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Original Article

Utility of Global Longitudinal Strain in Predicting Obstructive Coronary Artery Disease in Intermediate Risk Patients

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Abstract

Introduction: Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world and has nearing its epidemic proportions. Although CAD mortality rates worldwide have declined over the past four decades, CAD remains responsible for about one-third or more of all deaths in individuals overage.

Aims and Objectives: The primary objective of the study is to see the correlation between global longitudinal strain assessed by tissue Doppler imaging or two-dimensional (2D) speckle tracking echocardiography and CAD as assessed by coronary angiography in intermediate-risk patients.

Materials and Methods: This was a prospective clinical study, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad. Patients admitted with symptoms of stable CAD during the period June 12 to November 30, 2017 were studied.

Results: Total number of patients with a clinical diagnosis of stable angina at intermediate risk of CAD as per Framingham Risk Score admitted to the hospital during the study period is 50. Out of 50 patients, five patients refused coronary angiogram.

Conclusion: Global longitudinal strain (GLS) assessed by 2D-STE at rest is a predictor of significant CAD. GLS has high sensitivity for early detection of significant CAD in intermediate risk patients. 2D-STE has the potential to improve the value of chocardiography in the detection of the CAD, identifying high-risk patients.

Key words: Intermediate risk patients, Longitudinal Strain, Significant CAD

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world and has nearing its epidemic proportions. Although CAD mortality rates worldwide have declined over the past four decades, CAD remains responsible for about one-third or more of all deaths in individuals overage 35.[1-3] CAD causes 9.4% of total deaths (25 lakhs) in underdeveloped countries and 16.3% (13 lakhs) of all deaths in developed countries.[1] The World Health Organization has calculated the year of 2002 alone, 12.6% of deaths in the world were because of CAD.[2] The proportion of CAD is expected to increase as it is the disease of aging and the world population getting older.

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India has a similar scenario. Indian studies have revealed that cardiovascular diseases (CVD) cause about 40% of deaths in the urban areas and 30% of deaths in rural areas in India.[3] Prevalence of CVD in the adult population has multiplied in urban areas from around 2% in early 1960s to 6.5% in late 1970s, 7% during the year 1980, to close 10% in 1990, and to a critical 10.5% in the year 2000. At the same time in rural areas, it is increased to a smaller extent from about 2% during 1970 to 2.5% in late 1980s, and to calculate 4% in 1990, at last the prevalence has reached 4.5% in 2000.

Hence, prevention of CVDs among people is more important. If CVD occurs, the earlier detection and

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treatment are required for the prevention of complications and death. Moreover, identification of risk factors and prevention of CAD are more important than treatment itself. Early detection of CAD among people with or without symptoms is main task to reduce morbidity and mortality. There are various invasive and non-invasive methods to detect CAD among people with symptoms. Always invasive methods have their own advantages and disadvantages, so non-invasive tests are low-cost modalities of CAD detection and are need of the hour. Various non-invasive methods used are electrocardiogram (ECG), echocardiogram (ECHO), computed tomography (CT), magnetic resonance imaging, and nuclear imaging. Exercise stress testing such as treadmill test, stress echocardiography, and stress single-photon emission computed tomography is routinely used for the non-invasive assessment of CAD and is considered safe procedures.

In recent years, it has become increasingly apparent that a large number of patients classified as low risk or intermediate risk for acute coronary syndrome (ACS) and without diagnostic cardiac biomarkers represent the most prevalent group of patients admitted to hospital with chest pain.[4,5] Up to one-third of patients with chest pain who are referred to coronary angiography have no significant coronary artery stenosis.[6] Although this investigation is generally safe, it has well-known risk of complications and is also costly. Exercise testing is widely used for selecting patients for coronary angiography but has its clear limitations as emphasized in the European guidelines for stable CAD.[7] In stable CAD, coronary CT angiography (CTA) is a non-invasive alternative to assess coronary anatomy, but according to expert consensus only selected patients should be considered for CTA.[7] Thus, we are in need of a simple, non-invasive method to improve the selection of patients who are referred for coronary angiography.

Recently, quantification of left ventricular (LV) longitudinal strain and strain rate using two-dimensional (2D) speckle tracking echocardiography (2D STE) was shown to be a sensitive method for identifying significant CAD, transmural myocardial infarction[8,9] as well as acute or subacute ischemia.[10,11]

The present study is done to see the correlation between global longitudinal strain (GLS) and CAD as assessed by coronary angiography in intermediate risk patients admitted in Nizam's Institute of Medical Sciences, Hyderabad, between June 1, 2017, and November 30, 2017.

