Left Ventricular Systolic Dyssynchrony in Patients with Hypertrophic Cardiomyopathy: The prevalence and its Relation to Syncope

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Background: The distribution and magnitude of left ventricular hypertrophy (LVH) are not uniform in patients with hypertrophic cardiomyopathy (HCM) , which results in regional heterogeneity of left ventricular (LV) systolic function. The aim of this study was to evaluate LV regional systolic dyssynchrony in patients with HCM by Tissue Doppler Imaging (TDI) and to find any correlation between TDI data and syncope.

Methods: A total of 44 consecutive patients with HCM are recruited in the present study. .All patients, underwent complete clinical and echocardiographic evaluation including TDI . The following were measured in 6 different basal and 6 mid-myocardial segments: systolic peak velocity(Sm), early diastolic myocardial velocity (Em), pre-contraction time(Q-Sm) from beginning of Q-wave of ECG to the onset of Sm, total asynchrony index ,interventricular mechanical delay(difference in Q-Aortic valve opening and Q-Pulmonic valve opening) and maximum difference in time to peak systolic velocity between 2 of 12 segments(ΔPVI).

Results: TDI analysis in HCM subgroup with syncope showed both significant interventricular (36.72±26.26 vs 14.74±11.30 msec, P<0.001) and intraventricular delays(39.40±22.38 vs27.70±17.32 msec, P=0.07). The prevalence of LV systolic dyssynchrony was from 20.5% to 38.6% based on different methods. Patients with syncope had greater impairment of regional systolic and early diastolic function, remarkably lower Sm and Em velocities.

Conclusion: The impairment of inter and intraventricular systolic synchronicity is significantly related to syncope in patients with HCM.TDI analysis may be able to select subgroups of HCM patients at increasing risk of syncope and major cardiac events.

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.[1-3] Histopathologically, it is associated with myocardial hypertrophy, fiber disarray and fibrosis, which are all thought to interfere with myocardial force generation and relaxation.[4] Regional myocardial hypertrophy, especially asymmetrical septal hypertrophy of the left ventricle, is the most characteristic feature of HCM and it has been classified morphologically.[1,5] Heterogeneity of left ventricular (LV) myocardial properties has been shown to result in delayed relaxation and significant regional heterogeneity in systolic synchronicity in patients with HCM.[6-8]

The greatest risk for sudden death has been suggested to be associated with one of the following clinical markers:[9-12] (1) Prior cardiac arrest or sustained ventricular tachycardia; (2) family history of one or more premature HCM-related deaths (3) syncope, (4) hypotensive or attenuated blood pressure response to exercise; (5) multiple, repetitive (or prolonged) non-sustained ventricular tachycardia on serial ambulatory (Holter) monitoring; and (6)

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massive LV hypertrophy (wall thickness, ≥30 mm).

It has recently suggested   that extreme myocardial systolic dyssynchrony assessed by tissue Doppler imaging (TDI) may provide additional information for identifying patients with HCM at increased risk of ventricular arrhythmias and sudden cardiac death.[8-13]

Considering regional heterogeneity of LV systolic and diastolic function we sought to evaluate dyssynchrony indices in HCM patients to find any correlation between dyssynchrony indices and syncope in these patients.

Patients and Methods

Study population: This study comprised 44 consecutive patients with HCM diagnosis referred to our echocardiography laboratory. Exclusion criteria were: history of hypertension, known or suggested coronary artery disease and valvular heart disease. The diagnosis of HCM was based on conventional echocardiographic demonstration of non-dilated, non-obstructed hypertrophic left ventricle in the absence of other cardiac or systemic diseases that might result in LV hypertrophy with detection of myocardial hypertrophy defined as having at least 15 mm LV wall thickness in anyone of lateral, anterior, inferior, septal or apical segments.[14-16]

Clinical data: Clinical records were reviewed to obtain demographic data, symptoms, New York Heart Association (NYHA) functional class, family history and medications at the time of index echocardiography. Patients with HCM were sub-

classified based on their positive history of syncope.

