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Two-dimensional Speckle -tracking Echocardiography Derived Longitudinal Strain in Patients with Unstable Angina and Normal Left Ventricular Ejection Fraction

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Abstract

Longitudinal strain (LS) measurements by Speckle Tracking Echocardiography (STE) is a point of care imaging modality that had been documented to have a role in NSTEMI/STEMI and stable Coronary artery disease (CAD). This study aims to determine the accuracy of LS parameters in diagnosis and predicting severity of CAD in unstable angina patients with no regional wall motion abnormalities. It was a prospective analytical study in which 143 low-risk Unstable angina patients underwent STE. Based on Coronary angiogram results, the study participants were divided into obstructive CAD and control group. Patients with obstructive CAD (n = 79) had significantly higher GLS_{Trans} and GLS₁₂ ($-18.2 \pm 3.5\%$ Vs $-20.4 \pm 3.2\%$, $p = 0.001$ and $-16.0 \pm 3.5\%$ Vs -18.1 ± 3.0 , $p = 0.001$ respectively) compared to patients with normal/non-obstructive coronaries (n = 45). Both GLS_{Trans} and GLS₁₂ were independent predictors of obstructive CAD by multivariate logistic regression. However, the diagnostic accuracy of GLS_{Trans} (AUC = 0.683) and GLS₁₂ (AUC = 0.687) were only modest. But the positive predictive value of grossly altered GLS $>-16.1\%$ was high (92.1%). Regional longitudinal strain (RLS) parameters were noted to be significantly higher in obstructive CAD group compared to the control one (RLS_{LAD}: -18.8 ± 4.8 Vs -21.2 ± 4.5 , $p = 0.007$; RLS_{LCX}: -16.0 ± 4.8 Vs -18.6 ± 3.5 , $p = 0.001$; RLS_{RCA}: -18.8 ± 3.6 Vs -20.2 ± 3.4 , $p = 0.031$). Diagnostic accuracy of GLS in patients with low-risk UA is only modest. However, the subgroup of patients with GLS $>-16.1\%$ have a high probability of having obstructive CAD and in particular multivessel disease and hence these patients can be subjected to CAG without further ischemic testing.

Keywords: Global longitudinal strain (GLS), GLS₁₂, Regional longitudinal strain (RLS), Unstable angina, Normal LV ejection Fraction

1. Introduction

Coronary artery disease (CAD) manifests clinically as either Stable ischemic heart disease or as an acute coronary syndrome (ACS). ACS in turn is sub grouped into ST elevation

myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA). Overall the use of highly sensitive assays for myocardial necrosis (cardiac troponin) has shifted the classification of NSTEMI-Acute Coronary Syndrome (ACS) away from UA to NSTEMI [1]. UA still constitute an

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important sub-group of CAD patients presenting with chest pain to both Emergency room (ER)/outpatient (OP) department.

Several non-invasive investigations such as exercise electrocardiogram, rest and stress echocardiography [2], stress myocardial perfusion imaging (MPI) [3], Computerized tomography coronary angiogram (CTCAG) [4] and cardiac magnetic resonance imaging (CMR) are used for both diagnosis and risk stratification in patients of UA without any high-risk features before taking up for an invasive Coronary angiogram (CAG). Stress MPI, stress echocardiography and CMR are more sensitive and specific than TMT. However, in actual clinical practice (particularly in a developing country like India) their use is diminished in view of cost issues, availability and the need for expertise in interpretation. Though CAG is still the gold standard, it is an invasive investigation which can cause certain complications albeit rare. Hence it is imperative to further risk stratify low risk unstable angina patients noninvasively and determine which subset of patients has increased probability of obstructive CAD and in turn need invasive angiogram.

Lately, myocardial deformation imaging by 2-D/3-D speckle tracking echocardiography (2-D/3-D STE) is identified as an important modality for assessing myocardial function. Impairment in several 2-D and 3-D strain parameters have been shown to have a role in predicting obstructive CAD both in SIHD patients [5,6] and NSTEMI/STEMI [7,8]. But the predictive value of strain imaging is still not defined in patients with UA and normal Left ventricular (LV) function with no regional wall motion abnormalities (RWMA) by studies with a large sample size. If strain imaging can predict the occurrence and severity of CAD in those presenting to ER or OP services with low-risk UA, it will drastically reduce the hospitalisation time and cost as it can be performed and interpreted within few minutes.

