Global Longitudinal Strain at Rest for Detection of Coronary Artery Disease in Patients without Diabetes Mellitus

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Summary: Global longitudinal strain (GLS) at rest on two-dimensional speckle tracking echocardiography (2D STE) was demonstrated to help detect coronary artery disease (CAD). However, the optimal cut-off point of GLS and its diagnostic power for detecting critical CAD in non-diabetes mellitus (DM) patients are unknown. In the present study, 211 patients with suspected CAD were prospectively included, with DM patients excluded. All patients underwent echocardiography and subsequently coronary angiography within 3 days. Left ventricular (LV) GLSs were quantified by 2D STE. Territorial peak systolic longitudinal strains (TLSs) were calculated based on the perfusion territories of the 3-epicardial coronary arteries in a 17-segment LV model. Critical CAD was defined as an area stenosis ≥70% in ≥1 epicardial coronary artery (≥50% in left main coronary artery). Totally 145 patients were diagnosed as having critical CAD by coronary angiography. Significant differences were observed in all strain parameters between patients with and without critical CAD. The area under the receiver operating charcteristic (ROC) curve (AUC) for GLS in the detection of left main (LM) or three-vessel CAD was 0.875 at a cut-off value of –19.05% with sensitivity of 78.1% and specificity of 72.7%, which increased to 0.926 after exclusion of apical segments (cut-off value –18.66%; sensitivity 84.4% and specificity 81.8%). The values of TLSs were significantly lower in regions supplied by stenotic arteries than in those by non-stenotic arteries. The AUC for the TLSs to identify critical stenosis of left circumflex (LCX) artery, left anterior descending (LAD) artery and right coronary artery (RCA), in order of diagnostic accuracy, was 0.818 for LCX, 0.764 for LAD and 0.723 for RCA, respectively. In conclusion, in non-DM patients with suspected CAD, GLS assessed by 2D STE is an excellent predictor for LM or three-vessel CAD with high diagnostic accuracy, and a higher cut-off point than reported before should be used. Excluding apical segments in the calculation of GLS can further improve the predictive accuracy of GLS. It is unsatisfactory for TLSs to be used to identify stenotic coronary arteries.
Key words: two-dimensional strain; coronary heart disease; global longitudinal strain; territorial longitudinal strain

Non-invasive diagnosis of coronary artery disease (CAD) in patients with no acute or previous myocardial infarction has been a clinical challenge. Two-dimensional speckle tracking echocardiography (2D STE) is clinically used to measure myocardial strains by tracking myocardial speckle patterns and generate longitudinal, radial and circumferential strains. These strain parameters have been validated to be useful in the quantitative assessment of systolic and diastolic heart function, both regionally and globally[1, 2]. Recent studies also reported that strains by 2D STE could be used to quantify the deformation of the myocardial

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ischemia area and thus to detect CAD[3, 4].

Among all strain measures, the longitudinal strain was found to be mostly reduced in myocardial segments subtended by stenotic coronary arteries[4–6] and it is the most sensitive and reproducible indicator of ischemia[7, 8]. Studies have shown the valuable role of global longitudinal strain (GLS) as an independent predictor for significant CAD[4, 5, 9]. When combined with stress echocardiography, GLS could improve diagnostic concordance between observers and enhance the accuracy of novice readers[10]. However, most of these studies were in small scale and investigated the value of GLS for detecting advanced CAD. The findings were also inconsistent in terms of the value of territorial longitudinal strain (TLS) for locating the stenotic coronary artery[5, 11, 12].

Myocardial strains were found to be affected independently by diabetes mellitus (DM)[13, 14]. A certain number of patients with DM were often included in the previous studies that evaluated the performance of GLS for detection of CAD[5, 9, 15]. We suppose that the presence of DM may affect the diagnostic accuracy of GLS in detecting CAD. Our previous study examined the strains of CAD patients with DM and compared them with those in non-DM patients and we found that both global and segmental longitudinal strains were significantly lower in CAD patients with DM than those without[16]. We further hypothesized that the values of myocardial strains at rest for detecting CAD and identifying stenotic coronary artery may be also different in non-DM CAD patients from those in CAD patients concomitant with DM.

