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Value of Resting and Stress Myocardial Deformation Assessment by Two Dimensional Speckle Tracking Echocardiography to Predict the Presence, Extent and Localization of Coronary Artery Affection in Patients with Suspected Stable Coronary Artery Disease

Dr. T. Suresh Babu[1], Dr. D. Rajasekhar[2], Dr. Vanajakshamma[3], Dr. B. Raghuram[4], Dr. Madhava Naidu[5]

Abstract: ***Background: Myocardial deformation indices are considered as sensitive markers of ischemia. They are useful in the quantification of hemodynamic significance of coronary artery disease (CAD). Dobutamine stress echocardiography (DSE) is a non-invasive method with established diagnostic accuracy. Limited studies have been published exploring the implementation of speckle tracking imaging during DSE. Hence we sought to evaluate the utility of speckle tracking echocardiography (STE) for detection of left ventricular strain and strain rate during DSE in patients with stable coronary artery disease (SCAD). Materials and Methods: 50 patients of SCAD were prospectively recruited. All patients underwent dobutamine speckle tracking echocardiography and coronary angiogram. Global longitudinal strain (GLS%) /strain rate(GLSR 1/S) and Global radial strain (GRS%)/strain rate (GRSR1/S), Global circumferential strain (GCS%)/strain rate (GCSR1/S) were calculated at rest, at dobutamine dose 5mcg/kg/min, at peak stress and at early recovery (3min after stress). Obstructive CAD was defined as > 50% of coronary artery luminal narrowing. Results: Out of 50 patients, significant stenosis on coronary angiogram was observed in 22(44%) patients. Among them 10 (45%) had single vessel disease (SVD), 5 (22%) had double vessel disease (DVD) and 7 (33%) had triple vessel disease (TVD). Left anterior descending artery (LAD) involvement was seen in 18 (82%) patients, Left circumflex (LCX) in 15(68%) and Right coronary artery (RCA) in 8 (36%) patients. Patients with significant CAD were more frequently male (68%). All analysed STE parameters at peak dobutamine doses and during recovery were significantly lower in patients with significant stenosis than in patients without siginificant stenosis. GLS(%)(-16.55±2.75 vs -21.11±2.50, p value 0.02) and GLSR (1/S)(-1.54±0.25 vs -1.75±0.84 p value=0.04), GRS(%) (34.45±3.50 vs 49.54±2.85, p value <0.05) and GRSR (2.26±0.33 vs 2.95±0.75 p <0.05), GCR (%) (-17.98±4.06% vs -23.84±4.25%, p value 0.03) and GCSR (1/S) (-1.54±0.34 vs -1.97±0.25, p value 0.01) were lower in significant stenotic patients during peak stress when compared to patients without significant stenosis. The sensitivity, specificity of GLS for detecting significant CAD were 86.4% and 96.4% respectively, for GRS were 80.6% and 73.5% respectively and for circumferential strain were 83.6% and 75.8% respectively. There was incremental significant decrease in GLS with increasing number of coronary vessels involved. Conclusions: Left ventricular strain and strain rate analyses in dobutamine speckle tracking echocardiography during peak stress and recovery can help in prediction of hemodynamically significant coronary artery stenosis in patients with stable CAD.***

Keywords: Myocardial deformation; Speckle tracking echocardiography; Stable coronary artery disease, Global longitudinal strain, Global radial strain, Global circumferential strain

