Section A-Research paper

COMPARISON OF LEFT VENTRICULAR DEFORMATION BY ECHOCARDIOGRAPHY WITH AND WITHOUT CORONARY ARTERY DISEASE AMONG CHRONIC STABLE ANGINA PATIENTS

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ABSTRACT

Objective: Myocardial deformation is assessed by 2Dimensional Speckle Tracking Echocardiography which is the way of analysing resting Left Ventricular myocardial function in patients with chronic stable angina, as well as in predicting underlined ischemia.

Methods: 50 consecutive patients with positive stress test & preserved Left ventricular Ejection Fraction were included in the study. Included patients were subjected to exercise test, Echo and coronary angiogram. Strain analysis was performed offline using Echo-Pac by averaging peak systolic longitudinal, circumferential and radial strain of 18 segments. Torsion parameter was assessed by net difference between basal and apical LV rotation obtained from short axis view. Dukes score and metabolic equivalents were used as outcome of exercise test. Coronary stenosis of ≥70% reduction of the arterial lumen area was considered to be significant Coronary Artery Disease (CAD).

Results: Total of 50 patients enrolled had a mean age of 57.82±10.32 years. 25(50%) were non-significant coronaries and 25(50%) were significant coronary artery disease. Global longitudinal strain and Global radial strain were significantly reduced when compared between non-significant and significant coronary artery disease groups *(-18.4± 2.34 vs. -16.5± 2.11; p=0.004 and 39.65 ± 8.66 vs. 31.9 ± 10.36; p =0.006 respectively)*. Torsion was significantly reduced and statistically significant among non-significant and significant coronary artery disease groups *(2.74 ± 1.18 vs. 1.96± 1.17; p=0.024)*. The exercise capacity of patients with significant coronary artery disease between normal and significant coronary artery disease groups were impaired and statistically significant *(9.00 ±2.10 vs. 7.69± 2.05; p=0.039).*

Conclusions: In Chronic stable angina patients, the resting myocardial deformation analysis using 2-Dimentional Speckle Tracking Echocardiography will effectively differentiate between significant and non-significant coronary artery disease

Keywords: Speckle Tracking Echocardiography, Global Longitudinal strain, Torsion, Significant Coronary artery disease

Abbreviation List

CAD: Coronary Artery Disease

CAG: Coronary angiogram

CSA: Chronic stable angina

PCI: Percutaneous coronary intervention

STI: Speckle Tracking imaging

INTRODUCTION

Coronary artery disease (CAD) remains as the major cause of morbidity and mortality [1]. In 1772, William Heberden the English physician described Angina Pectoris (Angina) as one of the classic symptoms of CAD [2].

Myocardial fibers which are more prone to ischemia are oblique & transversely oriented. And the measurement of motion and deformation will be the sensitive marker for CAD. Injury to longitudinally oriented fibers can be demonstrated by longitudinal systolic and early diastolic velocities. These are measured by tissue Doppler imaging (TDI) which are the independent predictors of CAD [3]. Since TDI has angle dependency and tethering effect as the disadvantage [4], STE is considered as the better choice to detect the myocardial deformation at rest. Hence Speckle tracking echocardiography (STE) is used as the most recent technique that provides a global approach to find the myocardial mechanics. This will give information about the three spatial dimensions of cardiac deformation [5].

It is very rarely demonstrated that whether circumferential, radial deformation and torsion parameters measured by STE at rest are as useful as longitudinal deformation for the detection of significant coronary artery disease. Therefore, aim of the study is to determine whether the resting STE at rest can predict the presence of significant CAD in consecutive patients with chronic stable angina and with positive exercise stress test which can improve the diagnostic performance of a well-established non-invasive method

METHODS

1. Study population;

Subjects admitted for coronary angiogram with positive exercise stress test from June 2018 to December 2018 with normal resting LVEF (left ventricle ejection fraction) were included in the study. It's a prospective study took place in Department of Cardiology KMC, Manipal. Patients with prior History of Myocardial infarction, Coronary Artery Bypass Graft, Valvular heart disease and baseline LV dysfunction were excluded. All the included patients were subjected to echocardiographic evaluation including speckle tracking echocardiography (STE). The protocol was approved by institutional Ethics Committee KMC Manipal. Patients were enrolled after Clinical Trial Registry-India registration. Informed consent was taken from all the included patients.