In the present study, the strain assessment was performed in CAD patients in the absence of DM. We sought to investigate the optimal cut-point of GLS at rest in this population and its diagnostic value for detecting advanced CAD. The value of TLS for detecting stenosis in individual coronary artery in this population was assessed as well.

1 MATERIALS AND METHODS

This study was performed after the grant of the approval by the Research Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All patients were fully informed of the procedure and signed a written consent form. The study was conducted in compliance with Health Insurance Portability and Accountability (HIPAA) regulations.

1.1 Study Population

In this study, a total of 211 patients with suspected CAD (from Nov. 1, 2013 to Nov. 30, 2014) were prospectively included. All of them underwent resting echocardiography and subsequently coronary angiography within 3 days. Patients with DM were excluded. The exclusion criteria were as follows: (1) the patient had recorded history of DM; (2) the patient had no history of DM but was diagnosed as having DM by glucose tolerance test during hospitalization (fasting glucose ≥7.0 mmol/L or 2-h glucose after a 75 g oral glucose load ≥11.1 mmol/L); (3) patients had wall motion abnormalities (WMA) detected by resting echocardiography, reduced left ventricular ejection fraction (LVEF), severe valvular stenosis or regurgitation, poor echocardiography images and arrhythmias such as atrial fibrillation and frequent premature complexes that may affect the analysis of the images.

1.2 Conventional Echocardiographic Examination

Patients were scanned using a Vivid E9 ultrasound scanner (GE Vingmed; Horten, Norway). 2D echocardiographic measures including interventricular septum and left ventricular (LV) posterior wall thickness, LV end-diastolic dimensions (LVEDD), and left atrial (LA) dimensions (end-systole) were obtained from the parasternal long-axis view. LVEF was calculated by modified biplane Simpson method. Mitral E-wave and A-wave velocity was measured and the E/A ratio calculated. Pulsed-wave TDI tracings were done at the septal mitral annulus in the apical 4-chamber view to obtain E' velocity, and E/E' ratio was calculated.

1.3 Two-dimensional Speckle Tracking Echocardiography

Two dimensional gray scale images of three consecutive cardiac cycles for each of three standard apical (two-, three-, and four-chamber) views were saved at a frame rate of between 40 and 60 fps. An investigator who was blinded to the angiographic results conducted the strain analysis off-line by using EchoPAC software (GE Vingmed; Horten, Norway). As described previously[16], the LV endocardial border was traced by tracking algorithm throughout the cardiac cycle automatically and adjusted manually in case of poor tracking. The tracking quality was ascertained visually and segments with inadequate tracking were rejected. Segmental peak systolic longitudinal strains (PSLSs) were then quantified automatically by automated algorithm. A more negative value of strain represents a larger longitudinal strain. The strain analysis was summarized in a color-coded bull's eye display with a conventional 17-segment LV model (fig. 1). GLS was defined as the average value of the 17 segmental PSLSs, and segmental longitudinal strain (basal, mid- or apical segments) was defined as the average value of PSLSs of the corresponding six segments (five segments for the apex). In addition, TLS was the average of the corresponding segmental PSLSs based on the perfusion territories of the 3-epicardial coronary arteries [left circumflex artery (LCX), left anterior descending artery (LAD) and right coronary artery (RCA)] in the 17-segment LV model[17].

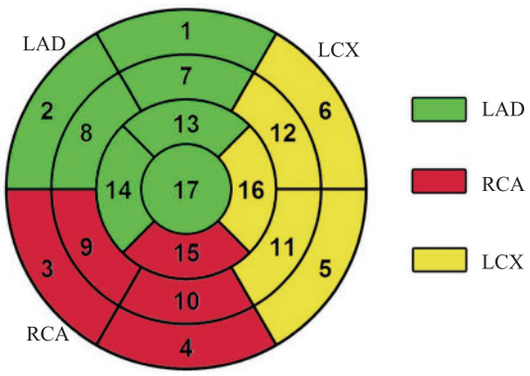

Fig. 1 A 17-segment LV model on a circumferential polar plot
This model shows the perfusion territories of the 3-epicardial coronary arteries (LAD, LCX and RCA) as suggested by AHA[17]. Segments numbered as 1, 7, 13, 2, 8, 14 and 17 are subtended by LAD (color green), segments 6, 12, 16, 5 and 11 by LCX (color yellow), and segments 4, 10, 15, 3 and 9 by RCA (color red).

