Original Article

Clinical and Echocardiographic Evaluation of Regional Systolic Function Detected by Tissue Doppler Imaging in Hypertrophic Cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is the most common type of the genetic cardiovascular diseases. Regarding to tremendous heterogeneity in the phenotypic expression of HCM, which is generally unrelated to genotype, we aimed to study, clinical and echocardiographic parameters such as Tissue Doppler Imaging (TDI) in various subtypes of HCM patients and evaluate the influence of race and gender in Iranian patients.
Methods: Patients with HCM underwent a complete clinical and echocardiographic study including TDI to assess regional systolic contraction(in the 12 segments) and early diastolic annular velocity (Em) from the septal mitral annulus.
Results: The study comprised 41 patients (20 women, mean age = 41 ± 15 years) with mean LVEF 55%±4.8% and mean maximal septal thickness 2.07cm. Considering LVOT gradient>30mmHg, hypertrophic obstructive cardiomyopathy (HOCM) was found in 18 (45%). Asymmetric septal hypertrophy (ASH) existed in 27 patients (67%), systolic anterior motion of anterior mitral leaflet (SAM) in 25 persons (64%). Nineteen patients (46.3%) were included in NYHA function class (FC) II and 6 (14.7%) in FC III or higher. We found syncope in 10 (24.4%), chest pain in 4 (9.8%), atrial fibrilation in 14.6 % and ventricular arrhythmias in (17.1%) of patients. History of ICD was seen in 7 (17.1%) and PPM in 9 cases. Mean E' velocity was 5.44± 1.65 cm/sec and S velocity 5.70± 1.49 cm/sec with significant lower S velocity and E' in syncope patients. Overall, HOCM patients had grade II diastolic dysfunction with E/É >15(17.54±7.46). Majority (25) of cases (61%) were categorized in type III of HCM. RV involvement was observed in 11 patients (28.2%).No significant differences existed between prevalence of syncope and dysrhythmia among HCM and HOCM patients.
Conclusion: In our study, we found lower detection of latent HOCM, compared to other studies, suggestive of inadequate use of appropriate provocative maneuvers such as exercise stress echocardiography and amyl nitrate. We detected remarkably lower S velocity (5.70± 1.49 cm/sec) and E' velocity (5.44± 1.65 cm/sec) in HCM patients compared to normal subjects, with more significant reductions in patients with syncope.

Keywords: Hypertrophic cardiomyopathy, Echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM), the most common type of the genetic cardiovascular diseases is a primary autosomal-dominant disorder of the myocardium caused by mutations in sarcomeric contractile proteins. Histopathologically, it is associated with myocardial hypertrophy, fiber disarray and fibrosis, which are all thought to interfere with myocardial force generation and relaxation.[1-3] There is tremendous heterogeneity in the phenotypic expression of HCM, which is generally unrelated to genotype. This is shown by the variability in the age of onset of clinical disease, degree and location of hypertrophy, and presence and site of intraventricular dynamic pressure gradients. Despite this heterogeneity, almost all patients with HCM have some degree of diastolic dysfunction. The presence of subtle changes in LV filling may even identify patients with preclini-

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cal disease without LV hypertrophy.

The origin of diastolic dysfunction in HCM is both multifactorial and complex, with changes at the molecular, myocardial tissue, and global LV levels. More than 400 mutations have been described in HCM, which result in the production of abnormal myocardial sarcomeric proteins that have altered contraction and relaxation characteristics.[3-4] Morphological factors that influence the degree of diastolic dysfunction include the degree of ventricular hypertrophy, myocardial disarray, and interstitial fibrosis.[5] Early diastolic (Ea) and systolic (Sa) velocities are reduced in patients with HCM as compared to normal controls.[6,7] The depressed Ea velocities found in HCM patients contrasts with the normal or above normal Ea velocities seen in trained athletes who may also have left ventricular hypertrophy.[8,9]

The ratio of mitral E to annular Ea (E/E') has been used to estimate left ventricular filling pressures in other settings, but may not be helpful in estimating filling pressures in individual HCM patients.[10]

