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Global Longitudinal Strain Measured by 2D Speckle Tracking Echocardiography in Stable Angina Patients and Their Angiographic Correlation.

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Abstract

Introduction & Objective: *Myocardial strain assessed by Speckle Tracking Echocardiography (STE) quantifies myocardial deformation which appears earlier than wall motion abnormality. Thus Global Longitudinal Strain (GLS) assess myocardial function in early stage of ischemic evolution. The aim of the study was to estimate GLS in coronary angiography undergoing intermediate to high risk stable angina patients which could correlate GLS with significant Coronary Artery Disease (CAD), determine cut-off value for identifying significant CAD and find sensitivity and specificity for the GLS cut-off value.*

Methods: *This was a cross-sectional study which included stable angina patients with normal left ventricular ejection fraction who were otherwise indicated to undergo coronary angiography. All the patients underwent STE and their GLS value was calculated. The coronary artery angiography findings were then correlated with GLS using appropriate statistics.*

Results: *A total of 89 patients were included. There was a strong negative correlation (r = -0.824) between GLS value and presence of significant CAD. The mean values of GLS for single vessel disease, double vessel disease and triple vessel disease were -15.94 ± 7.30, -15.28 ± 0.58 and -11.59 ± 1.35 (P <0.001) respectively. The GLS cut-off value ≤ -18.5 identified significant CAD and the sensitivity, specificity and area under curve for this cut-off value was 96.8%, 85.2% and 0.937 respectively (P<0.001).*

Conclusion: *Global longitudinal strain is a sensitive, specific and excellently accurate modality that had a strong negative correlation with presence and severity of significant CAD.*

Keywords: Coronary Artery Disease (CAD); Global Longitudinal Strain (GLS); Speckle Tracking Echocardiography (STE).

Introduction

Global Longitudinal Strain (GLS) measured by Speckle Tracking Echocardiography (STE) using myocardial deformation assess global myocardial contractile function which overcome limitations of conventional Left Ventricular Ejection Fraction (LVEF) based myocardial systolic functional assessment (Takigiku et al., 2012). Moreover, with temporal progression of myocardial ischemia, changes in strain occur earlier than that with regional wall motion abnormality or LVEF (which are the usual parameters for assessing ischemic heart disease) in conventional 2D trans-thoracic echocardiography (Collider et al., 2017, Amundsen et al., 2006). Hence, 2D-STE is helpful tool to assess myocardial function in early stage of ischemic evolution (Collider et al., 2017, Amundsen et al., 2006). There are not such studies done in our part of the world, so the present study was formulated. The objective of the study was to measure GLS in Coronary Angiography (CAG) undergoing intermediate to high-risk stable angina patients which would be effective for determining GLS values for different severity of CAD, correlating GLS with CAG findings, calculating GLS cut-off value for detection of significant Coronary Artery Disease (CAD) and finding sensitivity and specificity for GLS cut-off value.

Materials and Methods

It was a hospital based cross-sectional prospective study conducted between 1st July 2018 to 30th June 2019 for 12 months at Bir Hospital and Shahid Gangalal National Heart Center, Kathmandu, Nepal. Adult patient age ≥ 18 years undergoing CAG for their intermediate to high risk stable angina but with a normal left ventricular ejection fraction in echocardiography were included in the study. Patients with acute coronary syndrome, past h/o CAD or myocardial infarction, past h/o percutaneous coronary intervention, coronary artery bypass graft or any cardiac surgery, wall motion abnormality, overt

heart failure, rhythm abnormalities, severe valvular heart disease, concomitant disease, consuming cardiotoxic drugs and not giving consent for the study were excluded from the study. Sample size was calculated using the formula: $N=Z^2pq/e^2$, where "p" was the highest incidence of significant CAD in stable angina patients (Sultan et al., 2016)and the sample size came out to be 67. Patients were enrolled for the study until sample size was achieved or duration of the study terminated, whichever came later.

