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Original Article

Myocardial longitudinal strain reserve as a marker of severity of coronary artery disease during dobutamine stress echocardiography

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Abstract

Background

Timely and prompt detection of coronary artery disease (CAD) is of paramount importance for patient management in daily clinical practice. Several noninvasive stress tests are available for evaluating CAD, of which dobutamine stress echocardiogram (DSE) is widely available for localization and extent of CAD. However, wall-motion analysis during DSE is subjective, so two-dimensional speckle tracking-derived longitudinal strain has been recently presented to allow quantitative assessment of global and regional wall motions.

Aim

To assess longitudinal strain reserve (LSR) during DSE test in predicting severity of CAD in chronic stable patients.

Patients and methods

The study included 48 patients with chronic stable angina referred to DSE unit. Patients were classified into two groups according to Gensini score: group 1 had Gensini score less than 20 (mild CAD) and group 2 had Gensini score more than or equal to 20 (severe CAD). All patients were subjected to complete history taking, full general and cardiac examination, ECG analysis, DSE test, and two-dimensional speckle-tracking echocardiography, where global longitudinal strain was measured at rest and at peak dobutamine stress, then LSR was measured, then average territorial longitudinal strain (TLS) of the three major epicardial arteries [left anterior descending (LAD), left circumflex artery (LCX), and right coronary artery (RCA)] was measured, and then selective coronary angiography results were used for Gensini score calculation.

Results

There was a statistically significant difference between the study groups regarding stress global longitudinal strain and LSR. Regarding TLS of LAD, there was a statistically significant difference between the study groups regarding average stress and regional strain reserve of LAD territory. Regarding TLS of LCX, there was a statistically significant difference between the study groups regarding stress and regional strain reserve of LCX territory. There was a significant inverse correlation between LSR and Gensini score (r=−0.79, $P \leq 0.001$), with multivariate logistic regression stating age, smoking, and diabetes are significant predictors of low LSR in the study population. Regarding TLS of RCA, there was a statistically significant difference between the study groups regarding rest and stress RCA territory. We found a cutoff value of LSR that can significantly predict severe CAD, which was 2.9, and at a cut-off value of 2.7, LSR can significantly predict left main equivalent disease.

Conclusions

LSR is a significant predictor of severe CAD at a cutoff value of 2.9. In addition, LSR can significantly predict left main equivalent disease at a cutoff value of 2.7.

Keywords: Longitudinal strain reserve, predictors, severe coronary artery disease

Introduction

Stable coronary artery disease (CAD) is a very common disease, which is expected to further increase owing to

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population aging and improvements in survival after acute coronary syndromes. Chest pain accounts for approximately six million annual visits to emergency departments in the USA, making chest pain the second most common complaint in the emergency departments. As a result, more than 10 million stress tests are being performed in the USA every year, as well as at least one million diagnostic catheterizations. Recent guidelines also recommend noninvasive testing in patients with stable CAD with intermediate 15–85% pretest likelihood of CAD to identify patients who will need coronary angiography [1].

Exercise testing is widely used for selecting patients for coronary angiography, of which, dobutamine stress echocardiography (DSE) is frequently used for the detection, localization, and assessment of severity and extent of CAD because of its wide availability, low cost, and lack of ionizing radiation [2]. However, assessment of regional myocardial function on DSE relies on the semiquantitative evaluation of endocardial excursion and wall thickening and is therefore highly subjective and image quality dependent, even in the hands of expert observers [3].

The need for more quantitative techniques to objectively evaluate regional left ventricular (LV) myocardial performance during DSE has led to the incorporation of new deformation indices such as two-dimensional (2D) speckle-tracking echocardiography. Myocardial longitudinal strain quantification by speckle tracking echocardiography has been validated, and it accurately measures regional systolic LV function. It has also been shown to be superior to visual assessment of wall motion in detection and quantification of regional myocardial ischemia [4].

Recently, clinical studies have investigated the diagnostic value of 2D strain during DSE for inducible ischemia detection in patients with suspected CAD, with special emphasis on the myocardial longitudinal strain reserve (LSR) with speckle-tracking echo, defined as the reserve between peak stress and rest during DSE, which reflects the ability of the myocardium to improve its function during stress testing [5]. Although global deformation parameters have been increasingly used for myocardial function analysis, there are sparse data concerning segmental deformation of the LV. Moreover, some studies suggest heterogeneity of strain among LV segments, which may be especially significant during stress echocardiography [6].

The aim of our work is to highlight the value of LSR as a new concept of myocardial functional reserve to predict severe CAD and how global longitudinal strain (GLS) and territorial longitudinal strain (TLS) change from rest to peak dobutamine stress.

