Global Longitudinal Strain as Predictor of Inducible Ischemia in No Obstructive Coronary Artery Disease in the CIAO-ISCHEMIA Study

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Background: Global longitudinal strain (GLS) is a sensitive marker for identifying subclinical myocardial dysfunction in obstructive coronary artery disease (CAD). Little is known about the relationship between GLS and ischemia in patients with myocardial ischemia and no obstructive CAD (INOCA).

Objectives: To investigate the relationship between resting GLS and ischemia on stress echocardiography (SE) in patients with INOCA.

Methods: Left ventricular GLS was calculated offline on resting SE images at enrollment (n = 144) and 1-year follow-up (n = 120) in the CIAO-ISCHEMIA (Changes in Ischemia and Angina over One year in International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial screen failures with no obstructive CAD on computed tomography [CT] angiography) study, which enrolled participants with moderate or severe ischemia by local SE interpretation (≥3 segments with new or worsening wall motion abnormality and no obstructive (<50% stenosis) on coronary computed tomography angiography.

Results: Global longitudinal strain values were normal in 83.3% at enrollment and 94.2% at follow-up. Global longitudinal strain values were not associated with a positive SE at enrollment (GLS = –21.5% positive SE vs GLS = –19.9% negative SE, P = .443) or follow-up (GLS = –23.2% positive SE vs GLS = –23.1% negative SE, P = .859). Significant change in GLS was not associated with positive SE in follow-up (P = .401). Regional strain was not associated with colocalizing ischemia at enrollment or follow-up. Changes in GLS and number of ischemic segments from enrollment to follow-up showed a modest but not clinically meaningful correlation (β = 0.41; 95% CI, 0.16, 0.67; P = .002).

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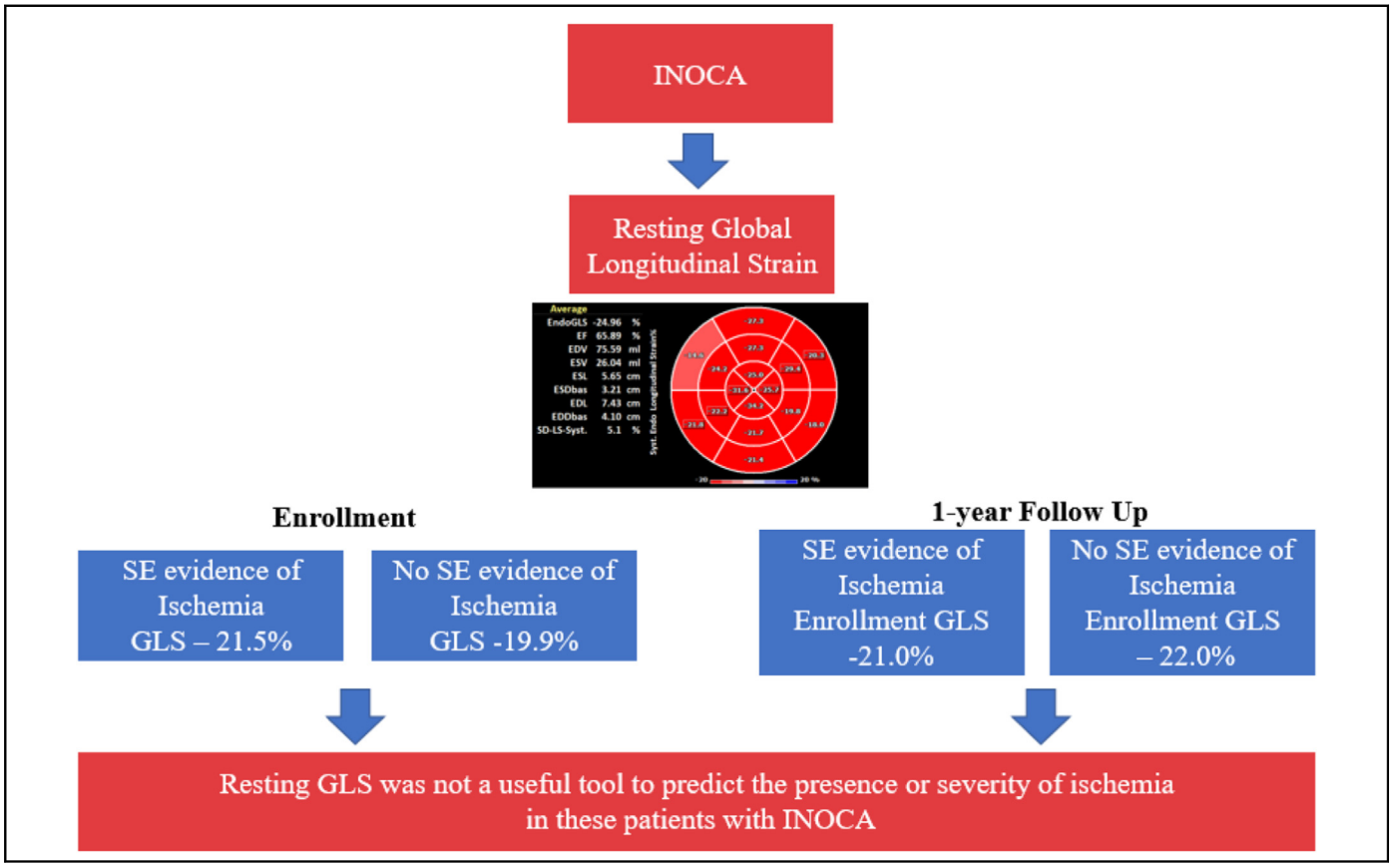
Conclusions: In this cohort of INOCA patients, resting GLS values were largely normal and did not associate with the presence, severity, or location of stress-induced ischemia. These findings may suggest the absence of subclinical myocardial dysfunction detectable by echocardiographic strain analysis at rest in INOCA. (J Am Soc Echocardiogr 2023;■:■-■.)