1. Introduction

Stable coronary artery disease (SCAD) is a very common disease. It is expected to increase further due to population aging and decline of mortality in acute coronary syndromes.[1,2]Echocardiography is the leading cardiac imaging technique in patients with suspected cardiac disease. However, conventional echocardiography at rest provides little information on the presence of coronary artery disease (CAD) in such patients. Longitudinally orientated myocardial fibers are located subendocardially, the area most susceptible to ischemia, that is why measurements of longitudinal motion and deformation may be the most sensitive markers of CAD using tissue Doppler imaging (TDI)[3,4] or 2-dimensional strain echocardiography (2DSE)[5-8]. Unlike tissue Doppler imaging, Speckle tracking derivatives are less susceptible to translational motion changes and tethering, which generally leads to erroneous qualitative evaluation of stress echo images. Myocardial deformation indices are considered as sensitive markers of ischemia. They may be useful in the quantification of hemodynamic significance of CAD. Dobutamine stress echocardiography (DSE) is a well-established imaging modality in the detection of CAD on the basis of regional wall motion abnormalities induced by myocardial ischemia. Wall motion analysis during DSE is subjective, and considerable expertise is required to achieve the published levels of accuracy. So far few studies have been published exploring the implementation and clinical utility of speckle tracking imaging during DSE[9-12]. The aim of the current study is to examine the value of LV strain (S) and strain rate (SR) using speckle tracking echocardiography to detect the presence, extent and localization of coronary artery affection in patients with suspected SCAD during rest and during dobutamine stress conditions.

2. Methods

2.1 Study population

It is a single centre, cross sectional prospective study. Patients with suspected SCAD admitted in the department

of Cardiology, SVIMS, Tirupati, a tertiary care teaching institute were included in the study.

2.2 Inclusion and exclusion criteria:

Fifty patients admitted in department of Cardiology SVIMS Tirupati, between June 2017 to July 2018 with diagnosis of SCAD were included in the study. Patients aged between 35 – 75 years, presenting with no wall motion abnormalities at rest and good left ventricle systolic function i.e LVEF > 55% were included in the study. Patients with evidence of acute coronary syndrome, segmental wall motion abnormalities at rest, LVEF < 50%, significant valvular heart diseases, rhythm other than normal sinus rhythm, congestive cardiac failure, patients not willing to participate in the study were excluded from the study. The research protocol was approved by the institutional ethics committee. Written, informed consent was obtained from each patient.

2.3 Conventional echocardiography

All echocardiographic examinations were obtained using ACCUSIONSEC2000 echocardiographic machine. LV diameters and wall thicknesses were measured. Pulsed wave Doppler was used to record trans-mitral flow in the four-chamber (4-CH) apical view as well as the trans-aortic flow in the five-chamber (5-CH) apical view. LVEF was determined using modified biplane Simpson's method in the 4-CH and the two-chamber (2-CH) apical views as recommended by the American Society of Echocardiography[13].

STE was done for all the patients at rest and during stress induced by dobutamine. An initial infusion of dobutamine at 2.5 ug/kg/min with gradual increase to 5, 7.5, 10, 20 ug/kg/min for every 3 minutes was used to induce stress. Atropine up to 1mg was used in the study. The infusion was terminated once 85% of the maximal predicted heart rate is reached. STE was done using the SIEMENS ACUSONSSEC2000 machine. Three consecutive end expiratory cardiac cycles using high frame rate (80–100 frames/sec) harmonic imaging was acquired in the apical 4-CH, 2-CH, the long axis (LAX) views and the short-axis (SAX) mitral valvular, papillary and apical ventricular levels. The 2D-STE analysis was performed offline on grayscale images of the LV obtained in these views. Thereafter, the endocardium and epicardium were delineated and the region of interest was divided into 6 segments automatically by the machine software. Once the regions of interest were optimized, the software generates automatically strain curves for different myocardial segments. From the apical 4-CH view, longitudinal strain/strain rate (LS/LSR) and radial strain/strain rate (RS/RSR) were assessed. From the apical 2-CH view, LS/LSR and RS/RSR were assessed. From the apical LAX view, LS/LSR and RS/RSR were assessed. The peak systolic (PS) global longitudinal strain/strain rate (GLS/GLSR) and the global radial strain/strain rate (GRS/GLSR) were calculated as the average of the LS and RS of the 16 myocardial segments of the 4-CH, 2-CH and apical LAX views. From the short axis view at the level of the mitral valve, papillary muscle and apical levels, the circumferential strain (CS) was assessed. The Global circumferential strain/strain rate (GCS/GCSR) were calculated as the average of S/SR of the 16 LV segments of the LV cavity at basal, mid, apical levels in SAX view.

2.4 Coronary angiography (CAG)

Angiograms were obtained for each coronary vessel in at least 2 projections. A reduction in arterial lumen area of <50% of any coronary vessel including left main coronary vessel was considered significant.