2. Echocardiography:

Transthoracic Echocardiography was performed to assess left ventricular deformation by using vivid 7-echocardiography system (GE) with a 2.5MHz transducer.

3. Conventional Echocardiography:

LV diameters and wall thicknesses were measured in the left parasternal long axis at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. LVEF was determined using modified biplane Simpson's method in Apical 4-CH and two-chamber (2-CH) apical views as recommended by the American Society of Echocardiography [6].

4. Two-dimensional Speckle Tracking Echocardiography:

Three consecutive cardiac cycles (80-100 frames/s) were acquired in Apical 4CH, 2CH, 3CH and Short axis at 3 levels (Base, Mid and Apex). The 2D STE analysis was done off-line by using Echo-Pac. Analysis was done by tracing the endocardial border and the region of interest was divided into 6 segments automatically by the software. After the region of interest was selected the software automatically gave the strain and strain rate curve patterns of different segments along with Bull's eye of 17 segments. Global strain values were obtained by averaging these segments. Apical 4CH, 2CH and 3CH gives longitudinal strain and strain rates, whereas Short axis views base, mid and apical level gives radial and circumferential strain and strain rates.

LV twist was calculated as difference between clockwise rotation of the base and counter-clockwise rotation of the apex expressed in degrees (°). While torsion was defined as LV twist per unit length and was obtained by dividing the total twist degree by the length of the ventricle (°/cm). LV torsion was obtained by tracing the endocardial border of base and apical region in short axis view. LV Length was defined as the maximum distance between the midpoints of the mitral annulus to the apex in the apical two- and four-chamber views [7, 8]

5. Exercise Electrocardiogram:

The exercise stress ECGs were analysed and categorised as either normal or abnormal. An abnormal exercise ST response was defined as ≥1mm of horizontal or downsloping ST depression (J point + 80 ms) or ≥1mm ST-segment elevation. Duke score was considered to be a strong prognostic and diagnostic index since it combines information regarding the exercise capacity, ECG alterations and symptoms during the exercise test [9].

6. Coronary Angiogram:

Coronary Angiogram was performed routinely by radial or femoral approach [10]. Coronary angiograms were obtained for each coronary vessel in at least two projections and stenosis with ≥70% reduction of the arterial lumen area was considered significant.

7. Statistical Analysis:

Statistical analysis was performed using the EZR (32 bit) version 1.37. Continuous data are expressed as mean ± SD and categorical data are presented as number (percentage). Independent t-test was performed to evaluate the comparison between significant and non-significant CAD groups. Pearson correlation was used to correlate between metabolic equivalent with Global Longitudinal Strain (GLS) and Torsion. Receiver Operating Characteristic (ROC) curve was performed to obtain the cut-off point for GLS, Global

Circumferential Strain (GCS), Global Radial Strain (GRS) and Torsion. A p value of <0.05 was considered as statistically significant.

RESULTS

Total of 67 subjects were selected, out of which 9 subjects were not willing to sign consent and 8 subjects' transthoracic window was not conducive for good image recording. Finally, 25 subjects without Coronary artery disease and 25 subjects with Coronary artery disease were considered for analysis. Both the groups had positive Treadmill test and underwent CAG.

1. Clinical data: Diabetes Mellitus and Hypertension were statistically significant between patients with significant and non-significant (CAD) coronary artery disease (Table 1).

2. Exercise ECG: Metabolic equivalents and Corrected QT interval were statistically significant between patients with significant and non-significant CAD (Table 2)

3. Conventional echocardiography: LV dimensions and LVEF by M-Mode and Simpson's method were not statistically significant between patients with significant and non-significant CAD (Table 3).

4. Speckle Tracking Echocardiography: Longitudinal, Radial and Circumferential Strains of 18 segments at base, mid and apex was averaged and these parameters were decreased in significant CAD groups compared to non-significant CAD. Global Longitudinal and Radial strain was found to be statistically significant (p value <0.05) with decreased strain among significant CAD patients (Table 4).