Keywords: Strain, Echocardiography, Ischemia, No obstructive disease, INOCA, Stress testing



Central Illustration Among a cohort of patients with ischemia on SE and no obstructive CAD on CCTA, resting GLS values on SE did not predict stress test positivity or presence of ischemia at enrollment or 1-year follow-up. Normal resting GLS is defined as <18.0%. Global longitudinal strain was largely normal and did not provide additional diagnostic utility in INOCA.

INTRODUCTION

Individuals with ischemia and no obstructive coronary artery disease (INOCA) experience high symptom burden, impaired quality of life, and increased adverse cardiac events compared with asymptomatic individuals.[1-3] Multiple studies demonstrate a high prevalence of coronary microvascular dysfunction (CMD), coronary vasospasm, or both in INOCA.[4-6] However, there is poor correlation between angina and ischemia on both invasive and noninvasive cardiac testing.[4,7-10] For example, in the CIAO-ISCHEMIA (Changes in Ischemia and Angina over One year in International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial screen failures with no obstructive coronary artery disease [CAD] on computed tomography [CT] angiography) study of patients with INOCA as determined by stress echocardiography (SE) and coronary CT angiography (CCTA), there was no association between the number of ischemic segments on SE and angina severity,[10] and half of patients with moderate or severe ischemia at baseline had normal SE 1 year later.[10]

Resting GLS has incremental diagnostic utility compared with conventional wall motion assessment in discriminating the presence and location of obstructive CAD[11,12] among symptomatic patients undergoing resting echocardiography for suspected CAD. The diagnostic utility of resting GLS among individuals with INOCA has not been rigorously studied.

To address this gap, we leveraged the international, multicenter CIAO-ISCHEMIA study to investigate (1) the frequency of abnormal GLS as a subclinical marker of myocardial dysfunction at rest and (2) the relationship between resting GLS and the presence and severity of ischemia on SE in INOCA. We hypothesized that GLS would be associated with subclinical myocardial dysfunction and predict stress-induced ischemia among patients with INOCA.

Abbreviations

BMI = Body mass index

CAD = Coronary artery disease

CCTA = Coronary computed tomography angiography

CIAO-ISCHEMIA = Changes in Ischemia and Angina over One year in International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial screen failures with no obstructive coronary artery disease on computed tomography angiography

CMD = Coronary microvascular dysfunction

CT = Computed tomography

GLS = Global longitudinal strain

INOCA = Ischemia and no obstructive coronary artery disease

IQR = Interquartile range

LVEF = Left ventricular ejection fraction

RLS = Regional longitudinal strain

SAQ = Seattle Angina Questionnaire

SBP = Systolic blood pressure

SE = Stress echocardiography

WMSI = Wall motion score index

MATERIALS AND METHODS

Study Population

Two hundred twelve participants were enrolled from 39 participating international sites into the CIAO-ISCHEMIA study.[10] CIAO-ISCHEMIA participants were enrolled but not randomized into the ISCHEMIA trial. They had ischemic symptoms (chest pain or other potential ischemic equivalent) and moderate to severe ischemia on SE (≥3 ischemic segments) as determined by the local enrolling site but no obstructive CAD on CCTA (no stenosis ≥50% in major epicardial vessel). Patients with <50% stenosis in all epicardial vessels are unlikely to have flow limitation based on invasive measurement of fractional flow reserve.[13] Demographics were assessed at enrollment. Angina status, assessed by the Seattle Angina Questionnaire (SAQ),[14] and ischemia as assessed by SE, were evaluated at enrollment and 1-year follow-up. Only patients who had SE images technically suitable for GLS analysis were included (Figure 1). The study was approved by the New York University Grossman School of Medicine Institutional Review Board and by each site's local Institutional Review Board or ethics committee. All participants provided written informed consent.

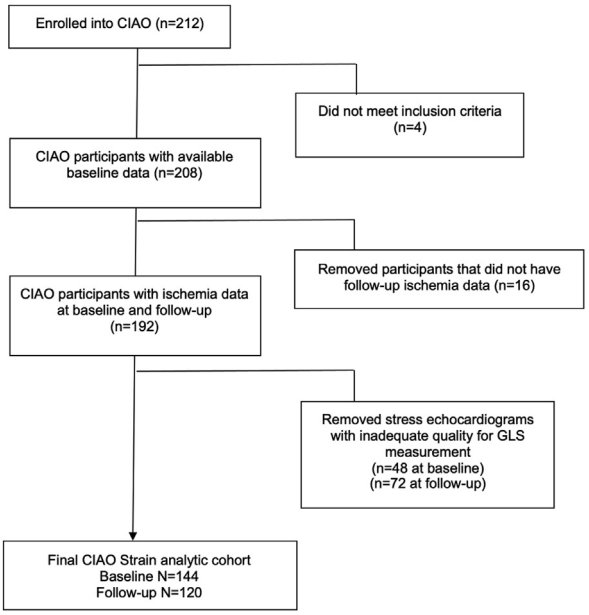


Figure 1 Study flow diagram. One hundred ninety-two CIAO participants with enrollment and 1-year SE images were eligible for inclusion in this analysis. Stress echocardiography images were analyzed on 144 individuals at enrollment. Forty-eight participants (25% of total eligible cohort) were excluded as resting images at enrollment were not suitable for strain analysis. At 1-year follow-up SE images were analyzed on 120 individuals. A further 24 participants were excluded between enrollment and 1-year follow-up due to poor image quality.

