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ORIGINAL ARTICLE

Increased deformation of the left ventricle during exercise test measured by global longitudinal strain can rule out significant coronary artery disease in patients with suspected unstable angina pectoris

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Abstract

Background: Noninvasive identification of significant coronary artery disease (CAD) in patients with unstable angina pectoris (UAP) is challenging. Exercise stress testing has been used for years in patients with suspected CAD but has low diagnostic accuracy. The use of Global longitudinal strain (GLS) by speckle tracking echocardiography is a highly sensitive and reproducible parameter for detection of myocardial ischemia. Our aim was to study if identification of normal or ischemic myocardium by measurement of GLS immediately after an ordinary bicycle exercise stress testing in patients with suspected UAP could identify or rule out significant CAD.

Methods: Seventy-eight patients referred for coronary angiography from outpatient clinics and the emergency department with chest pain, inconclusive ECG and normal values of Troponin-T was included. All patients underwent echocardiographic examination at rest and immediately after maximum stress by exercise on a stationary bicycle. Significant CAD was defined by diameter stenosis > 90% by coronary angiography. In patients with coronary stenosis between 50–90%, fractional flow reserve (FFR) was measured and defined abnormal < .80. Analysis of echocardiographic data were performed blinded for angiographic data. Patients were discharged diagnosed with CAD (n = 34) or non-coronary chest pain (NCCP, n = 44).

Results: In patients with NCCP, GLS at rest was -21.1 ± 1.7% and -25.5 ± 2.6% at maximum stress ($P < .01$). In patients with CAD, GLS at rest was -16.8 ± 4.0% and remained unchanged at maximum stress (-16.6 ± 4.6%, $P = .69$). In patients with NCCP, LVEF was 56.1% ± 6.0 and increased to 61.8% 5.2, $P < .01$. In CAD patients, LVEF at rest was 54.7% ± 8.6 and increased to 58.2% ± 9.5 during stress, $P = .16$. In NCCP patients, Wall Motion Score index decreased .02 ± .07, $P = .03$ during stress and was without significant changes in patients with CAD. Area under the curve (AUC) for distinguishing CAD for was .97 (.95-1.00), .63 (.49-.76), and .71 (.59-.83) for GLS, LVEF, and WMSi, respectively.

Conclusion: In patients with suspected UAP, increased deformation of the left ventricle measured by GLS immediately after exercise stress testing identified normal myocardium without CAD. Reduced LV contractile function by GLS without increase after exercise identified significant CAD.

KEYWORDS
coronary artery disease, global longitudinal strain, physiological stress echocardiography

1 | INTRODUCTION

Coronary artery disease (CAD) is the most common cause of death worldwide.[1] Morbidity and mortality are significantly improved through adequate revascularization and medical treatment in patients with both acute myocardial infarction and stable CAD.[2] Patients with chest pain, inconclusive ECG and negative Troponin represent a diagnostic challenge where identification or exclusion of CAD is a major issue. Echocardiography is recommended as part of early diagnostic workup and provides information about myocardial function and is useful in consideration of differential diagnosis and risk stratification.[3] We have previously demonstrated that the use of echocardiography and measurement of global longitudinal strain (GLS) in the emergency department may rule out CAD with high accuracy in patients with chest pain, inconclusive ECG and normal troponin.[4] Despite these findings a number of patients still remain with the question of whether they have significant CAD and should be referred for coronary angiography.

Exercise ECG has been used to identify or rule out CAD with inferior diagnostic accuracy compared to stress echocardiography in patients with suspected ACS.[5–7] Computer tomography coronary angiography is increasingly used but provides at present time only an anatomical and not functional evaluating of coronary pathology. Pharmacologic stress imaging is used and is preferred over exercise ECG in patients with suspected CAD but is time consuming, user dependent and resource demanding[3] but adding GLS measurements in dobutamine stress (DSE) imaging increases the diagnostic precision.[8] Evaluating contractile reserve by GLS during exercise is proven simple and feasible in healthy subjects.[9] Invasive assessment of coronary pathology and grading of stenosis can be challenging and assessment of diameter stenosis is mostly used. Functional evaluation is recommended in 50–90% stenosis and in multi vessel disease[10,11] where studies have shown favorable results when only treating lesions of hemodynamically significance[12]. The diagnostic performance of exercise ECG and physiologic stress echocardiography has not been studied in relation to angiography with hemodynamic measurements.[7] It is therefore of interest to detect ischemia related to possible CAD in these patients.