Patients and methods

The study included 48 patients with chronic stable angina referred to DSE unit.

Exclusion criteria of the study

The following were the exclusion criteria:

(1) Previous myocardial infarction.
(2) Inadequate image quality or inadequate tracking during DSE.
(3) Atrial fibrillation.
(4) Occurrence of DSE end points other than completion of protocol such as arrhythmias, hypotension/severe hypertension, or intolerable symptoms.
(5) Patients with contraindications for coronary angiography.

Ethical consideration

Consent was obtained from every patient after explanation of the procedure. Medical research and ethics committee approved the study.

Patients were classified into two groups according to Gensini score: group 1 had Gensini score less than 20 (mild CAD), and group 2 had Gensini score more than or equal to 20 (severe CAD).

All patients were subjected to complete history taking, full general and local cardiac examination, ECG analysis to exclude atrial fibrillation and previous myocardial infarction, and dobutamine stress echocardiography test to detect positive cases. Images were taken with patient in the left lateral position and were acquired from the parasternal long axis, parasternal short axis, mid ventricle, apical four chamber, and two chamber views with each stage of basal resting, low dose, intermediate, and peak stress. Test is considered positive if decreased wall thickening in two or more contiguous segments, and also 2D speckle-tracking echocardiography was done where GLS measured at rest and at peak dobutamine stress, then LSR [ΔGLS (peak-rest)] was measured, then average TLS of the three major epicardial arteries [left anterior descending (LAD), left circumflex artery (LCX), and right coronary artery (RCA)] was measured at resting and at stress and then regional strain reserve is calculated as Δ TLS (peak-rest). Elective coronary angiography for patients who showed dobutamine-positive stress test to assess the burden of atherosclerosis by number of diseased more than 70% stenosis is considered significant and Gensini score is calculated.

Statistical analysis

Statistical analysis was done using the following tests: paired t test, χ^2, Pearson correlation, receiver operating characteristic (ROC) curve, and univariate and multivariate logistic regression test.

Results

Regarding demographic data, the present study showed that there was a statistically significant difference between the study groups regarding, hypertension, diabetes mellitus, and smoking in favor of group 2, but there was no significant difference regarding age, sex, obesity, dyslipidemia, and family history.

There was a statistically significant difference between the study groups regarding stress GLS and LSR. Regarding TLS

of LAD, there was a statistically significant difference between the study groups regarding average stress and regional strain reserve of LAD territory. Regarding TLS of LCX, there was a statistically significant difference between the study groups regarding stress and regional strain reserve of LCX territory. Regarding TLS of RCA, there was a statistically significant difference between the study groups regarding rest and stress RCA territory. There was no significant difference regarding resting GLS, resting TLS of both LAD and LCX, regional strain reserve of RCA.

Our study showed that there was a statistically significant inverse correlation between LSR and Gensini score (r=−0.79, $P \leq 0.001$) (Fig. 1).

Multivariate regression analysis discovered that the factors that predict low LSR among the examined cases were age, smoking, and diabetes.

A ROC curve analysis was performed, and we found that a cutoff value of LSR that can significantly predict severe CAD was 2.9 [area under the curve (AUC)=0.89%; confidence interval (CI)=95%, sensitivity = 96.6%, specificity = 89.1%] (Fig. 2). Moreover, the present study conducted another ROC curve, and it was found that LSR can significantly predict left main (LM) equivalent disease at a cut-off value of 2.7 (AUC = 0.80%, CI = 95%, sensitivity = 84.6%, specificity = 72.7%) (Fig. 3 and Tables 1–5).

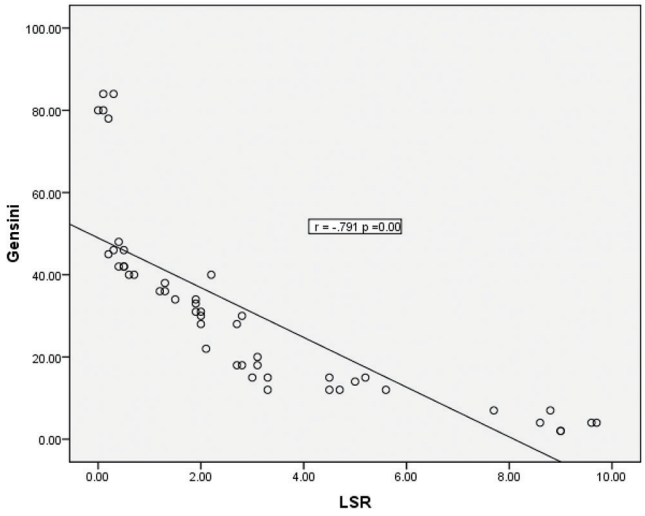

Figure 1: Significant inverse correlation between LSR and Gensini score (r=−0.79, P = 0.00). LSR, longitudinal strain reserve.