Segmental Regional Longitudinal, Circumferential and Radial strain & strain rate at base, mid and apex were significantly reduced in patients with CAD when compared to that of non-CAD group. Specific segments supplied by stenotic coronary artery showed lower regional strain when compared to segments supplied by non-stenotic coronary artery. Regional Longitudinal and Radial strain were statistically significant with p value< 0.05, and regional circumferential strain did not show any statistical significance (Table 5). Apical/Basal rotation, Torsion and Twist parameters were significantly reduced in patients with significant CAD when compared with Non-CAD. Only Torsion showed statistical significance with p value < 0.05 and other parameters were not statistically significant (Table 6).

5. Correlation analysis: Analysis showed weak negative linear correlation between METS and GLS *(p=0.118; r=-0.32)* and weak positive linear correlation between METS and Torsion *(p=0.46; r=0.153*) in patients with significant CAD.

6. Receiver Operating Characteristic (ROC) curve: Receiver Operating Characteristic (ROC) curve was plotted for Metabolic Equivalents, Torsion, Global longitudinal strain, Global radial strain and Global circumferential strain to obtain the optimal cut-off value for predicting the significance of coronary artery disease. ROC curve analysis showed higher area under the curve among Torsion, Global longitudinal and Global radial strain parameters followed by Metabolic Equivalents and Global circumferential strain (Table 7)

7. Logistic Regression: Univariate and Multivariate logistic regression was done to detect the association between independent variables and Coronary artery disease (Table 8). Univariate logistic regression analysis identified HTN *(OR= 4.333; p= 0.02)* & DM *(OR=5.63; p=0.006)* as independent predictors of Coronary artery disease. Multivariable logistic regression showed gender(female) *(OR=6.213; p=0.03)* as independent predictor of CAD.

DISCUSSION

This study examined the value of resting longitudinal, radial and circumferential deformation to detect the coronary affection on patients with significant CAD by using Speckle tracking imaging. HTN and DM are the risk factors for CAD and this study showed that these parameters were the clinical predictors of CAD *(Table 1).* Along with this univariate logistic regression identified that HTN *(OR= 4.333; p= 0.02)* & DM *(OR=5.63;*

p=0.006) as predictors of CAD and was statistically significant *(Table 8).* Mean Age and BMI were almost similar between significant CAD and normal coronary groups.

Logistic regression analysis was done to detect clinical and demographic predictors of CAD among patients with positive treadmill test. Multivariable logistic regression analysis identified Female gender as independent predictor of Coronary Artery Disease *(Table 8)*. Many studies have verified that CAD risk in men is higher comparing to pre-menopausal women. (11) A study was conducted which have proved that CAD risk accelerates in post-menopausal with higher age groups. In our study since we have included more adulthood and females of post-menopausal age group which could be an additional reason for females being at high risk for CAD among the study population.

This study even showed that different LV segmental resting longitudinal, radial or circumferential strain and strain rate parameters were significantly reduced in subjects with significant CAD compared to that of Non-CAD subjects. Similar findings were examined in the other studies which showed resting global strain can be a parameter to predict the presence of significant CAD (12,13). In addition to this present study proved that the resting Torsion parameters were significantly reduced in significant CAD subjects *(Table 6).*

As per the primary objective of this study the Global longitudinal, radial, circumferential strain and Torsion provided better value to predict CAD over conventional echocardiography and exercise testing *(Table 4&6).* Similar findings were even examined in Choi et al (14) where STE was proven better over conventional echocardiographic parameters. In addition to these segments supplied by the stenotic artery had impaired regional strain and strain rate values.

