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Evaluation of left ventricular global longitudinal strain as an adjunct to standard and ABCDE stress echocardiography for risk stratification in ischemic heart disease

Aim — In a prospective observational study of risk stratification in patients with ischemic heart disease (IHD) using stress echocardiography (Stress ECHO), to evaluate the significance of left ventricular (LV) global longitudinal strain (GLS) as an independent prognostic marker or as an adjunct to the existing markers.

Material and methods — This study included 273 patients (60.4% men, mean age 60.9±9.5 years) with known (n=109; 39.9%) or suspected (n=164; 60.1%; IHD pretest probability (PT): 17 [11-26]% (interquartile ranges: Me [Q1; Q3])) IHD. All patients underwent Stress ECHO with physical exercise (PE) on a recumbent bicycle ergometer (n=165; 60.4%), vasodilator (adenosine triphosphate (ATP), n=74; 27.1%), and other stress tests (n=34; 12.5%). The Stress ECHO protocol included assessment of local contractile disorders (LCD), B-lines, LV contractile reserve (CR), and heart rate reserve. Additionally, LV GLS was assessed at rest and at the test peak, and GLS reserve and GLS change (ΔGLS) were calculated. The prospective follow-up period was 20 [13-25] months. The composite cardiovascular end point (CVE) included death from cardiovascular causes, acute coronary syndrome, revascularization, and stroke/transient ischemic attack, and was calculated until the first event.

Results — Prognostic values were obtained for 272 (99.6%) patients. During the follow-up period, 114 cardiovascular complications (CVC) occurred in 87 (31.9%) patients (1 to 3 in each patient). According to the multivariate regression analysis of the Stress ECHO results, the independent predictors for the CVE were the emergence of new LCDs at the peak of stress testing (odds ratio (OR) 2.95; 95% confidence interval (CI): 1.51-5.76; p=0.02) and ΔGLS (OR 0.90; 95% CI: 0.81-0.99; p=0.039). With the use of ATP, the risk of developing CVC was described by a similar model, that had an even higher level of significance (OR for LCD 36.21; 95% CI: 3.09-424.09; p=0.004; OR for ΔGLS 0.48; 95% CI: 0.25-0.94; p=0.032). In PE Stress ECHO, the GLS index added to the LCD did not demonstrate an independent prognostic value. The ROC analysis identified a threshold value for ΔGLS as a predictor of unfavorable prognosis. The threshold absolute value was 1.2 in the entire group and 0.2 in the ATP Stress ECHO subgroup. In case of difficulties in assessing the LCD at the testing peak, an alternative model was used with evaluation of the IHD PT (OR 1.09; 95% CI: 1.04-1.14; p<0.001), emergence of angina at the testing peak (OR 5.07; 95% CI: 1.81-14.26; p=0.002), reduced LV CR (OR 2.18; 95% CI 0.73-6.53; p=0.162), and ΔGLS (OR 0.83; 95% CI 0.72-0.95; p=0.008).

Conclusion — In Stress ECHO performed for risk stratification in IHD, the ΔGLS value, regardless of and in addition to LCDs, is a predictor of CVC. The absolute value of ΔGLS <1.2 in the entire group and ΔGLS <0.2 in the ATP subgroup indicates an unfavorable prognosis for the next 1.5 years.

Keywords — Stress echocardiography; pretest probability; local contractile disorders; left ventricular global longitudinal strain, cardiovascular complications

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Introduction

The past years, the decrease of cardiovascular mortality (especially associated with the acute coronary syndrome) has been achieved in the Russian Federation due National Project of «The Healthcare» [1]. The potential for further improvement is connected with chronic non-inflammatory disease such as chronic coronary syndromes (CCS) and chronic heart failure as complication of the CCS [2]. According to data of the Russian Federal State Statistics Service of 2022, 7,604,000 patients have a diagnosis of CCS in the Russian Federation, and coronary artery disease (CAD) was newly diagnosed in 988,700 patients; more than 80% had CCS (stable forms of CAD) [1].

Several phenotypes of CCS associated with different risks of cardiovascular events, the main goal of cardiologists to verify myocardial ischemia as a key pathogenetic substrate for CCS, and to identify the patients at a high risk of developing cardiovascular complications with indications for myocardial revascularization [2, 3].