Discussion

We found that GLS reserve is the most sensitive predictor of severity of CAD as assessed by Gensini score. Moreover, we found significant inverse correlation between LSR and Gensini score (r=−0.79, P = 0.00). In addition, we did multivariate logistic regression test and we found that age, smoking, and diabetes were significant predictors of low LSR. Interestingly, we found that LSR at a cut-off value of 2.9 can significantly predict severe CAD and at a cut-off value of 2.7 can significantly predict LM equivalent disease.

We analyzed the average resting GLS, and we found no significant difference between the study groups. This was concordant with Rumbinaitė *et al.* [7]; Uusitalo *et al.* [3]; and Aggeli *et al.*[8]. However, longitudinal strain has been recognized as a sensitive parameter in the detecting CAD at rest even in the presence of normal LV wall motion in patients with severe CAD [9,10]. These discrepancies in our present study might be explained by the cross-matching mean value between our study groups. On the contrary, when

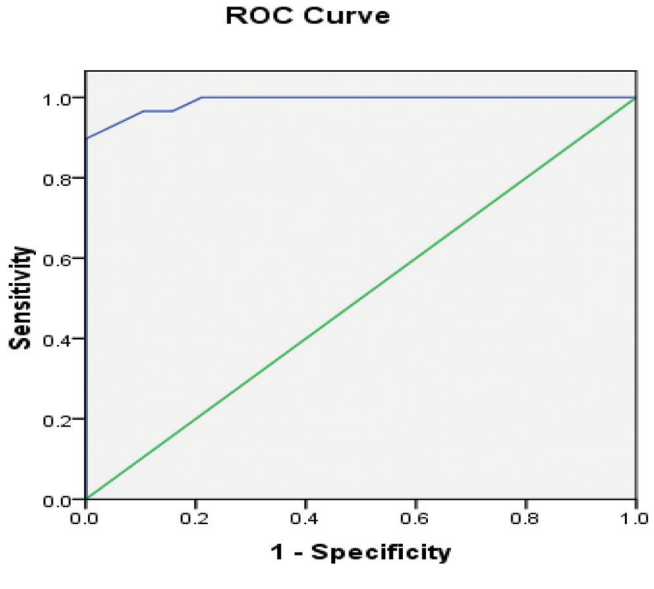

Figure 2: A ROC analysis was performed. The cutoff value of LSR to predict severe CAD was 2.9 (AUC = 0.89%, CI = 95%, sensitivity = 96.6%, specificity = 89.1%). AUC, area under the curve; CAD, coronary artery disease; CI, confidence interval; LSR, longitudinal strain reserve; ROC, receiver operating characteristic.

Table 1: Average global longitudinal strain, stress global longitudinal strain, and longitudinal strain reserve in the study groups

	Group 1 (n=19)	Group 2 (n=29)	Test value	P
	Mean±SD (range)	Mean±SD (range)		
Average resting GLS	−13.42±3.11 (−23.3 to−10.3)	−11.17±2.51 (−14.2 to−4.5)	−2.9	>0.05
Average stress GLS	−19.98±7.32 (−24 to−0.15)	−11.3±3.2 (−15.7 to−0.15)	−3.6	**<0.001**
LSR	6.56±2.61 (2.7 to 9.7)	0.13±0.93 (0.0 to 3.1)	8.71	**<0.05**

GLS, global longitudinal strain; LSR, longitudinal strain reserve.

Table 2: Average, stress, and regional strain reserve of left anterior descending territory in the study groups

LAD	Group 1 (n=19)	Group 2 (n=29)	Test value	P
	Mean±SD (range)	Mean±SD (range)		
Average resting strain	−13.33±2.71 (23.8 to−9.4)	−11.35±2.60 (−15.8 to−3.6)	−2.53	>0.05
Average stress strain	−19.91±5.85 (−28.1 to−10.5)	−12.88±2.99 (−17.1 to−5)	−5.486	<0.001
Strain reserve	−6.57±6.31 (−14.6 to−4)	−1.52±2.45 (−5.1 to−4.3)	−3.90	<0.001

LAD, left anterior descending.

