ORIGINAL ARTICLE

CME

Usefulness of Tissue Doppler Imaging to Identify Low Risk Patients with Diagnosis of Hypertrophic Cardiomyopathy

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ABSTRACT

Objectives
Pulsed tissue Doppler imaging is a useful tool for the early detection of hypertrophic cardiomyopathy and the differential diagnosis of this disease from other secondary causes of hypertrophy.

Objective
The aim of this study was to determine the prognostic significance of preserved systolic tissue velocities in patients with diagnosis of hypertrophic cardiomyopathy.

Methods
One hundred and forty six patients with diagnosis of hypertrophic cardiomyopathy were prospectively included by means of a Doppler echocardiography study. Systolic tissue velocities were obtained from the averaged septal and lateral velocities. Patients with preserved systolic tissue velocities (Sa ≥ 8 cm/s; upper quartile), were compared with those presenting decreased velocities. The primary endpoint was defined as the presence of sudden death, stroke, heart failure, or hospitalization for cardiovascular causes at follow up.

Results
Twenty nine percent of patients (n = 43) presented preserved systolic tissue velocities in the tissue Doppler images, mostly in men (76.7% vs. 53.4%, p = 0.009) and with no age differences. Ventricular diameter and thickness were similar between the two groups while the atrial area was significantly lower (23.7 ± 6.7 vs. 28.8 ± 8, p < 0.01). At follow-up (median of 2.7 years), the number of events increased significantly as systolic pulsed tissue Doppler velocities decreased. No patient from the group with preserved systolic tissue velocities presented the combined endpoint, with significant differences with respect to the control group (0% vs. 21.6%, p = 0.001), and a negative predictive value of 100%.

Conclusions
In our population with hypertrophic cardiomyopathy, the presence of preserved systolic tissue velocities in pulsed tissue Doppler imaging identified low-risk patients with a very low number of events at follow up and high negative predictive value.

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Key words > Cardiomyopathies – Hypertrophic cardiomyopathy – Doppler ultrasound – Prognosis

Abbreviations >

Aa	Late diastolic velocity	**LVEDP**	Left ventricular end-diastolic pressure
ADHF	Acute decompensated heart failure	**PSTV**	Preserved systolic tissue velocities
AF	Atrial Fibrillation	**PTD**	Pulsed tissue Doppler
CVA	stroke	**Sa**	Systolic velocity
Ea	Early diastolic velocity	**SAM**	Systolic anterior motion of the mitral valve
EF	Ejection fraction	**SD**	Sudden death
HCM	Hypertrophic cardiomyopathy	**SVT**	Sustained ventricular tachycardia
ICD	Implantable cardioverter defribillator		

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most frequent genetic cardiac disease, with a prevalence of approximately 0.2%. (1-4) Although its course is benign in most patients, there is a small subgroup who presents a complicated evolution, either with development of sudden death (SD) or quality of life deterioration due to symptom progression leading in some cases to end-stage heart failure. (1-9)

These reasons have prompted the use of clinical variables and those derived from different complementary methods to identify patients at higher future risk (10). However, despite technological advances and greater knowledge of the disease, results have not always been consistent. (11)

Echocardiography has been the most widely used method for the diagnosis and risk stratification of patients with HCM, as it allows establishing the degree of hypertrophy, estimate ventricular function, and assess the presence of dynamic left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve (SAM). (12, 13) The incorporation of pulsed tissue Doppler (PTD) to measure myocardial systolic (Sa) and early diastolic (Ea) velocity has been useful in the differential diagnosis of HCM from other causes of hypertrophy, as they may alter before hypertrophy develops in patients without phenotypic manifestations. (14, 15) The E/Ea ratio has been correlated with increased left ventricular end-diastolic pressure (LVEDP), (16) and has been associated with presence of SD at follow-up, a lower exercise capacity and a greater number of cardiovascular events. (17, 18) Conversely, the relationship between Sa velocities and cardiovascular events at follow-up in patients with diagnosis of HCM has not been systematically evaluated, and the clinical significance of preserved systolic tissue velocities (PSTV) in these patients is still unknown.