Echocardiographic Analysis

All SEs were evaluated by a blinded investigator (M.H.P.) at the ISCHEMIA trial echocardiography core laboratory (Massachusetts General Hospital) for the presence, severity, and location of ischemia based on a standardized 16-segment myocardial segmentation model.[15] Moderate or severe ischemia was defined as the presence of stress-induced moderate or severe hypokinesis, akinesis, or dyskinesis in ≥3 segments.[16] Presence and severity of ischemia was based on core lab adjudication. Offline cardiac strain analysis using TomTec 2D-CPA software (ver. TTA 2.3) was performed by 2 investigators (E.F.D., D.R.C.), blinded to patient SE results. Subendocardial GLS analysis was undertaken on apical 2-, 3-, and 4-chamber resting SE images. Strain analysis was performed if ≥12 of 16 cardiac segments were of adequate quality for analysis. Contrast-enhanced images were included as the feasibility and accuracy of such analysis had been previously established.[17]

Regional longitudinal strain (RLS) was defined based on coronary vascular supply as follows: anterior region (left anterior descending artery): basal anterior, basal anterior septum, midanterior, midanterior septum, apical anterior, and apical septal; inferior region (right coronary artery): basal inferoseptum, basal inferior, midinferoseptum, midinferior, and apical inferior; and lateral region (left circumflex artery): basal inferolateral, basal anterolateral, midinferolateral, midanterolateral, and apical lateral. An RLS value was calculated for each coronary territory, and ischemia was defined as stress-induced wall motion abnormalities in at least 2 segments of that region. Normal strain was defined as <−18.0% based on published values.[18-20] We defined *improvement* in GLS as change toward a more negative value (farther from 0) and *worsening* in GLS as change toward a more positive value (closer to 0). A significant change in GLS from enrollment to 1 year was defined as >15.0% relative change and/or absolute change of >3%.[21] Interobserver and intraobserver reproducibility of GLS was undertaken on a subset (15%, $n = 22$) of patients.

Statistical Methods

We computed descriptive statistics of baseline characteristics, stress test results, and symptoms, presented as median and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. We evaluated differences in patients' stress test characteristics between enrollment and 1 year using the Wilcoxon rank-sum test for continuous variables and McNemar's

HIGHLIGHTS

- Among patients with INOCA, resting GLS is largely normal.
- GLS did not predict the presence, severity, or location of stress-induced ischemia.
- Resting GLS was not discriminatory for presence or severity of inducible ischemia.

test for categorical variables. Comparison within each time point was conducted with Student *t* test and Pearson's chi-square test as appropriate.

We assessed whether changes in GLS measurements between baseline and follow-up were associated with key variables of interest, namely, stress test results, number of ischemic segments, and wall motion score index (WMSI). We fit separate linear mixed-effects models of GLS with each variable, including a random intercept to account for potential correlations among measurements belonging to the same patient. To examine both the cross-sectional and the within-subject (longitudinal) associations between each key variable and GLS measurements, we included the mean value for each participant and the time-varying value centered at the participant-level mean as covariates.[22,23] For example, for WMSI, we included the mean WMSI for a given participant, and the time-varying WMSI centered at the participant-level mean WMSI. Unadjusted modeling included only the variable of interest. In adjusted analysis, we extended each model to control for sex, age, body mass index (BMI), enrollment left ventricular ejection fraction (LVEF) at rest, SAQ Angina Frequency Score, and systolic blood pressure (SBP, in mm Hg). To facilitate interpretation, WMSI was scaled for a 0.1-unit change, while LVEF and SBP were each scaled to a 10-unit change. All analyses were conducted in R software. To evaluate statistical significance, we set the 2-tailed type 1 error to 0.05.

RESULTS

Enrollment Characteristics

One hundred forty-four patients had SE images suitable for GLS analysis at enrollment, and 120 of these had suitable SE images at both enrollment and 1-year follow-up (Figure 1). The intraclass correlation coefficient for interobserver reproducibility was 0.91 (95% CI, 0.79-0.96), and the coefficient of variance was 2.56%. Intraobserver intraclass correlation coefficients were 0.79 (D.R.C.: 95% CI, 0.56-0.91) and 0.94 (E.F.D.: 95% CI, 0.80-0.98). Among the 144 included individuals, 67% ($n = 97$) were female with a median age of 61 years (Table 1). Symptoms leading to SE and angina frequency are reported in Table 1. The median time from SE to enrollment was 63 days (IQR, 35-132 days). Apart from a lower BMI among included patients (28.4 kg/m^2 vs 30.9 kg/m^2, $P = .032$), there were no significant differences in demographic, clinical, or stress test characteristics between included versus excluded from analysis at either time point (tested variables as in Tables 1 and 2, data not shown).

Stress test characteristics at enrollment and follow-up are presented in Table 2. At least 85% of the maximal predicted heart rate was achieved in 82.1% of individuals at enrollment and 75.0% at follow-up. A hypertensive response to stress was present in 16.2% at enrollment and 18.0% at follow-up.

Table 1 Enrollment clinical and demographic characteristics

Characteristic	Value
Age, years	61.0 (56-70)
Sex, female, %	67.4 (*n* = 97)
BMI, kg/m^2	28.4 (25.0-31.5)
Race, %	
White	84.7 (*n* = 122)
Black	5.6 (*n* = 8)
Asian	6.9 (*n* = 10)
Other/unknown	2.8 (*n* = 4)
Ethnicity: Hispanic or Latino %	11.1 (*n* = 16)
Cardiovascular risk factors, %	
Hypertension	62.5 (*n* = 90)
Diabetes	15.4 (*n* = 22)
Active smoking	6.2 (*n* = 9)
Statin therapy	82.5 (*n* = 118)
Low-density lipoprotein cholesterol, mg/dL	99.0 (77.0-125.6)
Family history of premature coronary heart disease	36.8 (*n* = 53)
Cardiovascular history, %	
Prior myocardial infarction	2.1 (*n* = 3)
Prior revascularization	4.9 (*n* = 7)
Heart failure	0.7 (*n* = 1)
Atrial fibrillation	4.2 (*n* = 6)
Valvular heart disease	5.0 (*n* = 7)
Cardiovascular medications, %	
Antiplatelet	73.6 (*n* = 106)
Beta-blocker	55.6 (*n* = 80)
Calcium channel blocker	14.6 (*n* = 21)
Short acting nitrate	10.4 (*n* = 15)
Long-acting nitrate	9.7 (*n* = 14)
Anticoagulant	4.2 (*n* = 6)
Symptoms leading to SE, %	
Typical chest pain	49.3 (*n* = 71)
Atypical chest pain	34.0 (*n* = 49)
Shortness of breath	53.5 (*n* = 77)
Nausea	2.8 (*n* = 4)
Sweating	4.2 (*n* = 6)
Angina	
SAQ Angina Frequency Scale	83 (66-93)
SAQ Angina Frequency Scale score	90 (70-100)
Angina frequency at enrollment, %	
None	37.5 (*n* = 53)
Daily	2.1 (*n* = 3)
Weekly	13.6 (*n* = 19)
Monthly	46.4 (*n* = 65)

Data in parentheses are presented as *n* or 25th-75th percentiles.