1.4 Coronary Angiography

Coronary angiography was performed on all 211 patients within 3 days after echocardiography was completed. An experienced angiographer, blinded to patient's clinical information and echocardiography results, scored the angiograms with regard to the location and the severity of stenosis of the major 3-epicardial coronary arteries as defined by the American Heart Association classification. The severity of coronary stenosis was expressed as a percentage of the luminal area. Stenosis with ≥50% reduction of the arterial luminal area was considered significant. The patients were then stratified into three groups: group A, 3-vessel CAD including left main (LM) disease; group B, 1- or 2-vessel CAD; group C, control group (no CAD or no critical CAD). Critical CAD was defined as stenosis ≥70% in ≥1 epicardial coronary artery (or ≥50% in LM). 3-vessel CAD was defined as stenosis ≥70% in at least one epicardial vessel and concomitantly ≥50% in other epicardial vessels. One- or two-vessel CAD was defined as stenosis ≥70% in one or two vessels and <50% in other vessel(s).

1.5 Statistical Analysis

Data are expressed as $\bar{x}\pm s$ for continuous variables or numbers (percentages) for categorical variables. One-way analysis of variance with post hoc analysis by Bonferroni's was used to compare continuous variables and Chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) analysis was conducted to investigate the predictive value of GLS for critical CAD and the role of TLS in identifying stenotic coronary arteries. By ROC analysis of each strain parameter, the area under the ROC curve (AUC) was calculated and the optimal cut-off point with the highest sensitivity and specificity was determined.

To investigate inter- and intra-personal measurement reproducibility, measurements were performed off-line on 50 randomly selected studies by two independent investigators. The intra-class correlation coefficients (ICC) were calculated. All analysis was performed using SPSS version 20.0 software (SPSS, Inc., USA). Statistical tests were two-tailed and a *P* value of less than 0.05 was considered statistically significant.

2 RESULTS

2.1 Patients' Baseline Characteristics and Angiographic Data

A total of 211 patients with suspected CAD were included in the study. The patients' clinical characteristics are summarized in table 1. Detailed angiographic findings are shown in table 2. Coronary angiography revealed that there were 145 with critical CAD (68.7%) and 66 with no critical or no CAD (31.3%). Of the patients with critical CAD, 64 (30.3%) had 3-vessel and 81 (38.4%) had 1- or 2-vessel CAD. More patients had histories of cerebrovascular accident and hypertension, and were male and smokers in critical CAD group than in non-critical CAD group. Patients with 3-vessel CAD had higher incidence of dyslipidemia and higher serum level of total cholesterol and took ARB and/or ACE inhibitors and calcium channel blockers more frequently.

2.2 Echocardiographic Data

Representative Bull's eye displays with segmental PSLSs along with their coronary angiograms are shown in fig. 2. The baseline echocardiographic parameters are presented in table 3. There were no significant differences in LVEDD, interventricular septum and LV posterior wall thickness, and LVEF among the three groups. The patients with critical CAD had higher mitral A-wave velocity and lower E/A ratio than control patients. Moreover, the patients with 3-vessel CAD had significantly higher E/E' ratio and larger LA size than control patients. These findings indicated that the patients with critical CAD, particularly those with 3-vessel CAD, had worse LV diastolic dysfunction than those without critical CAD.

2.3 Longitudinal Strain Analysis

Comparison results of global and segmental PSLSs among the three groups are summarized in table 3. The Bull's eye displays with segmental PSLSs and coronary angiograms are presented in fig. 2, which are representatives from 5 selected patients including a patient without critical CAD, a patient with 3-vessel CAD, and 3 patients with 1-vessel CAD (LAD stenosis, LCX stenosis and RCA stenosis, respectively). Patients with critical CAD had significantly lower global and segmental longitudinal strain values than those without. Of patients with critical CAD, significant