The purpose of this study was to evaluate the usefulness of PTD, focusing on Sa myocardial contraction velocity in risk stratification of cardiovascular events in a subpopulation of patients with diagnosis of HCM.

METHODS

Patients

Among the total 601 patients with diagnosis of HCM who are currently under follow-up at our institution, 157 (26%) consecutive patients were selected to participate in this prospective study. The diagnosis of HCM was previously made after left ventricular hypertrophy evidence (> 15 mm wall thickness) by echocardiography or magnetic nuclear resonance imaging, without hypertension or any other cause that might have led to that degree of hypertrophy. Eleven patients were excluded from the study, four due to left ventricular systolic function (LVSF) impairment with ejection fraction (EF) ≤ 50% and seven because they presented no hypertrophy (three had progressed to a dilated stage of the disease and four had undergone another procedure as heart transplantation or septal myectomy). Finally, 146 patients fulfilled all the inclusion criteria to participate in the study. None of the patients under follow-up had previous history of infarction.

Procedures

The echocardiographic study was performed with a General Electric Vivid 7 ultrasound equipment (GE Vinmed Ultrasound, Horten, Norway) and the Echopac software (GE, Horten, Norway) was used for off-line image analysis. Images were acquired by one of the four operators specifically trained for image capture and processing (EG, FS, GG, and JPO) and were obtained with the patient lying in left lateral decubitus position. Both ventricular and atrial dimensions were measured according to the American Society of Echocardiography (ASE) guidelines. (19) The magnitude and distribution of ventricular hypertrophy was assessed in left ventricular short axis sections at basal, mid-ventricular, and apical levels, dividing each level into six equal segments (anterior, anteroseptal, inferoseptal, inferior, inferolateral and anterolateral). Despite ASE recommendations, the apical section was divided into six segments instead of four as this is the procedure employed by the equipment software for off-line analysis. Maximum wall thickness in any of these 18 segments was considered as maximum left ventricular wall thickness. Three morphological HCM subtypes were defined according to the echocardiographic findings: non-obstructive HCM, apical HCM (maximum wall thickness predominantly at the left ventricular apical level above the papillary muscles), and obstructive HCM (maximum instantaneous gradient at the left ventricular outflow tract or at mid-ventricular level obtained at rest with continuous wave Doppler echocardiography ≥ 30 mmHg). (20)

Pulsed tissue Doppler imaging (TDI) was used to measure Sa, Ea and Aa, positioning the sample volume at the myocardial level in the septal and lateral portions of the mitral annulus in the apical 4-chamber view. (21, 22) Maximum E and A wave velocities, as well as the deceleration time of the transmitral flow E wave were also obtained from the apical 4-chamber view, by positioning the sample volume at the level of the mitral leaflet tips during diastole. Signals were obtained from a cardiac cycle at end expiration in patients with sinus rhythm, and from the average of three cardiac cycles in patients with atrial fribrillation (AF) (30 patients).

There is no general consensus to establish which of the myocardial systolic velocities (Sa) is more adequate as evaluation parameter; some previous studies have used both septal as well as lateral measurements while others have employed the average of these two measurements. The same occurs with the measurement of Ea velocity for the subsequent estimation of left ventricular filling pressure by means of the E/Ea ratio. The present study adopted average velocities both for Sa and Ea because these measurements had less dispersion in the linear regression analysis, and hence seemed subject to less variability. An E/Ea value >15 was used as cutoff point to assume a high left ventricular filling pressure.

Data validation and endpoints

Patient data were collected from personal interviews and available admission clinical history reviews to confirm endpoints. In the case of patients undergoing follow-up outside our institution, or who missed appointments, the interview was performed by telephone with the patient or a near relative.