While enrolling sites interpreted all participants as having moderate or severe ischemia, by core echocardiography lab adjudication, the SE was positive in 93.1% at enrollment, and moderate or severe ischemia was

Table 2 Stress test characteristics—enrollment and follow-up

	Enrollment			
	Whole cohort (*n* = 144)	Participants with 1-year follow-up (*n* = 120)	Follow-up	*P* value*
SE type, %				.070
Exercise	86.0 (*n* = 123)	84.9 (*n* = 101)	80 (*n* = 96)	
Pharmacological	14.0 (*n* = 20)	15.1 (*n* = 18)	20.0 (*n* = 24)	
MET achieved (MET)	7 (6.1-9.2)	7 (6.1-9.2)	7.9 (6.8-10.1)	.013
85% maximum heart rate achieved, %†	82.1 (*n* = 115)	84 (*n* = 97)	75 (*n* = 90)	.076
Baseline SBP, mm Hg	139 (124-150)	137 (123-150)	134.5 (120, 149)	.535
Baseline DBP, mm Hg	81 (76-87.5)	81 (76-87)	80 (70, 86)	.010
Systolic hypertension at baseline	48.9% (*n* = 67)	45% (*n* = 51)	45% (*n* = 54)	1.00
Diastolic hypertension at baseline	20% (*n* = 23)	19% (*n* = 19)	18% (*n* = 20)	1.00
SBP, stress	170 (156-190)	170 (156-190)	166 (151.2, 189.8)	.109
DBP, stress	84 (80-95)	84 (80-95)	80 (72, 90.2)	.014
Hypertensive response to stress	16.2% (*n* = 22)	16.1% (*n* = 18)	18.0% (*n* = 21)	1.00
Resting LVEF, %	62 (58-66)	62 (58-66)	63 (59-67)	.065
LVEF stress, %	61 (58-67)	61 (58-67)	67 (60-72)	<.001
Stress test positive, %	93.1 (*n* = 134)	92 (*n* = 111)	42 (*n* = 51)	<.001
Number of ischemic segments	4.0 (3.0-4.0)	4.0 (2.8-4.0)	0.0 (0.0-2.0)	<.001
Ischemia location, %				
Anterior	44.4 (*n* = 64)	42.5 (*n* = 51)	15.0 (*n* = 18)	<.001
Inferior	38.2 (*n* = 55)	38.3 (*n* = 46)	11.0 (*n* = 13)	<.001
Lateral	27.8 (*n* = 40)	25.8 (*n* = 31)	6.0 (*n* = 7)	<.001
Anterior and Lateral	14.6 (*n* = 21)	12.5 (*n* = 15)	4.0 (*n* = 5)	.041
Anterior and Inferior	11.8 (*n* = 17)	10.8 (*n* = 13)	3.0 (*n* = 4)	.012
Inferior and Lateral	7.6 (*n* = 11)	6.7 (*n* = 8)	2.0 (*n* = 3)	.180
Symptoms during stress, %				
Limiting chest pain	11.9 (*n* = 17)	10.9 (*n* = 13)	2.0 (*n* = 2)	.003
Non-limiting chest pain	11.2 (*n* = 16)	10.9 (*n* = 13)	7.0 (*n* = 8)	.267
Dyspnea, %	24.5 (*n* = 35)	26.1 (*n* = 31)	18.0 (*n* = 22)	.136
Claudication, %	0.7 (*n* = 1)	0.8 (*n* = 1)	0 (*n* = 0)	1.00
Other, %	7.0 (*n* = 10)	7.6 (*n* = 9)	16.0 (*n* = 19)	.052

DBP, Diastolic blood pressure; *MET*, metabolic equivalent.
Data in parentheses are presented as *n* or 25th-75th percentiles.
*Reported *P* values are for subjects with paired enrollment and 1-year follow-up data.
†Patients who underwent exercise testing only.

present in 77.8%. At 1-year follow-up, SE was positive for ischemia in 42.5%, with moderate or severe ischemia at 1 year in 22.5%. At enrollment, there was no statistical difference in demographic or clinical characteristics between those with positive and those with negative SE (Table 3). At 1-year follow-up, those with positive SE had a higher (more favorable) SAQ angina frequency subscale score than those with negative SE (median, 95; IQR, 80-100 with positive SE, vs median, 80; IQR, 70-100 with negative SE; $P = .030$). Cardiovascular risk factors were not associated with SE positivity at either time point. At 1-year follow-up there was an increase in the use of calcium channel blockers from 17% at baseline to 29% at follow-up ($P = .022$). There were no other significant changes in medical therapy.

