



ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC DYSSYNCHRONY IN HYPERTENSIVE PATIENTS WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION USING TWO DIMENSIONAL SPECKLE TRACKING METHOD.

Physiology

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ABSTRACT

Background: Left Ventricular (LV) systolic dyssynchrony is common in patients with hypertension who are susceptible to the development of heart failure. The early detection of systolic dysfunction is thus a valuable information for implementing interventions for prevention of progression of heart failure. Patterns and degree of alterations in mechanical dyssynchrony in different segments of LV and its determinants in hypertensive patients have not been studied well. The present study thus aimed to evaluate the prevalence of LV systolic dyssynchrony in stable, asymptomatic patients with hypertension.

Material and Method: 2-dimensional echocardiographic (2DE) images of the LV were acquired in apical 4-chamber and parasternal short-axis view at mid ventricular levels to assess systolic dyssynchrony in 72 hypertensive patients with normal Left Ventricular Ejection Fraction (LVEF) and 57 healthy controls using speckle tracking method. LV Mass and LVEF were measured using 2D guided M Mode scan and diastolic function was assessed in early diastole with tissue Doppler imaging.

Results: The QRS complex was significantly prolonged in the hypertensive group as compared to the controls (109.5 ± 20.4 vs 86.5 ± 9.4 , $P < .01$). Also the systolic dyssynchrony indices were significantly higher in patients with hypertension than in the normal controls in between all the segments of the septum and the lateral wall of the LV ($P < .01$).

Conclusions: Sub clinical Left ventricular dyssynchrony is common among hypertensive patients with normal LV systolic function and no evidence of congestive heart failure.

KEYWORDS

Speckle tracking, Systemic hypertension, Left ventricular function.

INTRODUCTION

Hypertension is one of the earliest recorded medical conditions which has shaped the course of modern history and the consequences of hypertension (myocardial infarction, stroke, and heart failure) are predicted to be the leading global cause of death and is one of the major health issues worldwide. It is estimated to cause around 7.5 million deaths globally, about 12.8% of the total of all annual deaths. This accounts for 57 million DALYs or 3.7% of total DALYs.¹

The presence of hypertension may affect cardiac function not only by impairing myocardial function, but also by disturbing the coordination between regions of the ventricle, resulting in ineffective contraction. Thus, mechanical dyssynchrony, the incoordinate wall motion of different ventricular segments in systole and diastole, is also an important contributor to left ventricular dysfunction in hypertensive patients. Intraventricular dyssynchrony is a reflection of left ventricular remodeling, myocardial scarring and impaired LV function and that, accordingly, it should be detectable in all patients with LV dysfunction.^{2,3} Intra and Interventricular dyssynchrony have emerged as important mechanisms contributing to the progression of heart failure and left ventricular remodeling, and is the subject of debate.⁴ Although systolic mechanical dyssynchrony has been studied more than diastolic mechanical dyssynchrony, diastolic dyssynchrony is more common than systolic dyssynchrony in adults with both systolic and diastolic heart failure and may be associated with ventricular dysfunction and poor outcome.⁵ Also several studies have shown that the presence of intra-left ventricular dyssynchrony is one of the main predictors of response to Cardiac Resynchronization therapy (CRT).^{6,7,8}

Patients who have LV systolic dysfunction and dilatation frequently have a prolonged QRS complex. QRS prolongation is generally associated with delayed electrical activation of the left ventricle, leading to uncoordinated ventricular motion, decreased stroke volume, and mitral regurgitation. Because of this association, QRS duration has been used as a surrogate marker for ventricular dyssynchrony.⁹ The frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex ranges from 30% to as high as 50%, suggesting that dyssynchronous contractions can be present without substantially increasing the QRS duration on the electrocardiogram. The surface electrocardiogram may thus not be optimal for patient selection because electrical dyssynchrony (wide QRS complex) does not accurately reflect intra-LV dyssynchrony and may underestimate

it.¹⁰ Therefore, echocardiography is the most practical approach for identifying dyssynchronous contractions and has a key role in assessing LV dyssynchrony, i.e. the mechanical delay between septum and lateral wall contraction.¹¹

More recently volumetric real time two-dimensional echocardiography has been used in conjunction with semi-automatic border detection algorithms to evaluate heart-failure patients for the presence of mechanical asynchrony.¹² Myocardial wall motion has been shown to be accurately quantified by volume-time curve analysis with 2D analysis software.¹³ The two dimensional echocardiography has been described as the ideal imaging modality for assessment of global and regional myocardial function. By slicing the heart in multiple tomographic planes, real time imaging of endocardial motion and wall thickening of the entire myocardium is possible. The major advantages of echocardiography are that it is noninvasive, fast, atraumatic, portable and widely available at all cardiac centers.