Echocardiographic studies: Echocardiograhic studies were performed with a Vivid Seven digital ultrasound system (GE VingMed Ultrasound, Horten, Norway with a M3S transducer). LV volume and EF were evaluated by visual assessment and Simpson's method and graded according to ASE guidelines. They were classified as follows: Type I: HCM patients   with hypertrophy limited to anterior segment of ventricular septum. Type II: hypertrophy of both anterior and posterior segments of ventricular septum , Type III: involvement of both septum and free wall of LV , Type IV: atypical form, and Type V: apical HCM.[5]

Color TDI was performed on completion of the standard 2D, M-mode and Doppler echocardiographic measurements. Digital data were transferred for offline analysis with the software incorporated in the Vivid Seven system. Scanning was carried out longitudinally from the apex to acquire apical four, two and three chamber views with a 3.0 MHz phased-array transducer and a frame rate of 150 frames per second.

Images were acquired with a sweep speed of 100 cm/s, with gains and filters optimized. TDI measurements were sampled from 3 cardiac cycles at each location and the results averaged. Systolic peak velocity (Sm) and early diastolic myocardial velocity (Em) ,diastolic peak velocities of base of anteroseptal , peak systolic velocity and time from Q wave to peak systolic velocity of the 12 left ventricular segments; basal and mid anterior, inferior,

Figure 1. Intraventricular dyssynchrony assessment by measuring time from Q wave to peak systolic velocity of the basal septum

lateral, septal, posterior and anteroseptal were assessed by offline TDI (Fig. 1).

Interventricular Dyssynchrony

Interventricular dyssynchrony (IVMD) was defined as a time difference between Q-Aortic valve opening and Q-pulmonic valve opening with value greater than 40 milliseconds considered to be abnormal.

Echocardiographic Determination Of Interaventricular Dyssynchrony

Intraventricular dyssynchrony was evaluated using following methods. (1) Basal septum to basal lateral mechanical delay. A difference longer than 65 milliseconds was considered as an intraventricular dyssynchrony marker. (2) Maximum difference in time to peak systolic velocity of all 12 segments(in 6 basal and 6 mid myocardial segments, Maximum difference in time to peak systolic velocity between 2 of 12 segmets (ΔPVI) compared and intraventricular dyssynchrony was established when a maximum difference greater than 100 milliseconds was present. (3) Intraventricular dyssynchrony assessment using the SD of the time from the Q wave to the peak of the systolic wave of all 12 segments (total asynchrony index, TAI), presence of intraventricular dyssynchrony established when total asynchrony index was greater than 32.6[17]. (4) Intraventricular dyssynchrony assessment using septal to posterior mechanichal delay (SPW-MD). A difference longer than 130 milliseconds was considered as an intraventricular dyssynchrony marker.

Statistical Analysis

Mean±standard deviation and count (percentage) were used to describe the quantitative and qualitative data, respectively. One sample t test was used to compare the mean of dyssynchrony indices with standard cut-points. Pearson's correlation coefficient was the statistics for showing the linear correlations between each pair of these indices. In addition, Cochran's Q was used for determining the difference of dyssynchrony prevalence, based on different indices. Pairwise comparisons performed by McNemar test (with Bonferroni correction for significance level). Subgroup analysis performed by independent sample t or Mann Whitney U test (for interval) and Chi square or Fisher's exact test (for categorical) data. P value less than 0.05 considered as statistically significant using SPSS 15 for Windows (SPSS Corp., Chicago, Illinois).

Table 1. Echocardiographic findings in patients with hypertrophic cardiomyopathy

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Left Ventricular Ejection Fraction (%)	55.0±4.8
Left Atrium Area (cm²)	22.0±8.6
Maximum Septal Thickness (cm)	2.0±0.7
Left Ventricular outflow Tract Gradient (mmHg)	31.6±34.4
E' velocity (cm/sec)	5.4± 1.7
S velocity (cm/sec)	5.7± 1.5
E/E'	14.8±5.9
E/A	1.2±0.6
Deceleration Time (msec)	205±85.8

Intra-Observer Reliability

For investigating the variability of measurements, 15 patients were selected randomly and interventricular mechanical delay was measured again by the rater. The results were compared by one-sample t test and no statistically significant difference were observed (mean was 32.6±25.2 msec in the first and 32.4±20.9 msec in the second measurements; P=0.790). Also, there was a high correlation between two measurements (Pearson's r=0.90; P<0.001)

Results
Background Data

There were 23 women, mean age : 39 ± 14.9 years (range 12 to 66 years). Mean LV EF was 55 ± 4.8%.Twenty patients (45.5%) were in New York Heart Association (NYHA) functional class II. Eleven patients (25%) had the history of syncope. Chest pain was observed in 5 (11.4%) cases. Six patients (13.6%) had a history of atrial fibrillation and also six (13.6%) had previously implanted ICD. Left bundle branch block was found in two cases (4.5%).