In the Russia, stress echocardiography (SE) with various stress agents remains the most accessible, cheaper method for specific diagnosis of CCS in patients with a moderate (>15–50%) or with a low pre-test likelihood of obstructive atherosclerotic CAD (≤15%) in combination with factors that increase the pre-test likelihood of obstructive atherosclerotic CAD [2]. The regional wall motion abnormalities (RWMA) of three or more segments of the left ventricle (LV) at peak stress are the main marker of high-risk patient and the reason for myocardial revascularization, if obstructive coronary atherosclerosis was revealed [2, 3]. The detection of two or more segments with WMA is increasingly considered as a predictor for a high risk of cardiovascular events and myocardial revascularization in a modern cohort of comorbid patients receiving multicomponent drug therapy [2–4]. However, in recent years, even for this «mild» criterion, the value of a negative test result for the prognosis of patients has decreased along with a reduced sensitivity of the WMA itself in the diagnosis of CCS (a negative test result does not always exclude CCS and indicates a favorable prognosis) [4]. To increase the sensitivity and prognostic value of negative SE results, it has been proposed to supplement the study protocol with assessment B-lines, LV contractile reserve (LVCR), coronary flow reserve (CFVR) in the left anterior descending artery (LAD), and heart rate reserve (HRR) (ABCDE protocol) as the markers that have previously shown an independent diagnostic and prognostic value [4–6]. In the STRESS ECHO 2020 and STRESS ECHO 2030 multicenter clinical studies in a modern heterogeneous group, the assessment of several indicators allowed a more accurate phenotyping of patients by identifying a group with indications for invasive diagnostics, and stratifying a high risk of death based on the ABCDE score [5, 7]. However, the assessment of CFVR, which is the second in the prognostic significance after WMA, often causes difficulties in clinical practice, especially when conducting an exercise echocardiography.

In the 2024 clinical consensus statement from the European Association of Cardiovascular Imaging the assessment of Global Longitudinal Strain (GLS) of LV (GLS LV) is proposed as an alternative and/or supplemental method that reduces the dependence of test results on the qualification of the examining physician and increases the diagnostic and prognostic accuracy [4]. The role of resting GLS LV has been previously determined as an isolated earlier marker of impaired LV contractility [8, 9]. Analysis of GLS LV during SE (including exercise echocardiography) was shown to be technically feasible and to have independent significance in identifying obstructive and clinically significant CAD (including microvascular) [4]. However, at present, there are practically no reports on the technical feasibility of assessing GLS LV in SE (especially exercise echocardiography) as a prognostic marker for risk stratification. The threshold values GLS LV and its dynamics during stress test as prognosis marker have not been determined.

Aim

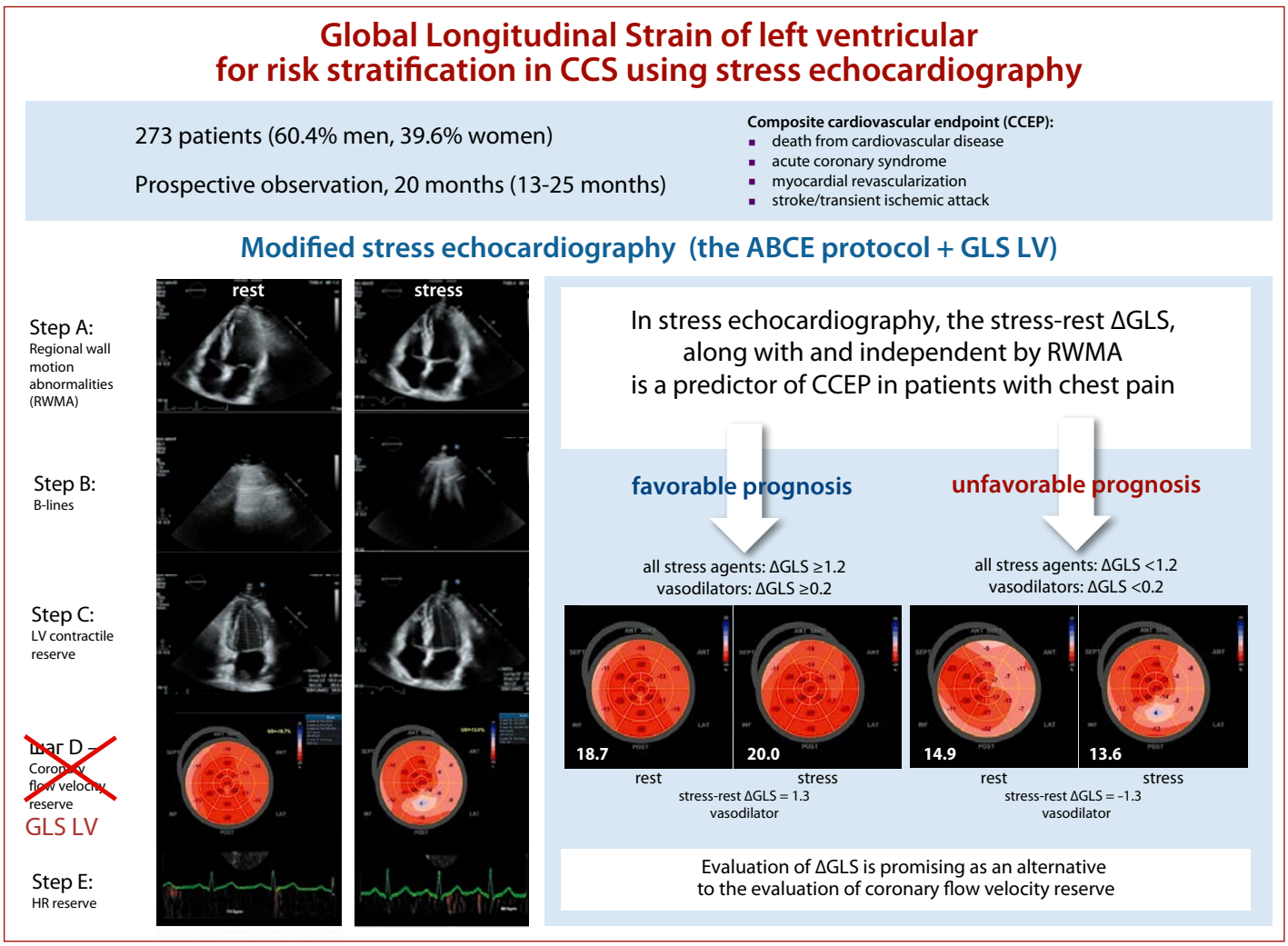
To evaluate the prognostic value of GLS LV during SE in CAD patients in prospective observational study.