Measuring LV deformation by GLS has been shown to be a reproducible and sensitive measure of ischemia and myocardial infarction.[4,13,14] It is therefore of great interest and the aim of this study to measure changes in LV deformation by GLS after physiological stress in patients with chest pain without myocardial infarction and examine the impact on the diagnosis of CAD. To ensure a feasible protocol, the study was designed with image acquisitions before and after physiologic stress.

2 | METHODS

2.1 | Study population

In this prospective study, patients referred from the emergency department and outpatient clinics for invasive coronary angiography with suspected CAD between 2014–2020 were evaluated for inclusion. Four hundred twenty-seven patients were screened for inclusion and 78 were included in this study. Three hundred forty-nine patients were dismissed due to lack of indication for coronary angiography. All the following criteria for inclusion were met: (1) Acute chest pain lasting > 10 minutes without myocardial infarction, (2) episode of chest pain within last 3 days and no myocardial infarction, and (3) indication for coronary angiography according to current guidelines.[3,10] Exclusion criteria were: (1) Age < 18 years, (2) QRS duration > 0.12 seconds, (3) Severe valve dysfunction as defined in the ESC guidelines on the management of valvular heart disease,[15] (4) Atrial fibrillation with heart rate > 100 beats/min or other continuous arrhythmia, (5) Prior myocardial infarction, (6) Severe mental disorder, (7) Abnormal initial cardiac troponin T (cTnT), (8) Abnormal ECG suggestive for ongoing ischemia, (9) Short life expectancy of extra-cardiac reason. The patients included were categorized as non-coronary chest pain (NCCP) or coronary artery disease (CAD).[3,16]

2.2 | Echocardiography

Echocardiographic examinations were performed at rest and immediately after maximum exercise using a Vivid 7 and E9 Scanner (GE Ultrasound, Horten, Norway) with images and Cineloops stored digitally. Three consecutive cycles from three apical and parasternal image planes were recorded using two-dimensional grayscale echocardiography. Post hoc analysis of echocardiographic recordings was performed using commercially available software (EchoPAC version 202, GE Ultrasound). Post hoc analysis was performed blinded to clinical and angiographic data. Closure of the aortic valve defined the end of systole and was determined by Doppler flow of the left ventricular outflow tract (LVOT). Peak systolic strain was defined as the maximum

value of peak negative strain (myocardial shortening) or peak positive strain (myocardial lengthening) during systole. Global peak systolic longitudinal strain by speckle-tracking echocardiography was calculated in an 18-segment left ventricular (LV) model as the average segmental value on the basis of three apical imaging planes.[17] Software for semi-automatic measurement of GLS by 2D-strain was used in this study (EchoPAC version 202, GE Ultrasound). LVEF was calculated using Simpson's biplane method. Wall motion score was visually assessed in a 16-segment model as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic.[17] Wall motion score index (WMSi) was calculated by averaging all analyzed segments.

2.3 | Exercise ECG

Exercise ECG was performed on a stationary bicycle. Initial power load was set to 50W increasing 25 W/min. Lateral ECG electrodes were carefully placed not obstructing the apical acoustic window for stress imaging. ECG, heart rate and blood pressure were monitored. Exercise capacity is expressed in metabolic equivalents (METS). 1 MET correspond to an estimated resting metabolic rate with O_2 consumption of 3.5 ml O_2/kg body weight per minute.[18] The patients were instructed to assume the left lateral position on the echo exam table immediately after stopping at maximum exercise. Echocardiography was performed as soon as possible focusing on the left ventricle. Three apical images (four chamber, two chamber, and apical long axis) were analyzed for the measurement of GLS. Interpretation of exercise ECG was according to guidelines.[19]

2.4 | Coronary angiography

All patients underwent coronary angiography. In patients with a visually estimated diameter stenosis > 90% was defined as significant CAD. In visually estimated stenosis ranging between 50–90%, fractional flow reserve (FFR) was measured. FFR values < .80 were defined as significant CAD.

2.5 | Statistical analysis

Continuous data are presented as mean ± SD or median (inter quartile range). Categorical data are presented as numbers (percentage). Comparisons of means were analyzed using paired samples *t*-tests. Mann-Whitney *U* tests were used for non-parametric data and Fischer's exact test for comparing nominal data. Statistical analysis was performed using SPSS 27.0 (SPSS Inc., Chicago, Illinois, USA).