2. Methods

2.1. Study population

It was a prospective analytical study in which one forty-three consecutive patients more than 18 years of age with a diagnosis of unstable angina to whom CAG was planned were enrolled. All those included should have normal LV systolic function with no RWMA on echocardiogram and a negative highly sensitive troponin assay result.

Abbreviations list

CAD	Coronary artery disease
ACS	acute coronary syndrome
STEMI	ST elevation myocardial infarction
NSTEMI	Non- ST elevation myocardial infarction
UA	Unstable angina
ER	emergency room
STE	speckle tracking echocardiography
LV	left ventricle
EF	ejection fraction
RWMA	regional wall motion abnormality
CAG	coronary angiogram
LAD	left anterior descending artery
LCX	left circumflex coronary artery
RCA	right coronary artery
LS	Longitudinal strain
GLSTRANS	Transmural longitudinal strain
RLS	Region specific longitudinal strain
ROC	Receiver operating characteristic curve
MVD	Multi vessel disease
PPV	Positive predictive value

Patients with prior CAD, previous history of myocardial infarction, presence of significant valvular heart disease, patients receiving chemotherapy, those with Stage 4 & 5 Chronic kidney disease, Presence of Left bundle branch block/pacemaker and those cases who developed NSTEMI/STEMI during hospital stay were excluded. The study was approved by our institutional ethics committee, Mahatma Gandhi Medical College and Research Institute. All participants signed an informed consent form.

Baseline parameters like patients age, gender, Body Mass Index (BMI), presence of risk factors such as diabetes mellitus, systemic hypertension, dyslipidaemia, obesity, current smoking status, angina NYHA class, Global Registry of Acute Coronary Events (GRACE)score, resting ECG findings were collected.

2.2. Image acquisition and analysis

2-D echocardiography was done for all the patients using Vivid E –95 system (GE healthcare) equipped with a 4 V phased array matrix transducer (1.5–4.0 MHz). All routine echocardiographic measurements were obtained according to American Society of Echocardiography guidelines. A single cardiologist experienced in strain echocardiogram performed the test and he was blinded to patient's clinical and angiographic details. Cine loops with 3 cardiac cycles in apical 3 chamber (A3C), apical 4 chamber (A4C) and apical 2 chamber (A2C) views

were recorded at a frame rate of 50–80 per second and stored.

Longitudinal strain (LS) was measured from the three standard planes (A3C, A4C, A2C) by 2D STE using 17 segment model of LV. In each of the apical planes, tracing of LV myocardium was automatically performed by the software. Manual adjustments were made whenever it was deemed necessary. Software calculated the strain values of individual segments in all 3 views. After processing all 3 apical views, a 17-segment bull's eye map was generated. Transmural Global longitudinal strain (GLS_{Trans}) was provided automatically by the software. Based on the standardised model of myocardial perfusion territories [9], region specific longitudinal strain (RLS) were calculated as the average value of the segments belonging to each perfusion territory in the LAD, LCX and RCA respectively. GLS_{12} was derived manually from 6 basal and 6 mid ventricular segments whereas GLS_{11} obtained from 6 mid and 5 apical segments.

2.3. Coronary angiogram

Angiographic images were studied meticulously by an interventionist who was blinded to the patient data. Patients with a lesion of >70% stenosis in one or more major epicardial coronary vessel and those with less than TIMI 3 flow distally were considered to have obstructive CAD. Participants with normal coronaries and non-obstructive disease were taken as the control group. Patients with >70% stenosis in Obtuse marginal, posterior descending artery, posterolateral branch, ramus were considered obstructive only if the vessel diameter was more than 2.25 mm.

2.4. Reproducibility

Fifteen patients were randomly chosen and their intra and inter-observer reliability were assessed for GLS and RLS values. The inter-class correlation coefficient for intra-observer comparisons of GLS and GLS_{12} were 0.985 (95% CI:0.957–0.995) and 0.939 (95% CI:0.818–0.979) respectively. The inter-class correlation coefficients for inter-observer reliability were 0.979 (95% CI: 0.937–0.993) and 0.945 (95% CI: 0.825–0.982) respectively.

2.5. Statistical analysis

SPSS version 16 was used to perform statistical analysis. Quantitative variables were expressed as mean $\pm$ standard deviation, while categorical variables were expressed as numbers and percentages.

