ORIGINAL ARTICLE

SUBCLINICAL SYSTOLIC DYSFUNCTION AMONG NEWLY DIAGNOSED HYPERTENSIVES WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION USING TWO DIMENSIONAL STRAIN IMAGING METHOD: HOSPITAL BASED OBSERVATIONAL STUDY

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ABSTRACT

Background: Heart failure is the major cause of morbidity and mortality in hypertension. Early detection of subclinical systolic heart failure thus is an important step in prevention of clinical heart failure. There are limited studies evaluating the presence and determinants of subclinical heart failure along axial, circumferential and radial axis among hypertensives with normal Left Ventricular Ejection Fraction (LVEF) using strain imaging methods. Present study aimed to detect the subclinical global and regional systolic dysfunction in longitudinal, circumferential and radial axis and its determinants in hypertensive patients with normal LVEF.

Material and Method: 2-dimensional echocardiographic (2DE) images of the Left Ventricle (LV) were acquired in apical 4-chamber and parasternal short-axis view at mid ventricular levels to assess global and regional strain in longitudinal, radial and circumferential axis in 72 hypertensive patients with normal 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 regional strain in longitudinal axis was significantly reduced at Apex and Apico lateral segment of LV in hypertensive population compared to normotensive group (-17.99± 5.21 Vs-19.77±4.17; $p<0.01$ and -14.78 ±5.69 Vs -17.40± 5.23; $p<0.01$) respectively. However the mean Global Longitudinal and circumferential systolic Strain was not significantly reduced in the hypertensive group when compared to the normotensive group.

Conclusions: The regional LV systolic function in longitudinal axis at apex and apico lateral wall was significantly reduced while the global systolic function in longitudinal and circumferential axis was preserved in hypertensive patients compared to normotensive healthy individuals.

Keywords: Speckle tracking, Systemic hypertension, Left ventricular function.

ABBREVIATIONS

EF: Ejection Fraction
EWDT: E Wave Deceleration Time
GLS: Global longitudinal strain
GCS: Global circumferential strain
HC: Hip Circumference
HHD: Hypertensive heart disease
LS: Longitudinal Strain
LVEF: Left Ventricle Ejection Fraction
LVEDV: Left Ventricle End Diastolic Volume
LVESV: Left Ventricle End Systolic Volume
LVH: Left Ventricle Hypertrophy
LVMI: Left Ventricular mass index
MAP: Mean arterial Pressure
RS: Radial Strain
WHR: Waist hip ratio

INTRODUCTION

The burden of hypertension is increasing globally[1] and ranks number one among risk factors for DALY. [2] Hypertensive heart disease is an important cause of morbidity and mortality in patients of hypertension.[3] Hypertension is an important risk factor for development and progression of systolic dysfunction. Systemic hypertension increases LV wall stress that triggers activation of various neurohormonal pathways leading to expression of genes regulating structural remodeling of myocardium and extra cellular matrix leading to increase in LV Mass and sets the stage for progression of systolic and diastolic dysfunction.[4] Moreover, while conventional echocardiography can detect changes in LV diastolic dysfunction associated with Left Ventricular Hypertrophy(LVH), global LV systolic function often remains preserved until late in the course of the disease, making subtle changes in LV contractile function difficult to interpret in the early stages.[5,6,7]

The early detection of subclinical systolic dysfunction is a valuable information for implementing interventions for prevention and control of progression of heart failure. LV emptying during systole is a result of shortening of LV myocardial fibers in longitudinal, circumferential and radial axis.[8] Thus understanding of alterations in regional myocardial shortening in three different axis is of great importance in identification, quantification and prognostication of patients with myocardial dysfunction. The noninvasive quantification of regional myocardial systolic function is an important goal in clinical cardiology.[9] Currently available routine methods for assessment of regional myocardial function are subjective and best semiquantitative.[10] Echocardiographic strain imaging (deformation imaging) has emerged as a novel method to quantify myocardial strain in different axis, and due to its ability to differentiate between active and passive movements of myocardial segments and to evaluate components of myocardial function, such as longitudinal myocardial shortening, that are not visually assessable, it allows comprehensive assessment of myocardial function and the spectrum of potential clinical applications is very wide.[11]