Aims and Objectives

The primary objective of the study is to see the correlation between GLS assessed by tissue Doppler imaging or 2D STE and CAD as assessed by coronary angiography in intermediate risk patients so that strain imaging can be used as a reliable non-invasive tool to predict obstructive CAD, and invasive coronary angiography and its complications can be avoided in selected patients.

MATERIALS AND METHODS

Design

This was a prospective clinical study.

Setting

This study was conducted at Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad.

Subjects

Patients admitted with symptoms of stable CAD during the period June 1, 2017–November 30, 2017.

Inclusion Criteria

Adult patients (age > 18 years) who presented to the hospital by clinically suspected stable CAD (symptoms felt to be related to CAD such as angina or angina equivalents) were included in the study.

Patients with no regional wall motion (WM) abnormality and preserved LV ejection fraction (LVEF) on conventional 2D echocardiography.

Patients at intermediate risk of CAD based on Framingham Risk Score (10-year risk of MI or death of 10–20%) who underwent coronary angiogram were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

- ACSs
- Known ischemic heart disease
- Congestive heart failure
- Significant valvular disease
- Rhythm other than sinus rhythm
- LVEF <50% or regional WM abnormalities at rest as detected by echocardiography
- Prior history of percutaneous coronary intervention or coronary artery bypass grafting
- Patients who refused coronary angiogram.

Investigations

- Complete blood picture
- Blood urea, serum creatinine
- Serum electrolytes
- Fasting lipid profile
- ECG
- Cardiac biomarkers (LDH, CPK-MB)
- Chest X-ray
- 2D ECHO including strain imaging.

After the clinical evaluation, including review of medical history, relevant physical examination, and relevant investigations as detailed above, all the patients who gave consent underwent coronary angiogram in the same hospital admission.

All echocardiographic examinations are obtained using Philips HD11XE machine. LV diameters and wall thicknesses are 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. Pulsed wave Doppler is used to record transmitral flow at the tips of the mitral leaflets in the four-chamber (4-CH) apical view as well as the trans-aortic flow in the five-chamber apical view. Peak velocity of early (E) and atrial (A) diastolic filling of the Doppler mitral flow and E/A ratio is calculated. 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.

Strain Analysis

Two consecutive heart cycles at rest, from the three standard apical planes (4-CH, 2-CH, and long-axis), are considered by conventional 2D grayscale echocardiography. In each of the apical views, the endocardial contour was manually drawn and tracking of deformation was automatically performed by the software, once visual confirmation of good quality tracking was given by the operator. The software algorithm automatically segmented the LV into six equidistant segments and selected suitable speckles in the myocardium for tracking. The software algorithm then tracked the speckle patterns on a frame by frame basis using the sum of absolute difference algorithm. Regional longitudinal peak systolic strain was measured in all views between aortic valve opening and closing for the six basal, six midventricular, and four apical segments and 17^{th} segment was apical cap and averaged from the 17 segments to provide Global Longitudinal peak systole strain (GLSS).

Coronary angiography is performed by either a radial or femoral approach. A reduction in arterial lumen area of >50% of left main coronary artery (LMCA) and >70% of any other coronary artery is considered significant.

Statistical Analysis

All analyses were made using the Minitab 16 software package. Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as percentages. Independent *t*-test is used to compare means, ANOVA to compare multiple groups.

The research protocol is approved by the Institutional Ethics Committee, Nizam's Institute of Medical Sciences, Hyderabad. Written, informed consent is obtained from each patient.

RESULTS

A total number of patients with clinical diagnosis of Stable Angina at intermediate risk of CAD as per Framingham Risk Score admitted to the hospital during the study period is 50. Out of 50 patients, five patients refused coronary angiogram so they are excluded from the data analysis.

Clinical Data

Most of the patients fell in the age groups of 41–50 years and 51–60 years (22 and 24, respectively) Table 1. Three patients were in the age group of 31–40 years and one patient in the age group of 61–70 years.

The relative frequency of males and females presenting with stable angina and intermediate risk of CAD is 54% (27 patients) and 46% (23 patients), respectively Table 2.

Out of 50 patients, 27 (54%) were smokers Table 3. Forty-four (88%) patients had hypertension. Of them, 37 were on medical therapy for hypertension. Thirty-four patients had dyslipidemia and 22 (44%) had family history of CAD.