Material and methods

We enrolled 273 patients (60.4% men, 60.9±9.5 years) with known (n=109; 39.9%) or suspected (n=164; 60.1%) CCS with pre-test likelihood of obstructive atherosclerotic CAD 17 [11–26] % (Table 1). Inclusion criteria were age 18–80 years; indications for SE to verify myocardial ischemia and risk stratification in accordance with clinical guidelines (primary diagnosis of CCS in individuals with preserved LV ejection fraction (LVEF) with pre-test likelihood of obstructive atherosclerotic CAD >15% or with pre-test likelihood of obstructive atherosclerotic CAD 5–15% in the presence of factors its increase; risk restratification and assessment of prognosis in patients with a known diagnosis of CCS without LV dysfunction) [2, 3].

Exclusion criteria were: clinical signs of chronic heart failure of NYHA class III and higher; cardiomyopathy; valvular heart disease of grade >1; absolute contraindications to SE; acute coronary syndrome (ACS) within <1 month; absence of endocardial visualization of more than 3 LV segments on resting echocardiogra-

Central illustration. Assessment of global longitudinal strain of left ventricular as addition to standard and extended stress echocardiography for risk stratification in chronic coronary syndromes (CCS)



phy; neuropsychiatric diseases that make it difficult to interact with the physician.

During the selection stage of the study anthropometry, blood pressure (BP) and HR were assessed; pretest likelihood of obstructive atherosclerotic CAD was determined in patients with primary diagnosis; 12-lead electrocardiogram (ECG); echocardiography, ultrasound examination of the carotid arteries were performed; blood concentrations of glucose, creatinine, total cholesterol, triglycerides, low-density and high-density lipoprotein cholesterol were determined.

Adenosine triphosphate (ATP) SE (n=74; 27.1%), transesophageal pacing SE (n=28; 10.3%), dobutamine SE (n=6; 2.2%) and exercise (semi-supine bike) SE (n=165; 60.4%) were performed. The type of stress was determined by the cardiologist based on the patient's clinical data. Anti-anginal drugs were discontinued at least 24 hours prior to the study.

Stress echo was performed on Vivid 9 (GE Healthcare, USA), Vivid 095 (GE Healthcare, USA) ultrasound diagnostic systems using the M5S-D matrix sector phased array transducer (1.5–4.6 MHz) or Philips Affiniti 70 (Philips, USA) using the S4–2 sector transducer (2–4 MHz) in the second tissue harmonic mode without echo signal enhancement.

ATP as a stressor was used as an infusion of 140 μg/kg/min for 6 minutes. In case of negative test results and in the absence of contraindications, atropine 1 mg was additionally administered by intravenous injection. Transesophageal pacing was initiated when the contraction rate exceeded the spontaneous rate by 10%. The stimulation rate was then increased stepwise every 2 minutes in the range 100→120→140→160 HR with 1-minute intervals between steps. A protocol of continuous infusion of dobutamine 10→20→30→40 μg/kg/min + atropine 0.25 mg/min up to 1.0 mg was used, with dose escalation every 3 minutes. Exercise echocardiography was performed on a semi-supine bike with a table rotated 10–40° to the left to obtain the best visualization point of the heart. The exercise was started with a load of 25 W and increased continuously by 25 W every 2 minutes.