3 | RESULTS

Seventy-eight patients were eligible for inclusion. Thirty-four (43.6%) patients had significant CAD. Twenty-five (32.1%) patients had single vessel disease, nine (11.5%) patients had two-vessel disease, and none had three-vessel/left main stem disease. Forty-four (56.4%) patients did not have significant CAD and were diagnosed NCCP. There were no complications reported after coronary angiography or intervention.

There were no significant differences in demographical, clinical data, preexisting medications or risk of CAD (Table 1).

All patients underwent exercise testing. During exercise, systolic blood pressure increased significantly in both groups, but diastolic blood pressure did not change. There was no significant difference in exercise capacity, systolic blood pressure response and exercise duration between the groups. Patients with CAD demonstrated a higher pulse frequency both at rest (mean difference 12.2 ± 3.3, $P < .01$) and during exercise (15.0 ± 5.7, $P = .01$) (Table 2). Feasibility and image quality were excellent and 16.1±1.9 of 18 segments (89.4%) were analyzed at rest, while 14.8 ± 2.7 segments (82.2%, $P < .01$) could be analyzed at post stress imaging with no significant difference between the groups. No adverse events occurred during stress.

Table 3 lists all results from the echocardiographical examination both during rest and post stress.

When comparing the groups at rest, there was no difference in LVEF, but GLS showed higher absolute values and WMSi was lower in the NCCP patients.

In patients with NCCP, LVEF and systolic deformation (GLS absolute value) increased whereas WMSi decreased during stress testing (Table 3).

In patients with CAD, LVEF and GLS showed no significant change during stress test but there was an increase in WMSi (Table 3).

When analyzing difference in extent of CAD there was no significant difference in WMSi. GLS demonstrated a numerical but not significant difference comparing one- and two-vessel disease at rest with GLS -17.4±3.4 versus -14.9±3.8, $P = .83$. LVEF showed a significant difference at rest with 56.9±7.9 versus 48.3±7.8, $P = .01$. The difference disappeared in both GLS and LVEF during exercise.

The results of the ROC analysis are listed in detail in Table 4. AUC of GLS was higher than both LVEF ($P < .001$) and WMSi ($P < .001$). There was no significant difference in AUC comparing LVEF and WMSi ($P = .6$). With the optimal cut-off values, two patients with CAD had GLS and WMSi values reclassifying them as NCCP patients. In the NCCP group two patients were reclassified based on GLS and four patients based on WMSi.

4 | DISCUSSION

To our knowledge, this study is the first to demonstrate that LV deformation measured by GLS increases during physiologic stress in a normal myocardium and remains slightly depressed and unchanged in the ischemic myocardium in patients with UAP. GLS measured immediately after physiologic stress may therefore be a valuable tool to separate patients with CAD from patients without suspected UAP. Measurement of GLS is easy to perform after an ordinary exercise ECG on a stationary bicycle or on the treadmill in an everyday clinical practice. Our findings are in accordance with a number of previous studies who have demonstrated that GLS may detect ischemia with high accuracy compared to visual assessment.[4,20] However, this study extends previ-

TABLE 1 Clinical and demographic characteristics of included patients

Patient characteristics	NCCPn = 44	CADn = 34	*P*-values
Male/female	24/20	25/9	.09
Age (years)	58.8 ± 13.0	65.0 ± 10.1	.03
Systolic blood pressure (mm Hg)	136.4 ± 22.0	141.1 ± 19.3	.33
Diastolic blood pressure (mm Hg)	80.5 ± 12.8	81.5 ± 10.9	.71
Body mass index UNIT (kg/m^2)	26.9 ± 5.0	27.4 ± 3.9	.60
Currently smoking (n)	13 (29.5%)	10 (29.4%)	.13
Family history of CAD (n)	30 (68.2%)	18 (52.9%)	.17
Dyslipidemia (n)	13 (29.5%)	16 (47.1%)	.12
Diabetes (n)	6 (13.6%)	6 (17.6%)	.63
Medication			
Acetylsalicylic acid (n)	12 (27.3%)	12 (35.3%)	.45
Beta blocker (n)	6 (13.6%)	9 (26.5%)	.16
RAAS inhibitor (n)	8 (18.2%)	13 (38.2%)	.05
Calcium antagonist (n)	7 (15.9%)	7 (20.6%)	.60
Statin (n)	11 (25.0%)	17 (50.0%)	.02

CAD, Coronary artery disease; Continuous data are presented as mean ±SD; NCCP, Non-coronary chest pain; RAAS, Renin angiotensin aldosterone system.