2.5 Statistical analysis

Data was collected in pre-designed Microsoft excel spread sheets. Data was presented as mean and standard deviation for continuous variables and numbers with percentages for categorical variables. Differences observed if any was tested for significance with unpaired student's t-test for continuous data and with Chi-square test for categorical data. Receiver operator characteristic (ROC) curves were constructed and an area under curve (AUC) was calculated. From the ROC curves constructed for different LV deformation variables, the optimal cut off values with the highest sensitivity and specificity for diagnosing, predicting severity or localization of CAD were identified. All the statistical analysis was performed on Microsoft Excel spread sheets and Statistical Package for Social sciences (SPSS) for Microsoft Windows, Version 20.0.IBM. A p-value of ≤0.05 was considered as significant.

3. Results

As per the results of coronary angiography patients were classified into those with significant stenosis (Group A) which included 22(44%) patients and patients without significant stenosis (Group B) which included 28(56%) patients. Out of the 22 patients, single vessel disease (SVD) was seen in 10 (45%) of patients, double vessel disease was seen in 5 (22%) patients and three vessel disease was seen in 7 (33%) patients.

Clinical data: There was no statistically significant difference in age, gender, smoking status, incidence of diabetes mellitus, dyslipidaemia between two groups (Table 1).

Table 1: Major risk factor distribution among study population

Risk factors	Group A	Group B	p value
AGE	63.5±5.9	60.5±4.5	0.32
DM	12	10	0.24
HTN	13	11	0.31
Dyslipidemia	6	5	0.27
Smoking	18	12	0.09

*** p value of <0.05 is statistically siginificant,** HTN – Hypertension , DM- Diabetes mellitis.
The mean age of the study population was 62.5±9.4 years. Majority of the patients were in the age group of 60 to 70 years.

Table 2: Age distribution of population studied

Age in years	Number of patients	Percentage (%)
30-40	1	2
41-50	8	16
51-60	15	30
61-70	22	44
71-80	4	8
Total	50	100

Conventional echocardiography: There was no statistically significant difference in LV dimensions or LV EF between two groups (Table 3).

Table 3: Conventional echocardiographic data

Variable	Group A	Group B	p value
LVEDD(mm)	48.6±5.5	51.8±10.7	0.12
LVESS(mm)	30.4±4.8	31.4±8.6	0.48
SWT(mm)	0.99±0.05	1.1±0.05	0.75
PWT(mm)	0.95±0.05	0.96±0.05	0.81
FS(%)	37.7±6.3	37.5±8.4	0.65
EF(%)	65.2±5.5	66.5±9.5	0.81
Trans mitral E wave velocity (cm/sec)	0.73±0.14	0.84±0.11	0.95
Transmitral A wave velocity. (cm/sec).	0.79±0.15	0.88±0.1	0.2

***p value of <0.05 is statistically significant**

LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; SWT: septal wall thickness; PWT: posterior wall thickness; FS = fractional shortening; EF = ejection fraction.

Speckle tracking echocardiography:

Baseline speckle tracking echocardiography : The baseline STE parameters like GLS/GLSR, Global radial strain (GRS)/strain rate (GRSR) and GCS/ GCSR did not show any between two groups(Table 4, Figure 1).

Table 4: Baseline speckle tracking echocardiography

	Group A	Group B	p Value (<0.05)
GLS%	-19.95±2.85	-20.55±2.54	0.15
GLSR 1/S	-1.87±0.34	-1.95±0.35	0.09
GRS%	46.56±3.55	47.85±2.85	0.23
GRSR 1/S	2.85±3.25	2.97±3.95	0.31
GCS %	-21.52±2.52	-22.54±3.25	0.21
GCSR 1/S	-1.85±0.42	-1.98±0.35	0.32

*** p value of <0.05 is statistically significant**

GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, GRS: Global radial strain, GRSR: Global radial strain rate, GCS: Global circumferential strain, GCSR: Global circumferential strain rate.