All the patients underwent a coronary angiogram Table 4. Twenty-nine patients (58%) had normal coronaries or nonobstructive CAD. Fifteen patients (30%) had single-vessel disease and four patients (8%) had double vessel disease. One patient had triple vessel disease, and one patient had left main coronary disease with bifurcation

Table 1: Age distribution of patients

Age group (in years)	Total	Percentage
31–40	3	6
41–50	22	44
51–60	24	48
61–70	1	2
All	126	100

Table 2: Sex distribution of the patients

Sex	No. of patients	Percentage
Male	27	54
Female	23	46
Total	50	100

Table 3: Other baseline characteristics

	Number of patients	Percentage
Smoking	27	54
Hypertension	44	88
Hypertension on treatment	37	74
Diabetes mellitus	24	48
Family history of CAD	22	44
Dyslipidemia	34	68

CAD: Coronary artery disease

lesion (distal LMCA with ostial left anterior descending [LAD] and ostial LCX).

The difference in the mean age of presentation between patients with and without significant CAD is not statistically significant ($P = 0.40$). There is also no difference among patients with single-vessel disease, double-vessel disease, triple vessel disease, and LMCA disease in respect to mean age of presentation. Similarly, there is no statistically significant difference between the patients with and without significant CAD with regard to body mass index (BMI) ($P = 0.99$).

All the baseline characteristics are relatively comparable among the different patient groups as depicted in Table 5.

Table 4: Coronary angiography results

	No. of patients	Percentage
Normal coronaries/Non obstructive CAD	29	58
Single vessel disease	15	30
Double vessel disease	4	8
Triple vessel disease/LMCA disease	2	4

CAD: Coronary artery disease, LMCA: Left main coronary artery

There were no statistically significant differences between the normal, single vessel, two vessels and three vessels disease groups as regard of septal wall thickness ($P - 0.39$), posterior wall thickness ($P - 0.31$), LV end diastolic diameter ($P = 0.44$), LV end systolic diameter ($p = 0.07$), ejection fraction ($P = 0.77$), E wave velocity ($P = 0.63$), A wave velocity ($P = 0.82$) and E/A ratio ($P = 0.89$) as shown in Table 6.

There is a statistically significant difference in mean of GLPSS between those with normal coronaries versus patients with CAD (P value 0.00). Mean GLPSS is -20.4 ± 0.83, -18.33 ± 0.5 , -17.32 ± 0.41 and -16 ±0.14 for normal, single vessel, two vessels and three vessels disease respectively (Table 7) (Fig. 11). There is also a statistically significant difference in mean of peak systolic global longitudinal strain rate between those with normal coronaries versus patients with CAD (P value 0.00). Mean GLPSS is 1.5 ± 0.22, 0.7 ± 0.17, 0.65 ± 0.17 and 0.4 ± 0 normal, single vessel, two vessel and three vessel disease respectively Table 7.

DISCUSSION

Many patients who are at intermediate risk for CAD present with stable angina or angina equivalents. Patients

Table 5: Demographic data as regard to extent of cad

	Normal coronaries/non-obstructive CAD (%)	SVD (%)	DVD (%)	TVD/LMCA disease (%)
Males	14 (51.85)	9 (33.33)	2 (7.4)	2 (7.4)
Females	15 (65)	6 (26)	2 (8.6)	0 (0)
Smoking	14 (51.85)	10 (37.03)	2 (7.40	1 (3.7)
Hypertension	26 (59.09)	13 (29.54)	3 (6.8)	2 (4.5)
Dyslipidemia	22 (64.7)	9 (26.4)	3 (8.8)	0 (0)
Diabetes	17 (70.83)	5 (20.83)	1 (4.16)	1 (4.16)
Family H/o CAD	12 (54.54)	5 (22.72)	3 (13.63)	2 (9.09)