According to the trial protocol, the date of the baseline echocardiographic study was established as clinical follow-up initiation. The primary endpoint was defined as the combined endpoint of death from cardiovascular causes, hospitalization due to a condition compatible with acute decompensated heart failure (ADHF), stroke (CVA, defined

by a neurologist blinded to the study during hospitalization, or acute ischemic injury confirmed by computed axial tomography or nuclear magnetic resonance imaging), SD at follow-up (unexpected death within the first hour of symptom initiation in a previously stable patient), and sustained ventricular tachycardia (SVT) detected by Holter monitoring, or cardiac implantable electrical device interrogation, or implantable cardioverter defribillator (ICD) appropriate therapies. The latter, as well as the initial points, were separately analyzed as secondary endpoints.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and groups were compared using the Mann-Whitney test. Discrete variables were expressed as integers (percent of the total number) and compared with the chi square test or Fisher´s exact test, as appropriate. Survival curves were built with the Kaplan-Meier method and were compared using the log-rank test. A multivariate multiple logistic regression analysis (step down method) was performed to determine endpoint-associated factors: event-associated variables with $p < 0.10$ in the univariate analysis were incorporated into the model. A p value < 0.05 was considered statistically significant. Data were analyzed using SPSS Statistics, version 2.1 (IBM Corp, Chicago, Illinois) software.

RESULTS

Among the 146 patients participating in the study, 23 (15.7%) presented the primary endpoint after a median follow-up of 2.7 years (95% CI 1.09-3.38): 2 patients (1.3%) died from cardiovascular causes, 5 (3.4%) had SVT or appropriate, effective ICD shock, and from the remaining 16 patients, 4 (2.7%) suffered a CVA during follow-up and 12 (8.6%) were hospitalized due to ADHF or its progression to functional class III-IV.

Table 1 shows baseline population characteristics in patients with and without events at follow-up. Most patients were men (70% from the total population), with mean age 49.78 ± 17.8 years. Women presented a significantly higher number of major events compared with men (15/58, 25.9% vs. 8/87, 9.2%; $p = 0.007$). Similarly, in the group presenting the primary endpoint, family history of SD and AF were more prevalent.

Table 2 compares the echocardiographic characteristics between the two populations.

The obstructive variant of HCM was associated with higher prevalence of the primary endpoint, same as moderate to severe mitral regurgitation, although SAM was similar in both groups. No differences were found in systolic and diastolic diameters, EF and the percentage of patients with extreme hypertrophy ≥ 30 mm, though there was a trend of greater septal thickness in the event group, with a significantly higher left atrial area. Among PTD-evaluated variables, there were no differences among diastolic function parameters: the E/Ea ratio was similar between groups, and there were no differences between patients presenting a significantly increased LVEDP (E/Ea > 15). Conversely, Sa velocity was significantly lower in the group with the primary endpoint (5.4 ± 1.3 vs. 7.1 ± 1.9 cm/s; $p < 0.001$).

Table 3 shows combined endpoint predictive variables: family history of SD, AF, III-IV grade mitral regurgitation, maximum septal thickness and Sa velocity.

The population was divided in quartiles according to the Sa values, and PSTV was defined as Sa ≥ 8 cm/s (upper quartile). As shown in Figure 1, as Sa velocities in the PTD decreased, the presence of the primary endpoint increased significantly, as well as the secondary endpoint, though in this case in the limit of statistical significance.

Similar findings can be seen in the freedom from events curves (Figure 2A).

None of the patients with PSTV had events at follow-up, a result that was significantly different from the group with decreased systolic tissue velocities (Figure 2B), with a 100% negative predictive value. A similar finding was observed regarding the new AF incidence at follow-up (2.3% vs. 24.2%, $p = 0.002$).

DISCUSSION

The present study established the usefulness of PTD for risk stratification and prognosis in a population of patients with diagnosis of HCM.

Among the PTD measurements, Sa velocity showed the greatest usefulness, since it was not only a predictive variable of events in the multivariate analysis, but also identified the subgroup of PSTV patients who presented a good prognosis in the long-term follow-up. The event predictive variables at follow-up are in agreement with previously described studies, and some of them probably have higher association with some combined endpoint variables: AF with CVA, first degree family history of SD and maximum septal thickness with SD or SVT, (23) and III-IV grade mitral regurgitation with functional class progression or development of ADHF. (24)

Even though maximum wall thickness ≥ 30 mm has been classically associated with greater risk at follow-up, (25) no significant differences were observed in this study. This could have been attributed to a reduced sample number; however, recent publications question the prognostic value of this cutoff point, especially in the elderly population. (11, 26)

Pulsed tissue Doppler is easy to perform, highly reproducible and widely used in HCM. Among the various measurements obtained with PTD, the E/EA ratio has probably been the most extensively assessed as a diastolic left ventricular dysfunction parameter, which is very difficult to evaluate in this pathology with conventional Doppler classical parameters. (27) However, although some authors have found that an E/Ea ratio > 15 is associated with a higher number of SD episodes and events related to HCM, this relationship was not established in the present study.