Resting GLS

Median GLS was −21.4% (−24.1% to −19.0%) at enrollment and −23.1% (−25.6% to −20.9%) at 1-year follow-up. Global longitudinal strain was normal in the majority at both enrollment (83.3%,

Table 3 Characteristics associated with abnormal stress test at enrollment and 1-year follow-up

	Enrollment			1-Year follow-up		
	Stress test negative	Stress test positive	*P* value	Stress test negative	Stress test positive	*P* value
Enrollment	*n* = 8	*n* = 136		*n* = 69	*n* = 51	
Age, years	59.0 (58.0-60.2)	62 (55.8-70.0)	.450	61.0 (56.0-67.0)	62.0 (55.0-71.5)	.505
Sex. emale, %	50.0 (*n* = 4)	68.4 (*n* = 93)	.438	66.7 (*n* = 46)	70.6 (*n* = 36)	.796
Race, %			.076			.696
White	62.5 (*n* = 5)	86.0 (*n* = 117)		79.7 (*n* = 55)	86.3 (*n* = 44)	
Black	25.0 (*n* = 2)	4.4 (*n* = 6)		7.2 (*n* = 5)	3.9 (*n* = 2)	
Asian	12.5 (*n* = 1)	6.6 (*n* = 9)		10.1 (*n* = 7)	5.9 (*n* = 3)	
Other	0 (*n* = 0)	2.9 (*n* = 4)		2.9 (*n* = 2)	3.9 (*n* = 2)	
Hypertension, %	75.0 (*n* = 6)	61.8 (*n* = 84)	.710	55.1 (*n* = 38)	68.6 (*n* = 35)	.189
Diabetes, %	0 (*n* = 0)	16.3 (*n* = 22)	.609	13.0 (*n* = 9)	14.0 (*n* = 7)	1.00
BMI, kg/m^2	30.3 (26.6-33.2)	28.4 (25.0-31.2)	.297	28.1 (24.8-31.0)	29.4 (26.5-32.2)	.154
Low-density lipoprotein, mg/dL	101.0 (83.1-107.0)	99 (76.2-125.7)	.974	100.0 (75.9-124.5)	99.0 (80.0-127.0)	.668
Smoking, %	0 (*n* = 0)	6.6 (*n* = 9)	1.00	5.8 (*n* = 4)	5.9 (*n* = 3)	1.00
Prior myocardial infarction, %	0 (*n* = 0)	2.2 (*n* = 3)	1.00	2.9 (*n* = 2)	2 (*n* = 1)	1.00
Prior Revascularization, %	12.5 (*n* = 1)	4.4 (*n* = 6)	.336	5.8 (*n* = 4)	3.9 (*n* = 2)	1.00
Angina						.030
SAQ Angina Frequency Scale score	70.0 (65.8-80.0)	84.0 (66.0-93.0)	.138	80.0 (70.0-100.0)	95 (80.0-100.0)	.073
Angina frequency, %						
None	12.5 (*n* = 1)	39.4 (*n* = 52)	.104	26.5 (*n* = 18)	50.0 (*n* = 24)	
Daily	12.5 (*n* = 1)	1.5 (*n* = 2)		2.9 (*n* = 2)	2.1 (*n* = 1)	
Weekly	12.5 (*n* = 1)	13.6 (*n* = 18)		14.7 (*n* = 10)	12.5 (*n* = 6)	
Monthly	62.5 (*n* = 5)	45.5 (*n* = 60)		55.9 (*n* = 38)	35.4 (*n* 17)	
Medications, %						
Beta-blocker	12.5 (*n* = 1)	25.7 (*n* = 35)	.680	27.5 (*n* = 19)	23.5 (*n* = 12)	.776
Calcium channel blocker	25 (*n* = 2)	8.1 (*n* = 11)	.155	15.9 (*n* = 11)	3.9 (*n* = 2)	.072
Long acting nitrate	0 (*n* = 0)	6.6 (*n* = 9)	1.00	8.7 (*n* = 6)	2 (*n* = 1)	.236
GLS on enrollment echo	−19.95 (−22.10 to −18.68)	−21.50 (−24.07 to −19.09)	.443	−21.00 (−23.82 to −19.11)	−22.02 (−24.46 to −18.50)	.627
GLS on follow-up echo	−21.94 (−23.64 to −20.50)	−23.16 (−25.68 to −21.08)	.502	−23.09 (−25.68 to −21.19)	23.19 (−25.52 to −20.16)	.859
Abnormal GLS, %	25.0 (*n* = 2)	16.2 (*n* = 22)	.621	4.3 (*n* = 3)	7.8 (*n* = 4)	.456

Data in parentheses are presented as *n* or 25th-75th percentiles.

n = 120) and follow-up (94.2%, *n* = 113). Clinical factors associated with normal and abnormal enrollment GLS are presented in Table 4. Abnormal GLS was associated with higher BMI (31.0 vs 28.1 kg/m^2; *P* = .023) and Hispanic ethnicity (*P* = .006).

The median change in GLS between enrollment and follow-up was −2.1 percentage points (−4.3 to 1.1). Global longitudinal strain improved in 38.3% of individuals (*n* = 46; median change in GLS, −5.2%) and worsened in 10.8% of individuals (*n* = 13; median change in GLS, +4.3%).

Global Longitudinal Strain and Stress Test Results

At enrollment, GLS was not significantly different between those with a positive or negative SE (GLS, −21.5% positive SE vs GLS, −19.9% negative SE; *P* = .443; Figure 2). Abnormal GLS was not more common in those with a positive SE (*P* = .673; Table 3) or in those with moderate or severe ischemia on SE (*P* = .093) compared to those with mild or no ischemia, although few patients had abnormal GLS (16.7%, *n* = 24). There was no correlation between GLS and number

Table 4 Clinical, demographic, and stress test factors associated with normal and abnormal GLS at enrollment