Tissue Doppler imaging (TDI) in addition to its role in establishing the diagnosis of HCM in patients with left ventricular hypertrophy (LVH), can identify abnormalities in myocardial contraction and relaxation velocities before hypertrophy is manifest.[6,12,13] In a TDI study, myocardial contraction and relaxation velocities were significantly reduced compared to controls in both patients with overt HCM and those with HCM mutations without LVH. The sensitivity and specificity of reduced Tissue Doppler (TD) velocities for identifying patients with a mutation without LVH was 100 and 93 percent, respectively.[6] A two year follow-up study of 12 patients with HCM mutations without LVH found that septal thickness and LV mass increased and early and late diastolic TD velocities decreased.[13]

However, subgroups at higher risk for important disease complications and premature death reside within a HCM patient population. Many patients proceed along specific adverse pathways, punctuated by underlying clinical events that ultimately dictate treatment strategies. These include:

1) premature sudden and unexpected death, most commonly in adolescents and young adults; 2) progressive symptoms of heart failure with exertional dyspnea and functional limitation (often accompanied by chest pain) in the presence of preserved LV systolic function; 3) advanced heart failure (end-stage phase) characterized by systolic dysfunction and LV remodeling; and 4) complications attributable to artrial fibrillation (AF), such as embolic stroke and heart failure.[14]

Tissue Doppler echocardiography (TDE) has become an established component of the diagnostic ultrasound examination; it permits an assessment of myocardial motion using Doppler ultrasound imaging.

Regarding to tremendous heterogeneity in the phenotypic expression of HCM, which is generally unrelated to genotype, we decided to study clinical and echocardiographic parameters such as S-TDI in various subtype of HCM patients and evaluate the influence of race and gender on Iranian patients.

Patients and Methods

Forty-one patients (21 men) with HCM diagnosis underwent a complete clinical and echocardiographic studies including TDI. HCM diagnosis was made based on having at least 15 mm Left Ventricular wall thickness in any of lateral, anterior, inferior, septal or apical walls

without such confounding factors as history of hypertension or aortic stenosis (AS). They comprised Type I HCM patients with hypertrophy limited to anterior segment of ventricular septum, Type II having hypertrophy of both anterior and posterior segments of ventricular septum, Type III with involvement of both septum and free wall of LV, Type IV with atypical form, and Type V showing apical HCM.

Baseline data were age, sex, and the reason for referral, symptoms duration, New York Heart Association (NYHA) FC, Familial History of syncope or arrhythmia , presence or absence of syncope or ventricular arrhythmia , LVH in ECG, ICD or PPM History. Doppler echocardiograms were performed without changes in medications.

Echocardiography-Doppler Evaluation

The ultrasound equipment was a vivid seven digital ultrasound system, GE Vingmed, Horten, Norway, with a 2.5 MHZ transducer. Studies were performed in the left lateral decubitus in the apical four chamber and the long-and short axis parasternal views. Measurements were performed according to the recommendations of the American Society of Echocardiography.

All patients had complete M-mode, 2-D, and pulsed wave Doppler studies by standard approaches.

Doppler echocardiograms were recorded on high-fidelity video tape and analyzed off-line using a commercially available digital lab computer.

The presence of systolic anterior motion of the mitral valve apparatus was noted if present in any 2-D or M mode view. The severity of mitral systolic anterior motion was assessed by measurement of the septal-mitral valve distance at the onset of systole. The Doppler left ventricular outflow wave form was assessed for its contour and peak velocity.

The presence of mitral valve regurgitation and its severity was noted if present in 2-D and color doppler view according to recommendations of the American Society of echocardiography.

Tissue Doppler imaging

TDI was performed on completion of the standard echocardiographic measurements.