Stable angina patients with intermediate pretest probability were instructed to undergo exercise Tread Mill Test (TMT) and those with TMT results positive were suggested for CAG. On the other hand, those patients with high pretest probability were directly encouraged to undergo CAG without TMT. Meanwhile, 2D STE images from each patient were stored offline. For STE, electrocardiography gated echocardiographic images were captured from at least three longitudinal views i.e., parasternal long axis view, apical four chamber view and apical three chamber view. Care were taken to include images with good endocardial border in all standard views and a minimum of three consecutive cardiac cycles with a high frame rate of 30- 90 frames per second settings were applied to the echo machine. These offline images were later analyzed using QLAB Cardiac Analysis software of Phillips high end echocardiography machine (AFFINITI 50C, EPIQ 7) to generate Global peak longitudinal strain of entire myocardial segment using LV Global L Peak-aCMQ technique and were plotted in strain graph. To improve diagnostic accuracy, these offline images were scrutinized by an experienced second operator. After few exclusions, patients underwent CAG by a team of experienced cardiologists. Coronary angiography was transacted in ≥ 2 projections for each coronary artery. Angiographic details including presence or absence of significant CAD, involvement of specific coronary artery and severity of CAD were portrayed in working proforma.

Simultaneously, detail clinical history, history of cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia, family history of CAD, smoking history, past medical/surgical history, general physical examination, systemic evaluation, Chest X-ray (CXR), Electrocardiography (ECG), necessary laboratory investigations and 2D TTE were recorded and drafted over working proforma. Ethical clearance for the study was obtained from Institutional Review Board, National Academy of Medical Sciences.

Patients were categorized into two groups i.e., patient without significant CAD (group 1) and patient with significant CAD (group 2). Data were then listed into worksheet (Microsoft excel) and statistical analysis was accomplished using IBM Statistical Package for Social Science (SPSS) statistics, version 20. Continuous variables were arrayed as mean ± standard deviation and categorical variables were indexed as number, percentages or proportions. . A 2x2 contingency table was sketched. Spearman's rank correlation was applied to assess strength of relationship between GLS and angiographic findings (non-parametric). Sensitivity and specificity were derived using Receiver Operating Characteristic (ROC) curve which also formulated cut-off value of GLS for diagnosing CAD. Concurrently, Area Under Curve (AUC) was reported. Finally, Confidence Interval (CI) of 95% and P value were computed to conclude the result obtained. Value of $P < 0.05$ was considered significant.