Continuous variables were compared using independent samples t-test. Pearson chi-square test and fisher exact tests were used for categorical variables. Univariate and multivariate regression analysis were done to study the predictors of obstructive CAD. Receiver operator characteristic curves (ROCs) were constructed for strain parameters to detect their sensitivity and specificity in identifying obstructive CAD. Inter- and intra-observer reliability were studied using Blant-Altman analysis and using inter class correlation co-efficient.

3. Results

Total of 124 patients out of 143 participants were taken for final analysis. Sixteen patients had issues with image quality and hence were excluded. Three other patients' cardiac enzymes turned positive during hospital stay. The clinical details are provided in Table 1. The mean age was 55.2 years and there were 87 (70.2%) males. The GRACE score ranged between 30 and 128 with a mean of 79.6 indicating that the study group indeed had only low to intermediate risk patients. Only 25 (20.2%) patients had ischemic changes on resting ECG while the rest had normal or non-diagnostic ECG.

The 2-D echocardiographic parameters are presented in Table 2. The mean ejection fraction was 64.2% suggesting the fact that included group had only those with preserved EF. Out of these 124, 79 patients had obstructive CAD and 45 patients had normal coronaries/nonobstructive disease (control group). Among 79 patients with obstructive CAD, eight patients had slow flow coronaries suggestive of probable microvascular dysfunction. The angiographic results are displayed in Table 3. Most of the patients with obstructive CAD had lesion in LAD. There were no significant differences between the control and obstructive group as far as the traditional risk factors were concerned except for sex and hypertension. Females recruited in our study more often had normal coronaries compared to males.

GLS_{Trans} as well as GLS_{12} , GLS_{11} were significantly higher (less negative) in the obstructive CAD group (GLS_{Trans} : $-20.4 \pm 3.2\%$ vs $-18.2 \pm 3.5\%$, $p = 0.001$; GLS_{12} : $-18.1 \pm 3.0\%$ vs $-16.0 \pm 3.5\%$, $p = 0.001$; GLS_{11} : $-21.9 \pm 3.9\%$ vs $-19.7 \pm 4.7\%$, $p = 0.007$). RLS values are provided in Table 2. The longitudinal deformation indices in individual territories were significantly reduced in patients with obstructive CAD.

Receiver operating characteristic (ROC) curves were constructed for GLS_{Trans} and GLS_{12} in patients with obstructive lesion (Fig. 1). The analysis of the

Table 1. Clinical profile of study population.

	All (n = 124)	Normal/non-obstructive CAD (n = 45)	Obstructive CAD (n = 79)	P value
Age in years ($\pm$ SD)	55.2 $\pm$ 9.7	54.42 $\pm$ 9.61	55.62 $\pm$ 9.7	0.508
Gender n (%)				0.044
Male = 87 (70.2%)		26 (29.9%)	61 (70.1%)	
Female = 37 (20.8%)		19 (51.4%)	18 (48.6%)	
BMI (kg/m ²)	24.6 $\pm$ 2.7	24.4 $\pm$ 2.5	24.8 $\pm$ 2.9	0.462
Hypertension n (%)	75 (60.5%)	22 (48.9%)	53 (67.1%)	0.046
Diabetes n (%)	68 (54.8%)	22 (48.9%)	46 (58.2%)	0.315
Dyslipidemia n (%)	31 (25%)	11 (24.4%)	20 (25.3%)	0.914
Smoking n (%)	17 (13.7%)	6 (13.3%)	11 (13.9%)	0.927
Diastolic BP mm Hg	83.2 $\pm$ 10.1	82.6 $\pm$ 12.0	83.5 $\pm$ 8.9	0.668
B blockers n (%)	59 (47.6%)	18 (40%)	41 (51.9%)	0.202
ACE Inhibitors n (%)	43 (34.7%)	13 (28.9%)	30 (38%)	0.307
GRACE score ($\pm$ SD)	79.6 $\pm$ 19.7	79.6 $\pm$ 21.3	79.6 $\pm$ 18.9	0.987

Continuous data are expressed as mean $\pm$ SD and categorical variables are presented as number (percentage).

CAD Coronary artery disease, BMI Body-mass index, ACE angiotensin converting enzyme, TIMI Thrombolysis in myocardial infarction, GRACE Global registry of acute coronary events.