Mirsky and Parmley initially introduced the concept of strain to facilitate the understanding of elastic stiffness in heart muscle. They defined strain as a dimensionless quantity that represents the percentage change in dimension from a resting state to one achieved following application of a force (stress).[12] Edvarsden et al[13] and Gotte et al[14] too reported on the utility of strain measurements for assessment of the regional contractile properties of the myocardium, the former by tissue Doppler echocardiography and the latter by Magnetic Resonance Imaging. Two-dimensional (2D) speckle tracking is one of the latest echocardiographic techniques for rapid, offline, bedside analysis of regional LV strains in the longitudinal, radial, and circumferential directions.[15, 16, 17]

The effect of hemodynamic loading conditions operative in patients of hypertension with normal LVEF on systolic deformations in axial, circumferential and radial axis has not been evaluated adequately. Thus we conducted this study with an aim to detect subclinical impaired systolic shortening in global longitudinal, circumferential and radial axis and in regional myocardial segments in patients of hypertension with normal LVEF using two-dimensional strain imaging.

MATERIAL AND METHODS

Setting and study design; Tertiary care hospital based 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 5-10minutes of rest. Two readings were recorded at an interval of 3-5 minutes in sitting position. Averages of two readings were 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 strain, 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 were recorded to measure LV dimensions at the end of systole and diastole following guidelines of American society of echocardiography.[18] 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 É 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 was recorded in cine mode for measurement of systolic strain imaging in longitudinal, circumferential and radial axis. The study was recorded on DVD for offline analysis. 18 segments model was used to measure regional systolic strain in longitudinal, circumferential and radial axis. Strain imaging 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 7 segments (the apex, apical septum, mid inferior septum, basal inferior septum, basal anterolateral wall, mid anterolateral wall and apicolateral walls. Three cardiac cycles were analyzed and averaged value was taken as mean of regional and global longitudinal strain. Peak systolic radial strain (RS) and circumferential strain (CS) were 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 values were averaged and taken as the mean RS and CS, respectively.

Definition of decreased global systolic strain: The cutoff value taken for labeling depressed global systolic strain in any axis was taken as value $\leq 10^{th}$ percentile of the distribution among normal healthy population of control group.

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 (Backmancoulter) of central biochemistry lab of IGMC .

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±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 X^2 test and unpaired t test or Mann Whitney test as appropriate respectively. The distribution of clinical characteristics among group with decreased global systolic strain with group having preserved global systolic strain was done using X^2 and unpaired t test for categorical and continuous variables respectively. Variables found to have significant associations with depressed global systolic strain was modeled in linear regression model to determine the independent predictor of global systolic strain using global longitudinal strain as the dependent variable. 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 Table1.

Table 1: Clinical Characteristics of the study groups

Characteristics	Normotensives (N=57)	Hypertensives (N=72)	P value
Age (yrs) (mean±sd)	39.1±7.3	46.1±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±35.1	194.9±43.8	0.08
LDL-C(mg/dl)	106.8±30.1	115.7±35.4	0.13
HDL-C(mg/dl)	44.5±11.1	44.3±13.6	0.58
TG(mg/dl)	152.4±100.3	173.3±115.3	0.09
TG/HDL	3.8±3.2	4.2±2.8	0.05
DBP(mmHg)	84.5±5.9	96.5±9.1	0.01
MAP(mmHg)	98.6±6.0	115.1±8.6	0.01
QRS Duration (msec)	86.5±9.4	109.5±20.4	0.01
LVEDV (ml)	89.6±22.5	94.1±22.1	0.15
LVESV (ml)	31.7±9.7	32.3±11.4	0.88
LVEF (%)	64.9±5.2	65.3±6.5	0.54
LV mass (gms)	127.1±27.5	142.8±32.1	0.01
E/A ratio	1.2±.3	1.1±.3	0.07
EWDT(msec.)	177.3±35.6	172.7±33.4	0.57
E(m/sec)	70.8±13.1	70.4±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

Table 2: Comparison of global and regional systolic strain in longitudinal, circumferential and radial axis in hypertensive and normotensive groups