	Normal strain (n = 120)	Abnormal strain (n = 24)	P value
Age, years	61 (56, 70)	61.5 (56.2, 70)	.944
Sex, female, %	70.8 (n = 90)	50.0 (n = 12)	.080
Race, %			.819
White	85.0 (n = 102)	83.3 (n = 20)	
Black	5.0 (n = 6)	8.3 (n = 2)	
Asian	7.5 (n = 9)	4.2 (n = 1)	
Other	2.5 (n = 3)	4.2 (n = 1)	
Ethnicity: Hispanic or Latino, %	7.5 (n = 9)	29.2 (n = 7)	
Hypertension, %	60.8 (n = 73)	70.8 (n = 17)	.488
Diabetes, %	15.1 (n = 18)	16.7 (n = 4)	.765
BMI, kg/m^2	28 (24.7-31.1)	30.9 (28-32.7)	.023
Low-density lipoprotein, mg/dL	94.0 (74.9-121.5)	115.3 (93.1-138.1)	.036
Smoking, %	5.8 (n = 7)	8.3 (n = 2)	.645
Family history of premature coronary heart disease, %	38.3 (n = 46)	29.2 (n = 7)	.237
Prior myocardial infarction, %	2.5 (n = 3)	0 (n = 0)	1.000
Prior revascularization, %	5.0 (n = 6)	4.2 (n = 1)	1.000
Symptoms precipitating stress test, %			
Typical chest pain	51.7 (n = 62)	37.5 (n = 9)	.297
Atypical chest pain	34.2 (n = 41)	33.3 (n = 8)	1.000
Shortness of breath	50.8 (n = 61)	66.7 (n = 16)	.232
Nausea	3.3 (n = 4)	0 (n = 0)	1.000
Sweating	2.5 (n = 3)	12.5 (n = 3)	.058
LVEF at rest, %	63 (59-66)	57 (55-60.2)	<.001
LVEF with stress, %	61 (57.5-67)	60 (57.5-67.2)	.468
Exercise stress test, %	85.7 (n = 102)	87.5 (n = 21)	1.000
Exercise time, seconds	395 (300-510.8)	420 (345-563)	.472
Metabolic equivalent	7.0 (6.1-9.4)	7.6 (6.1-8.4)	.879
Baseline SBP, mm Hg	138 (123-150)	140 (128-150)	.663
Baseline diastolic blood pressure, mm Hg	80 (76-89)	82 (79.2-86.2)	.855
Peak SBP, mm Hg	170 (156-189.5)	170 (152.5-189)	.946
Peak diastolic blood pressure, mm Hg	85 (80-95)	80.0 (77.5-88.5)	.173
Hypertensive response to stress, %	16.7 (n = 19)	13.6 (n = 3)	1.000
Stress test positive, %	93.3 (n = 112)	91.7 (n = 22)	.673
Ischemic segments, n	3 (3-4)	4 (2.8-5)	.232
WMSI	1.3 (1.3-1.4)	1.4 (1.2-1.5)	.410
Symptoms during stress			
Limiting chest pain	10.9% (n = 13)	16.7% (n = 4)	.488
Nonlimiting chest pain	10.9% (n = 13)	12.5% (n = 3)	.733
Dyspnea	27.7% (n = 33)	8.3% (n = 2)	.079
Claudication	0.8% (n = 1)	0% (n = 0)	1.000
Other	5.9% (n = 7)	12.5% (n = 3)	.372
SAQ Frequency Scale	83.5 (63.2-92.8)	83 (69-93.5)	.838
SAQ Angina Frequency Scale score	90 (70-100)	90 (80-100)	.271

(Continued)

Table 4 (*Continued*)

	Normal strain (*n* = 120)	Abnormal strain (*n* = 24)	*P* value
Medications, %			
Antiplatelet	72.5 (*n* = 87)	79.2 (*n* = 19)	.672
Beta-blocker	52.5 (*n* = 63)	70.8 (*n* = 17)	.154
Calcium channel blocker	15.8 (*n* = 19)	8.3 (*n* = 2)	.528
Short-acting nitrate	10.8 (*n* = 13)	8.3 (*n* = 2)	1.000
Long-acting nitrate	9.2 (*n* = 11)	12.5 (*n* = 3)	.704
Statin	84.9 (*n* = 101)	70.8 (*n* = 17)	.137
GLS	−22.4 (−24.6 to −20.1)	−16.7 (−17.5 to −16.1)	Not applicable

Data in parentheses are presented as *n* or 25th-75th percentiles.

of ischemic segments (rho = 0.079, $P = .344$) or stress WMSI (rho = 0.078, $P = .352$) at enrollment.

At 1-year follow-up, there was no difference in GLS between those with a positive or negative SE at that time point (GLS, −23.2% positive SE vs GLS −23.1% negative SE; $P = .859$; Figure 3). Abnormal GLS was not more common in participants with a positive SE at 1 year ($P = .456$; Table 3). Moderate or severe ischemia was not more common ($P = .654$) among the patients with abnormal GLS at 1 year (5.8%, $n = 7$). There was no correlation between 1-year GLS and 1-year number of ischemic segments (rho = −0.002, $P = .984$) or WMSI (rho = −0.005, $P = .954$). Enrollment GLS did not differ between those with positive and negative SE at 1-year follow-up (GLS, −22.0% positive SE vs GLS, −21.1% negative SE; $P = .678$).

Regional Longitudinal Strain and Regional Ischemia

Regional longitudinal strain was not significantly different in corresponding areas of regional ischemia at enrollment or follow-up (Table 5). Regional longitudinal strain was not worse in the presence of corresponding segmental ischemia at either enrollment or follow-up.

Change in GLS and Stress Test Results

Patients who experienced a significant change in GLS between enrollment and follow-up did not show differences in the rates of positive SE ($P = .401$), number of ischemic segments ($P = .545$), or stress WMSI ($P = .544$) at 1 year compared to those who did not experience a significant change in GLS.

Longitudinal Modeling of GLS

There was no significant cross-sectional association across the entire population between GLS and ischemia on SE whether ischemia was defined as a positive stress test (unadjusted $\beta = -0.43$, $P = .669$), the number of ischemic segments (unadjusted $\beta = 0.11$, $P = .516$), or the stress WMSI (unadjusted $\beta = 0.15$, $P = .372$). For example, a 0.1-unit increase in stress WMSI was not associated with mean GLS. In contrast, for an individual patient, longitudinal change in these ischemia measures was associated with change in GLS between baseline and follow-up, but the magnitude of the associations was small: change in SE positivity (unadjusted $\beta = 1.91$, $P = .001$), change in number of ischemic segments (unadjusted $\beta = 0.43$, $P < .001$), and the stress WMSI (unadjusted $\beta = 0.44$, $P = .001$). For both the population as a whole and for individual patients, the associations of GLS and exposures of interest were largely unchanged after adjustment for hypothesized confounders (Supplemental Table 1). Left ventricular ejection fraction and SBP were independently associated with GLS in all models. Unadjusted and adjusted models for the relationship between GLS and ischemic and other variables are presented in Supplemental Table 1.