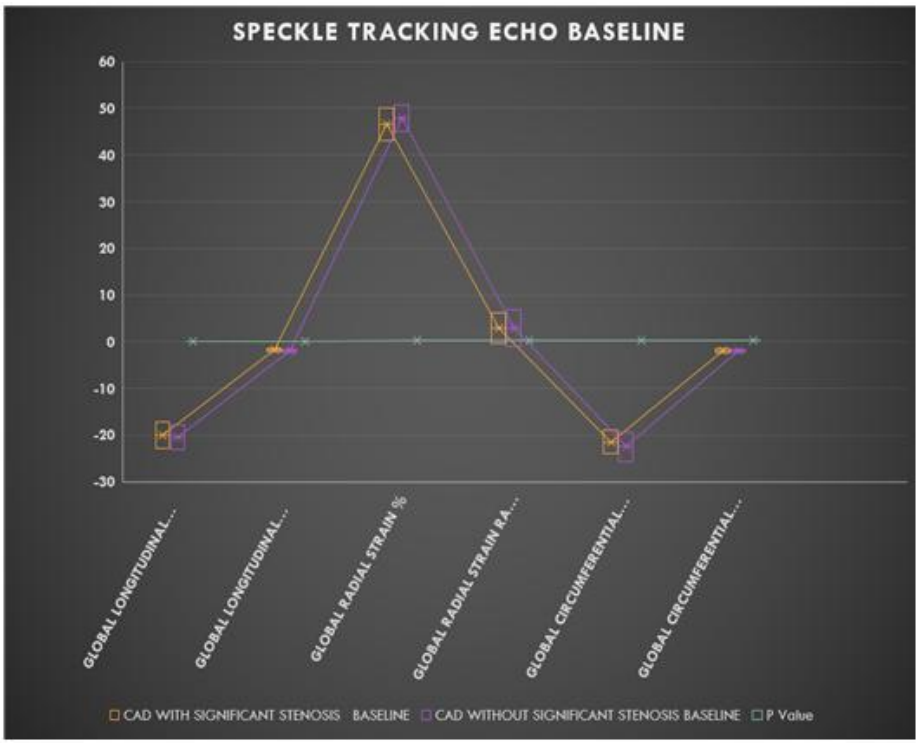

Figure 1: Box and Whisker diagram showing Baseline STE

Speckle tracking echocardiography at low dose of dobutamine, GLS and GLSR showed statistically significant difference (p value < 0.05) in Group A when compared to Group B. Remaining parameters like GCS/GCSR and GRS/GRSR did not show any significant difference between two groups.(Table 5).

Table 5: Low dose dobutamine STE

	Group A	*Group B*	*p Value*
GLS%	-18.95±2.75	-22.55±2.60	0.04*
GLSR 1/S	-1.79±0.35	-2.05±0.28	0.03*
GRS%	46.56±3.55	49.85±2.85	0.12
GRSR 1/S	2.95±0.25	3.52±0.75	0.09
GCS %	-21.52±2.52	-23.54±3.45	0.08
GCSR 1/S	-1.90±0.42	-2.15±0.35	0.1

***p value of <0.05 is statistically significant**

GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, GRS: Global radial strain, GRSR: Global radial

strain rate, GCS: Global circumferential strain, GCSR: Global circumferential strain rate.

STE at peak dose of dobutamine, GLS and GLSR, GCS/GCSR and GRS/GRSR showed statistically significant difference (p value < 0.05) (Table 6, Figure 2)

Table 6: Peak dose of dobutamine STE

	Group A	GROUP B	p VALUE
GLS%	-16.55±2.75	-21.11±2.50	0.02*
GLSR 1/S	-1.54±0.25	-1.75±2.84	0.04*
GRS%	34.5±3.50	49.85±2.85	<0.05*
GRSR 1/S	2.26±0.33	2.95±0.75	<0.05*
GCS %	-17.98±4.06	-23.84±4.25	0.03*
GCSR 1/S	-1.54±0.34	-1.97±0.25	0.01*

*** p value of <0.05 is statistically significant**

GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, GRS: Global radial strain, GRSR: Global radial strain rate, GCS: Global circumferential strain, GCSR: Global circumferential strain rate.