Systolic myocardial tissue velocities (Sa) have been useful to differentiate HCM from other causes of secondary hypertrophy and from the physiological hypertrophy of athletes. (28) Together with myocardial

	Without events (n=123)	With events (n=23)	p
Age, years	48.13 ± 17.7	55.17 ± 1.6	0.083
Male gender, n (%)	79 (64.8)	8 (34.8)	0.007
Treatment			
Beta-blockers, n (%)	75 (64,1)	16 (69.6)	0.61
ACEI, n (%)	28 (23.9)	4 (17.,4)	0.49
OAC, n (%)	13 (11.1)	10 (43.5)	<0.001
Pacemaker, n (%)	12 (10.3)	3 (13)	0.69
ICD, n (%)	23 (19.7)	12 (52.2)	0.001
History			
DM, n (%)	5 (4.1)	1 (4.3)	0.96
HT, n (%)	25 (20.7)	9 (39.1)	0.056
DYS, n (%)	34 (28.1)	10 (43.5)	0.142
Smoking, n (%)	39 (32.2)	6 (26.1)	0.56
Family history of SD, n (%)	16 (13.6)	11 (47.8)	0.001
Symptoms			
Dyspnea, n (%)	35 (28.9)	10 (43.5)	0.168
Angina, n (%)	24 (19.8)	6 (26.1)	0.49
Syncope, n (%)	20 (16.5)	7 (30.4)	0.144
AF, n (%)	19 (16.1)	11 (47.8)	0.002

ACEI: Angiotensin-converting enzyme inhibitors. AF: Atrial fibrillation. DM: Diabetes mellitus. DYS: Dyslipidemia. HT: Hypertension. ICD: Implantable cardioverter defibrillator. OAC: Oral anticoagulation. SD: Sudden death.

Table 1. Baseline population characteristics

	Without events (n=123)	With events (n=23)	p
HCM Subtypes			
Non-obstructive, n (%)	67 (54.4)	9 (39)	0.068
Obstructive, n (%)	44 (36.1)	13 (56.5)	0.065
Apical, n (%)	12 (15.8)	1 (7.7)	0.68
LVDD	44.8 ± 5.9	45.2 ± 6.9	0.88
LVSD	25.1 ± 5.5	25.8 ± 7.3	0.83
LVS	20.2 ± 5.4	22.6 ± 6.6	0.09
PW	12.4 ± 2.7	13.5 ± 3.8	0.22
LA area	26.3 ± 7.6	32.5 ± 8.6	0.001
Maximum wall thickness	22.6 ± 5.7	24.6 ± 5.9	0.22
E wave	0.86 ± 0.24	0.90 ± 0.33	0.94
A wave	0.64 ± 0.27	0.72 ± 0.39	0.83
E/Ea ratio	13.19 ± 5.6	16.5 ± 9.3	0.106
E dec T	229 ± 90	243 ± 105	0.123
CSF	43.3 ± 8.4	44.9 ± 8.6	0.35
LVEF	65.4 ± 7.1	63.7 ± 9.6	0.33
PASP	36.2 ± 8.8	39.6 ± 15.7	<0.001
Sa (mean)	7.1 ± 1.9	5.4 ± 1.3	0.001
Sa ≥ 8 cm/seg	43 (35.2%)	0 (0%)	0.001
SAM	38 (31.1%)	10 (43.5%)	0.249
MR III-IV	5 (4.1%)	5 (21.7%)	0.01

LA: Left atrium. E dec T: E wave deceleration time. HCM: Hypertrophic cardiomyopathy. LVDD: Left ventricular diastolic diameter. LVEF: Left ventricular ejection fraction. LVS: Left ventricular septum. LVSD: Left ventricular systolic diameter. MR III-IV: Moderate-severe mitral regurgitation. PASP: Systolic pulmonary artery pressure. PW: Posterior wall. Sa: Systolic velocity. SAM: Systolic anterior motion of the mitral valve. SF: Shortening fraction.