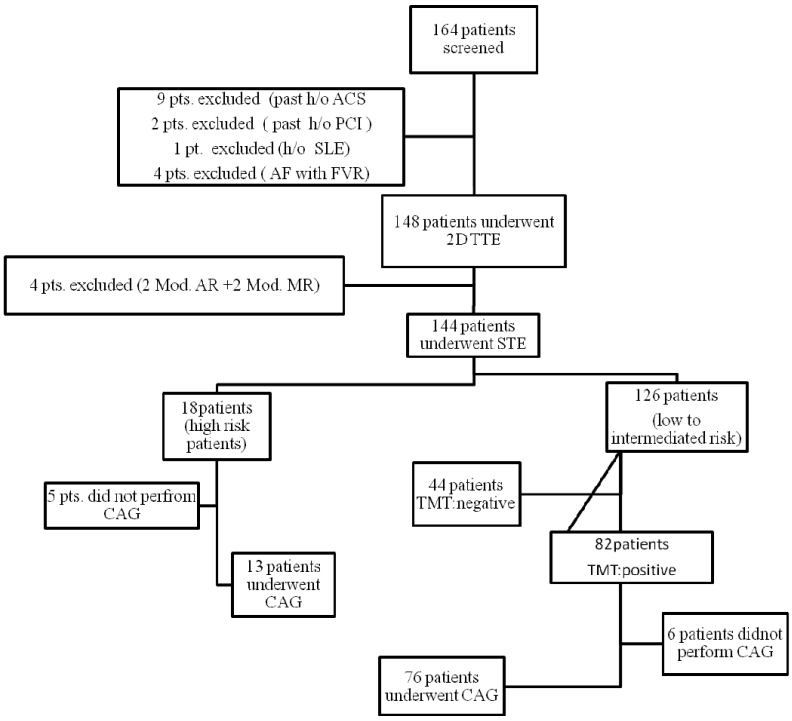

Figure 1: Patient selection algorithm (Note:2D: Two Dimensional, ACS: Acute Coronary Syndrome, AF: Atrial Fibrillation, AR: Aortic Regurgitation, CAG: Coronary Angiography, FVR: Fast Ventricular Rate, MR: Mitral Regurgitation, PCI: Percutaneous Coronary Intervention, SLE: Systemic Lupus Erythematosus, STE: Speckle Tracking Echocardiography, TMT: Tread Mill Test, TTE: Trans-Thoracic Echocardiography)

Results

There were a total of 89 patients in the study and the mean age was 58.36 ± 9.54 years. More than two-third (69.7%) of the patients had significant CAD and the mean GLS was -15.96 ± 6.72. The baseline characteristics are listed in table 1.

Characteristics	Frequency (%)
Total Patients	89
Age (mean ± SD)	58.36 ± 9.54 years
Male Female	65 (73%) 24 (27%)
Smoking	41 (46.1%)
Tobacco Chewing	10 (11.2%)
HTN	52 (58.4%)
DM-II	23 (25.8%)
Obesity	17 (19.1%)
Dyslipidemia	7 (7.9%)
PAD	1 (1.1%)
LVEF (mean ± SD)	61.8 ± 2.6%
Significant CAD	62 (69.7%)
GLS (mean ± SD)	-15.96 ± 6.72

Table 1: Baseline characteristics

(Note: CAD: Coronary Artery Disease, DM-II: Diabetes Mellitus- type 2, GLS: Global Longitudinal Strain, HTN: Hypertension, LVEF: Left Ventricular Ejection Fraction, PAD: Peripheral Artery Disease, SD: Standard Deviation)

Table 2 depicts various baseline characteristics among group 1 and group 2 patients. The mean GLS was -19.84 ± 8.64 in group 1 and -14.27 ± 4.87 in group 2 patients with p value of <0.001.

Characteristics	Group 1 (CAD -)	Group 2 (CAD +)	P Value
Age (mean ± SD)	55.48 ± 6.41 years	59.61 ± 10.41 years	0.060
Male Female	15 (16.9%) 12 (13.5%)	50 (56.2%) 12 (13.5%)	0.014
Smoking	9 (10.1%)	32 (36.0%)	0.112
Tobacco Chewing	0 (0%)	10 (11.2%)	0.027
HTN	17(19.1%)	35 (39.3%)	0.567
DM-II	6 (6.7%)	17 (19.1%)	0.607
Obesity	6 (6.7%)	11 (12.4%)	0.621
Dyslipidemia	4 (4.5%)	3 (3.4%)	0.108
PAD	0 (0%)	1 (1.1%)	0.507
LVEF (mean ± SD)	61.9 ± 2.7%	61.7 ± 2.6%	0.740
GLS (mean ± SD)	-19.84 ± 8.64	-14.27 ± 4.87	< 0.001

Table 2: Baseline characteristics between two groups

(Note: CAD: Coronary Artery Disease, DM-II: Diabetes Mellitus- type 2, GLS: Global Longitudinal Strain, HTN: Hypertension, LVEF: Left Ventricular Ejection Fraction, PAD: Peripheral Artery Disease, SD: Standard Deviation)

Table 3 illustrates mean GLS value for different severity of CAD.