ROC curves suggested only modest accuracy for both GLS_{trans} and GLS₁₂ (see Table 4) and there was no significant difference in diagnostic performance between them. Univariate analysis of traditional risk factors for CAD, GRACE risk score and LVEF for prediction of CAD were assessed which revealed that only sex, hypertension, GLS_{trans} and GLS₁₂ had statistically significant association. After multivariate regression analysis, GLS_{trans} and GLS₁₂ were found to be independent predictors of obstructive CAD ($p = 0.006$ and $p = 0.007$ respectively). The optimal cut off values for GLS_{trans} and GLS₁₂ in diagnosing obstructive CAD was -18.5% and -17.0% with sensitivity of 53.2%, 62% and specificity of 74.3%, 60% respectively.

Table 2. Echocardiographic parameters of study group.

	Normal/non-obstructive CAD (n = 45)	Obstructive CAD (n = 79)	P value
LV EF, % ($\pm$ SD)	64.2 $\pm$ 4.74	64.1 $\pm$ 3.2	0.937
LV Mass, g/m ²	82.9 $\pm$ 11.5	85.1 $\pm$ 11.3	0.299
LV E/e'	10.4 $\pm$ 2.8	10.8 $\pm$ 3.2	0.511
GLS _{Trans} , %	-20.4 $\pm$ 3.2	-18.2 $\pm$ 3.5	0.001
GLS ₁₂ , %	-18.1 $\pm$ 3.0	-16.0 $\pm$ 3.5	0.001
GLS ₁₁ , %	-21.9 $\pm$ 3.9	-19.7 $\pm$ 4.7	0.007
RLS _{LAD}	-21.2 $\pm$ 4.5	-18.8 $\pm$ 4.8	0.007
RLS _{LCX}	-18.6 $\pm$ 3.5	-16.0 $\pm$ 4.8	0.001
RLS _{RCA}	-20.2 $\pm$ 3.4	-18.8 $\pm$ 3.6	0.031

LV left ventricle, EF ejection fraction, E-trans mitral early diastolic velocity, e'- early myocardial diastolic velocity, GLS_{Trans}-transmural global longitudinal strain, RLS- regional longitudinal strain, LAD-left anterior descending artery, LCX-left circumflex artery, RCA-right coronary artery.

Table 3. Coronary angiographic profile of study participants.

Angiographic finding	Frequency
Normal/non-obstructive CAD n (%)	45 (36.3%)
Single vessel disease	31 (25%)
Double vessel disease	21 (16.9%)
Triple vessel disease	15 (12.1%)
Left main disease	4 (3.2%)
Microvascular dysfunction	8 (6.4%)
LAD disease	62 (50%)
LCX disease	37 (29.8%)
RCA disease	39 (31.5%)

LAD-left anterior descending artery, LCX-left circumflex artery, RCA-right coronary artery.

Fig. 1. Receiver operating characteristic curves demonstrating value of transmural GLS, GLS₁₂ in the diagnosis of obstructive CAD. GLS-Global longitudinal strain.

Table 4. Analysis of ROC curves and cut-off values for longitudinal strain.

	AUC	Cut-off value	Sensitivity	Specificity
GLS _{trans}	0.683	−18.5%	53.2%	74.3%
GLS ₁₂	0.687	−17.0%	62%	60%
RLS _{LAD}	0.564	−18.3%	50%	70%
RLS _{LCX}	0.781	−16.1%	78.4%	74.7%
RLS _{RCA}	0.633	−19.1%	59%	60%

AUC- area under the curve, GLS_{Trans}-transmural global longitudinal strain, RLS_{LAD}-regional longitudinal strain in LAD territory, RLS_{LCX}-regional longitudinal strain in LCX territory, RLS_{RCA}-regional longitudinal strain in RCA territory.

3.1. RLS in identifying specific territory involvement

ROC curves for RLS are shown in Fig. 2. The predictive power of RLS in detecting significant

stenosis in the subtending coronary vessel are presented in Table 4 (also see Fig. 5). RLS_{LCX} had good accuracy in localising obstructive circumflex lesions with an optimal cut off value of greater than −16.1% with a sensitivity and specificity of 78.4% and 74.7% respectively. RLS_{RCA} showed moderate accuracy whereas RLS_{LAD} was not accurate in pointing obstructive disease in LAD.

3.2. Longitudinal strain and multivessel disease

GLS_{Trans} and GLS₁₂ increased significantly (less negative values) with increasing severity of CAD (see Table 5). The diagnostic accuracy of GLS_{trans} and GLS₁₂ in identifying multivessel disease (MVD) was good with an AUC of 0.735 and 0.747 respectively (see Fig. 3). GLS_{trans} greater than −18.9% had

Fig. 2. a–c: Receiver operating characteristic curves demonstrating value of RLS_{LAD}, RLS_{LCX}, RLS_{RCA} respectively in the diagnosis of obstructive CAD in their corresponding territories.