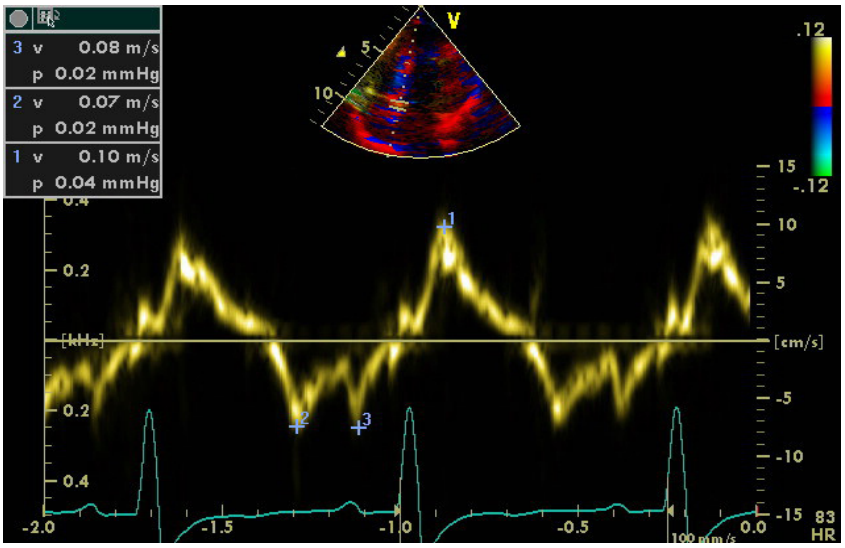

Figure 1. Septal Tissue Doppler imaging (TDI) tracing in a Patient with HCM

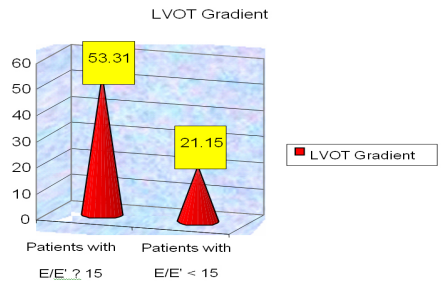

Figure 2. Comparison between Mean value of Left Ventricular Outflow Tract(LVOT) Gradient in Hypertrophic CardioMyopathy patients considering E/E' Ratio.

Digital data were transferred for off line analyses with the software incorporated in the vivid seven system to assess regional systolic contraction, in the 9 segments (Base septal, Mid septal, Base Lateral, Mid Lateral, Base Inferior, Mid Inferior, Base Anterior, Mid Anterior, Mid Anteroseptal). Early diastolic annular velocity (Em) was obtained by placing a tissue Doppler sample volume at the septal mitral annulus in the 4 -chamber view, and E/Em ratio was calculated (Fig. 1).

Statistical Analysis

Data were described as mean ± standard deviation for interval and count (%) for categorical variables. Subgroup analysis performed by Chi-square or Fisher's exact tests for qualitative data and Student's t, Mann Whitney U or Kruskal Wallis tests for quantitative variables. Multivariable analysis was done by a binary logistic regression model. P value < 0.05 was considered as statistically significant. SPSS 15 for Windows (SPSS corp., Chicago, Illinois) was used for statistical analysis.

Results

Forty-one patients aged from12 to 66 years (20 women, mean age = 41 ± 15 years) participated the study. Mean LVEF was 55%±4.8%. Mean maximal septal thickness was 2.07cm. Considering LVOT gradient>30mmHg, Hypertrophic obstructive cardiomyopathy (HOCM) was found in 18 (45%). Asymmetric septal hypertrophy existed in 27 patients (67%) and SAM in 25 person (64%). Table 1 presents the echocardiographic findings. Nineteen patients (46.3%) had been stated in NYHA function class II and 6 (14.7%) in function class III