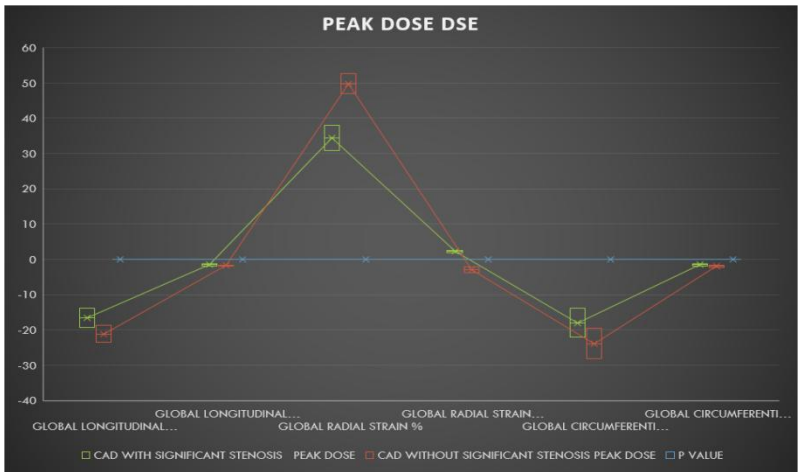

Figure 2: Box and Whisker diagram during peak dose of STE

STE during recovery phase of dobutamine stress, GLS and GLSR, GCS/GCSR and GRS/GRSR showed statistically significant difference (p value < 0.05) between two groups.(Table 7)

Table 7: Recovery phase of dobutamine STE

	Group A	Group B	P VALUE
GLS%	-17.55±2.75	-20.11±2.50	0.02*
GLSR 1/S	-1.64±0.25	-1.85±0.12	0.04*
GRS%	38.45±3.50	45.85±2.85	<0.05*
GRSR 1/S	2.36±0.35	2.75±0.75	<0.05*
GCS %	-18.98±4.50	-21.84±4.75	0.03*
GCSR 1/S	-1.64±0.35	-1.85±0.35	0.01*

*** p value of <0.05 Statistically significant**

GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, GRS: Global radial strain, GRSR: Global radial strain rate, GCS: Global circumferential strain, GCSR: Global circumferential strain rate.

During peak dose of dobutamine STE, GLS with cut off value of -20.50 showed sensitivity, specifity and AUC of 86.4%, 96.4% and 0.89 respectively. GLSR with cut off value of -1.90 showed sensitivity, specificity and AUC of 86.4%, 96.4% and 0.89 respectively.(Table 8, Figure 3)

Table 8: ROC curve analysis for the detection of CAD

	Cut Off Value	Sensitivity	Specificity	AUC	p value
GLS%	-20.5	86.40%	96.40%	0.89	<0.05*
GLSR 1/S	-1.9	90%	96%	0.92	<0.05*

*** p value of <0.05 is statistically significant**

GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, AUC: area under curve

Reciever operator characteristic (ROC) curves during peak dose of dobutamine STE showed GLS with cut off value of -20.50 had sensitivity, specifity and AUC of 86.4%, 96.4% and 0.89 respectively and GLSR with cut off value of -1.90 showed sensitivity, specificity and AUC of 86.4%, 96.4% and 0.89 respectively.(Figure 3,4)