Table 1 Characteristics of the patients in different groups

Variables	Three-vessel CAD (*n*=64)	One- or 2-vessel CAD (*n*=81)	Control (*n*=66)	Total (*n*=211)	*P* value
Male, *n* (%)	44 (68.75)*	55 (67.9)*	33 (50.00)	132 (62.56)	0.039
Age (years)	60.52±9.59*	57.00±8.40*	53.02±10.06	56.82±9.59	<0.001
Height (cm)	164.31±7.37	165.32±6.84	164.59±6.89	164.79±7.00	0.667
Weight (kg)	65.73±10.24	67.24±10.95	65.68±10.81	66.29±10.67	0.6
Body surface area (m^2)	1.73±0.16	1.74±0.16	1.71±0.15	1.73±0.16	0.532
Body mass index (kg/m^2)	24.26±2.95	24.49±2.89	23.91±3.19	24.24±3.00	0.507
Systolic blood pressure (mmHg)	137.05±20.92*	132.59±16.69	129.21±16.38	132.89±18.17	0.047
Diastolic blood pressure (mmHg)	80.67±13.56	80.78±11.11	79.18±1081	80.25±11.79	0.667
Heart rate (beats/min)	73.00±10.60	71.70±11.38	70.77±9.69	71.81±10.62	0.489
Risk factors					
Diabetes, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	—
Hypertension, *n* (%)	44 (68.75)*	55 (67.9)*	21 (31.8)	120 (56.9)	<0.001
Smoking, *n* (%)	26 (40.6)*	36 (44.4)*	15 (22.7)	77 (36.5)	0.018
Cerebrovascular accident, *n* (%)	5 (7.8)*	4 (4.9)	0 (0)	9 (4.3)	0.042
Dyslipidemia, *n* (%)	21 (32.8)#	12 (14.8)	15 (22.7)	48 (22.7)	0.037
Serum markers					
Cholesterol (mmol/L)	4.21±1.18#	3.74±0.79	3.93±0.88	3.94±0.97	0.015
Triglycerides (mmol/L)	1.66±1.17	1.37±0.98	1.44±1.00	1.48±1.05	0.249
HDL (mmol/L)	0.95±0.22*	0.99±0.24	1.07±0.29	1.00±0.25	0.028
LDL (mmol/L)	2.51±1.13	2.16±0.68	2.21±0.80	2.28±0.88	0.056
Creatinine (μmol/L)	79.71±19.46*	75.11±16.95	68.38±15.68	74.77±17.78	0.004
Glucose (mg/dL)	5.31±0.64	5.30±0.63	5.26±0.56	5.29±0.61	0.884
Medication prior to coronary angiography					
Aspirin, *n* (%)	9 (14.1)	23 (28.4)	12 (18.2)	44 (20.9)	0.088
Statin, *n* (%)	11 (17.2)	16 (19.8)	6 (9.1)	33 (15.6)	0.192
β-blocker, *n* (%)	8 (12.5)	15 (18.5)	7 (10.6)	30 (14.2)	0.352
ARB and/or ACE inhibitor, *n* (%)	4 (6.2)#	17 (23.9)*	2 (3)	23 (11.4)	<0.001
Calcium channel blocker, *n* (%)	9 (14.1)	20 (24.7)*	4 (6.1)	33 (15.6)	0.008
Nitrate agent, *n* (%)	7 (10.9)	8 (9.9)	8 (12.1)	23 (10.9)	0.91

CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; ARB, angiotensin II receptor antagonist; ACE, angiotensin converting enzyme. Values are expressed as $\bar{x}\pm s$ or *n* (%).
P-value was calculated by using Chi-square test or one-way analysis of variance. *$P<0.05$ *vs*. control group, #$P< 0.05$ *vs*. one- or 2-vessel CDA group

Table 2 Angiographic findings in different groups

Variables	Three-vessel CAD [*n*=64, n (%)]	One- or 2-vessel CAD [*n*=81, *n* (%)]	Control [*n*=66, *n* (%)]	Total (*n*=211)	*P* value
Diseased vessel					
LMCA	9 (14.1)	0 (0)	0 (0)	9 (6.2)	—
LAD	51 (79.7)	67 (82.7)	0 (0)	118 (81.4)	0.642
LCX	54 (84.4)*	12 (14.8)	0 (0)	66 (45.5)	<0.001
RCA	44 (68.8)*	13 (16)	0 (0)	57 (39.3)	<0.001
Number of disease vessel					
3-vessel disease	64 (100%)	0 (0)	0 (0)	64 (44.1)	—
2-vessel disease	–	28 (34.6)	0 (0)	28 (19.3)	—
1-vessel disease	–	53 (65.4)	0 (0)	53 (36.6)	—