TABLE 2 Patient performance during exercise ECG

Parameter	NCCP	CAD	*P*-value
Exercise duration (min)	5.9 ± 2.0	5.7 ± 2.1	.69
METS	6.7 ± 2.0	6.3 ± 1.70	.32
At rest			
Systolic blood pressure (mm Hg)	136.4 ± 22.0	141.1 ± 19.3	.34
Pulse (beats/min)	65.4 ± 10.4	77.4 ± 18.4	<.01
Maximum exercise			
% of estimated maximum HR	92.3 ± 13.4	88.6 ± 11.5	.63
Post exercise			
Systolic blood pressure (mm Hg)	181.4 ± 38.8	185.6 ± 33.3	.62
Pulse (beats/min)	100.2 ± 22.3	115.1 ± 27.7	.01
% of achieved maximum HR during exercise	65.5 ± 10.4	63.9 ± 9.5	.55
NCCP	**At rest**	**Post exercise**	
Systolic blood pressure (mm Hg)	136.4 ± 22.0	185.6 ± 33.3	<.01
Pulse (beats/min)	65.4 ± 10.4	100.2 ± 22.3	<.01
CAD			
Systolic blood pressure (mm Hg)	141.1 ± 19.3	185.6 ± 33.3	<.01
Pulse (beats/min)	77.4 ± 18.4	115.1 ± 27.7	<.01

CAD, Coronary artery disease; Continuous data are presented as mean ±SD; METS, metabolic equivalents; NCCP, Non-coronary chest pain; HR, heart rate.

ous findings by the identification of ischemic myocardium in patients with chest pain without myocardial infarction. LVEF was not able to separate normal from ischemic myocardium with clinical significance in the present study. This finding is supported by previous studies that describe LVEF as a suboptimal parameter in diagnosing and excluding CAD.[4,20–22]

WMSi differed between the groups and changed during stress but demonstrated inferior diagnostic accuracy compared to GLS. This difference between WMSi and GLS in a post exercise situation might be due to an important difference between WMSi and strain: whereas strain measures myocardial deformation on a continuous scale, there is no separate wall motion score for hyperdynamic deformation. Thus,

TABLE 3 Echocardiographic parameters comparing NCCP and CAD

Parameter		NCCP	CAD	*P*-value
LVEF	resting	56.1 % ± 6.0	54.7 % ± 8.6	.40
LVEF	post exercise	61.8 % ± 5.2	58.2 % ± 9.5	0.05
P-value		<.01	.16	
WMSi	resting	1.03 ± .07	1.00 ± .27	.31
WMSi	post exercise	1.01 ± .03	1.12 ± .18	<.01
P-value		.03	.01	
GLS	resting	-21.1 % ± 1.7	-16.8 % ± 4.0	<.01
GLS	post exercise	-25.5 % ± 2.7	-16.6 % ± 4.6	<.01
P-value		<.01	.69	

CAD, Coronary artery disease; Continuous data are presented as mean ±SD; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NCCP, Non-coronary chest pain; WMSi, Wall Motion Score index.

TABLE 4 ROC analyses with AUC for identifying CAD immediately after stress

	Cutoff	Sensitivity	Specificity	AUC (95% CI)	NPV	PPV
GLS	-21.8%	93.9	93.2	.97 (.95 – 1.00)	95.4	91.0
WMSi	1.10	45.5	91.1	.71 (.59 – .83)	69.5	78.9
LVEF	59.5%	62.5	59.1	.63 (.49 – .76)	68.2	52.8

Abbreviations: AUC, Area under the curve; CI, Confidence interval; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NPV, Negative predictive value; PPV, Positive predictive value; WMSi, Wall Motion Score index.

in contrast to WMSi, strain is able to measure the hyperdynamic deformation induced by exercise. Peteiro et al[23] demonstrated in their study that WMSi performs best at peak exercise vs. post exercise. This might partly explain the lower diagnostic accuracy of WMSi in this study.

Another advantage of GLS for ischemia detection in patients with significant CAD is that onset of transient ischemia is initially subendocardial and not transmural. Subendocardial myocardial fibers are predominantly longitudinally oriented in the left ventricle.[23] In addition, physiologic stress led to an increased blood pressure response at maximal exercise which may contribute to increased subendocardial ischemia due to increase endocardial wall stress and perfusion mismatch in the patients with significant CAD. These effects of physiologic stress may contribute to the separation between normal and ischemic myocardial deformation expressed by GLS in this study. As a consequence, the measurement of LV longitudinal deformation by GLS seems to be a sensitive measure of subendocardial function and therefore act as a sensitive marker of ischemia.