Table 3: Average stress and regional strain reserve of left circumflex artery territory in the study groups

LCX	Group 1 (n=19)	Group 2 (n=29)	Test value	P
	Mean±SD (range)	Mean±SD (range)		
Average resting strain	−10.52±5.92 (−28.2 to−4.2)	−8.14±3.03 (−14 to−4)	−1.833	>0.05
Average stress strain	−15.19±5.76 (−22.7 to−5.2)	−9.52±3.92 (−17.5 to−3.2)	−4.05	0.000
Strain reserve	−4.67±5.60 (−15.2 to−9.2)	−1.37±3.56 (−10.2 to−5.5)	−2.49	<0.05

LCX, left circumflex artery.

Table 4: Average, stress, and regional strain reserve of right coronary artery territory in the study groups

RCA	Group 1 (n=19)	Group 2 (n=29)	Test value	P
	Mean±SD (range)	Mean±SD (range)		
Average resting strain	−15.50±6.01 (−23.6 to−5)	−11±5.39 (−16.6 to−0.33)	−2.7	**<0.05**
Average stress strain	−14.42±1.7 (−16.6 to−11)	−11.14±4.13 (−16.3 to−4.6)	−3.2	**<0.05**
Strain reserve	−1.08±4.7 (−8.67 to−6.7)	−0.149±3.16 (−6.67 to−5.3)	−1.08	>0.05

RCA, right coronary artery.

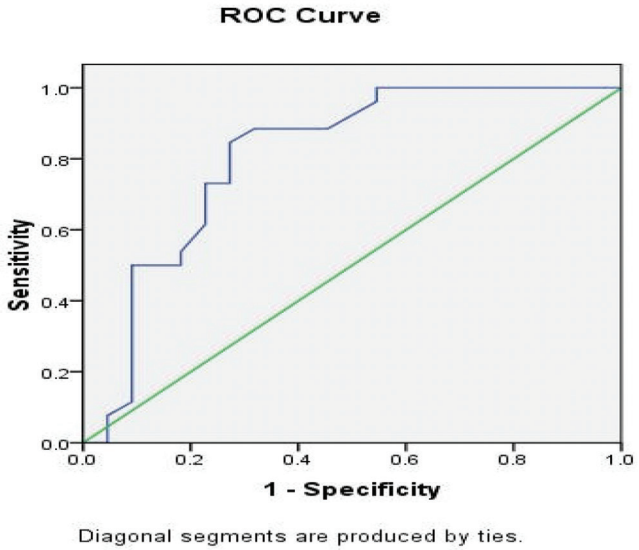

Figure 3: (Showing a ROC curve of LSR predicting LM equivalent with a cut off value 2.7(AUC = 0.80 %, CI=95 %, sensitivity= 84.6%, specificity= 72.7 %). AUC, area under the curve; CI, confidence interval; LM, left main; LSR, longitudinal strain reserve; ROC, receiver operating characteristic.

we analyzed the average stress GLS, we found significant difference between the study groups. This was concordant with Norum *et al.* [11]. On the contrary, this was discordant with Uusitalo *et al.* [3], who found no significant difference regarding stress GLS in their study groups. This might be explained by the cross-matching mean value of their study groups.

In addition, we analyzed LSR [ΔGLS (peak-rest)] and found a significant difference between the study groups. This was concordant with Aggeli *et al.* [8], and this agrees with that fact that the ischemic myocardium has a lower capability to withstand the stress owing to lower contractile reserve [7].

Moreover, we investigated the relationship between LSR and severity of CAD and we found a strong inverse correlation between LSR and Gensini score (r=−0.791, P = 0.00). This was concordant with Vrettos *et al.* [12] and Elrabat *et al.* [13], who found a significant negative correlation between longitudinal strain and severity of CAD as assessed by coronary angiography. This agrees with the fact that longitudinal mechanics predominate in the ischemia-vulnerable subendocardium as subendocardial myocardial fibers are mainly longitudinal oriented and abnormalities of myocardial deformation in the longitudinal axis are seen in the development of many pathophysiologic states, including CAD and myocardial infarction [14].