The patterns and degree of alterations in mechanical dyssynchrony in different segments of LV in hypertensive patients have not been studied well. Thus we conducted this study with an aim to assess LV dyssynchrony in hypertensive patients with normal LVEF, using the novel two dimensional speckle tracking method.

MATERIAL AND METHODS

Setting and study design; Tertiary care hospital based prospective case control observational study.

Study subjects and selection method; patients of hypertension diagnosed on the basis of recording of Blood Pressure (BP) $>140/90$ mmHg on two occasions at an interval of 2-4 weeks and known hypertensives with BP $>140/90$ mmHg not on anti hypertensive medications were the patient population screened for enrollment in the study. Patients with LV systolic dysfunction with LVEF of $<50\%$, patients with regional wall motion abnormalities, patients with documented Myocardial Infarction (MI), valvular heart disease, or any other structural heart disease, patients with atrial fibrillation, chronic kidney disease were excluded from the study. The eligible patients consenting to participate after informed consent were enrolled in the study. Apparently healthy individuals visiting Cardiology OPD of IGMC for evaluation of symptoms related to chest pain, breathlessness etc. not found to have any significant heart disease and having

BP<140/90 mmHg were enrolled as control subjects after obtaining informed consent. The study protocol was approved by the ethical committee of the institution.

Data Collection; Data related to demographics, behavioral risk factors, clinical characteristics, anthropometry and BP were recorded using standard and validated tools and following standard guidelines. BP was recorded with mercury based sphygmomanometer using appropriate size BP cuff and observing all precautions after 5-10 minutes of rest. Two readings were recorded at an interval of 3-5 minutes in sitting position. Average of two readings was taken as the BP value. Weight was measured using flat surfaced weighing machine in light clothes with shoes off. Before recording weight zero error was corrected if found. Weighing machine was calibrated against standard weight periodically to ensure valid recording of weight. Height was measured using wall mounted calibration scale with off shoes and cap if any, subject standing erect with heels touching wall. Waist circumference was measured using non stretchable measuring tape in erect posture at the end of exhalation during normal breathing at point mid way between anterior superior iliac spine and lowest rib with the measuring tape parallel to the ground.

Measurement of LV systolic dyssynchrony, LVEF, LV Mass and LV Diastolic function; Echocardiography study was performed with echocardiography machine model I 33 of Philips Medical System using adult probe. All acquisitions were performed by the same experienced operator with the patients in the left lateral decubitus position. 2D guided M mode recording at tips of Mitral leaflets in Parasternal long axis view with simultaneous ECG signals recording to measure LV dimensions at the end of systole and diastole following guidelines of American society of echocardiography.¹⁴ Three consecutive cardiac cycles were analyzed to measure the Left ventricular end diastolic volume (LVEDV), Left ventricular end systolic volume (LVESV), LVEF and LV mass by averaging the three values. End systolic and end diastolic points were selected corresponding to end of T wave and peak of R wave of simultaneous recorded ECG tracing. Doppler inflow signals across MV during diastole with pulse wave Doppler and mitral annular velocity in longitudinal axis at medial septal and lateral wall annular points in early diastole E' was recorded with tissue Doppler imaging to measure E/A ratio, E wave deceleration time, e' and E/e' ratio as the indices of LV diastolic functions. 4 cardiac cycles of 2D images in apical four chamber and parasternal short axis view at mid cavity level were recorded in cine mode for measurement of systolic dyssynchrony of the LV. The study was recorded on DVD for offline analysis. Systolic dyssynchrony was analyzed using QLAB commercial software of Phillips for 2D strain imaging with speckle tracking method. After manual tracing of the endocardial border of 2D tomographic images of LV in longitudinal and short axis plane at mid cavity level at the end-systolic frame and selecting the appropriate region of interest, including the entire transmural wall, the software automatically determined six segments in each view. Each segmental strain curve was obtained by frame-by-frame tracking of the acoustic markers in the myocardial tissue. The tracking quality was scored as valid or poor. Segments with poor tracking despite manual readjustments of the region of interest were excluded from analysis. Peak systolic longitudinal strain (LS) was measured in 6 segments (the apical septum, mid inferior septum, basal inferior septum, basal anterolateral wall, mid anterolateral wall and apicolateral walls). Peak systolic radial strain (RS) was measured in six segments (mid anterior, mid anterior septum, mid inferior septum, mid inferior, mid inferior lateral wall and mid anterolateral wall) from a mid-LV short-axis view. Three cardiac cycles were analyzed and the peak radial and longitudinal strain, and time to peak radial and longitudinal strain were measured. Systolic dyssynchrony index of septum with lateral wall, anterior with inferior wall at mid LV plane were recorded by measuring differences in the time interval between peaks of negative strains between opposing walls e.g. anterior with inferior and septum with lateral wall.