The mean myocardial wall thickness was 2 ± 0.7 cm, with a subaortic gradient 30 mm Hg or higher in 19 (43.2%) cases. Asymmetric septal hypertrophy existed in 27 patients (62%). Among the 44 cases of HCM or HOCM, 26 (59.1%) were in common type (type III) and 11 (25%) in atypical type (type IV). Twelve patients (27.3%) had moderate mitral regurgitation (MR) and 32 (72.7%) had none or mild MR. Mean Em velocity was 5.44± 1.65 cm/sec and Sm velocity was 5.70± 1.49 cm/sec (Table 1). S-TDI values were reduced in all 12 segments with significantly lower Sm velocity and Em in syncope patients (Fig. 2).
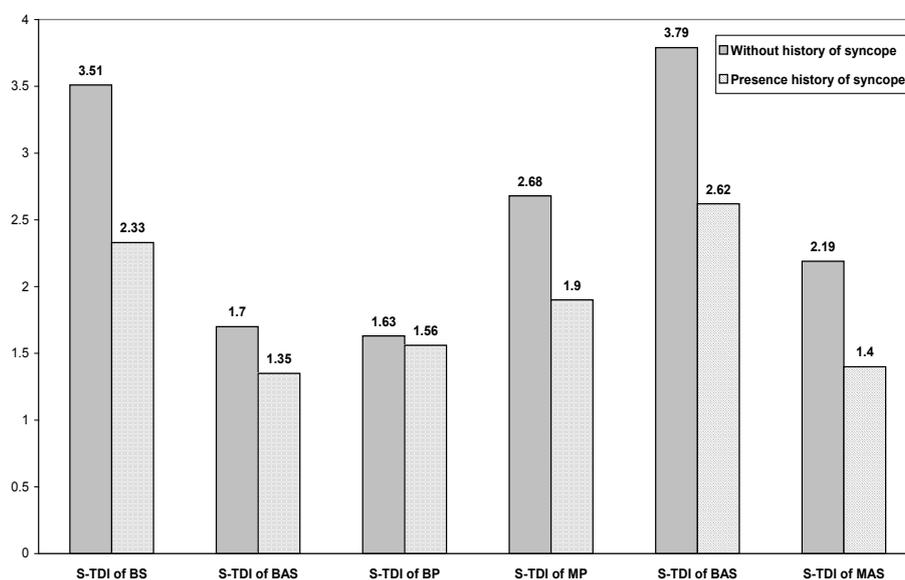
Figure 2. Comparison between mean value of S velocity in patients with and without history of syncope in hypertrophic cardiomyopathy

Dyssynchrony Indices

Different indices for LV dyssynchrony determined in subjects under study. Each index was compared to its reference values. Regarding the predefined threshold for significant dyssynchrony, the prevalence of LV systolic dyssynchrony was 16 (36.4%), ΔPVI 17 (38.6%) TAI, 11(25%), SPWMD 9 (20.5%) and 6 (13. 6%) IVMD. Cochran's Q test proposed a difference among the results of these methods (P=0.01). However, McNemar's test for pairwise comparisons (with Bonferroni's adjustment for significance level), did not confirm any significant differences. Pearson's r correlation coefficient was also used to investigate the linear correlations between each pair of the above indices. The mean±SD of these coefficients was 0.34±0.32 (range 0.04–0.98). Only the correlations between

SLWMD and other indices were statistically significant (all P<0.05). In addition, correlation between Δ PVI and TAI was strong and significant (r=0.98; P=0.01). These findings showed considerable differences among various dyssynchrony indices in HCM patients.

Associations between dyssynchrony indices and Patients Characteristics

To investigate the relations between different dyssynchrony indices and some important factors in HCM patients, we compared the mean of each index among subgroups of our study participants.

The prevalence of dyssynchrony based on ΔPVI was greater in HOCM patients (52.6% versus 24%, P=0.05). The mean of TAI was also greater in patients with HOCM (34.4±21.8 versus 27.8±16.8).