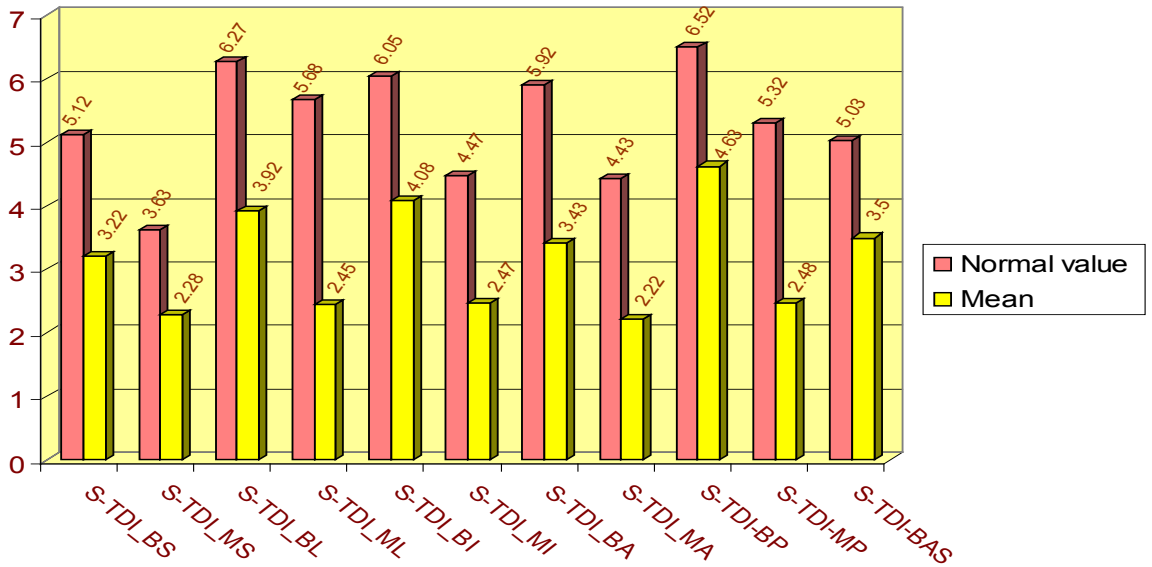

Figure 3. Normal values and calculated mean and standard deviation for S-Wave velocity in Tissue Doppler Imaging(S-TDI) in Hypertrophic CardioMyopathy patients (All p-values were < 0.001)

Table 1: Echocardiographic findings in 41 patients with hypertrophic cardiomyopathy

Left Ventricular Ejection Fraction (%)	55 ± 4.8
Left Atrium Area (cm2)	22 ± 8.6
Maximum Septal Thickness (cm)	2 ± 0.7
Asymmetric Septal Hypertrophy	27 (67%)
Left Ventricular outflow Tract Gradient (mmHg)	31.6 ± 34.4
Left Ventricular outflow Tract Gradient > 30 mmHg	18 (45%)
Systolic Anterior Motion of Mitral Valve	25 (64.1%)
Mitral Regurgitation	34 (92.5%)
Right Ventricular Involvement	11 (28.2%)
E/E'	14.8 ± 5.9
E' velocity (cm/sec)	5.44± 1.65
S velocity (cm/sec)	5.70± 1.49
E/A	1.2 ± 0.6
Deceleration Time (msec)	205 ± 85.8

* Data are presented as mean ± standard deviation for interval and count (%) for nominal variables

or higher. Other main clinical presentations were syncope in 10 (24.4%), chest pain in four (9.8%), atrial fibrilation in 14.6 % and ventricular arrhythmias in (17.1%) of patients, history of ICD implantation was present in 7 (17.1%) and PPM in 9 cases. LVH in ECG was found in 68.3 % of patients.

Mean E' velocity was 5.44± 1.65 cm/sec and S velocity was 5.70± 1.49 cm/sec(Fig. 3)

As shown in Fig.2, overall HOCM patients had grade II diastolic dysfunction with E/É >15(17.54±7.46) (P=0.008). Majority of cases (25 [61%]) were categorized in type III of HCM. RV involvement was observed in 11 patients (28.2%).

Clinical and Echocardiographic findings in HOCM

Important clinical findings and echocardiographic indices, such as diastolic dysfunction of LV in HOCM patients, compared to other HCM patients are presented in Table 2. It can be observed that F/M ratio is approximately reversed in HOCM, compared to HCM (P=0.04). No significant differences existed between prevalence of syncope ,dysrhythmia and the positive family history between two groups.

LVEF is significantly greater in patients with

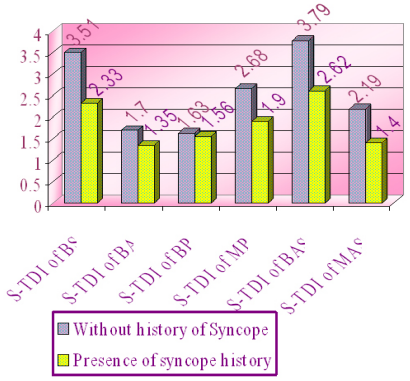

Figure 4. Comparison between Mean value of significant results considering history of syncope in Hypertrophic CardioMyopathy (HCM) patients (All p-values were < 0.05)