Blood Biochemistry; 5 cc of venous blood sample was drawn in fasting state for estimation of blood sugar and lipid profile. Blood sugar and lipid profile was done using standard kits in fully automatic auto analyzer Model Konelab (Backman Coulter) of central biochemistry lab of IGMCC.

Statistics; Data was entered in Microsoft Excel spread sheet and Epi Info version 3.4.3 statistical software was used for statistical analysis. The clinical characteristics of the study population were reported as

percentages and Mean \pm sd for categorical and continuous variables respectively. Comparison of significance of differences in the distribution of categorical variables and study population means of continuous variables between group with and without Hypertension was analyzed by X2 test and unpaired t test or Mann Whitney test as appropriate respectively. Statistical significance of various clinical and metabolic determinants for impaired mechanical dyssynchrony were analyzed by calculating odds ratios and its 95% C.I. 2 tailed significance at <0.05 was taken as statistical significance.

Results

Clinical characteristics; of the study population of group with and without hypertension is described in detail in Table 1. In brief the mean age of the hypertensive group was significantly higher compared to normotensive group (46.12 \pm 11.17 yrs vs. 39.08 \pm 7.25 yrs; p <0.01) but the gender distribution was similar in both the groups (59.7% vs. 61.4%; p = 0.98). The study group means of Body Mass Index (BMI), Waist circumference (WC) and Waist Hip Ratio (WHR) among hypertensive and normotensive groups respectively was not significantly different. The mean QRS duration measure in 12 lead ECG was significantly higher among hypertensive group (109.5 \pm 20.4 vs. 86.4 \pm 22.5 msec.; p <0.01). As expected the mean Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were significantly higher among hypertensive groups than in normotensive group.

The mean fasting blood sugar, total cholesterol, LDL-C and TG were not significantly different in hypertensives and normotensive study groups but the TG/HDL ratio was significantly increased in the hypertensives when compared to the normotensives (4.18 \pm 2.76 Vs 3.79 \pm 3.22; p <0.05).

Table 1. Clinical Characteristics of the study groups

CHARACTERISTICS	NORMOTENSIVES (n=57)	HYPERTENSIVES (n=72)	P value
Age (yrs) (mean \pm sd)	39.1 \pm 7.3	46.1 \pm 11.1	0.01
Sex (Male) %	35(61.4%)	43(59.7%)	0.98
Diabetic Status (yes)%	14(24.6%)	16(22.2%)	0.91
Total-C(mg/dl)	183.3 \pm 35.1	194.9 \pm 43.8	0.08
LDL-C(mg/dl)	106.8 \pm 30.1	115.7 \pm 35.4	0.13
HDL-C(mg/dl)	44.5 \pm 11.1	44.3 \pm 13.6	0.58
TG(mg/dl)	152.4 \pm 100.3	173.3 \pm 115.3	0.09
TG/HDL	3.8 \pm 3.2	4.2 \pm 2.8	.058
DBP(mmHg)	84.5 \pm 5.9	96.5 \pm 9.1	0.01
MAP(mmHg)	98.6 \pm 6.0	115.1 \pm 8.6	0.01
QRS Duration (msec)	86.5 \pm 9.4	109.5 \pm 20.4	0.01