Table 2. Relationships between dyssynchrony indices and some characteristics of the patients with hypertrophic cardiomyopathy

	Cardiac Rhythm			Mitral Regurgitation		
	AF (n = 6)	Sinus (n = 38)	P	Moderate (n = 12)	No/Mild (n = 32)	P
Δ PVI	130±59.6	75±43.9	0.03	101.7±66.3	80.9±48.5	0.26
IVMD	34.2±22.7	16.9±16.5	0.06	27.3±26.5	17.8±14.5	0.14
TAI	47.3±18.5	26.5±15.8	0.02	35.2±24.4	28.9±16.9	0.33
SPWMD	122±74.2	82.2±53.9	0.39	139.6±76.3	78±51.9	0.01
SLWMD	63.3±39.3	26.1±30.5	0.04	24.2±29.1	35.9±35.5	0.31

Δ PVI: Maximum difference in time to peak systolic velocity between 2 of 12 segments; IVMD: Inter-Ventricular Mechanical Delay; TAI: Total Asynchrony Index; SPWMD: Septal-to-Posterior Wall Motion Delay; SLWMD: Septal-to-Lateral Wall Motion Delay
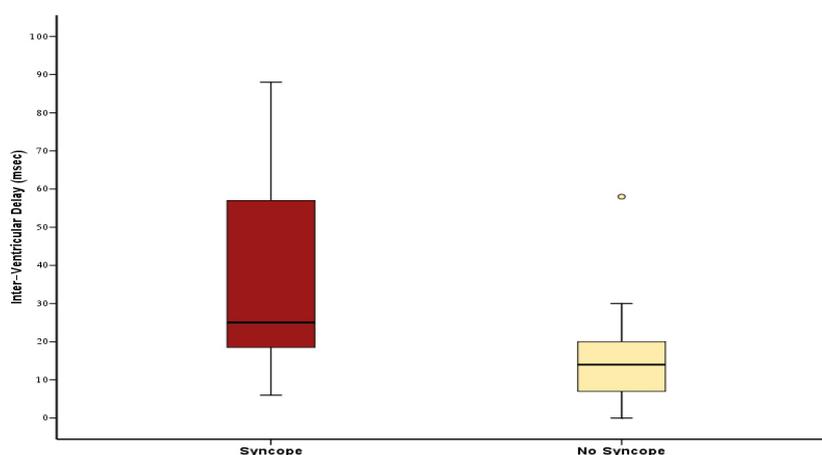
Figure 3. Significant correlation between interventricular dyssynchrony and syncope.

The differences between the mean of other indices in HOCM and HCM patients were not statistically significant. The mean of all dyssynchrony indices were greater in patients with atrial fibrillation (AF), compared to patients with normal sinus rhythm, but statistically significant results existed in corresponding ΔPVI, IVMD, TAI and SLWMD (Table 2). The mean of SPWMD was below the defined cutoff-point (130 ms) in both groups. However, the prevalence of dyssynchrony was more in AF group (66% versus 22%, P=0.02). Another finding was the greater mean of SPWMD in patients with moderate MR compared to those with none or mild MR (P=0.01). The difference in the prevalence of dyssynchrony also verified this finding (55.6% versus 21.4%, P=0.05).

As shown in Figure 3 and Table 3, all of the indices had greater means in patients with history of syncope. Interventricular delay was 36.72±26.26 msec in syncope vs 14.74±11.30 msec in non-syncope patients (P<0.001). Total asynchrony index in syncope and non-syncope groups were 39.40±22.38 msec and 27.70±17.32 msec respectively (P=0.08), , Maximum difference in time to

peak systolic velocity between 2 of 12 segments (ΔPVI) were 112.72±61.17 msec vs 77.87±49.22 msec (P=0.06).

Similarly, the mean of IVMD was higher in patients with an implanted ICD (P<0.001). Prevalence of dyssynchrony was higher in these group, too (50% versus 8.3%, P=0.007).