Variables	Normotensives	Hypertensives	P value
Global Longitudinal strain(%)	-18.3±3.4	-17.5±3.7	0.16
Global Circumferential strain(%)	-16.6±5.9	-17.1±6.3	0.69
Regional axial strain			
Apical segment(%)	-19.8±4.2	-17.9± 5.2	0.02
Apical septum(%)	-22.5± 3.8	-21.9± 5.4	0.85
Mid Inferior Septum(%)	-21.5± 4.8	-20.21± 5.5	0.09
Basal Inferior Septum(%)	-16.8± 5.1	-16.3± 5.8	0.58
Basal Anterior lateral(%)	-22.2 ±6.8	-22.3 ±6.7	0.65
Mid anterior lateral(%)	-21.4± 8.1	-20.4± 7.9	0.46
Apico lateral(%)	-17.4± 5.2	-14.8 ±5.7	0.01
Regional Circumferential strain			
Mid anterior(%)	-22.5± 8.9	-24.9 ±10.5	0.30
Mid anterior septum(%)	-22.1 ±7.6	-20.9± 8.1	0.27
Mid Inferior septum(%)	-18.7 ±8.8	-19.3 ±9.1	0.87
Mid Inferior(%)	-21.5 ±9.2	-22.5 ±7.3	0.24
Mid Inferior lateral(%)	-19.1± 7.3	-20.1± 9.8	0.82
Mid anterior lateral(%)	-17.6± 7.8	-17.5 ±7.4	0.90
Regional Radial strain			
Mid Anterior(%)	23.9± 9.3	23.1 ±10.1	0.47
Mid Anterior Septum(%)	27.9± 8.7	22.9± 8.9	0.01
Mid Inferior Septum(%)	23.6± 8.4	21.92±8.6	0.29
Mid Inferior(%)	24.1 ±8.9	24.5 ±8.3	0.47
Mid Inferior Lateral(%)	24.1 ±10.1	24.5± 8.9	0.49
Mid Anterior Lateral(%)	25.2 ±11.3	23.8± 10.1	0.51

In brief the mean age of the hypertensive group was significantly higher compared to normotensive group (46.12±11.17 yrs vs. 39.08±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±20.4 vs. 86.4±22.5 msec.; p<0.01). As expected mean the Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were significantly higher among hypertensive groups than in normotensive group.

Echocadiographic characteristics; the mean LV mass was significantly higher among hypertensive group (142.85±32.0 vs. 127.1±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±3.54 Vs 12.42±3.01; p<0.01, medial annular velocity e' 7.59±2.22 Vs 8.43±2.01; p<0.02) and E/e´medial annular ratio of 9.68±2.33 Vs 8.67±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.

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±2.76 Vs 3.79±3.22; p<.05).

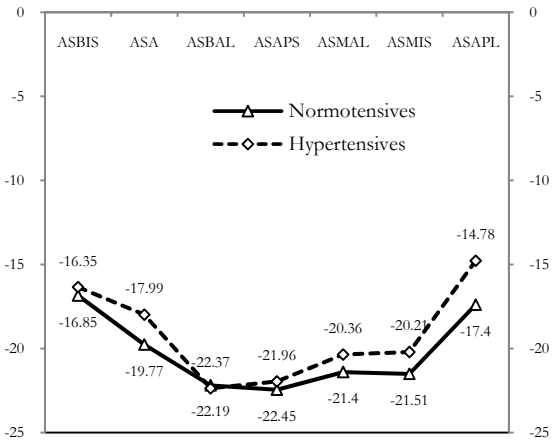

Fig.1 Echo based regional Longitudinal Strain

Global and regional systolic functions in Axial, Circumferential and radial axis; The regional longitudinal strain was significantly reduced in the Apex (-17.99± 5.21 Vs -19.77±4.17; p<.05) and the Apico lateral segment (-14.78 ±5.69 Vs -17.40± 5.23; p<.05) of LV (Table 2, Fig.1) . However no significant difference in remaining segments in longitudinal, circumferential and radial axis was observed. There was no statistically significant difference in the global systolic strain along longitudinal and circumferential axis between the study groups.

Table 3: Distribution characteristics of population with decreased global axial strain [<10th percentile of normotensive group (13.0)]

Variables	GLS≤13 (n=18)	GLS>13 (n=111)	P value
Age(years)	45.8±9.7	42.5±20.3	0.21
Sex (male) %	16(88.9%)	62(55.9%)	0.01
Smoking status (yes) %	1(5.6%)	7(6.3%)	0.68
Alcohol consumption(yes) %	5(27.8%)	16(14.4%)	0.28
BMI(kg/m^2)	26.7±3.2	25.7±3.9	0.27
W.C.(cm)	94.2±6.9	88.1±10.0	0.01
WHR	0.95±0.04	0.9±0.06	0.01
SBP(mmHg)	149.1±17.6	139.9±15.4	0.02
DBP(mmHg)	97.6±12.5	90.1±8.9	0.01
MAP(mmHg)	114.8±13.6	106.7±10.3	0.01
QRS Duration (msec)	102.5±21.5	98.7±19.8	0.46
FBS(mg/dl)	105.4±37.3	91.8±10.7	0.01
TG/HDL	5.1±3.4	3.8±2.9	0.09