Echocardiographic characteristics; of the study population of group with and without hypertension is described in detail in Table 2. The mean LV mass was significantly higher among hypertensive group (142.85 \pm 32.0 vs. 127.1 \pm 27.5 gm; p <0.01) however LV volumes at end diastole and end systole were not significantly different. The mean LVEF of hypertensive and normotensive population was also not different statistically. The indices of LV diastolic function were significantly deranged among hypertensive groups when compared to the normotensive group [lateral mitral annular early diastolic velocity e' 10.90 \pm 3.54 Vs 12.42 \pm 3.01; p <0.01, medial annular velocity e' 7.59 \pm 2.22 Vs 8.43 \pm 2.01; p <0.02) and E/e' medial annular ratio of 9.68 \pm 2.33 Vs 8.67 \pm 1.79; p <0.01]. However there was no significant difference in E/A ratio and E wave deceleration time of mitral inflow doppler signals among the two groups.

Table 2. Conventional echo parameters in the study groups

Characteristics	Normotensives (n=57)	Hypertensives (n=72)	P value
LVEDV (ml)	89.6 \pm 22.5	94.1 \pm 22.1	0.15
LVESV (ml)	31.7 \pm 9.7	32.3 \pm 11.4	0.88
LVEF (%)	64.9 \pm 5.2	65.3 \pm 6.5	0.54
LV mass (gms)	127.1 \pm 27.5	142.8 \pm 32.1	0.01
E/A ratio	1.2 \pm 0.3	1.1 \pm 0.3	0.07
EWDT (msec.)	177.3 \pm 35.6	172.7 \pm 33.4	0.57
E (m/sec)	70.8 \pm 13.1	70.4 \pm 16.8	0.85

A (m/sec)	62.6±12.1	67.3±14.3	0.07
Medial mitral annular E' (m/sec)	8.4±2.1	7.6±2.2	0.07
Lateral mitral annular E' (m/sec)	12.4±3.1	10.9±3.5	0.01
E/E' (Medial annular)	8.7±1.8	9.7±2.3	0.01

Correlates of Left Ventricular Dyssynchrony; of the study population of group with and without hypertension is described in detail in Table 3. The systolic dyssynchrony indices were found to be significantly higher in patients with hypertension than in the normal controls in between all the segments of the Septum and the Lateral wall of the LV in both the Apical four chamber ($p < .05$) and the Short axis view ($p < .05$).

TABLE 3: Echo Based Systolic Dyssynchrony Index Among Hypertensive And Normotensive Study Population

VARIABLES	NORMOTENSIVE	HYPERTENSIVE	P value
(4CV)APS-APL (ms)	23.58 ± 7.17	55.18 ± 9.41	0.03
MIS-MAL(ms)	22.52 ± 6.51	57.94 ± 14.01	0.01
BIS-BAL(ms)	24.22 ± 6.34	57.22 ± 10.92	0.01
(SXV)MA-MI(ms)	19.73 ± 6.66	59.78 ± 10.43	0.01
MAS-MIL(ms)	21.50 ± 5.31	60.78 ± 8.82	0.00
MIS-MAL(ms)	21.88 ± 6.22	57.08 ± 9.70	0.01

Discussion

Present study aimed to evaluate the prevalence of systolic LV asynchrony in patients with newly detected hypertension with normal LVEF using Speckle Tracking 2D Echocardiography. On measuring the differences in the time to peak systolic strain between two opposing LV segments in the four chamber view there was a consistent trend of longer time to peak systolic strain across the different opposing LV wall segments in the hypertensive population compared to controls which was statistically significant in between all the segments [APS-APL (55.18 ± 9.41ms vs. 23.58 ± 7.17ms; $p < .05$), MIS-MAL (57.94 ± 14.01 ms vs. 22.52 ± 6.51 ms; $p < .05$) and BIS-BAL (57.22 ± 10.92 ms vs. 24.22 ± 6.34 ms; $p < .05$)]. This trend was also noticed in the short axis view (between MA-MI - 59.78 ± 10.43 ms vs. 19.73 ± 6.66 ms; $p < .05$, MAS-MIL - 60.78 ± 8.82ms vs. 21.50 ± 5.31 ms; $p < .05$, MIS-MAL - 57.08 ± 9.70 ms vs. 21.88 ± 6.22 ms; $p < .05$). This mechanical dyssynchrony was further supported by the presence of electrical dyssynchrony on electrocardiogram which showed a significantly higher QRS duration in the hypertensive population than the normotensives (109.47±20.38 ms vs. 86.45±9.42 ms; $p < 0.001$).

