine a non-uniform dispersion of cardiac impulse and a regional delay in systolic activation of LV ventricular wall (that is, prolongation of intraventricular delay), and on the other hand establish a single macroscopic or multiple microscopic re-entry circuits, generating polymorphic life threatening ventricular tachyarrhythmias and sudden cardiac death.

Study limitations

The first limitation, intrinsic to the Doppler technique, is the angle dependence of pulsed DMI. However, we used the same angle incidence of transmitral Doppler, and our DMI reproducibility was good. Secondly, cardiac overall motion in the space influences DMI regional velocities, thus limiting evaluation of myocardial heterogeneity. In our study, however, the concept of impaired myocardial function rises from comparison of regional DMI variables between two different groups.

In addition, our study only investigated the relationship between intraventricular delays and sudden cardiac death in a selected population of young patients with HCM with mild hypertrophy. Extrapolation to the general HCM population

Figure 4 Cumulative risk of sudden cardiac death at follow up in patients with HCM with a cutoff point of 45 ms for DMI intraventricular delay.

What is already known on this topic

- It is well known that the distribution and magnitude of left ventricular (LV) hypertrophy are not uniform in patients with hypertrophic cardiomyopathy (HCM), which results in regional heterogeneity of both left and right ventricular systolic and diastolic function
- Mildly increased LV wall thicknesses due to HCM should be distinguished from certain extreme manifestations of the physiologically based "athlete's heart"
- Although standard Doppler echocardiography has been widely used to distinct athlete's heart from pathologic LV hypertrophy, few reports have described myocardial systolic adaptation to extensive physical exercise

What this study adds

- The present study highlights for the first time the existence of extreme myocardial systolic non-uniformity and asynchrony in patients with HCM, even in presence of mild septal hypertrophy, in contrast with homogeneous myocardial systolic activation assessed in power athletes
- Furthermore, in patients with HCM, Doppler myocardial imaging parameters of intra-left ventricular electromechanical asynchrony were the most powerful predictors of sudden cardiac death in the subsequent 4 years, and provided significant incremental prognostic value compared with clinical information and other instrumental data

(including patients with severe hypertrophy) might therefore not hold true. The role of DMI for stratifying the extent of myocardial abnormalities and future risk in HCM needs therefore further prospective evaluation.

CONCLUSIONS

Pulsed DMI may represent an effective non-invasive and easily repeatable technique for assessing the severity of regional delay in activation of LV walls and therefore for the differential diagnosis between patients with either physiological or pathological LV hypertrophy. In patients with HCM with mild septal hypertrophy, DMI analysis may provide additional information for selecting subgroups of patients at increased risk of ventricular arrhythmias and sudden cardiac death who might benefit from more accurate risk stratification, taking into account the overall clinical profile, and possibly treatment with a prophylactic implantable cardioverter defibrillator.

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Competing interests: none

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COMMENTARY

Risk stratification in hypertrophic cardiomyopathy (HCM) remains a problem. Sudden death (SD) is more frequent in adolescents and young adults and is the most common cause of cardiovascular related SD in competitive athletes, especially basketball and football. Tissue Doppler imaging has emerged as a new echocardiographic technique that provides additional information compared with conventional echocardiography concerning subclinical regional myocardial dysfunction and electromechanical coupling. The study of D'Andrea *et al* introduces a new simple and easy to detect marker of tissue Doppler derived ventricular asynchrony that could represent a prognostic indicator of poor prognosis and could have important clinical implication in patients with HCM. On these grounds, ventricular asynchrony should be assessed using tissue Doppler in patients with HCM who practise sporting activities.

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