Characteristics	GLS (mean ± SD)	P Value
Normal/ Non-Critical Coronaries	-19.84 ± 8.64	< 0.001
SVD	-15.94 ± 7.30	
DVD	-15.28 ± 0.58	
TVD	-11.59 ± 1.35	

Table 3: GLS value for CAD

(Note: CAD: Coronary Artery Disease, DVD: Double Vessel Disease, GLS: Global Longitudinal Strain, SVD: Single Vessel Disease, SD: Standard Deviation, TVD: Triple Vessel Disease)

The bi-variate correlation between significant CAD and GLS is demonstrated in table 4.

Correlations		Significant CAD	GLS
Significant CAD	Correlation Coefficient Sig. (2-tailed) N	1.0 89	-0.824 <0.001 89
GLS	Correlation Coefficient Sig. (2-tailed) N	-0.824 <0.001 89	1.0 89

Table 4: Correlation between Significant CAD and GLS

(Note: CAD: Coronary Artery Disease, GLS: Global Longitudinal Strain)

The GLS cut-off value of ≤ -18.50 predicted occurrence of significant CAD with a sensitivity of 96.8% and specificity of 85.2%. The Area under Curve (AUC) was 0.937 (95% confidence interval, 0.861- 1.000), P<0.001 suggestive of excellent accuracy (Figure 2).

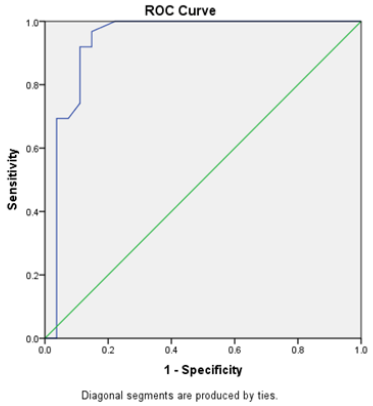

Figure 2: Receiver Operating Characteristic (ROC) curve

Discussion

The baseline demographics of this study consisted predominantly of male patients (73%) with mean age of 58.36 ± 9.54 years. Similar demographics were also observed in study done by Moustafa S, et al. (2018) and study done by Anwar, et al. (2013) with majority of male patients and mean age of 51.0 ± 8.7 years. Analogous findings were also reported in study done by Hussain et al. (2018) Congruency between our study findings of slightly older patients in significant CAD group (59.61 ± 10.41 years) compared to those without significant CAD group (55.48 ± 6.41 years) were also common in studies done by Montgomery et al. (2012), Rumbinaite et al. (2016), Gaibazzi et al. (2014), Choi et al. (2009), Mahjoob et al. (2017), and Eljersen et al. (2017).

Various studies have demonstrated presence of numerous atherosclerotic risk factors. Coincidental with our finding was an Egyptian study (Moustafa et al., 2018) which revealed that hypertension (64%) to be the most frequent risk factor which was succeeded by diabetes (62.5%), dyslipidemia (57%), smoking (39.5%) and family history of CAD (13.5%). Hypertension, hyperlipidemia and diabetes in decreasing pattern were depicted as risk factor by a study from Italy (Giabazzi et al., 2014). A research conducted in London found that common risk factors were hypertension (56%), dyslipidemia (45%), smoking (37%), chronic kidney disease (15%) and obesity (56%) (Vrettos et al., 2016). Contrarily to our study, a study from Iraq (Husein et al., 2018) displayed that the commonest risk factor were diabetes (73.6%), hyperlipidemia (58.3%), smoking (51.4%) and hypertension (33.3%). This variability in frequencies of risk factors may be explained by different population genetics and environmental factors between our population and these researches population.