Interestingly, the present study showed that LSR at a cut off value of 2.9 can significantly predict severe CAD with AUC = 0.89, sensitivity 96.6%, and specificity 89.1%. Our result was concordant with Aggeli *et al.* [8], who got cutoff value of 2 (AUC = 0.80, 87% sensitivity, and 73% specificity) for LSR in their study, and also it was concordant with Joyce *et al.* [15], who found an optimal cutoff of ΔPLSS for the

Table 5: Univariate and multivariate logistic refression analysis of predictor of global longitudinal strain reserve

Parameter	Univariate analysis			Multivariate regression		
	Confidence interval lower bond	upper bond	*P*	Confidence interval lower bond	upper bond	*P*
Age	−0.265	−0.193	0.001	−0.239	−0.125	0.009
Sex	−1.147	−4.310	0.219	-	-	-
Smoking	−3.380	−0.162	0.000	−1.582	−0.041	0.040
HTN	−3.370	0.083	0.004	-	-	0.166
DM	−5.368	−3.099	0.000	−2.362	−0.088	0.035
Dyslipidemia	0.719	5.896	0.003	−1.542	3.61.232	0.823
Obesity	−0.419	3.797	0.98	-	-	-
Family history	−3.464	1.284	0.23	-	-	-
GLS (constant)	14.257	18.514	0.001	11.750	17.665	0.005

DM, diabetes mellitus; HTN, hypertension; GLS, global longitudinal strain.

detection of significant CAD on ROC curve analysis was 1.9 (AUC = 0.70, sensitivity = 87%, specificity = 46%).

The present study showed that with multivariate logistic regression test, it was found that age, diabetes and smoking are significant predictors for low LSR. This was concordant with Cognet *et al.* [5], which agrees with the fact the consequences of aging on myocardial deformation; GLS declines at rest with aging in a healthy population, and these results could be partly explained by a reduced coronary flow reserve with aging as described with myocardial ischemia [16]. In addition, diabetes was found to be a predictor of LSR. This also was concordant with Wierzbowska-Drabik *et al.* [17], who found that diabetes is a predictor of LV longitudinal strain reduction at rest and at dobutamine stress in patients with significant CAD. This agrees with the fact that diabetes induce complex metabolic disturbances in cardiomyocytes, impairment microcirculation, and endothelial dysfunction leading to morphological and functional abnormalities of the myocardium [18]. Moreover, smoking was found to be a predictor of LSR. This agrees with the fact that smoking has acute and chronic deleterious effect on myocardial function and deformations [19].

Regarding TLS of LAD, the present study showed significant difference between the study groups regarding average stress and regional strain reserve of LAD territory. This was concordant with one study [8]. This agrees with the fact that 2D strain can be calculated at any stage of DSE, giving significant information regarding the presence of ischemia, even at low-dose stage, when meticulous evaluation of segmental function can be repeated at least at baseline and peak stage. it was found that high percentage of segments amenable to quantification (>90%) with limited interobserver variability, especially when systolic longitudinal strain was measured during significant tachycardia (mean value of heart rate 139 ± 17 beat/min) at peak stage of test [20]. On the contrary, our finding was discordant with Park *et al.* [21], who found that strain was significantly more impaired at low-dose dobutamine than resting or recovery phase in their study groups.

Regarding TLS of LCX, the present study showed significant difference between the study groups regarding stress and regional strain reserve of LCX territory. This was concordant with Aggeli *et al.*[8]. On the contrary, this was discordant with Park *et al.* [21], who found that LCX strain was significantly more impaired at recovery phase of dobutamine than resting or low-dose dobutamine phase in their study groups.

Regarding TLS of RCA, we found a significant difference between the study groups regarding rest and stress RCA strain. This was concordant with Aggeli *et al.*[8]. On the contrary, this was discordant with Park *et al.* [21], who found that RCA strain was significantly more impaired at recovery phase of dobutamine than resting or low-dose dobutamine phase in their study groups.

Interestingly, the present study showed that LSR at a cutoff value of 2.7 can significantly predict LM equivalent disease with AUC = 0.80, sensitivity 84.6%, and specificity 72.7%. This was concordant with Choi *et al.* [22], who found that longitudinal strain was significantly lower in patients with LM or three-vessel CAD without RWMA. This agrees with the fact that patients with LM equivalent CAD are a well-known high-risk subset. However, resting LV wall motions are usually normal at rest in these patients, unless there is a history of previous myocardial infarction or myocardial stunning. With advances in 2D echocardiography, LV longitudinal strain can now be measured using the 2D speckle tracking method, which provides a useful means of detection subtle changes in LV systolic function that could be caused by myocardial ischemia [23].

Conclusions

Our study found that GLS reserve is an independent predictor of CAD severity as assessed by Gensini score. Furthermore, we observed a cut-off value of 2.9 is a significant predictor of severe CAD. In addition, we observed a cutoff value of 2.7 is a significant predictor of LM equivalent disease.

So, GLS reserve might be used for risk stratification of patients with chronic stable angina during dobutamine stress test.

Limitations

The major limitations of the present study are that it is based on a single-center experience and may be limited by the small number of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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