Discussion

Detection of subgroups at higher risk for important disease complications and premature death is a major objective in HCM screening evaluation. It has been suggested that TDI enable us to select subgroups of HCM patients at an increased risk of ventricular tachyarrhythmias.[8] We found significant interventricular dyssynchrony in patients with HCM with syncope compared with non-syncope groups. Andrea et al, found significant relationship between LV intraventricular systolic dyssynchrony and increased risk of sudden cardiac death in patients with HCM and also have suggested intra-ventricular systolic dyssynchronicity as the most powerful predictors of sudden cardiac death in the subsequent 5 years.[13] Regional systolic function in

Table 3. Dyssynchrony indices in HCM patients with syncope, compared to patients without syncope

	All HCM n=44	HCM with syncope n=11(25%)	HCM without syncope n=33(75%)	P
Interventricular delay(msec)	20.50±18.90	36.72±26.26*	14.74±11.30	<0.001
Total asynchrony index(msec)	30.62±19.13	39.40±22.38†	27.70±17.32	0.08
ΔPVI (msec)	86.59±53.91	112.72±61.17‡	77.87±49.22	0.06
Septal posterior wall motion delay (msec)	93.00±63.46	117.37±88.19	86.27±54.93	0.23
Septal to lateral delay(msec)	32.72±33.98	44.54±35.59	28.78±33.04	0.19

healthy heart is uniform and there is no significant regional dyssynchrony in basal and mid myocardial segments. The prevalence of LV systolic dyssynchrony in our study was from 20.5% to 38.6% based on different methods. Andrea et al, also reported a significant systolic dyssynchrony in a regional contraction in the basal and mid myocardial segments . They studied 35 HCM patients along with 45 age and sex-matched controls and found both significant Inter- and Intraventricular delays in HCM group(P<0.0001), despite the absence of intraventricular conduction defects by surface ECG and also suggested that an Intraventricular delay > 45 msec can identifiy a subgroup of HCM patients with unsustained ventricular tachycardia.[8,13] In our study we found higher intra and interventricular systolic dyssynchrony indices in patients with history of syncope and ICD implantation. It remains uncertain if ventricular dyssynchrony, ventricular arrhythmia and syncope have significant correlation to each other and that ventricular dyssynchrony is causes ventricular arrhythmia and syncope.

In our study we evaluated regional systolic and early diastolic velocities of all 12 segments. Both Sm and Em velocities have reduced values in all 12 segments and were significantly lower in syncope patients which can be an additional finding in diagnosis of malignant form of HCM. Regional systolic dysfunction despite normal global systolic function have been demonstrated by other studies [18-24] .Dumont demonstrated inverse correlation between intra LV systolic asynchrony and mean peak systolic velocity and suggested the mean Sm as a good index of global systolic function and even more sensitive than ejection fraction for detecting LV systolic dysfunction; while it is also associated with more severe systolic asynchrony.[25]

There is a controversy about the correlation between the intraventricular systolic dyssynchrony and the morphologic markers of disease severity. We found a significant intraventricular dyssynchrony in patients with HOCM (52.6% versus 24%, P=0.05), AF rhythm (66% versus 22%, P=0.020) and more than moderate MR.[8,24] In the other study it has been suggested that patients with LVOT obstruction have more symptoms, a dismal prognosis and are at higher risk for AF, heart failure, ventricular arrhythmia, and sudden death. Our study demonstrated that intraventricular dyssynchrony is also related to LVOT obstruction, AF rhythm and significant MR and concluded that LV dyssynchrony can be assumed as a marker of important disease complications. The main limitation of our study was that we could not establish the direct effect of LV systolic dyssynchrony on sudden cardiac death in HCM patients which needs long term follow up of such patients but found significant correlation between other markers of malignant form of HCM and LV systolic dyssynchrony.

Ventricular systolic dyssynchrony is more common in HCM patients with syncope. Patients with syncope have greater impairment of regional systolic and early diastolic function (remarkably lower Sm and Em velocities). These abnormalities provide further support for TDI analysis in determining high risk HCM groups who may benefit from ICD implantation.

References

1 Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. *Circulation* 1995;**92**:1680-92. [7671349]

2 Maron BJ, Ferrans VJ, Henry WL, Clark CE, Redwood DR, Roberts WC, et al. Differences in distribution of myocardial abnormalities in patients with obstructive and non obstructive asymmetric septal hypertrophy (ASH): light and electron microscopic findings. *Circulation* 1974;**50**:436-46. [4278057]

3 Spindler M, Saupe KW, Christe ME, Sweeney HL, Seidman CE, Seidman JG, et al. Diastolic dysfunction and altered energetics in the alphaMHC403/+ mouse model of familial hypertrophic cardiomyopathy. *J Clin Invest* 1998;**101**:1775-83. [9541509]