Our findings demonstrate that exercise induced subendocardial ischemia due to CAD affected LV function sufficiently to be identified by GLS but not by WMSi or LVEF in post stress exercise echocardiography.

Former studies have correlated echocardiographic findings with angiographic assessment of CAD.[7] The FAME study addressed the problem with angiographic assessment of CAD which to a certain degree misinterpret the degree of stenosis compared to functional assessment with FFR measurements.[24] The diagnosis of significant CAD in our study was documented by FFR and the correlation between angiographic and echocardiographic findings is a strength. Several studies on pharmacological stress echo have demonstrated an incremental value of GLS in detecting CAD and were all correlated to angiographical assessment of coronary stenosis.[8,25,26]

We have previously demonstrated that GLS may exclude but not identify CAD in a resting echocardiographic examination at admittance in patients with chest pain, inconclusive ECG, and negative troponins. The present study extends these findings and demonstrates both identification and exclusion of significant CAD by measuring GLS by echocardiography immediately after physiological stress in order to separate normal from ischemic myocardium in a population with chest pain without AMI. Compared to pharmacologic stress echocardiography, GLS after physiologic stress is more physiologic, fast and simple to perform, less resource demanding and require no administration of intravenous medication. Thus, the measurement of GLS before and after physiologic stress in patients with chest pain may be used as a simple and feasible diagnostic method in an everyday clinical practice. Finally, a number of studies have demonstrated that GLS is a highly reproducible method with low inter observer variability which makes it highly suitable in clinical practice.[9,27,28]

This study was performed in patients with chest pain and negative cardiac troponins which indicate absence of myocardial necrosis. This suggest that the findings in this study might apply in the population of stable angina but needs to be further studied.

4.1 | Clinical implications

The present study has demonstrated that evaluating the LV deformation by GLS pre- and immediately post-stress may both identify and

rule out CAD in patients with chest pain without myocardial infarction. This finding may have significant clinical implications since patients with increased contractile response after physiologic stress have a low risk of ischemia or significant CAD. On the other hand, patients with inhibited contractile response after physiologic stress as shown by GLS are likely to have ischemia and significant CAD and should be referred to invasive coronary angiography. The clinical advantage of post-stress GLS is that it is an inexpensive and easy to perform method with low inter observer variability and high diagnostic capability. In addition, the simple comparison of GLS before and after physiologic stress test is easy to perform in an everyday clinical practice without extensive training.

4.2 | Limitations

The use of GLS by echocardiography may be limited by high heart rate since GLS by speckle tracking is measured with ideal frame rate 60–90. This is however, solved by measuring GLS shortly after peak exercise with somewhat lower heart rate, but still detectable ischemia.

This is a relatively small study. However, the contrast between groups with and without significant CAD is clear and the study is strengthened by the documentation of significant CAD as measured by FFR during angiography. The diagnostic accuracy reported in this study need to be further validated in a separate study. Measuring GLS at different stages of the exercise test including the restitution phase might add important knowledge of reversible myocardial ischemia and LV deformation. The sensitivity for WMSi to identify coronary ischemia was lower compared to some previous studies. This might be due to the heart rate during image acquisition post exercise in our study which was only 63.9-65.5% of achieved maximum during exercise.

This study has excluded patients with previous myocardial infarction, abnormal ECG suggestive for ongoing ischemia and prolonged QRS. The effect of exercise on myocardial deformation expressed by GLS needs to be further studied in these clinical settings.

Our data in patients with CAD demonstrated a significant increase in wall motion score index during stress but inferior diagnostic accuracy compared to GLS. We believe that our data are too limited to make firm conclusions regarding the specific vessel involvement. The issue of the degree of stenosis is extremely challenging with a functional test and also partly eliminated by doing functional testing with FFR in stenosis that are not high grade.

There was a decrease in total analyzed segments during stress imaging. Optimal image quality is more difficult to achieve in a patient after a maximal exercise with heavy breathing than in a patient examined with pharmacological stress.

5 | CONCLUSIONS

Measurement of LV contractility by echocardiographic GLS after physiologic stress in patients with chest pain without prior and ongoing myocardial infarction may identify and rule out significant CAD. The use of GLS in these patients may improve selection of patients for invasive coronary angiography and safely avoid further invasive diagnostics in those without detectable ischemia.

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CONFLICTS OF INTEREST

None.

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