Table 6: Echocardiographic data according to extent of coronary artery disease

	Normal coronaries/non-obstructive CAD	SVD	DVD	TVD/LMCA Disease	One way anova test	
					F	*P* value
SWT (cm)	1.05±0.13	1±0.06	1.07±0.09	1.05±0.07	1.01	0.39
PWT (cm)	1.07±013	1±0.07	1.07±0.09	1±0	1.21	0.31
LVEDD (cm)	4.64±0.48	4.53±0.33	4.47±0.39	5±0	0.9	0.44
LVESD (cm)	2.78±0.32	2.56±0.22	2.6±0.21	3±0.28	2.7	0.07
EF (%)	61.75±3.67	61.8±3.78	60.5±3.41	59.5±2.12	0.37	0.77
E WAVE (cm/s)	0.85±0.10	0.86±0.14	0.89±0.08	0.95±0.06	0.57	0.63
A WAVE (cm/s)	0.96±0.15	0.94±0.16	1.04±0.35	0.96±0.19	0.3	0.82
E/A RATIO	0.90±0.16	0.91±0.16	0.93±0.33	1±0.14	0.21	0.89

Table 7: Global longitudinal peak systolic strain in the studied population

	Normal coronaries/Non-obstructive CAD	SVD	DVD	TVD/LMCA disease	One way anova	
					F	*P* value
PS GLS (%)	−20.40±0.83	−18.33±0.5	−17.32±0.41	−16±014	8.11	0.00
PS GLSR (s^{-1})	1.50±0.22	0.70±0.17	0.65±0.17	0.4±0	73.83	0.00

with regional WM abnormality on echocardiography do not pose a problem in diagnosis. The subset of patients without regional WM abnormality on echocardiography needs to be further evaluated before subjecting them to invasive procedures like coronary angiography.

We generally have a higher threshold for investigation as long as the patient has good LV function. Questions persist regarding the appropriateness and cost effectiveness of screening for CAD along with the optimal approach to screening. GLS measured by 2D STE at rest has been recognized as a sensitive parameter in the detection of significant CAD.

In the present study, the value of GLPSS at rest to predict the presence, extent, and severity of CAD in patients with suspected stable angina pectoris has been evaluated. The present study included 50 patients with suspected stable angina pectoris without regional WM abnormality and with normal systolic function. These patients were subjected to 2D-STE and coronary angiography. Global LPSS are calculated and are correlated to the results of coronary angiography for each patient.

Of the 50 patients included in the present study, 29 patients had normal coronary arteries or mild non-obstructive CAD and 21 had significant CAD. Fifteen patients had single-vessel disease, four patients had two-vessel diseases, one patient had three-vessel diseases, and one patient had distal LMCA bifurcation lesion involving the ostia of LAD artery and left circumflex artery. There was statistically insignificant difference between the groups of patients with non-obstructive CAD and obstructive CAD (LMCA >50% stenosis and other coronary arteries >70% stenosis) as regard to the conventional echo parameters (dimensions, ejection fraction, and mitral E and A velocities) which were concordant with Biering-Sørensen *et al.*, Montgomery *et al.*, and Nicola *et al.* who showed statistically insignificant difference between the two groups with and without CAD in terms of EF and LV internal diameters. However, the present study is not in agreement with Radwan *et al.* study where there was a lower EF in the group of CAD (59.3 ± 3.2% vs. 65.7 ± 4.7%; $P < 0.000$).

In the present study, there is a statistically significant lower GLSS and strain rate in patients with CAD compared to those with normal coronary arteries or mild non-obstructive CAD ($P = 0.00$). There are no statistically significant differences in terms of age and BMI with $P = 0.40$ and 0.99, respectively. There are no significant differences in respect to other baseline demographic variables such as diabetes mellitus, hypertension, smoking, dyslipidemia, or family history of CAD.

There is a statistically significant difference in mean of GLPSS between those with normal coronaries or mild non-obstructive CAD and patients with CAD ($P = 0.00$). There is also a statistically significant difference in mean of peak systolic GLS rate between those with normal coronaries or mild non-obstructive CAD and patients with CAD ($P = 0.00$). These observations are in agreement and consistent with the studies of Biering-Sørensen *et al.*, Montgomery *et al.*, Nicola *et al.*, Radwan *et al.*, Smedsrud *et al.*, and Shimoni *et al.*

Biering-Sørensen *et al.* studied 296 consecutive patients with clinically suspected stable angina pectoris, no previous cardiac history, and normal LVEF. GLSS was significantly lower in patients with CAD compared with patients without CAD (17.1 ± 2.5% vs. 18.8 ± 2.6%; $P < 0.001$). They concluded that in patients with suspected stable angina pectoris, GLSS assessed at rest is an independent predictor of significant CAD.