4 Carasso S, Yang H, Woo A, Vannan M, Jamorski M, Wigle E, et al. Systolic myocardial mechanics in HCM: Novel concepts implications for clinical status. *J Am Soc Echocardiogr* 2008;**21**:675-83. [18187306]

5 Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. *Am J Cardiol* 1981;**48**:418-28. [7196689]

6 Kato T, Izawa H, Komamura K, Noda A, Asano H, Nagata K, et al. Heterogeneity of regional systolic function detected by tissue Doppler imaging is linked to impaired global left ventricular relaxation in hypertrophic cardiomyopathy. *Heart* 2008;**94**:1302-6. [18198205]

7 De Marchi SF, Allemann Y, Seiler C. Relaxation in hypertrophic cardiomyopathy and hypertensive heart disease: relations between hypertrophy and diastolic function. *Heart* 2000;**83**:678–84. [10814629]

8 Andrea AD, Caso P, Severino S, Scotto di Uccio F, Vigorito F, Ascione L, et al . Association between intraventricular myocardial systolic dyssynchrony and ventricular arrhythmias in patients with HCM. *Echocardiography* 2005;**22**:571-8. [16060893]

9 Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ.Magnitude of left ventricular hypertrophy predicts the risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;**342**:1778-85. [10853000]

10 Monserrat L, Elliott PM, Gimeno JR, Tome M, Shah J, Ward D, et al. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: An independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;**42**:873-9. [12957435]

11 Elliott PM, Gimeno B, Mahon NG, Poloniecki JD, Mc-Kenna WJ.Relation between severity of left ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:420-4. [11273061]

12 Maron BJ, Estes NA3rd, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. *Circulation* 2003;**107**:2872-5. [12814983]

13 Andrea AD, Caso P, Severino S, CuomoA S, Cappozzi AG, Calabr A P, et al. A Prognostic value of intra-left ventricular electromechanical asynchrony in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2006;**27**:1311-8. [16364972]

14 Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;**287**:1308-20. [11886323]

15 Elliot AP, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;**363**:1881-91. [15183628]

16 Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy; a report of American College of Cardiology foundation task force on clinical expert consensus documents and the European Society of Cardiology committee for practice guidelines. *Eur Heart J* 2003;**24**:1965-91. [14585256]

17 Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;**105**:438-45. [11815425]

18 Usyk TP, Omens JH, McCulloch AD. Regional septal dysfunction in a three-dimensional computational model of focal myofiber disarray. *Am J Physiol Heart Circ Physiol* 2001;**281**:506-14. [11454551]

19 Dong SJ, MacGregor JH, Crawley AP, McVeigh E, Belenkie I, Smith ER, et al. Left ventricular wall thickness and regional systolic function in patients with hypertrophic cardiomyopathy: a three-dimensional tagged magnetic resonance imaging study. *Circulation* 1994;**90**:1200-9. [8087929]

20 Severino S, Caso P, Galderisi M, De Simone L, Petrocelli A, De Divitiis O, et al. Use of pulsed Doppler tissue imaging to assess regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;**82**:1394-8. [9856926]

21 Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with HCM and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation* 2001;**104**:128-30. [11447072]

22 Yang H, Sun J, Lever H, Popovic Z, Drinko J, Greenberg N, et al. Use of strain imaging in detecting segmental dysfunction in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2003;**16**:233-9. [12618731]

23 Carasso S, Rakowski H. Myocardial Fibrosis and Regional Function in Hypertrophic Cardiomyopathy: May the Force Be with You. *J Am Soc Echocardiogr* 2008 ;**21**:1306-8. [19041573]Kiavar M, Behzadnia N, Sadeghpour A, Maddadi SH. Clinical and Echocardiographic Evaluation of Regional Systolic Function Detected by Tissue Doppler Imaging in Hypertrophic Cardiomyopathy. *Iran Cardiovasc Res J* 2009;**3**:137-43.

24 Dumont CA, Monserrat L, Rodriguez E, Peteiro J, Fernedez X, Rodrguez A ,et al. Left Ventricular Asynchrony in Patients with Hypertrophic Cardiomyopathy: Its Determinants and its Relation to Left Ventricular Function. *J Am Soc Echocardiography* 2007;**20**:1247-52. [17604956]