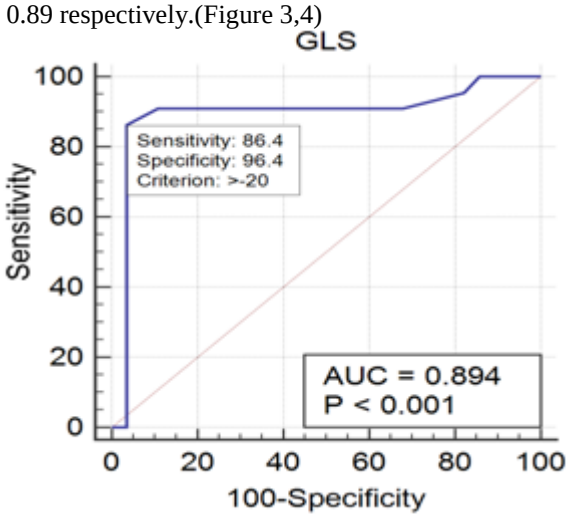

Figure 3: ROC curve of GLS

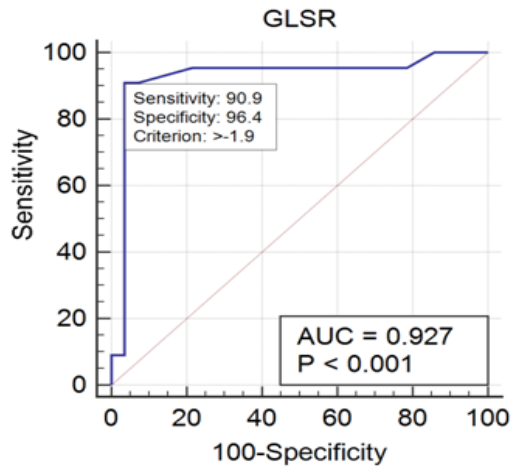

Figure 4: ROC curve of GLSR

During peak dose of dobutamine STE, GCS with cut off value of -19.50 showed sensitivity and specificity of 83.4% and 75.8% respectively. GRS with cut off value of 39.35 showed sensitivity and specificity of 80.6% and 73.5% respectively.(Table 9)

Table 9: ROC curve analysis for the detection of CAD

	Cut Off Value	Sensitivity	Specificity	P value
GLS %	-20.55	86.40%	96.40%	0.01*
GCS%	-19.55	83.50%	75.80%	0.01*
GRS %	39.35	80.60%	73.50%	0.01*

*** p value of <0.05 is statistically significant**
GLS: Global longitudinal strain, GRS: Global radial strain, GCS: Global circumferential strain.

- STE during peak dose of dobutamine stress echocardiography showed statistically significant difference (p value < 0.05) in GLS and GLSR, GCS/GCSR and GRS/GRSR in patients with TVD when compared to patients with SVD,DVD
- Regional longitudinal strain for Left anterior descending artery segments in the present study had cut off value of -18.50 that showed sensitivity and specificity of 91.4% and 94% respectively which is statistically significant. Regional longitudinal strain for left circumflex artery segments had cut off value of -19.55 which showed sensitivity and specificity of 85.5% and 82.8% respectively which is statistically significant. Regional longitudinal strain for right coronary artery segments with cut off value of -19.55 showed sensitivity and specificity of 80.6% and 76.5% respectively which is statistically significant. (Table 10)

Table 10: ROC curve analysis for localization of CAD

	Cut Off Value	Sensitivity %	Specificity %	P value
Regional longitudinal strain % for LAD segments	-18.5	91.40%	94.00%	0.01*
Regional longitudinal strain % for LCX segments	-19.55	85.50%	82.80%	0.01*
Regional circumferential strain % for RCA	-20.5	80.60%	76.50%	0.01*

*** p value of <0.05 is statistically significant**
LAD- left anterior descending artery, LCX-left circumflex artery, RCA- right coronary artery

4. Discussion

A total of 50 cases of SCAD were considered and were evaluated with ECG, conventional echocardiography and 2D STE at baseline and during stress with dobutamine. Subsequently, CAG was done.