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Table 1. Clinical characteristics of patients

Parameter	All patients (n=273)	Endpoint (+) (n=87)	Endpoint (–) (n=186)	p
Clinical and demographic data				
Age, years	60.9±9.5	62.7±9.3	60.0±9.6	0.022
Male patients, n (%)	165 (60.4)	55 (63.2)	110 (59.1)	0.554
BMI, kg/m^2	27.8±4.0	27.4±3.7	28.0±4.2	0.215
GFR (EPI), ml/min/1.73 m^2	76 [66; 90]	73 [65; 88]	77 [66; 90]	0.455
Pre-test likelihood of obstructive atherosclerotic CAD, %	17 [11; 26]	27 [13; 34]	16 [11; 22]	0.0003
Medical history, n (%)				
History of MI	43 (15.8)	18 (20.7)	25 (13.4)	0.130
History of PCI	49 (17.9)	19 (21.8)	30 (16.1)	0.260
History of CABG	2 (0.7)	1 (1.1)	1 (0.5)	0.537
Arterial hypertension	243 (89.0)	82 (94.3)	161 (86.6)	0.072
Obesity	67 (24.5)	17 (19.5)	50 (26.9)	0.189
Diabetes mellitus type 2	31 (11.4)	13 (14.9)	18 (9.7)	0.207
Atrial fibrillation	34 (12.5)	9 (10.3)	25 (13.4)	0.461
Smoking	52 (19.0)	18 (20.7)	34 (18.3)	0.666
Dyslipidemia	199 (72.9)	74 (85.1)	125 (67.2)	0.002
Carotid stenosis	207 (75.8)	77 (88.5)	130 (69.9)	0.001
Peripheral atherosclerosis	141 (51.6)	52 (59.8)	89 (47.8)	0.087
COPD	17 (6.2)	2 (2.3)	15 (8.1)	0.104
COVID-19 during follow-up	41 (15.0)	15 (17.2)	26 (14.0)	0.493
Cancer found during follow-up	15 (5.5)	4 (4.6)	11 (5.9)	0.781
Treatment, n (%)				
Beta-blockers	169 (61.9)	62 (71.3)	107 (57.5)	0.033
Calcium channel blockers	131 (48.0)	49 (56.3)	82 (44.1)	0.065
Angiotensinconverting enzyme inhibitors	105 (38.5)	38 (43.7)	67 (36.0)	0.238
Angiotensin II receptor blockers	77 (28.2)	27 (31.0)	50 (26.9)	0.494
Diuretics	80 (29.3)	26 (29.9)	54 (29.0)	0.907
Acetylsalicylic acid	194 (71.1)	75 (86.2)	119 (64.0)	0.0002
Other antiplatelets	87 (31.9)	42 (48.3)	45 (24.2)	0.0001
Statins	228 (83.5)	78 (89.7)	150 (80.6)	0.073

Data are presented as absolute number (%), M ± SD, or Me [Q1; Q3]. BMI, body mass index; GFR, glomerular filtration rate; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease.

BP, HR, ECG, cardiac echo videoclips including sequential images of the heart over three cardiac cycles in the cardiac apical two-, four-, and five-chamber views were recorded in all patients at baseline, at intermediate load stages, peak load, and during the recovery period. The frame rate was at least 60/s. At rest and at peak stress, global and regional contractility with WMA, the occurrence of local wall motion abnormalities were analyzed, and wall motion stress index (WMSI) and ΔWMSI were calculated (step A). B-lines were recorded before the test and during the early recovery period using a four-point scanning protocol (step B). LVCR was estimated as the ratio of systolic BP to LV end-systolic index at peak load and at rest (step C). HRR was estimated as HR at peak/rest HR (step E) [4–7].

The positive test criteria were as follows: appearance of RWMA or worsening in 2 or more LV segments (RWMA (+)); presence of B-lines at rest or their appearance during stress ≥ 2 (B-lines (+)); LVCR ≤ 1.1 in vasodilator test, ≤ 2.0 with other stressors (LVCR (+)); HRR ≤ 1.22 in vasodilator test, ≤ 1.8 with other stressors (HRR (+)) [4, 6].

Additionally, GLS LV was assessed at rest and at the peak load. GLS LV was calculated off-line semi-automatically using the Automated Functional Imaging (AFI) option (Vivid 9, Vivid 095, GE) or QLAB/aCMQ Affiniti (Philips). Cardiac echo videoclips from the apical two-, four-, and five-chamber positions were automatically stopped at the end of systole, and the endocardial boundaries were contoured to form the region of interest on the LV walls. GLS LV was determined automatically or by the formula:

$$GLS = (GLS_{2C}+GLS_{4C}+GLS_{5C})/3.$$

The GLS reserve was calculated as the ratio GLSstress/GLSrest, and the dynamics of GLS (ΔGLS) – as the difference between GLS at the peak of stress test and at rest [4, 8, 9].