In the present study ROC curve analysis showed a cut-off point of -18.56% for Global longitudinal strain with Sensitivity of 88% & Specificity of 56% and a cut-off point of 36.86% for Global radial strain with Sensitivity of 72% & Specificity of 68%. Torsion had a cut-off point of 2.4 deg/cm with a Sensitivity of 80% & Specificity of 56%. All these parameters were found to be the better deformation parameters to differentiate between subjects with significant CAD and those with non-significant CAD. Even Global Circumferential Strain had a cut-off point of -22.08% with Sensitivity of 96% and Specificity of 24% to diagnose significant CAD *(Table7).*

A study conducted by Biering-Sorensen et al [(15)] examined that the GLS was significantly lower in patients with CAD compared with patients without CAD. GLS remained an independent predictor of CAD after multivariable adjustment for baseline data, exercise test and conventional echocardiography data. In the present study GLS, GCS, GRS *(Table 4)* and torsion *(Table 6)* had a higher sensitivity and specificity which was not considered in the above study. These parameters had better value to predict significant CAD over the conventional echocardiographic parameters. Similar to the above study results even the present study showed decreased exercise capacity in patients with significant CAD and was statistically significant. Decrease in exercise capacity may be due to myocardial ischemia causing wall tension leading to increase in oxygen demand.

Muhammad Asrar et al [(16)] conducted a study to observe whether post-exercise torsion can assess LV deformation with normal LVEF. Comparison was made between LV torsional dynamics and LV diastolic filing parameters (E/e') to correlate with metabolic equivalents to predict exercise capacity. There was no correlation found between resting torsion and METS which had a similar finding to the present study. But there was statistically significant correlation between METS and post-exercise LV torsion (r=0.34, p=0.001) which was not assessed in the present study. Apart from this the present study found correlation between METS and GLS (r=-0.32, p=0.118) which may be a useful tool to assess LV myocardial function in subjects with normal LVEF.

Study limitations: Unequal gender distribution is the major limitation in our study due to constricted time limit. We have not segregated and data was not analysed based on age groups. If images were acquired immediately after post-exercise would give better torsional dynamics.

CONCLUSION

In patients with Chronic stable angina, the resting myocardial deformation analysis using speckle tracking was able to differentiate between significant CAD and non-significant CAD. The analysis of specific segmental deformation parameters was also able to predict the stenosed coronary artery. Torsion parameter was significantly reduced in subjects with significant CAD and could differentiate between significant and non-significant CAD groups. Speckle Tracking Imaging is the way of analysing the resting ventricular myocardial function as well as in detecting the presence of ischemia.

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FIGURE AND TABLE LEGENDS:

Figures: NA

Table1: Clinical and Demographic characteristic of subjects in group of CAD.

		Non-CAD N=25	**CAD N=25**	
Clinical Characteristic	**Group**	**Frequency (percent)**	**Frequency (percent)**	**P value**
Diabetes Mellitus (DM)	Non-diabetic	80 %	36 %	**0.004**
	Diabetic	20 %	64 %	
Gender	Male	32 %	12 %	0.171
	Female	68 %	88 %	
Hypertension	Non-hypertensive	52 %	20 %	**0.038**
	Hypertensive	48 %	80 %	
Demographic Characteristic		**mean±SD**	**mean±SD**	**P value**
Age (Years)		56.3 ± 11.05	59.28 ± 9.54	0.322
Body Mass Index (Kg/m^2)		162 ± 10.01	164.5 ± 11.0	0.398
Diastolic Blood Pressure (mmHg)		65.0 ± 10.99	69.70 ± 11.7	0.156
Height (cm)		24.8 ± 4.43	31.87 ± 31.4	0.277
Systolic Blood Pressure (mmHg)		78.40 ± 8.98	81.60 ± 4.73	0.121

Table 2: Electrocardiographic exercise testing

	Non-CAD N=25	**CAD N=25**	
Parameters	**mean±SD**	**mean±SD**	**P value**
QTC Interval (seconds)	0.40 ±0.04	0.44 ±0.06	**0.013**
Metabolic Equivalents	9.00 ±2.10	7.69± 2.05	**0.039**
Duke Score	-7.80 (4.51)	-9.88 (4.77)	0.120

Table 3: Conventional Echocardiographic parameters.