Table 2: Clinical and echocardiographic characteristics in patients with hypertrophic obstructive cardiomyopathy, compared to hypertrophic cardiomyopathy patients

	HOCM (n = 18)	HCM (n = 23)	P value
Age (years)	41 ± 15	39 ± 14.8	0.76
Sex (F/M)	12/6	8/15	0.04
Syncope	4 (22.2%)	6 (26%)	0.71
Dysrhythmia	3 (16.7%)	4 (17.4%)	> 0.99
Chest pain	1 (5.5%)	3 (13%)	0.61
PPM	3 (16.7%)	6 (26%)	0.48
ICD	1 (5.5%)	6 (26%)	0.11
LVEF (%)	58 ± 2.5	54 ± 5.8	0.03
E/E'	17.5 ± 7.5	12.7 ± 3.1	0.01
E/A	1.1 ± 0.5	1.3 ± 0.8	0.73
Deceleration Time (msec)	211 ± 86.9	197 ± 88.2	0.62
SAM	13 (72.2%)	12 (52.2%)	0.16
ASH	13 (72.2%)	13 (56.5%)	0.25
MR	17 (94.4%)	15 (65.2%)	0.10

PPM: Permanent Pacemaker; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; ASH: Asymmetric Septal Hypertrophy; SAM: Systolic Anterior Motion of Mitral Valve; MR: Mitral Regurgitation

HOCM. However, it seems that this finding has no clinical significance (58 ± 2.5 versus 54 ± 5.8 percent, p = 0.03). No associations were observed between E' velocity, S velocity and HOCM/HCM. On the other hand, E/E' ratio is higher in HOCM group (17.5 ± 7.5 compared to 12.7 ± 3.1 in HCM group, p = 0.01). Relative frequency of MR are much greater in HOCM patients (94.4% versus 65.2% in HCM patients), however, this difference was not statistically significant (P=0.10).

No differences were found between two groups of patients, in prevalence of implanted PPM or ICD. A considerable difference was observed in the case of ICD (5.5% in HOCM and 26% in HCM), but this was not statistically significant (P=0.11).

Adjusted association between the above factors and presence of HOCM was investigated by a logistic regression model. No significant relations were found after adjustment.

There was significant difference between HCM subtypes (I-V) considering SAM and ASH. It should be considered that based on the sample size of study, the power maybe not statistical sufficient for comparison between the groups. However, it can be observed that the association between SAM and ASH, and the type of HCM were significant. Prevalence of SAM was lower in type IV (P=0.03) and prevalence of ASH was lower in type IV and V (P=0.008), compared to other types of HCM.

Comparison between HCM benign and malignant subtypes considering history of ICD, history of syncope and TDI parameters showed some interesting results (Fig 4, Table 3).

Discussion

The natural history of HCM is characterized by a pronounced anatomic-functional diversity, and presents itself in a mild or massive, focal or diffuse, concentric or asymmetric way. Similarly the clinical manifestations or the natural disease history varies in the affected individu-

als. There is no single or classic morphologic form in HCM; virtually all possible patterns of LV hypertrophy have been reported. HCM should be diagnosed as obstructive or nonobstructive for all patients identified with this disorder.15 A large proportion of HCM patients without SAM or outflow obstruction at rest may nevertheless generate outflow gradients with physiological exercise. Whether or not symptoms are present, overall 70 percent of an unselected hospital-based HCM cohort have the propensity to develop an outflow gradient ≥30 mm Hg (and ≥50 mm Hg in the majority), either at rest or with exercise. Only 30 percent of HCM patients have the true nonobstructive form14, 15. Assessment of subaortic gradients with exercise echocardiography has an important role in the evaluation of those HCM patients without obstruction at rest.

The detection of latent form of HOCM, in our study was lower than the other studies, suggestive of inadequate use of other appropriate provocative maneuvers. We used valsalva maneuver in our study because amyl nitrate or exercise test are not commonly practiced provocative maneuvers in our country. In the other studies about 43 percent of patients had resting LVOTO, 30 percent latent LVOTO, and 27 percent true HCM 16- 17. Classification of patients with HCM according to the nature and severity of LVOTO may have important therapeutic and prognostic implications.