All angiograms were performed after SE. The Axiom Artis angiographic system (Siemens; Erlangen, Germany) was used in 209 (76.6%) patients to perform invasive coronary angiography. Multi-slice computed tomography (MSCT) angiography of the coronary arteries was performed on a Discovery NM/CT 570s hybrid CT scanner (GE Healthcare, USA) in 36 (13.2%) patients. In 28 (10.2%) patients, coronary angiography was not performed due to the negative result of SE and the second test for ischemia. Arterial stenosis was assessed by diameter; stenosis ≥50% (obstructive lesion) was considered anatomically significant.

The prospective follow-up period was 20 [13; 25] months with two control points in the form of a face-to-face visit and/or telephone contact and/or medical record review. The composite cardiovascular endpoint (CCEP) included cardiovascular death, ACS, and revascularization and stroke/transient ischemic attack (TIA) and was calculated before the first event. Patients were divided into 2 groups based on the presence or absence of CCEP, and predictors of cardiovascular events were analyzed.

The study was conducted in accordance with the tenets of the Helsinki Declaration and approved by the local Biomedical Ethics Committee. All patients signed the informed consent before being included in the study.

Statistical analysis was performed using Statistica 16.0 (StatSoft, USA) and SPSS Statistics 23.0 (USA). The normality of data distribution was tested with the Shapiro-Wilk test. Categorical indicators are presented as absolute values and relative frequencies (n (%)), quantitative indicators were described by means and standard deviations (M ± SD) for normally distributed indicators or medians and interquartile ranges (Me [Q1; Q3]) for non-normally distributed indicators. Student's t-test and MannWhitney U-test were used to evaluate the differences of normally distributed quantitative indicators and abnormally distributed indicators in two independent groups, respectively. Pearson's chi-squared test or Fisher's exact test was used to analyze differences in categorical indicators in independent patient groups. Statistically significant predictors of the CVE occurrence were identified with constructed multivariate logistic regression models; sensitivity and specificity were calculated; and ROC analysis of the obtained models was performed. The area under the ROC curve (AUC) was used to assess the prognostic quality of the models, and the Youden criterion was used to determine the threshold value of the predictor in single-factor models. Differences were considered statistically significant at $p<0.05$.

Results

WMSI and HRR were assessed in all patients, LVCR in 98.5%, B-lines in 93%, GLS LV in 68.9%. Obstructive CAD was detected in 162 (66.1%) patients.

Prognostic data were available for 272 (99.6%) patients. During the follow-up period, CCEP was reported in 87 (31.9%) patients. One to three cardiovascular events occurred: there were 18 cases of ACS (6.6%; 11 cases of acute MI, 7 cases of unstable angina) and 93 (31.5%) cases of myocardial revascularization by either stenting (n = 80) or coronary artery bypass grafting (n=13), 2 (0.7%) cases stroke/TIA. Patients with cardiovascular events were assigned to the CCEP (+) group and the remaining patients to the CCEP (–) group (n=186) (Table 1). During the follow-up period, 5 patients died from causes not related with cardiovascular diseases.

In the CCEP (+) group, patients were older, had a higher pre-test likelihood of obstructive atherosclerotic CAD, more frequent dyslipidemia, carotid atherosclerosis. The prevalence of diabetes mellitus, atrial fibrillation, smoking, obesity, history of revascularization, and COVID-19 disease did not differ between the groups.

All preload stress echocardiographic parameters were comparable in both groups (Table 2). At peak stress CCEP (+) group had lower LVEF and LV strength, HRR, LVCR, GLS reserve, ΔGLS and higher WMSI, ΔWMSI, more frequent phenotypes of RWMA (+), LVCR (+), HRR (+) and typical anginal pain. There were no differences in the comparison of B-lines and ST-segment depression >1 mm at the peak load in the CCEP (+) and CCEP (-) groups.

In the total group (all stress agents) all factors that were significantly different between the groups, were predictors ($p<0.05$) of the CCEP except for carotid atherosclerosis and HR at the peak load by the univariate regression analysis. The absolute value of the threshold ΔGLS as a predictor of the risk of CCEP was 1.2 using to the ROC analysis.

In the multivariate Cox regression analysis, including all noncollinear factors that showed significance in the univariate analysis, 2 models were constructed to predict the risk of CCEP: a model based on the results of stress echocardiography (Table 3), and a model based on clinical data and on the results of stress echocardiography (Table 4). First model included RWMA (+) and ΔGLS, the diagnostic accuracy of the model was 64.9%, specificity 64.7%, sensitivity 65.3%, AUC=0.684, and statistical significance of the model was $p< 0.001$. Second model included pre-test likelihood of obstructive atherosclerotic CAD, typical anginal pain at the peak load, ΔGLS and reduced LVCR, the diagnostic accu-

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Table 2. Symptoms, electrocardiographic data, and systemic and cardiac hemodynamics during SE in the total group of patients