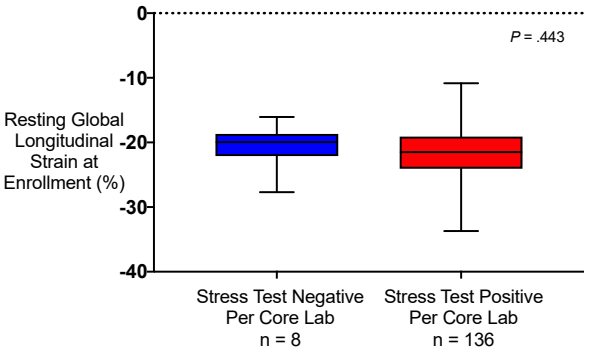


Figure 2 Resting GLS at enrollment and enrollment SE outcome. Resting GLS values at enrollment in individuals with a positive (*n* = 136 in *red*) and negative (*n* = 8 in *blue*) SE enrollment. Values were not significantly different between those with a positive or negative SE (*P* = .443).

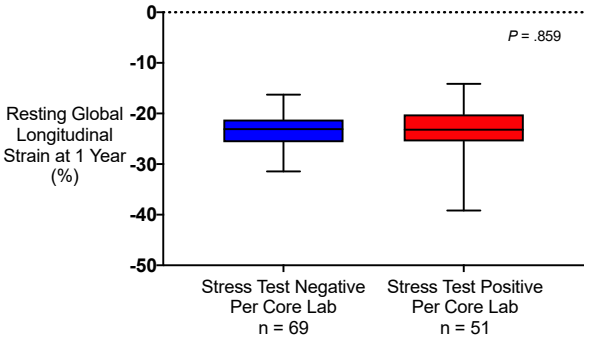


Figure 3 Resting 1-year GLS and 1-year stress test outcome. Global longitudinal strain values at 1-year follow-up in individuals with a positive (*n* = 51 in *red*) and negative (*n* = 69 in *blue*) SE at 1-year follow-up. Values were not significantly different between those with a positive or negative SE (*P* = .859).

Table 5 Regional longitudinal strain in the presence and absence of corresponding regional ischemia at enrollment and 1-year follow-up

	Enrollment			1-Year follow-up		
	Anterior ischemia absent (n = 79)	Anterior ischemia present (n = 63)	P value	Anterior ischemia absent (n = 101)	Anterior ischemia present (n = 18)	P value
Anterior regional strain	−21.7 (−25.9, −19.7)	−22.2 (−25.7, −19.5)	.833	−23.9 (−27.0, −20.7)	−24.3 (−27.9, −19.9)	.982
	Lateral ischemia absent (n = 101)	Lateral ischemia present (n = 39)		Lateral ischemia absent (n = 112)	Lateral ischemia present (n = 6)	
Lateral regional strain	−21.0 (−24.0, −16.9)	−21.3 (−24.5, −18.9)	.671	−21.8 (−24.3, −19.6)	−23.2 (−25.8, −19.9)	.557
	Inferior ischemia absent (n = 87)	Inferior ischemia present (n = 54)		Inferior ischemia absent (n = 104)	Inferior ischemia present (n = 12)	
Inferior regional strain	−18.5 (−21.0, −16.2)	−17.7 (−20.9, −16.0)	.678	−19.9 (−21.8, −17.3)	−19.6 (−20.7, −18.1)	.906

DISCUSSION

Although GLS has been associated with improved diagnostic accuracy in patients with obstructive CAD, our study may suggest that in INOCA, GLS is (1) largely normal, (2) not correlated with inducible ischemia, and (3) not predictive of SE findings.

In this cohort of patients with INOCA, GLS values were normal in 83% at enrollment and 94% at follow-up. As thresholds for normal GLS ranges have not been previously defined in this population, we defined abnormal GLS as worse than −18.0% based on accepted values among healthy individuals.[19,20,24] Women, who represented two-thirds of our cohort, have been reported to have higher GLS values than men;[19,25] however, in our cohort, female sex was not associated with GLS. Whereas GLS is load dependent and higher systemic blood pressures associate with worse GLS values,[19] we found that hypertension was not associated with abnormal GLS, potentially reflecting the reasonable level of blood pressure control in this cohort at the time of SE. It is possible that on an individual patient level changes in blood pressure between baseline and follow-up were also responsible for the improvement in GLS between baseline and follow-up seen in 38% of the population and the worsening seen in 11% of participants; however, our relatively small numbers meant that such changes did not reach statistical significance. Given the influence of SBP, assessment of myocardial work in the INOCA population may be of interest in the future. Although further study is warranted, our results provide insight regarding the range of GLS values among patients with INOCA.

In INOCA, myocardial ischemia occurs secondary to CMD from fixed structural remodeling of the microvasculature, functional dynamic obstruction of the microcirculation, or epicardial vasospasm.[2,26] Multiple studies have demonstrated worse GLS values among patients with obstructive CAD suggestive of myocardial dysfunction at rest secondary to irreversible myocardial injury and/or fibrosis resulting from repetitive ischemia.[11,12] A similar mechanism has been hypothesized to underlie the observation that patients with INOCA have increased risk of heart failure with preserved ejection fraction.[27] The predominantly normal GLS values seen in our population, despite inducible ischemia on SE, argue against the presence of subclinical myocardial dysfunction, detectable by echocardiographic strain analysis at rest, in the majority of individuals. Normal myocardial function at rest among patients with INOCA is further supported by the absence of myocardial fibrosis on cardiac magnetic resonance imaging among symptomatic patients with no obstructive CAD and CMD.[7,28]