LMCA, left main coronary artery; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.
*P value by Chi-square analysis for three-vessel CAD group *vs*. one- or 2-vessel CAD group

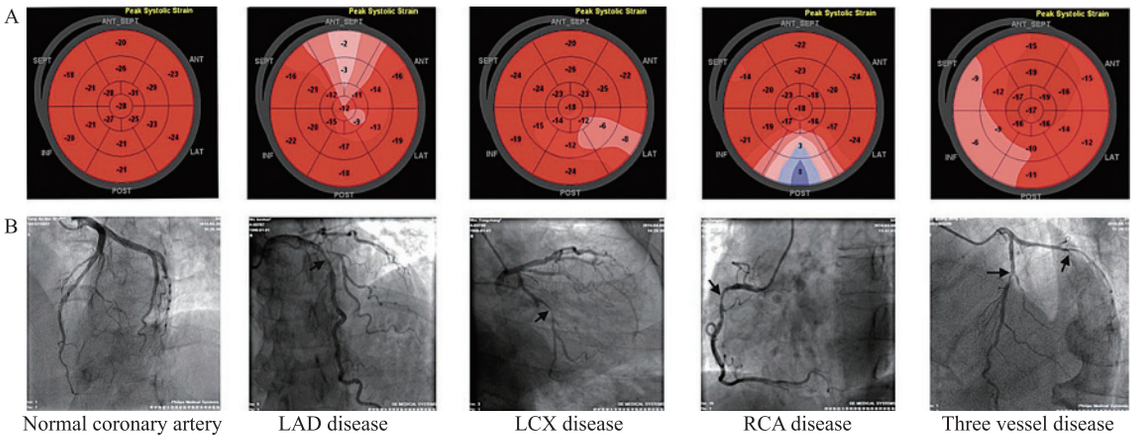

Fig. 2 Representative Bull's eye displays with segmental PSLSs along with their coronary angiograms
A: The 17-segment polar maps are presented as 'bull's eye' displays with the segmental values of PSLS. From left to right, the first polar map is from a patient with no critical CAD and shows no significant reduction of PSLSs. The second one is from a patient with 80 % stenosis in LAD and shows the significant reduction of PSLSs in basal-, mid-, apical-anterior and anteroseptal segments. The third one is from a patient with 80% stenosis in LCX and shows the significant reduction of PSLSs in basal-, mid- and apical-lateral segments. The forth one is the image of a patient with 85 % stenosis in RCA and shows the significant reduction of PSLSs in basal-, mid-, apical-inferior and posterior segments. The fifth one is the image of a patient with 3-vessel CAD and the significant reduction of PSLSs is almost throughout all segments. B: the coronary angiograms of corresponding patients as panel A are shown.

Table 3 Comparison of global and segmental PSLSs and baseline echocardiographic parameters among the three groups

Parameters	Three-vessel CAD (n=64)	One- or 2-vessel CAD (n=81)	Control (n=66)	Total (n=211)	P value
IVS (mm)	0.90±0.14	0.89±0.13	0.86±0.11	0.89±0.13	0.128
LVPW (mm)	0.91±0.12	0.91±0.12	0.88±0.11	0.90±0.12	0.161
LV end-diastolic dimension (mm)	4.64±0.43	4.68±0.39	4.53±0.38	4.62±0.40	0.078
LV ejection fraction (%)	65.91±8.82	67.1±6.96	68.76±7.15	67.26±7.68	0.103
LV end-diastolic volume (mL)	110±19	109±18	107±26	108±20	0.258
LV end-systolic volume (mL)	39±10	40±12	33±12	37±11	0.895
E (cm/sec)	62.40±18.41	60.14±14.63*	69.26±18.54	63.68±17.45	0.005
A (cm/sec)	84.21±18.26*#	73.38±15.15*	71.8±21.72	76.13±19.02	<0.001
E/A	0.77±0.32*	0.85±0.28*	1.04±0.41	0.89±0.36	<0.001
E/E'	12.91±3.58*#	10.73±3.03	9.96±3.61	11.13±3.58	<0.001
LA size	3.66±0.48*	3.59±0.50	3.43±0.46	3.56±0.49	0.023
Global PSLS (%)	−17.06±2.39*#	−18.51±2.91*	−20.82±2.05	−18.79±2.91	<0.001
Basal PSLS (%)	−14.85±2.90*#	−16.38±2.56*	−18.44±2.14	−16.56±2.91	<0.001
Middle PSLS (%)	−16.64±2.60*#	−18.17±2.77*	−20.41±1.98	−18.40±2.90	<0.001
Apical PSLS (%)	−19.94±3.94*#	−21.07±5.56*	−24.02±3.64	−21.67±4.83	<0.001
Mid and basal PSLS (%)	−15.75±2.58*#	−17.26±2.51*	−20.41±1.98	−17.79±3.03	<0.001