Table 5. Longitudinal Strain and CAD severity.

	Non-obstructive (n = 45)	Single vessel disease (n = 31)	Double vessel disease (n = 21)	Triple vessel disease (n = 15)	P value
GLS _{Trans} %	-20.4 ± 3.2	-19.1 ± 4.2	-17.1 ± 2.5	-17.3 ± 2.2	0.074
GLS ₁₂	-18.1 ± 3.0	-17.0 ± 4.3	-14.8 ± 2.5	-14.9 ± 2.1	0.036
GLS ₁₁	-21.9 ± 3.9	-20.8 ± 5.5	-17.8 ± 3.7	-19.3 ± 3.2	0.067

GLS_{Trans}-transmural global longitudinal strain.

a sensitivity and specificity of 75% and 62.5% respectively in detecting MVD (see Fig. 4).

4. Discussion

The important information's generated from our study are a) patients with obstructive CAD have significantly higher (less negative) longitudinal strain values; b) GLS_{trans} and GLS₁₂ have only modest accuracy in identifying obstructive CAD; c) though regional strain parameters were significantly altered in obstructive CAD, their role in localising the territory involved was accurate only with RLS_{LCX}; d) there was graded increase in LS values as the severity of CAD increased.

Compared to those with NSTEMI, people with UA have lower risk of cardiovascular events and appear to benefit less with potent dual antiplatelet therapy as well as early invasive revascularisation strategy within 72 h [10,11]. Hence the 2020 ESC guidelines recommend early invasive strategy (<24 h) only in those ACS patients with certain high-risk features such as positive cardiac troponins, dynamic ST segment changes suggestive of ischemia and a GRACE score > 140. Whereas in patients with low

risk UA, invasive strategy is selectively recommended only in those who have imaging evidence of ischemia or obstructive CAD by CTCAG [12]. Hence there is a need for a non-invasive imaging modality which is cost effective, provides point of care results at the ER/OP services and not need much of expertise in interpretation to risk stratify these low-risk unstable angina patients.

In the subgroup of ACS patients without any high risk features as included here, both GLS_{trans} and GLS₁₂ are better predictors of obstructive CAD than the traditional risk factors, GRACE score or the standard echocardiographic parameters. In ischemia there is flow heterogeneity noted in the watershed sub-endocardial layer (which has a preponderance of longitudinally oriented fibres) causing a reduction in longitudinal strain values even when there are no identifiable wall motion abnormalities/reduced EF by 2-D echocardiogram. Studies have demonstrated significantly higher values of GLS and RLS in stable CAD [5,13,14] as well as in NSTEMI [7,15] patients with obstructive disease and apparently normal LV systolic function. To our knowledge this paper appears to be the first prospective study in analysing the role of longitudinal strain indices in low-risk UA patients (without RWMA) and that too with a large sample size.

The accuracy of GLS from six different studies particularly involving stable CAD patients undergoing diagnostic angiography was only modest and it varied with a AUC ranging from 0.68 to 0.80 [5,16–18]. Though higher LS values were noted in obstructive CAD group, the overlap in distribution of GLS values between the two groups were considerable [19]. There is so much variation in GLS values such that in a meta-analysis of 24 studies including 2597 healthy volunteers it varied even in normal persons from -15.9% to -22.1% (mean: -19.7%; 95% confidence interval [CI]: -18.9 to -20.4%) [20]. So, the ASE guidelines do not recommend any normal range for GLS [21]. Hence it is not easy to diagnose obstructive CAD by picking a single GLS_{trans} or GLS₁₂ value. Our analysis also points to the same fact that the ability to diagnose CAD in patients presenting to ER with chest pain is only moderate owing to the inhomogeneity of GLS

Fig. 3. Receiver operating characteristic curves demonstrating value of transmural GLS, GLS₁₂ in the diagnosis of multivessel CAD.

Fig. 4. Representative bulls eye map of a patient with triple vessel disease and grossly deranged GLS_{trans} and GLS₁₂. GLS- global longitudinal strain, Trans-transmural.

values even among normal people. However, from our data we were able to identify a cut off value for GLS with high positive predictive value meaning that those patients are most likely to have CAD. A GLS value $> -16.1\%$ had an excellent positive predictive value of 92% in our study suggesting a

definite role for CAG in them without further ischemia testing. In a retrospective analysis done on 48 unstable angina patients, the discriminative power of GLS was found to be good with an AUC of 0.86 [22]. To summarise, low risk UA patients with a definitely abnormal GLS value (say $> -16.1\%$ in our

Fig. 5. Depiction of deranged regional longitudinal strain values in LAD territory in a patient with significant LAD disease (RLS_{LAD}: -13.0% & GLS_{trans}: -21.4%).

study) can be subjected to CAG without further provokable ischemia testing. But the remaining patients will require some other form of evaluation prior to catheterisation.