Table 4: Multi variable Linear Regression modeling

Variable	Coefficient	Std Error	F-test	P-Value
DBP	-0.119	0.044	7.2286	0.008178
FBS Status	-1.355	0.672	4.0633	0.046022
LV Mass	-0.031	0.010	9.9774	0.001998
SBP	0.032	0.028	1.3749	0.243265
WC cm	-0.038	0.031	1.5214	0.219777
Constant	31.990	3.339	91.8037	0.000000

Correlation Coefficient: r^2=0.22

Characteristics of study population with impaired global axial strain; 13 (18.1% with 95% C.I. of 0.145-1.30) patients from the hypertensive group had impaired GLS (Table 3). The study group with depressed global longitudinal strain had significantly higher WC (94.2±6.9 Vs 88.1±10.0 cm; p<.05), WHR (.95±.04 Vs .90±.06; p<.05) and FBS (105.44±37.3 vs. 91.85±10.7 mg/dl; p<.05). The mean SBP (149.11±17.653 Vs 139.91±15.406; p<.05), DBP (97.67±12.57 Vs 90.13±8.99; p<.05) and MAP (114.81±13.59 Vs 106.71±10.36; p<.05) was also significantly higher in the study group with depressed global systolic strain.

Independent predictors of depressed Global axial strain(Table 4):- multi variable linear regression modeling by fitting variables found to have significant association with depressed global systolic strain revealed Diastolic Blood pressure, LV mass, and impaired fasting glucose were independent predictors of impaired global axial strain.

DISCUSSION

Present study aimed to detect subclinical LV systolic dysfunction in longitudinal, circumferential and radial axis and their determinants in patients with newly detected hypertension with normal LVEF using strain imaging. The global strain in longitudinal and circumferential axis was not significantly different in hypertensive and normotensive groups. The regional longitudinal strain at apex and apicolateral segment was significantly reduced in hypertensive group while there was no significant difference in axial strain in other segments. The reduction in global and regional systolic strain in axial direction in hypertensive population with normal LVEF was also reported by Kouzu et al [19] and Galderisi et al [20, 21].The absence of significant reduction in global axial strain in present study could be related to differences in hypertensive patients recruited based on different methods of LVEF measured; M Mode based in present study and biplane area length method used by other investigators (Galderisi et al [21]).

The global circumferential and regional radial axis strain were also reported to be preserved in hypertensive patients in the studies done by Galderisi et al [20], Sengupta et al [22] and Imbalzano et al[23]. LV mass, DBP, impaired fasting sugar were found to be independent predictors of reduced global strain in longitudinal axis. Similar observations were also reported by Narayanan et al[24] and Chen et al[25] in their respective studies.

Thus the findings of the present study supports the observations made by other investigators that the early features of LV systolic dysfunction in hypertension with apparently normal appearing LV systolic function is in the axial axis while systolic shortening in circumferential and radial axis are preserved. This could be related to differential wall stress experienced by myocardial fibers oriented in different planes. Increased LV mass, Diastolic hypertension and impaired fasting sugar are associated with reduced axial strain and thus are risk factors for subclinical LV systolic dysfunction. The association of reduced medial and lateral early diastolic mitral annular velocity with reduced axial systolic strain is a surrogate marker rather than a predisposing factor.

The documentation of subclinical LV systolic dysfunction in axial plane is an important observation and has implications for close monitoring and better control of BP with agents that not only control BP but also achieve regression of LVH and control of blood sugar in patients with dysglycemia. But these interventions needs to be proven in randomized controlled trial as evidence based intervention for prevention of development of hypertensive heart disease.

Limitations: The results of the present study are applicable to only newly diagnosed hypertensive population where the duration of the hypertension is likely to be short. The sample size was small so the trends of reduced regional systolic strain observed in longitudinal axis might be truly reduced but due to limited power of the study the true differences in regional and global strain could not be detected. The reproducibility of the estimates of systolic strain using the speckle tracking method was not recorded thus there could have been measurement bias especially in small sample size study population. 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 global systolic dysfunction in longitudinal

axis in about 18.1% (95% C.I. of 0.145-1.30). Apical and apicolateral regions are the first one to show significant reduction in longitudinal systolic strain

The global as well as regional strain in circumferential and radial axis remained preserved. Increased LV mass, Diastolic hypertension and impaired fasting glucose were independent predictors of reduced global axial systolic strain.

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