Table 2. Echocardiographic parameters

relaxation variables, they have also been able to predict the development of HCM in patients with subclinical disease (without ventricular hypertrophy). (29) However, their usefulness as prognostic value within a group of patients with confirmed disease has not been completely evaluated. Our findings show that there is an inverse relationship between the development of events associated with HCM and Sa, with a progressive decrease of events as these velocities reach normal values. It was possible to identify a subgroup of patients with PSTV (in our case those with average septal and lateral Sa velocities ≥ 8 cm/s) presenting no events at follow-up, with a negative predictive value of 100%. The confirmation of these results in studies with a larger number of patients with greater power could have important clinical consequences, as it would allow by a simpler, efficient and highly reproducible method, the selection of a subpopulation of patients presenting low risk of events, and who would therefore not benefit from common prevention strategies.

Table 3. Event (primary endpoint) predictors in the multivariate analysis

Variable	Odds ratio	95% CI
AF	3.9178	1.0005 to 15.3418
III-IV MR	8.9542	1.5276 to 52.4861
Sa	0.5518	0.3474 to 0.8765
IAS	1.1624	1.0270 to 1.3158
Family history of SD	4.3158	1.1764 to 15.8324

AF: Atrial fibrillation. IAS: Interatrial septum. MR: Mitral regurgitation. Sa: Systolic velocity. SD: Sudden death.

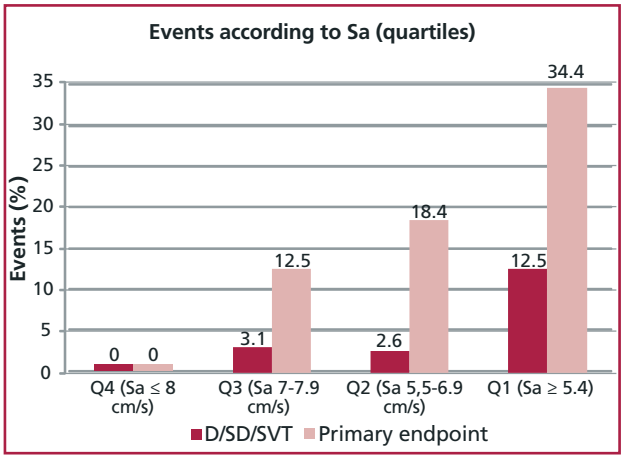


Fig. 1. Events according to myocardial tissue contraction velocities (Sa) divided in quartiles (Q). It can be seen that there is a progressive increase in the incidence of the primary endpoint (light bars; p = 0.001) and of the secondary endpoint (dark bars; p = 0.05) as myocardial tissue contraction velocities decrease (from Q4 to Q1).

Limitations

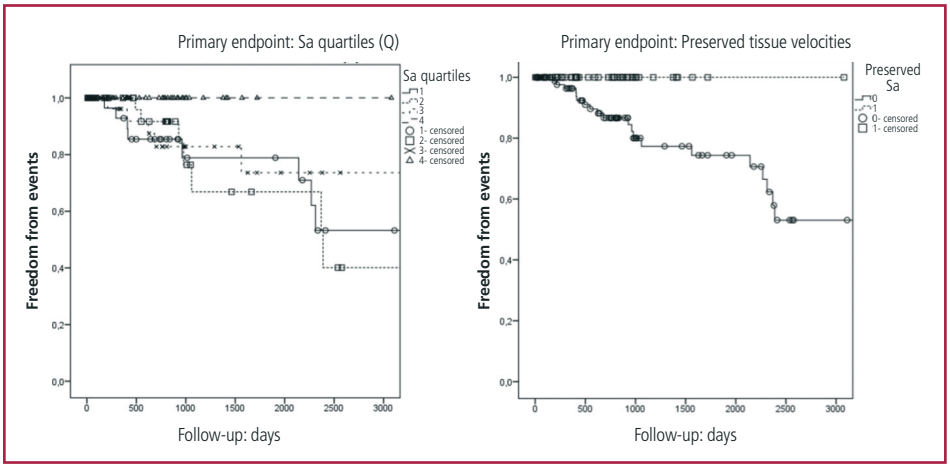
The greatest limitations of the present study are the relatively small sample number, a certain heterogeneity in patient age, lack of a control group, and that a genetic study was performed in only one patient of the study group. Moreover, although it was a prospective study, the enrollment period was very long, introducing bias in follow-up time, despite there were no substantial changes in treatment and prevention strategies during its course. Another important point is that the study design contemplated a single echocardiographic test at the beginning of the study; perhaps it would have been more useful to perform another test at a defined follow-up time to answer some questions about the prognosis of patients when changes are produced in some echocardiographic parameters (for example, decreased myocardial contraction velocities in patients with previously preserved ones). This statement induces caution in the generalization of results.