The present study classified the study subjects into two groups following Coronary Angiogram (CAG) i.e patients with significant CAD (Group A) (n= 22, 44%) and those without significant CAD Group B (n= 28, 56%). Major portion of the study population was contributed by patients aged between 60-70 years. In the present study, males constituted 68% of total cases (n=34). Obstructive CAD was more common in men. The above findings are supported by data from **INTERHEART study**[14], which showed a 3 fold rise in CAD incidence in males compared to females and increased incidence with aging, an approximate 50% incidence in the age group greater than 60 years. Baseline echocardiographic parameters like left ventricle diameters, wall thickness, LV function parameters like EF, and fractional shorting (FS) and Doppler velocities did not show any statistically significant difference between the two groups similar to previous studies[15-17].The present study has not observed any differences in STE parameters between two groups at rest, although longitudinal strain was shown to be useful for detecting CAD at rest in several previous studies.[15,18] Present study showed that longitudinal strain and strain rate were the only parameters which identified the significant CAD with low dose dobutamine STE similar to the study conducted by **Hanekom et al.**[19] Longitudinal strain and SR were found to be the most sensitive markers for ischemia because longitudinally orientated myocardial fibers are located subendocardially, the area most susceptible to ischemia.[20] Longitudinal, circumferential and radial strain parameters were significantly decreased from baseline to high dobutamine dose in Group A patients when compared to Group B patients similar to the sudy done by **E. Rumbanaite et al.**[21] Longitudinal, circumferential and radial strain parameters were significantly decreased from baseline to recovery in Group A patients when compared to Group B patients similar to study conducted by **Hui-Jeong Hwang et al**[22].
During peak dose of dobutamine STE, GLS with cut off value of -20.50 showed sensitivity, specifity and AUC of 86.4%, 96.4% and 0.89 respectively whereas **Rumbinaite et al. study** GLS with cut off value of -19.2 showed sensitivity of 89.4%. GLSR with cut off value of -1.90 showed sensitivity, specificity and AUC of 86.4%, 96.4% and 0.89 respectively. During peak dose of dobutamine, GCS with cut off value of -19.50 showed sensitivityand specifity of 83.4% and 75.8% respectively. GRS with cut off value of 39.35 showed sensitivity and specificity of 80.6% and 73.5% respectively. When compared to longitudinal strain, circumferential strain and radial strain and strain rates had lower sensitivities and specificities.

Regarding **extent of CAD**, GLS was significantly lower in patients with severe CAD (three vessels CAD) when compared to patients with one or two vessel CAD.

Identification of patients with three vessel CAD is important because of the significantly lower long term survival whether treated surgically or medically and the significantly higher operative mortality in this group of patients compared to patients with single or two vessel disease. Similar to our results, **Choi et al** [23] study had shown that resting GLS was significantly lower in patients with severe CAD (three vessel/left main CAD) without resting echocardiographic regional wall motion abnormalities compared to patients with one or two vessel CAD. Segmental deformation trying to localize the affected coronary vessel was also performed in the present study.

ROC curve analysis showed that the average of regional longitudinal strains (RLS) of the anterior wall and infero-septal segments best predicted LAD affection (sensitivity: 91.4%, specificity: 94.0%), while that of the infero-lateral and antero-lateral wall segments best predicted LCX affection (sensitivity: 85.5%, specificity: 82.8%), while the Circumferential strain of the mid segment of the inferior wall best predicted RCA (sensitivity: 80.6%, specificity: 76.5%). The present study showed results similar with study conducted by **Montgomery et al.**[24] with peak segmental strain measurements significantly lower in the LAD territory in patients with significant LAD stenosis compared to patients without significant LAD stenosis. The diagnostic content of 2D strain was less in the RCA and the LCX territory than in the anterior coronary circulation.

The lower sensitivity for detection of disease in the posterior-lateral circulation may be due to problems with image quality in the inferior, lateral, and posterior walls, evidenced by a higher tracking score compared with the anterior segments. ROC analysis confirmed that the strain and strain rate parameters were valuable in detecting significant CAD in patients with SCAD patients. So far very few studies in dobutamine stress STE are done in India. Further studies are needed to assess the diagnostic value of regional and global myocardial deformation parameters in large population.

5. Limitations

First, sample size is small in number to generalize the results and it is a conducted in a single centre. Second was inability to get good images in all patients and third, GLS lacks sensitivity in the regions supplied by the RCA and LCX, most likely a function of overlap in the posterior circulation and anatomical variation between the subjects.

6. Conclusion

Longitudinal strain and strain rate were the best parameters which identified the significant CAD even with low dose dobutamine STE. Longitudinal, circumferential and radial strain parameters showed good sensitivity and specificity during peak dobutamine dose and during recovery phases. However when compared to longitudinal strain, circumferential strain and radial strain had lower sensitivities and specificities. Longitudinal strain parameters are very useful in detecting the extent and localization of the CAD when compared to radial and circumferential strains. The present study concludes that the strain parameters mainly longitudinal strain parameters can be used to predict the presence, extent and localization of coronary artery affection in patients with suspected SCAD mainly during peak dobutamine stress and during recovery phases.

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