IVS, interventricular septum; LVPW, posterior wall of left ventricle; LV, left ventricle; E, mitral E velocity; A, mitral A velocity; LA, left atrial; LAVI, left atrial volume index; PSLS, peak systolic longitudinal strain; Global PSLS, including apical, mid and basal PSLS%
P values were calculated using one-way analysis of variance with post hoc analysis with Bonferroni's correction. *P<0.05 *vs*. control group; #P< 0.05 *vs*. one- or 2-vessel CAD group

strain difference was also seen between patients with 3-vessel CAD and those with 1- or 2-vessel CAD. Global PSLS was –17.06±2.39% in patients with 3-vessel CAD, –18.51±2.91% in patients with 1- or 2-vessel CAD, and –20.82±2.05% in control patients. The reduced level of GLS was proportional to the severity of CAD or to the increased number of stenotic coronary vessels.

TLS value based on the perfusion regions of LAD, LCX and RCA in the 17-segment LV model is shown in table 4. TLS was calculated by adding values of all corresponding segments or the corresponding

segments but excluding the 5 apical segments (TLS-nonapical). As shown in table 4–6, both TLS and TLS-nonapical were significantly lower in regions supplied by stenotic arteries than in regions by non-stenotic arteries (stenosis <50%). The distributing pattern of reduced segmental strains closely corresponded to the myocardial perfusion area supplied by stenotic artery as shown in fig. 1. Thus, it is possible that TLS could identify the stenotic coronary artery.

Table 4 Comparison of TLS in the perfusion territory supplied by stenotic or non-stenotic LAD

Strain	Control (*n*=66)	LAD stenosis (*n*=118)	*P*
TLSLAD (%)	−21.84±2.76	−18.34±3.96	<0.001
TLSLAD-nonapical (%)	−20.31±2.69	−16.88±4.11	<0.001

Table 5 Comparison of TLS in the perfusion territory supplied by stenotic or non-stenotic LCX

Strain	Control (*n*=66)	LCX stenosis (*n*=66)	*P*
TLSLCX (%)	−19.71±3.10	−14.87±4.76	<0.001
TLSLCX-nonapical (%)	−19.01±3.41	−14.40±4.67	<0.001

Table 6 Comparison of TLS in the perfusion territory supplied by stenotic or non-stenotic RCA

Strain	Control (*n*=66)	RCA stenosis (*n*=57)	*P*
TLSRCA (%)	−19.97±2.43	−17.11±3.70	<0.001
TLSRCA-nonapical (%)	−18.94±2.69	−16.41±3.91	<0.001

TLSLAD: strain in the perfusion territory supplied by LAD; TLSLAD-nonapical: TLSLAD after excluding apical segments and apex; TLSLCX: strain in the perfusion territory supplied by LCX; TLSLCX-nonapical: TLSLCX after excluding apical segments; TLSRCA: strain in the perfusion territory supplied by RCA; TLSRCA-nonapical: TLSRCA after excluding apical segments

2.4 Diagnostic Accuracy of Longitudinal Strain for Detecting CAD

ROC plots with the AUC and *P* values in table 7 illustrate the predictive power of GLS for detecting 3-vessel CAD, and that of TLS (TLSLAD, TLSLCX and TLSRCA) for identifying stenotic coronary arteries, i.e., LAD, LCX and RCA stenosis. The ROC was analyzed in two manners, one with all segments included (basal, mid and apical segments) and the other with apical segments excluded.