This study manifested that 69.7% of the patients had significant CAD which was one of the highest among studies done so far. Literatures have shown varied prevalence of significant CAD in stable angina patients. Study done by Bakhoum et al. (2016) found the frequency of significant CAD to be 75.3%, Moustafa et al. (2018) found it to be 75%, Radwan et al. (2017) found it to be 72.5%, El-Hefeny et al. (2016) found it to be 66.66%, Norum et al. (2015) found it to be 60%, Giabazzi et al. (2014) showed it to be 59.75%, Shahriar et al. (2018) found it to be 53%, Rostamzadeh et al. (2015) found it to be 504%, Teferici et al. (2014) found it to be 47.4%, Montgomery et al. (2012) found it to be 45.5%, Biering-Sorensen et al. (2014) found it to be 36.5%, Hagemann et al. (2017) found it to be 36% and Eljersen et al. (2017) found it to be 35%. Lower prevalence of significant CAD in these studies could be justified by presence of younger patients with low risk factors compared to our studies with contrasting features.

Spearman's rank correlation analysis observed linear association between GLS value (continuous variable) and presence of significant CAD (non-parametric variable). The correlation coefficient was tracked out to be -0.824 with p< 0.001, implying strong down-hill (inverse) relationship i.e., Low GLS value was associated with presence of significant CAD. This finding was in agreement with findings of Anwar (2013) where he found strong negative correlation(r: -0.88, p< 0.001) between GLS and CAD.

Till date, there is no single universal value of GLS to define normality or abnormality as all researches of speckle tracking echocardiography (GLS) were with different sets of machine and software provided by different vendors and this lacks uniformity in averaging a value for it. Several articles have proposed a range of values for GLS. The European Association of Cardio Vascular Imaging (EACVI) study group labeled average value of GLS to be -18% to -21.5%. (Farsalinos et al., 2015), Fiegenbaum et al. (2012) proposed normal value of GLS: -16 to -18. Yingchoncharoen et al. (2013) further narrowed down cutoff value of GLS and defined normal value of GLS: -15.9 to -22.1 (mean -19.7; 95% CI, -20.4 to -18.9) (Yingchoncharoen et al., 2013).

Mean GLS in our study was -15.96 ± 6.72 and mean GLS in patient with significant CAD was -14.27 ± 4.87 (P < 0.001) with mean GLS value in patient without significant CAD was -19.84 ± 8.64 (P < 0.001). Various researches have shown various values of GLS between significant and non-significant CAD groups. Study performed by Radwan, et al. (2017) where mean GLS between patient with significant CAD (-11.86 ± 2.89) and non-significant CAD (-18.65 ± 0.79) matches with our study. Biering-Sorensen, et al. (2014) observed the mean GLS was -17.1 ± 2.5 and -18.8 ± 2.6 (P<0.001) between patients with significant and non-significant CAD. Similarly, mean GLS between significant and non-significant CAD groups in study done by Montgomery et al. (2012) were -16.7 ± 3.18 and -19.05 ± 3.42 (P=0.002) respectively. Liou et al. (2016) documented mean GLS of -16.5 and -19.7, Norum et al. (2015) demonstrated mean GLS of -17.2 ± 2.6 and -19.2 ± 2.8, Giabazzi et al. (2014) found mean GLS of -19.02 ± 2.45 and -22.73 ± 2.74, Bakhoum et al. (2016) reported mean GLS of -16.55 ± 2.77 and -21.11 ± 0.8 (P<0.001) in patients with significant and non-significant CAD respectively. Lower mean value of GLS in our study compared to all these studies could be explained by the fact that our study population had higher percentage of significant CAD patient which resulted in lower GLS mean values.

The GLS cut-off value to identify significant CAD in our study was ≤ -18.5. Studies having similar findings as ours were conducted by Shahriar et al. (2018) where they found GLS cutoff value of -18.77 and Mahjoob et al. (2017) where they found GLS cutoff value of < -18.0. On the contrary, studies done by Giabazzi et al. (2014) reported cut-off GLS value to diagnose significant CAD to be -20.72, Bakhoum et al. (2016) documented it to be -20.44, Norum et al. (2015) demonstrated it to be -19.7 to -17.4 and Choi et al. (2009) sketched it to be -19.4. These researches have higher threshold GLS cutoff value as compared to our study. Moreover, there are various studies where GLS cut-off value was lower compared to our study. Patient with significant CAD had a GLS cut-off value of -17.77 in a study done by Montgomery et al. (2012), a value of -17.4 in a study done by Nucifora et al. (2010) a value