Parameter	All patients (n=273)	Endpoint (+) (n=87)	Endpoint (–) (n=186)	p
Rest				
HR, bpm	66.9±11.4	66.8±9.8	66.9±12.0	0.732
SBP, mm Hg	128 [117.5; 140]	128 [118; 137]	128 [117; 141]	0.957
DBP, mm Hg	80 [72; 87]	79.5 [70; 88]	80 [73; 87]	0.917
LVEDV, ml	90 [76; 104]	86 [73; 104]	91 [76; 104]	0.248
LVESV ml	29 [22; 36]	29 [20; 36]	29 [24; 35]	0.436
LVEF, %	67.0 [63.2; 71.3]	66.7 [62.5; 72.4]	67.0 [63.3; 70.9]	0.657
LV strength, dyne	8.3[6.8; 10.8]	8.3 [6.9; 11.9]	8.4 [6.7; 10.5]	0.591
WMSI, units	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	0.497
B-lines, units	0.00 [0.0; 1.0]	0.00 [0.0; 2.0]	0.00 [0.0; 1.0]	0.239
GLS LV	17.0 [14.3; 18.7]	17.0 [14.6; 18.5]	17.0 [14.2; 18.8]	0.746
Peak stress				
HR, bpm	115.4±24.5	108.5±21.0	118.6±25.4	0.0006
SBP, mm Hg	167 [132; 188]	163.5 [130; 186]	169 [136; 188]	0.601
DBP, mm Hg	86 [76; 97]	86 [76; 97]	86 [75; 97]	0.935
LVEDV, ml	83 [70; 99]	80 [68; 103]	83.5 [71.5; 97]	0.751
LVESV, ml	24 [18; 31]	26 [18; 37]	23 [18; 28.5]	0.073
LVEF, %	71.3 [64.5; 76]	66.7 [61.8; 75.0]	72.0 [66.7; 76.2]	0.0006
LV strength, dyne	13.3 [9.5; 17.6]	12.4 [8.1; 16.3]	13.7 [10.3; 18.2]	0.035
WMSI, units	1.0 [1.0; 1.19]	1.13 [1.0; 1.25]	1.0 [1.0; 1.10]	0.0001
Δ WMSI	0 [0; 0.13]	0.12 [0; 0.19]	0 [0; 0.10]	<0.0001
B-lines, units	0.00 [0.00; 2.00]	0.00 [0.00; 2.00]	0.00 [0.00; 2.50]	0.496
LVCR	1.5 [1.1; 1.96]	1.26 [1.01; 1.84]	1.60 [1.20; 2.0]	0.005
HR reserve	1.70±0.39	1.64±0.34	1.80±0.40	0.002
GLS LV	18.0 [16; 20.1]	17.3 [15; 19]	18.5 [16.4; 20.8]	0.01
GLS reserve	1.10 [1.0; 1.21]	1.05 [0.93; 1.53]	1.12 [1.02; 1.23]	0.018
ΔGLS	1.7 [–0.4; 3.25]	0.8 [–1.1; 2.6]	2.0 [0.4; 3.5]	0.019
RWMA (+), n (%)	111 (40.7)	53 (60.9)	58 (31.2)	<0.0001
B-lines (+), n (%)	84 (32.6)	25 (31.3)	59 (33.1)	0.764
LVCR (+), n (%)	162 (60.4)	59 (69.4)	103 (56.3)	0.041
HR reserve (+), n (%)	97 (35.5)	39 (44.8)	58 (31.2)	0.025
Typical anginal pain at the peak load, n (%)	38 (13.9)	18 (20.9)	20 (10.8)	0.024
ST segment depression ≥1 mm at the peak load, n (%)	96 (35.2)	31 (35.6)	65 (34.9)	0.936

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; RWMA – regional wall motion abnormalities; WMSI, wall motion stress index; GLS LV, global longitudinal strain of left ventricular; LVCR, left ventricular contractile reserve.

racy of the model was 81.0%, specificity 81.5%, sensitivity 80.0%, AUC=0.834, and statistical significance p<0.0001. Although the LVCR significance was greater than 0.05, its inclusion significantly improved the prognostic value of the model.

GLS, ΔGLS and GLS reserve did not demonstrate an independent prognostic value for the risk of CCEP by exercise SE group.

In the ATP SE group, patients had a more frequent obesity (36.5 and 20.1%; p=0.005), obstructive CAD (71.6 and 54.8%; p=0.012), and had a tendency towards a higher incidence of the CCEP (40.5 and 28.6%; p=0.061) vs other stress agents. At peak stress ATP SE CCEP (+) group had lower GLS LV, GLS reserve, ΔGLS and higher WMSI, ΔWMSI, more frequent phenotypes of RWMA (+) vs ATP SE CCEP (–) group.