Normally, the intraventricular septum is activated first followed by LV lateral wall, with delay not more than 25 ms which is the time taken by the impulse for spreading through the Purkinje fibers. In hypertensive patients, the septal-lateral delay becomes more significant and exceeds the normal limit owing to large ventricular mass and minor fibrosis between muscle fibers. The LV function is sustained not only by the contraction and relaxation of the myocardium, but also by the synchronicity of the left ventricle and the LV synchronicity in turn is influenced by many diseases, including dilated cardiomyopathy, coronary heart disease ,diabetes mellitus , hypertension , and diastolic heartfailure.^{15,16,17}

Kwon et al¹⁸ reported similar observations and confounded that systolic synchronicity was impaired in never treated hypertensives in comparison to normal controls. The main and novel finding of their study was that systolic dyssynchrony was independently impaired in the non LVH group with never treated hypertension when compared with controls, to a similar degree of that of the LVH group, suggesting that never treated hypertension in itself contributes to impaired systolic synchrony irrespective of LVH.

On the contrary Tan et al¹⁹ in their study divided the hypertensive population into LVH and Non LVH group on the basis of LVMI(LVMI>150g/m² as LVH) and compared their systolic synchronicity with the normal controls and reported that systolic synchronicity was more impaired in the LVH group than in the non LVH group and the controls. They further opined that the left ventricular geometry predicts the risk of cardiovascular events in hypertension and since LVH is not uncommon in hypertensive patients, it is generally agreed that hypertensive individuals with LVH are more prone to systolic dysfunction. The LV hypertrophy in hypertension is also associated with increased myocardial fibrosis.^{20, 21, 22} In addition, myocardial

ischemia caused by microvascular changes and an imbalance between oxygen demand and reduced coronary flow reserve may also contribute to the presence of impaired myocardial performance.²³ Chang et al²⁴ and Yang et al²⁵ also noticed similar findings in their studies and concluded that left ventricular dyssynchrony was significantly related to LV mass in hypertensives with normal LV systolic function.

Soliman et al²⁶ compared LV dyssynchrony among hypertensive patients and controls and found out that the delay between the septal and lateral walls was significantly higher in hypertensive patients than in controls. The severity of dyssynchrony was significantly related to LV mass, septal wall thickness, posterior wall thickness, and left ventricular end-diastolic dimension. Bae et al²⁷ evaluated LV dyssynchrony in 42 hypertensive patients pre and post antihypertensive treatment. The severity of Systolic dyssynchrony improved with antihypertensive treatment, and was associated with the regression of LV mass. LV systolic or diastolic dyssynchrony evaluated through the myocardial imaging techniques has been revealed to be more prevalent than expected with prevalence of 25.0 or 21.7%, respectively, in patients with a preserved LV systolic function (EF>50%), and these did not occur in parallel.

Our study extends the findings of these studies, and identifies LV dyssynchrony in hypertensive patients without any systolic dysfunction or clinical evidence of congestive heart failure. This could be related to differential wall stress experienced by myocardial fibers oriented in different planes. The increased LV mass, diastolic hypertension and impaired fasting sugar can be associated with mechanical nonuniformities (dyssynchrony), which lead to inefficient pump performance and energy expenditure and thus are risk factors for subclinical LV systolic dysfunction. The Left ventricular geometry predicts the risk of cardiovascular events in hypertension and thus needs to be evaluated accordingly.

Limitations; The present study was a single-center observational study thus plausible mechanisms relevant to the results in the current study and the potential clinical implications cannot be provided. Also the sample size was small so due to limited power of the study the null hypothesis may have been falsely accepted. Another limitation of our study was the lack of precise information about the time of onset and progression of the hypertension as most of our case patients were unaware of their hypertensive status before their first visit. The observations reported in the study are on hospital based patient population thus with inherent selection biases.

Conclusion

Hypertensive population with preserved LVEF had subclinical LV systolic dyssynchrony which was evident both in the 4 chamber as well as in the short axis view. Mid cavity regions were the first one to show significant prolongation.

As it is unknown whether subclinical LV systolic dyssynchrony could progress to severe overt heart failure or not, follow up of patients with positive findings is required periodically.

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