Coronary microvascular dysfunction among patients with INOCA is typically thought to cause diffuse subendocardial ischemia. Accordingly, noninvasive stress imaging including SE[9,29] has previously demonstrated significant variability in the detection of ischemia among patients with no obstructive CAD and symptoms of typical angina (previously termed cardiac syndrome X). It remains to be determined whether regional ischemia on SE or single-photon emission CT in the absence of obstructive CAD, as observed in up to 20% of patients with moderate or severe ischemia enrolled in ISCHEMIA, represents the same process as global ischemia as detected by stress CMR imaging or positron emission tomography.[10,28,30] We observed resolution of ischemia in 50% of our cohort at follow-up despite similar stress test characteristics and no significant changes in treatment. This variation likely reflects the heterogeneity in pathophysiological mechanisms among this patient population, the dynamic nature of CMD, and the lower sensitivity of SE for detecting global subendocardial ischemia compared with regional ischemic changes more commonly associated with obstructive CAD.[31,32] We hypothesized that GLS, as a global measure, might be associated with persistence of ischemic abnormalities at 1-year follow-up in the CIAO cohort, but this was not the case. The observed correlation between individual patients' changes in GLS and changes in stress test positivity, number of ischemic segments, and change in WMSI were in the clinically expected direction (worsening GLS was associated with more ischemia). These changes were statistically significant, but the magnitude of these changes was too small to be considered clinically relevant (<1.2% absolute difference in GLS) in an individual patient. These within-patient longitudinal trends serve to strengthen the overall plausibility of our results; however, the lack of association between GLS and ischemia on a population level continues to suggest that GLS may not be a useful predictor of ischemia on SE in this population.

Another possible explanation for the findings might be that GLS assesses subendocardial fibers, which are affected in obstructive CAD since ischemia due to this process affects the subendocardium first. In contrast, INOCA may occur due to CMD, which can spare the subendocardium, explaining the normal GLS values we observed.

Our results should be interpreted in the context of several limitations. We performed post hoc offline strain analysis on images acquired for the primary purpose of evaluating myocardial ischemia. These images were not optimized for strain analysis, and therefore, as noted in Figure 1, 25% of CIAO participants were excluded due to inadequate image quality, which could have led to attrition bias. However, the percentage of patients excluded was similar to prior studies undertaking strain analyses,[25] and with the exception of

BMI, there were no differences in characteristics between the included and excluded patient groups. We acknowledge that CMD has been previously associated with impairment of GLS at stress;[33] however, we set out to evaluate whether there was incremental value to the use of GLS *at rest* to predict ischemia among patients with INOCA. We performed strain analysis only on resting images given that our post hoc analysis was limited by variability of quality of stress images, in addition to the inherent technical challenges posed by measuring strain at peak stress, including suboptimal tracking in the setting of increased heart rate, hypercontractility, and excessive annular motion. A definitive cutoff for normal GLS values has not been defined; GLS ranging from −18% to −22% has been suggested in the literature among healthy individuals.[34,35] We used −18.0% as the cutoff for normal GLS, which was conservative based on the comparatively higher GLS values generated by the TomTec software in comparison with other strain software packages.[36] Given the known intervendor variability in GLS measurements, future studies using other GLS software packages will be needed to confirm our findings. As we were limited by our small cohort, we did not stratify GLS based on severity of ischemia and may be underpowered to detect differences in GLS between those with positive and those with negative SE particularly at enrollment. The findings related to SAQ should be interpreted with caution as the range of angina frequencies was not wide enough to allow for robust analysis; specifically, 83.6% of the population reported monthly or no angina at follow-up. Finally, it is important to acknowledge that given the imperfect sensitivity and specificity of SE, some participants may not have true INOCA. However, the ischemia severity required for study entry and high reproducibility of blinded assessment at the ISCHEMIA core laboratory curtail this limitation.

Although it is possible that the sensitivity of GLS at rest could vary depending on the severity of stress-induced ischemia present, the majority of our cohort had at least moderate ischemia, making this less likely. Although CMD is hypothesized to be the primary driver of ischemia in the CIAO cohort, we did not perform formal testing of invasive or noninvasive coronary flow for the diagnosis of CMD, thus limiting our ability to associate our findings directly with differences in coronary flow characteristics.

CONCLUSION

Among these individuals with INOCA, GLS was mostly normal and not associated with the presence or severity of inducible ischemia on SE at enrollment or follow-up. Global longitudinal strain at enrollment was not associated with ischemia on SE at follow-up.

CONFLICTS OF INTEREST

J.P. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. J.L.-S. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study; grants from Bayer; grants and personal fees from Pfizer; personal fees from Menarini; grants and personal fees from Sanofi; grants from Merck; grants and personal fees from Boeringher Infleheim; and grants from Amgen outside the submitted work. R.S. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study; he also reports speaker fees from Lantheus Medical Imaging, Bracco, and Philips Healthcare. M.D.S. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. He also serves on the Scientific Advisory Board for Regeneron and Amgen. P.A.P. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. K.A. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. K.A.-N. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. R.A. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. Y.X. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. D.M.K. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. J.A.S. reports grants from the National Heart, Lung, and Blood Institute, during the conduct of the study; personal fees from Bayer, Novartis, AstraZeneca, Amgen, Janssen, and United Healthcare; and grants from the American College of Cardiology, outside the submitted work. In addition, he has a patent Copyright to Seattle Angina Questionnaire with royalties paid and is on the Board of Directors for Blue Cross Blue Shield of Kansas City and Equity in Health Outcomes Sciences. J.H. is principal investigator for the ISCHEMIA trial for which, in addition to support by a National Heart, Lung, and Blood Institute grant, devices and medications were provided by Abbott Vascular, Medtronic, Abbott Laboratories (formerly St. Jude Medical), Royal Philips NV (formerly Volcano Corporation), Arbor Pharmaceuticals, AstraZeneca Pharmaceuticals, Merck Sharp & Dohme, Omron Healthcare, Sunovion Pharmaceuticals, Espero BioPharma; financial donations were provided by Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP. D.M. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. M.H.P. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. H.R.R. reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study, nonfinancial support from Abbott Vascular, Philips, SHL Telemedicine, and Siemens outside the submitted work. The remaining authors report no conflicts of interest.

REVIEW STATEMENT

Given her role as JASE Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Julius M. Gardin, MD, MBA.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2023.09.006.

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