Table 3. Results of multivariate analysis: predictors of CCEP development based on stress echocardiogram in the total group of patients

Factor	OR (95% CI)	p
RWMA (+)	2.95 (1.51–5.76)	0.002
ΔGLS	0.90 (0.81–0.99)	0.039

CCEP, composite cardiovascular endpoint; OR odds ratio; RWMA, regional wall motion abnormalities; ΔGLS, difference global longitudinal strain of left ventricular at peak load and at rest.

Table 4. Results of multivariate analysis: predictors of CCEP development based on clinical data and stress echocardiogram in the total group of patients

Factor	OR (95% CI)	p
Pre-test likelihood of obstructive atherosclerotic CAD	1.09 (1.04–1.14)	<0.001
Typical anginal pain at the peak load	5.07 (1.81–14.26)	0.002
ΔGLS	0.83 (0.72–0.95)	0.008
LVCR(+)	2.18 (0.73-6.53)	0.162

CCEP, composite cardiovascular endpoint; OR odds ratio; CAD, coronary artery disease; ΔGLS, difference global longitudinal strain of left ventricular at peak load and at rest; LVCR, left ventricular contractile reserve.

Table 5. Symptoms, electrocardiographic data, and systemic and cardiac hemodynamics during SE in the ATP group of patients

Parameter	All patients (n=74)	Endpoint (+) (n=30)	Endpoint (–) (n=44)	p
Rest				
HR, bpm	63.7±9.5	65.0±8.1	62.9±10.2	0.168
SBP, mm Hg	132 [118; 146]	130 [117; 144]	133 [118; 146]	0.942
DBP, mm Hg	80 [70; 86]	84 [71; 89]	77.5 [69.5; 85.5]	0.133
LVEDV, ml	84 [74; 100]	83.5 [67.5; 104]	86 [75; 99]	0.687
LVESV, ml	28 [22; 34]	26.5 [20; 35.5]	28 [24; 34]	0.884
LVEF, %	66.7 [63.2; 71.0]	66.5 [62.8; 70.7]	66.9 [63.2; 71.2]	0.619
LV strength, dyne	9.1 [7.7; 11.7]	8.7 [7.4; 12.0]	9.1 [7.9; 10.6]	0.670
WMSI, units	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	0.266
B-lines, units	0.00 [0.0; 1.0]	0.00 [0.0; 1.0]	0.00 [0.0; 1.0]	0.904
GLS LV	18.8 [16.9; 20.4]	18.2 [16.8; 19.8]	19.0 [16.9; 20.4]	0.685
Peak stress				
HR, bpm	87.8±13.1	90.1±12.7	86.2±13.3	0.315
SBP, mm Hg	122 [107; 134]	124 [112; 130]	120 [102.5; 135]	0.505
DBP, mm Hg	72 [63; 81]	76 [70; 83]	67.5 [60.5; 75.5]	0.011
LVEDV, ml	78 [70; 93]	77.5 [69.5; 97.5]	78 [70; 88]	0.730
LVESV, ml	23 [18; 28]	25.5 [18; 33]	23 [19; 26]	0.358
LVEF, %	71.3 [66.7; 74.7]	68.4 [64.5; 75.4]	72.1 [68.3; 74.7]	0.101
LV strength, dyne	10.2 [7.6; 13.4]	9.0 [6.8; 13.9]	10.6 [8.1; 13.0]	0.465
WMSI, units	1.0 [1.0; 1.13]	1.13 [1.0; 1.19]	1.0 [1.0; 1.0]	<0.0001
Δ WMSI	0 [0; 0.12]	0.12 [0; 0.17]	0 [0; 0]	0.0009
B-lines, units	0.00 [0.00; 1.00]	0.00 [0.00; 1.00]	0.00 [0.00; 1.00]	0.467
LVCR	1.1 [0.9; 1.3]	1.02 [0.86; 1.28]	1.1 [1.0; 1.3]	0.289
HR reserve	1.4±0.16	1.39±0.17	1.40±0.15	0.810
GLS LV	19.35 [17.3; 21.1]	17.4 [15.4; 19.1]	19.9 [18.7; 21.7]	0.007
GLS reserve	1.00 [1.00; 1.15]	0.93 [0.86; 1.05]	1.08 [1.03; 1.19]	0.004
ΔGLS	0.8 [–0.6; 2.9]	–1.35 [–2.45; 0.7]	1.6 [0.5; 3.2]	0.003
RWMA (+), n (%)	26 (35.1)	20 (66.7)	6 (13.6)	<0.0001
B-lines (+), n (%)	8 (11.9)	2 (8)	6 (14.3)	0.700
LVCR (+), n (%)	39 (54.9)	17 (60.7)	22 (51.2)	0.429
HR reserve (+), n (%)	11 (14.9)	5 (16.7)	6 (13.6)	0.744
Typical anginal pain at the peak load, n (%)	6 (8.1)	5 (16.7)	1 (2.9)	0.091
ST segment depression ≥1 mm at the peak load, n (%)	5 (6.8)	3 (10)	2 (4.5)	0.678

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; RWMA – regional wall motion abnormalities; WMSI, wall motion stress index; GLS LV, global longitudinal strain of left ventricular; LVCR, left ventricular contractile reserve.