	Non-CAD N=25	**CAD N=25**	
Parameters	**mean±SD**	**mean±SD**	**P value**
End Diastolic Dimension(cm)	4.70 ± 0.37	4.82± 0.40	0.241
End Systolic Dimension(cm)	3.01 ± 0.26	3.10 ± 0.26	0.200
Ejection Fraction (%)	65.72 ±2.75	65.12 ±2.13	0.392
Fractional Shortening (%)	36.04 ±2.11	35.84± 1.65	0.711
End Diastolic Volume(ml)	103 ±19.35	109±21.59	0.284

End Systolic Volume(ml)	35.72 ±7.71	38.12 ±7.87	0.281
Area Length Ejection Fraction (%)	65.65 ±2.91	65.34 ±2.29	0.678

Table 4: Global strain of 18 segments

	Non-CAD	CAD	
	N=25	**N=25**	
Parameters	**mean±SD**	**mean±SD**	**P value**
Global Longitudinal Strain of 18 segments (%)	-18.4± 2.34	-16.5± 2.11	**0.004**
Global Radial Strain of 18 segments (%)	39.65 ± 8.66	31.9 ± 10.36	**0.006**
Global Circumferential Strain of 18 segments (%)	-18.88 ± 4.6	-17.4 ± 3.35	0.211

Table 5: Regional Strain and Strain rate parameters of 18 segments

	Non-CAD	CAD	
	N=25	**N=25**	
Parameters (LV segments)	**mean±SD**	**mean±SD**	**P value**
Basal Anterior Wall Longitudinal Strain (%)	-19.3±5.3	-16.4± 5.4	**0.05**
Mid Anterior Wall Longitudinal Strain (%)	-15.8±4.9	-13.2± 3.4	**0.04**
Mid Anterior Wall Radial Strain (%)	36.9±16.6	26.4±17.8	**0.03**
Basal IVS Longitudinal Late Diastolic Strain Rate (s^{-1})	1.3± 0.4	1.03±0.3	**0.01**
Basal IVS Longitudinal Strain (%)	-19.4±4.5	-15.5±3.8	**0.002**
Basal Inferior Wall Longitudinal Early Diastolic Strain Rate (s^{-1})	1.6±0.5	1.2±0.4	**0.003**
Mid Inferior Wall Longitudinal Early Diastolic Strain Rate (s^{-1})	1.3± 0.5	1.06±0.3	**0.04**
Basal Inferior Wall Longitudinal Late Diastolic Strain Rate (s^{-1})	1.3±0.4	1.07±0.4	**0.02**
Basal Lateral Wall Longitudinal Strain (%)	-18.5±4.4	-15.5±4.6	**0.02**
Mid Lateral Wall Radial Strain (%)	40.5±19.3	27.6±18.5	**0.02**
Mid Posterior Wall Longitudinal Early Diastolic Strain Rate (s^{-1})	1.2±0.3	1.02± 0.3	**0.02**
Mid Posterior Wall Radial Strain (%)	43.8±22.8	29.06±21.1	**0.02**
Apical Posterior Wall Longitudinal Systolic Strain Rate (s^{-1})	-1.2±0.3	-1.08±0.3	**0.05**

Table 7: ROC curves for predicting significant coronary stenosis.

Parameters	Area under the curve (AUC)	Confidence Interval	Cut-off point	Sensitivity	Specificity
Metabolic Equivalent	0.63	0.47-0.79	8.40	0.68	0.66
Torsion	0.695	0.54-0.84	2.40	0.80	0.56
Global Longitudinal Strain of 18 segments (%)	0.70	0.56-0.85	-18.56	0.88	0.56
Global Radial Strain of 18 segments (%)	0.738	0.59-0.87	36.86	0.72	0.68
Global Circumferential Strain of 18 segments (%)	0.57	0.40-0.73	-22.08	0.96	0.24

Table 8: Unadjusted and adjusted association between independent variables and Coronary artery disease using logistic regression

Variables	Univariate		Multivariable	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**
Female (Gender)	4.125(0.961,17.704)	0.057	6.213(1.15,33.57)	***0.03***
HTN	4.333(1.235,15.206)	***0.02***	3.062(0.594,15.793)	0.181
DM	5.63(1.648,19.232)	***0.006***	3.989(0.783,20.309)	0.096
AGE	1.395(0.675,2.880)	0.369	1.016(0.952,1.085)	0.633
BMI	1.024(0.969,1.083)	0.401	0.966(0.812,1.149)	0.695

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