In the study conducted by Montgomery *et al.*, 2D STE characteristics of 123 consecutive patients who underwent stress echocardiography and subsequently coronary angiography within 10 days were assessed. In this study, in 56 patients with significant $CAD_{>50}$, GLS was 216.77 ± 3.18% compared with 219.05 ± 3.43% in the 67 patients without $CAD_{<50}$ ($P = 0.0002$). They concluded that non-obstructive CAD was identified by a reduced GLS measured by 2D STE in rest images with similar accuracy to the traditional WM score index measured in stress echocardiography.

Nicola *et al.* studied 82 patients who are referred for stress echocardiography. GLS was measured by STE in all the patients. Patients in the CAD group had significantly reduced rest GLS (−19 ± 2.4 vs. −22.7 ± 2.4, $P = 0.001$). They concluded that rest GLS demonstrated high accuracy in the detection of obstructive CAD, not different from, and possibly superior to, the visual assessment of regional WM during stress echocardiography. Rest GLS is synergistic with stress WM assessment, leading to the highest accuracy of detecting whether a patient is affected by obstructive CAD or not.

Radwan *et al.* studied 80 patients with suspected stable angina pectoris and no regional wall motion abnormalities with normal ejection fraction. There was a significant decrease in GLS in patients with obstructive CAD compared to patients without CAD (−11.86 ± 2.89% vs. −18.65 ± 0.79%, $P < 0.000$). The optimal cutoff value of GLS for prediction of significant CAD was −15.6% (AUC 0.88, 95% CI 0.78–0.96 $P < 0.000$). The sensitivity, specificity, and accuracy of GLS for detecting significant CAD were 93.1%, 81.8%, and 90%, respectively. There was a significant positive correlation between GLS and EF ($r = 0.33$; $P = 0.036$). There was incremental significant decrease in GLS with increasing number of coronary vessels involved. From these observations, they concluded that measurement of GLS using 2D STE is sensitive and accurate tool in the prediction of severe CAD.

Smedsrud *et al*. observed that 86 patients with suspected CAD referred to elective diagnostic coronary angiography. Global systolic strain was significantly lower in patients with CAD (−17.7 ± 3.0% vs. −19.5 ± 2.6%, $P = 0.003$).

Shimoni *et al*. observed that there are significant differences in all strain parameters between patients with and without CAD. They concluded that in patients hospitalized with angina who have significant CAD on coronary angiography, longitudinal systolic function is impaired.

Gopinath *et al*. concluded from their study that strain imaging has high sensitivity and high negative predictive value when compared to CAG (gold standard) in identifying obstructive CAD, making this a good test to rule out obstructive CAD in a low-risk population.

Moustafa *et al*. studied 200 patients with stable angina and normal conventional echocardiography. There was a statistically significant difference in the mean of GLSS between normal coronaries and different degrees of CAD (−20.11 ± 0.8 for normal, −18.34 ± 2.52 for single vessel, −16.14 ± 2.85 for two vessels, −14.81 ± 2.12 for three vessels, and −13.01 ± 2.92 for left main disease). GLPSS showed high sensitivity for the diagnosis of single-vessel CAD (90%, specificity 95.1%, cutoff value: −18.44, AUC: 0.954); two vessels disease (90%, sensitivity 88.9%, cutoff value −17.35, AUC: 0.906), and for three vessels CAD (cutoff value −15.33, sensitivity 63%, and specificity 72.2%, AUC 0.681). They concluded that 2D STE has good sensitivity and specificity to predict the presence, extent, and severity of CAD.

Bakhoum *et al*. studied 82 patients and found that GLS, global longitudinal strain rate, global radial strain, global radial strain rate, mid circumferential strain, and mid circumferential strain rate were significantly lower in patients with significant CAD compared to normal coronary arteries group (all $P = 0.000$).

CONCLUSIONS

GLS assessed by 2D-STE at rest is a predictor of significant CAD. GLS has high sensitivity for early detection of significant CAD in intermediate risk patients. 2D-STE has the potential to improve the value of echocardiography in the detection of the CAD, identifying high-risk patients.

Patients who are at intermediate risk for CAD who have normal or inconclusive ECG findings and normal conventional 2D echocardiography should be assessed by strain imaging. This approach helps in selecting the patients for invasive coronary angiography which in turn helps to decrease the risks and costs associated with coronary angiography. Patients who are stratified as low risk by strain imaging can be discharged earlier further decreasing the health-care costs. At the same time, early detection of subclinical LV dysfunction based on abnormal strain findings helps in evaluating such patients with a more aggressive approach such as coronary angiography and early appropriate revascularization if appropriate.

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