The prevalence of HOCM in our study was 45% which is close to resting LVOTO by other studies. This shows an underestimate in the detection of latent form of HOCM. The reason is that the Valsalva maneuver, is difficult to perform, ,frequently carried out incorrectly and often results in loss of the Doppler signal due to chest wall movement. Thus it has been suggested that inhalation of amyl nitrite in selected patients, permits an entirely noninvasive characterization of the nature and severity of left ventricular outflow obstruction 16. The Majority of our patients (n=25) were classified as HCM type III ([61%]) with involvement of septum and anterolateral free wall which is close to distribution by Maron classification (52%)18-19. Progression to severe functional limitation (NYHA Class III or IV) is uncommon, occurring in 10 to 15 percent of the overall patients population whereas in our study we found 6

Table 3: Comparison between Mean value, Standard Deviation(SD) of significant results considering history of syncope in Hypertrophic CardioMyopathy (HCM)

	Without history of Syncope (SD)	Presence of syncope history (SD)	p-value
Mean S-wave velocity (cm/s)	*6.07 (1.43)*	*4.60 (1.07)*	*<0.005*
Pulmonary vein S-wave Velocity (cm/s)	*55.82 (14.19)*	*28.50 (16.74)*	*<0.005*
Pulmonary vein D-wave velocity (cm/s)	*49.95 (17.01)*	*34.00 (16.00)*	*0.019*
S-TDI of BS (cm/s)	*3.51 (1.38)*	*2.33 (0.97)*	*0.035*
S-TDI of BA (cm/s)	*1.70 (0.30)*	*1.35 (0.42)*	*0.037*
S-TDI of BP (cm/s)	*1.63 (0.29)*	*1.56 (0.49)*	*0.021*
S-TDI of MP (cm/s)	*2.68 (1.10)*	*1.90 (0.96)*	*0.053*
S-TDI of BAS (cm/s)	*3.79 (1.54)*	*2.62 (1.23)*	*0.035*
S-TDI of MAS (cm/s)	*2.19 (1.10)*	*1.40 (0.63)*	*0.037*

(14.7%) patients in function class III or higher. AF has been suggested as the most common sustained arrhythmia in HCM which occurs in 20 percent of HCM patients,while atrial fibrilation occurred in 14.6 % of our patients.

Mean Left Ventricular outflow tract gradient (mmHg) in our study was 31.6 ± 34.4mmHg, with greater relative frequency of MR in HOCM patients compared to HCM patients (94.4% versus 65.2%).

There was significant association between SAM and ASH, and the type of HCM, Prevalence of SAM and ASH was high in HCM type III and low in type IV and V (P=0.008), compared to other types HCM. We found diastolic dysfunction grade II in most of our patients. It has been suggested that abnormalities in LV relaxation and filling which can be identified in about 80 percent of HCM patients presumably contribute to heart failure symptoms such as exertional dyspnea, and not consistently related to the severity of LV hypertrophy18.

The clinical course in HCM is typically variable. Mean value of EF in our patients was within normal limit (55.85±4.86 %) and we could not find more malignant forms of HCM in our study. However, S-TDI values were reduced in all 12 segments. Thus it seems that EF can not be regarded as a reliable marker for myocardial contractility, Tissue Doppler imaging parameters can show even subtle myocyte contractility dysfunction.

We detected remarkably lower S-TDI and early diastolic mitral annulus velocity values in HCM patients, which may reflect abnormal myocardial function as compared with those of normal subjects. In HCM patients with history of syncope, significant reductions in S-TDI, was seen, which can be an additional finding in diagnosis of malignant HCM parameters such as familial history of sudden cardiac death. However in the cases with history of arrhythmia and positive family history, these values were reduced in some but not all segments, which can be due to anisotropic distribution of conventional risk factors.

The detection of latent obstructive form of HCM in our study was lower than that of other studies[?], suggestive of inadequate use of provocative maneuver. We detected remarkably lower S velocity (5.70± 1.49 cm/sec) and E' velocity (5.44± 1.65 cm/sec) in HCM patients, as compared with normal values with more significant reductions in patients with syncope.

Conflicts of Interest no declare.

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