Secondly there is significant increase in both GLS_{trans} and GLS₁₂ values in participants with MVD as documented before in literature [5]. The accuracy of LS in diagnosis of MVD was found to be better (compare Figs. 1 and 3). Though the sensitivity to detect MVD in patients with grossly depressed GLS_{trans} >-16.1% is quite low (33.3%), the specificity is quite high (85%). Twenty-five study participants had GLS >16.1%. Among them only two had non-obstructive disease, 8 had single vessel disease and the rest 15 had MVD. Hence 2D-STE seems to have high specificity in identifying a sub group of low-risk UA patients who are at high risk of CV events (patients with MVD).

The role of RLS was investigated as CAD produces segmental variation in deformation indices. Though RLS of LAD, LCX and RCA were significantly reduced in the obstructive group, except for RLS_{LCX} they did not exhibit adequate diagnostic accuracy. Similarly the accuracy of regional strain to localise the culprit vessel was also poor in our analysis contrary to the data provided by Caspar et al. [7]. The explanation for this could be as follows a) the percentage of patients with multivessel disease was high in our study as opposed to only 20.7% in the study by Caspar thereby producing a more dispersed depression of deformation indices; b) studies reporting good predictive values for RLS have been predominantly done among patients with positive cardiac enzymes and hence more likely to have critical disease (subtotal/total occlusion) causing more localised drop in segmental functions [7,15]; c) obviously when segments are assigned to prespecified vascular territories there is always a chance of overlap between LAD and LCX as well as between LCX and RCA based on dominance and other anatomic variables which are difficult to analyse.

There are few limitations that needs to be addressed. A significant number of participants had hypertension and diabetes mellitus which are known to influence the strain measures. The derangement in GLS noted in control group could have been secondary to these known confounders or due to other forms of non-ischemic cardiomyopathy. Though multivariate regression analysis was performed for significant confounders and still GLS remained a powerful predictor of CAD, statistical significance always does not amount to clinical relevance. These could have been responsible for the modest accuracy noted. Adequately powered studies to assess the confounding role of cardiac risk

factors in patients presenting with chest pain are needed in future. Secondly due to logistic reasons radial, circumferential and layer specific strain analysis could not be performed.

5. Conclusion

In patients with low-risk UA (non-diagnostic resting ECG, negative troponin, apparently normal global and segmental LV function), both Transmural GLS and GLS₁₂ are independent predictors of CAD. But their accuracy in diagnosing obstructive disease is only moderate. However, it can be of practical use in pointing a subgroup of patients with grossly depressed LS (say GLS_{trans} >16.1% from our study) who have very high probability of having CAD (PPV of 92.0%) and in particular MVD. These patients can be subjected to CAG without further ischemia testing.

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Author's contribution

Conception and design of Study: Srinivasan Giridharan, Sasinthar Rangasamy. Literature review: Srinivasan Giridharan, Arumugam Aashish, Sasinthar Rangasamy. Acquisition of data: Arumugam Aashish, Selvaraj Karthikeyan, Pazhanivel Vijayalakshmi. Analysis and interpretation of data: Srinivasan Giridharan, Selvaraj Karthikeyan. Research investigation and analysis: Srinivasan Giridharan, Palamalai ArunPrasath. Data collection: Arumugam Aashish, Selvaraj Karthikeyan, Pazhanivel Vijayalakshmi. Drafting of manuscript: Srinivasan Giridharan, Palamalai ArunPrasath, Balasubramaniyan AmirthaGanesh. Revising and editing the manuscript critically for important intellectual contents: Srinivasan Giridharan, Selvaraj Karthikeyan. Data preparation and presentation: Arumugam Aashish, Pazhanivel Vijayalakshmi. Supervision of the research: Srinivasan Giridharan, Palamalai ArunPrasath, Balasubramaniyan AmirthaGanesh. Research coordination and management: Sasinthar Rangasamy, Balasubramaniyan AmirthaGanesh.

Declaration of competing interest

None.

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