CONCLUSIONS

Atrial longitudinal strain during the reservoir period by speckle tracking and atrial stiffness index are easily quantifiable and are altered in controlled mild hypertensive patients before other echocardiographic abnormalities are detected.

The differences appear to reflect a change in atrial function by the disease process itself and independently of other adaptive changes

Fig. 2. Freedom from events curves (Kaplan-Meier).
A: Freedom from the primary endpoint according to Sa myocardial tissue contraction velocities divided in quartiles (Q1 to Q4). Notice the absence of events in the upper curve (Q4, Sa ≥ 8 cm/s), and how these progressively increase from Q4 to Q1. Log-rank test = 0.078.
B: Freedom from the primary endpoint according to the presence of preserved or decreased systolic myocardial tissue contraction velocities (PSTV = 1, ≥ 8 cm/s vs. PSVT = 0, < 8 cm/s). Log-rank test = 0.019.



RESUMEN

Utilidad del Doppler tisular para identificar una subpoblación de riesgo bajo en pacientes con diagnóstico de miocardiopatía hipertrófica

Introducción
El Doppler pulsado tisular ha demostrado beneficio en la detección temprana de la miocardiopatía hipertrófica y en el diagnóstico diferencial de esta con otras causas secundarias de hipertrofia.

Objetivo
Determinar el valor pronóstico de las velocidades miocárdicas sistólicas tisulares preservadas en pacientes con diagnóstico de miocardiopatía hipertrófica.

Material y métodos
Se incluyeron 146 pacientes con diagnóstico de miocardiopatía hipertrófica, los cuales fueron evaluados en forma prospectiva mediante un estudio de ecocardiograma Doppler. Se obtuvieron las velocidades sistólicas tisulares del promedio de las velocidades septales y laterales; se compararon los pacientes con velocidades miocárdicas sistólicas tisulares preservadas (Sa >8 cm/seg; cuartil superior) con los que presentaban velocidades disminuidas. Se definió como punto final primario a la presencia de muerte súbita, accidente cerebrovascular, insuficiencia cardíaca o internación de causa cardiovascular en el seguimiento.

Resultados
El 29% (n = 43) presentó velocidades miocárdicas sistólicas tisulares preservadas en las imágenes del Doppler tisular, con más frecuencia de varones (76,7% vs. 53,4%; p = 0,009) y sin diferencias en la edad. Los diámetros ventriculares y los espesores fueron similares, en tanto que el área auricular fue significativamente menor (23,7 ± 6,7 cm2 vs. 28,8 ± 8 cm2; p < 0,001). En el seguimiento (mediana de 2,7 años), el número de eventos aumentó significativamente a medida que disminuyeron las velocidades sistólicas en el Doppler pulsado tisular. Ningún paciente del grupo velocidades miocárdicas sistólicas tisulares preservadas presentó el punto final combinado, con diferencias significativas con respecto al grupo control (0% vs. 21,6%; p = 0,001) y un valor predictivo negativo del 100%.

Conclusiones
En nuestra población de pacientes portadores de miocardiopatía hipertrófica, la presencia de velocidades miocárdicas sistólicas tisulares preservadas en el Doppler pulsado tisular permitió identificar a una subpoblación de pacientes de riesgo bajo, con un escaso número de eventos en el seguimiento, con un valor predictivo negativo elevado.

Palabras clave > Miocardiopatías - Miocardiopatía hipertrófica - Ecocardiografía Doppler - Pronóstico

Conflicts of interest
None declared.

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