The AUC for GLS in the detection of three-vessel CAD was 0.875 (cutoff value –19.05%; sensitivity 78.1% and specificity 72.7%). It dramatically increased to 0.926 after excluding apical segments (cutoff value –18.66%; sensitivity 84.4% and specificity 81.8%). In comparison, the diagnostic accuracy of TLS in the detection of individual coronary stenosis was lower. The AUC, in order of diagnostic accuracy, was 0.818 for LCX (cutoff value –18.1%; sensitivity 72.7% and specificity 74.2%), 0.764 for LAD (cutoff value –19.91%; sensitivity 66% and specificity 74.2%), and 0.723 for RCA (cutoff value –18.7%; sensitivity 66.7% and specificity 65.2%). Moreover, the AUC for TLS was not increased by excluding apical segments, which was 0.802, 0.753, and 0.688 for detecting LCX, LAD and RCA stenosis, respectively.

2.5 Reproducibility of Strain Measures

The inter-observer and intra-observer variability for 2D STE measurements are shown in table 8. These results of intra-class correlation coefficient (ICC) demonstrated that deformational characteristic measures had good intra-observer and inter-observer correlation.

3 DISCUSSION

The present study specifically explored the changes of myocardial longitudinal strains at rest in a population with suspected CAD in the absence of DM. Our previous study in a small group of patients (*n*=73) found that both global and segmental longitudinal strains were significantly higher in CAD patients without DM than those with DM , and a higher cutoff point was obtained with better accuracy for GLS to detect CAD in patients without DM[16]. In the present study, we included a larger cohort of patients with no DM, attempting to validate our previous findings and to identify an appropriate cutoff point for GLS to detect 1-vessle and 3-vessel CAD further. The predictive value of TLS for locating the stenotic coronary arteries specifically was studied as well.

Accumulating evidence shows that significant coronary stenosis can impair strains at rest and 2D STE is useful to detect CAD[4, 5, 9]. However, the power of the GLS in detecting the severity of CAD is uncertain. The present study included 211 patients without DM, of whom 145 patients were eventually diagnosed as having critical CAD by coronary angiography. We investigated the diagnostic value of GLS in this larger population for detecting critical CAD, especially 3-vessel CAD. First, we found that GLS declined incrementally with increased severity of CAD (the severity of coronary stenosis and the number of stenotic vessels). The GLS was mostly impaired in patients with LM or 3-vessel CAD (–17.06±2.39%) compared with control and moderate-risk patients (–20.82±2.05% and –18.51±2.91%, respectively). The GLSs in both CAD and control patients were higher than those reported by other studies[5, 11]. We speculate it is because myocardial ischemia in these two studies was actually less severe than that in our study according to the definition of CAD and furthermore, the two studies enrolled DM patients. Then, by AUC analysis, we demonstrated that GLS is an excellent predictor of LM or 3-vessel CAD with high sensitivity and specificity in patients with no

DM (AUC 0.875 with sensitivity 78.1% and specificity 72.7%). Both LM and 3-vessel CAD patients have poor prognosis and they are at high risk for other non-invasive diagnostic tests such as exercise test. It is of great clinical significance if GLS at rest could help distinguish this subset of patients.

More and more researches have been studying how to improve the diagnostic value of GLS in the identification of myocardial ischemia[11, 17]. Based on the previous data and our earlier study, we found that DM may be one of the most important factors to reduce the diagnostic power of GLS in the detection of CAD.