of -17.0 in a study done by Rostamzadeh et al. (2015) and a GLS cut-off value of -15.6 in a study done by Radwan et al. (2017). Different proportion of severity of CAD patients in sample population, different vendors, different speckle echocardiography machines and difference in sample size would have generated wide variability in GLS cut-off value between our study and the studies mentioned above.

There was inverse relation with increasing severity of CAD and GLS value. This could be explained by the fact that with increase in severity, more of the contractile myocardial units were affected and this resulted in less myocardial deformation producing low GLS value. Complying with this motif, mean GLS in our study was -15.94 ± 7.30 for SVD, -15.28 ± 0.58 for DVD and lowest for TVD -11.59 ± 1.35 with p value < 0.001. The distribution of SVD, DVD and TVD in our study was 25.9%, 20.2% and 23.6% respectively. Rawdan et al. (2017)also reported similar findings of mean GLS in SVD, DVD and TVD to be -15.13 ± 0.68, -12.25 ± 0.9 and -9.1 ± 1.94 respectively. Identical findings were demonstrated by Moustafa et al. (2018) where mean GLS values were in decreasing tendency with increasing severity of CAD and was -18.34 ± 2.52 for SVD, -16.14 ± 0.85 for DVD and -14.81 ± 0.12 for TVD. Concurrent were the findings of Giabazzi et al. (2014) which was -19.66 ± 2.66 for SVD, -19.20 ± 1.67 for DVD and -18.08 ± 2.5 for TVD.

This study demonstrated that the sensitivity and specificity for GLS cut-off value of ≤ -18.50 to detect significant CAD was 96.8% and 85.2% respectively with 95% confidence interval of 0.861- 1.000. This level of sensitivity and specificity can be decoded as a message that GLS cut-off value of ≤ -18.50 identifies almost all cases of significant CAD (96.8% sensitivity) and can highly reject cases of non-significant CAD (specificity of 85.2%). Moreover, AUC was summed up to be 0.937, P<0.001 suggesting excellent discriminating capability or accuracy of GLS for diagnosing significant CAD. These findings were in harmonious with studies done by Rawdan H, et al. (2017) where the sensitivity & specificity of GLS for detecting significant CAD were 93.1%, 81.8% and AUC:0.88, 95% CI 0.78-0.96,P< 0.001). Bakhoum et al. (2016) found sensitivity: 90%, specificity: 95.1% and accuracy: 95%, Mahjoob et al. (2017) graphed sensitivity: 91.1%, specificity: 63% and accuracy: 80.5% (P<0.001), Giabazzi et al. (2014) measured sensitivity: 81.63%, specificity: 84.85% and accuracy: 86.1% and Shahriar et al. (2018) outlined sensitivity, specificity and accuracy of 77.4%, 82.9% and 87.7% for diagnosing significant CAD. Research done by Vrettos et al. (2016) showed good sensitivity(71%) and high specificity(90%), P < 0.001 for GLS cut-off value -13.95 in predicting significant obstructive CAD.

There were few limitations of this study. Because of cross-sectional study design, causal relationship between the demographic characteristics could not be made. Selection bias always remains a part and parcel of such non-probability based random sampling technique. Moreover, small sample sized study like this should always be supplemented with a large population based randomized controlled trial where their inferences could be generalized to the population.

Conclusion

There was a strong negative correlation between GLS and presence of significant CAD. The GLS cut-off value of ≤ -18.5 for identifying significant CAD had a sensitivity of 96.8%, specificity of 85.2% and an excellent accuracy. Hence, GLS can be used as an effective alternative screening measure in patients planned for coronary angiography.

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