Table 7 ROC analysis of GLS for detecting 3-vessel CAD and TLS for identifying individual coronary artery stenosis

Vessel parameters	Cut-off value	Sensitivity	Specificity	AUC (95%CI)	*P*
Including apical PSLS					
GLS/3-vessel	–19.05	78.10%	72.70%	0.875 (0.819–0.932)	<0.001
TLS/LAD	–19.91	66%	74.20%	0.764 (0.696–0.832)	<0.001
TLS/LCX	–18.1	72.70%	74.20%	0.818 (0.746–0.889)	<0.001
TLS/RCA	–18.7	66.70%	65.20%	0.723 (0.630–0.817)	<0.001
Excluding apical PSLS					
GLS/3-vessel	–18.66	84.40%	81.80%	0.926 (0.884–0.967)	<0.001
TLS/LAD	–19.13	71.80%	62.10%	0.753 (0.683–0.822)	<0.001
TLS/LCX	–17.88	75.80%	76.70%	0.802 (0.727–0.877)	<0.001
TLS/ RCA	–18.63	63.20%	51.50%	0.688 (0.592–0.784)	<0.001

As it is reported, DM was an independent contributing factor for impaired LV GLS[18] and the level of strain reduction was correlated with duration of diabetes[19, 20]. Our previous study observed a lower cutoff value of GLS with inadequate sensitivity and specificity in the detection of obstructive CAD in DM patients[16]. The presence of DM would confound the predictive cut-off point of strain. Therefore, in the present study, DM patients were excluded from this cohort of patients. Diagnostic accuracy of GLS with a higher cut-off point was confirmed to be improved in non-DM CAD patients.

Table 8 Intra- and inter-observer variability for strain measurements

Variables	ICC	*P* value	95% Confidence interval
Intra-observer variability			
Global PSLS (%)	0.95	<0.001	0.91–0.97
Basal PSLS (%)	0.89	<0.001	0.82–0.93
Mid PSLS (%)	0.94	<0.001	0.89–0.96
Apical PSLS (%)	0.90	<0.001	0.84–0.94
Inter-observer variability			
Global PSLS (%)	0.94	<0.001	0.90–0.97
Basal PSLS (%)	0.88	<0.001	0.80–0.93
Mid PSLS (%)	0.94	<0.001	0.89–0.96
Apical PSLS (%)	0.89	<0.001	0.83–0.94

Myocardial fibers in the apical region are rather circular than longitudinal. Previous studies suggested that removing apical longitudinal strains from GLS calculation had better diagnostic performance in detection of CAD[9, 11, 21]. In the present study, the diagnostic accuracy was improved dramatically after excluding apical segments (AUC 0.925 with sensitivity 84.4% and specificity 81.8%). A GLS cut-off point at –19.05% or –18.66% after excluding apical segments in the present study was higher than that (–17.2% to –17.9%) reported by other studies[9, 11, 15]. The discrepancy may be due to the fact that only non-DM patients were enrolled in our study.

Another important finding in the present study is the predictive value of TLS in locating stenotic coronary artery. Studies reported that regional 2D strains were significantly lower in the corresponding segments supplied by the stenotic coronary artery and proposed that impaired regional longitudinal strains could help identify which coronary artery is stenotic[4, 11, 12]. However, its diagnostic value has not been fully established previously[21, 22]. In the present study, we found that the diagnostic accuracy of TLS was unsatisfactory, similar to that reported by other study[22], which suggested that excluding DM does not improve the diagnostic power of TLS in detecting stenotic arteries. Moreover, excluding apical segments in the calculation of TLS did not improve its accuracy as well. This was different from GLS in the detection of 3-vessel CAD. The reason might be related to the perfusion overlap of the 3-epicardial coronary arteries and the anatomical variability of coronary arteries in individual patient[23–25]. And microvascular networks between coronary arteries can give rise to zones of dual arterial perfusion[26], making strict regional analysis somewhat inaccurate.

There are some limitations in our study. It was of retrospective nature and was conducted in a single center. In addition to DM, other factors such as hypertension and age could affect 2D strains as well[27, 28]. In the present

study, there were more subjects with hypertension and advanced age in CAD group than in control group, which could influence the cut-off point of GLS in detecting CAD. Other baseline characteristics, such as sex, smoking and lipid disorders were also different between groups. Those differences might increase experimental-wise error rate in the present study.

In conclusion, the present study demonstrated that a great GLS reduction could predict CAD with LM or 3-vessel disease in non-DM patients. A higher threshold of GLS is proposed to be used in detection of advanced CAD in non-DM patients. Moreover, the present study also revealed that it is unsatisfactory for TLS to be used to identify stenotic coronary arteries in non-DM patients with CAD.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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