In the ATP SE group model to predict the risk of CCEP included RWMA (+) (OR 36.21; 95% CI: 3.09–424.09) and ΔGLS (OR 0.48; 95% CI: 0.25–0.94), the diagnostic accuracy of the model was 81.6%, specificity 80.8%, sensitivity 83.3%, AUC=0.921, and statistical significance of the model was p=0.000009. The absolute value of the threshold ΔGLS as a predictor of the risk of CCEP in ATP SE group was 0.2 using to the ROC analysis.

Clinical examples of using the ATP SE protocol with the assessment of GLS LV for prognosis of patients and choosing treatment tactics are presented in Figures 1 and 2.

Patient K., female,70 y.o. Pre-test likelihood of obstructive atherosclerotic CAD 27%. SE with ATP 140 μg/kg/min. No complaints or changes in ECG at the at the peak load, WMSI 1.0. GLS LV at rest 19.9, at the peak load 20.7. ΔGLS 0.8. Invasive coronary angiography – normal coronary arteries. Treatment tactics: optimal drug therapy. Prognosis for 25 months: without CCEP.

Patient B., male, 69 y.o. Pre-test likelihood of obstructive atherosclerotic CAD 44%. SE with ATP 140 μg/kg/min. No complaints or changes in the ECG at the at the peak load; WMA of the basal segment of the interventricular septum and the basal and middle segments of the anterior wall of LV, WMSI 1.19. GLS LV at rest 16.0; at the peak load 13.1. ΔGLS is 2.9. Invasive coronary angiography: stenosis of the LAD in the middle third 75%, 1st diagonal artery 85%, 2nd diagonal artery 85%, right CA in the proximal third 50%. The patient has a balanced type of myocardial blood supply with a high diagonal branches. Follow-up for 15 months; after two months, patient had PCI – stenting of middle third LAD; balloon dilation of the 1st and 2nd diagonal arteries.

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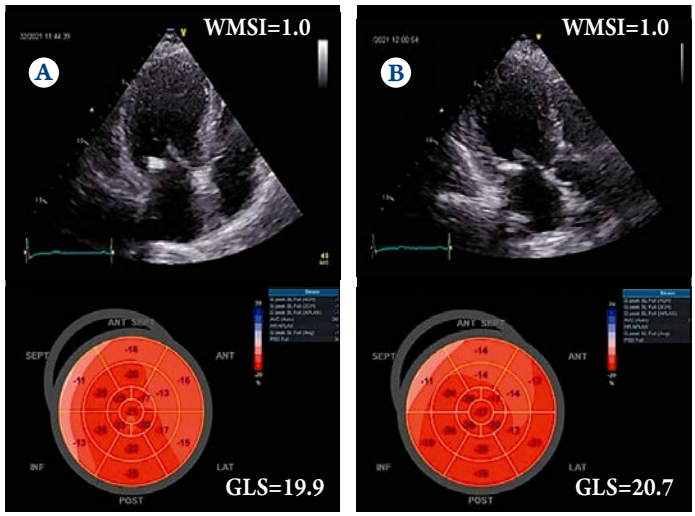
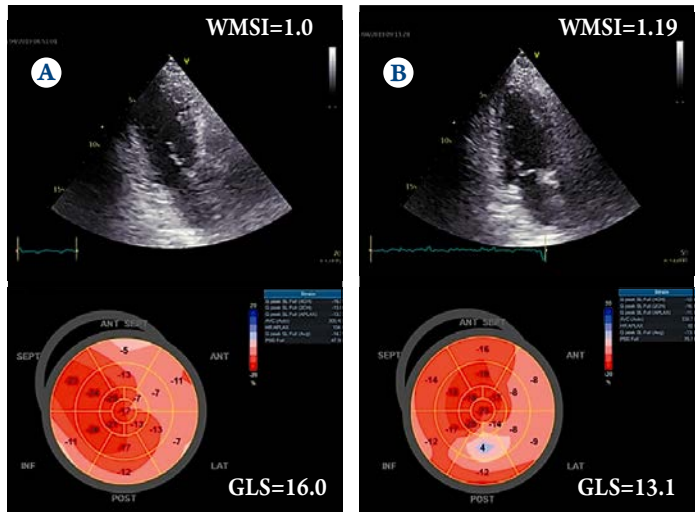
Figure 1. Echocardiograms of patient K., 70 years old. CAD: stable angina, functional class II



A: rest; **B**: peak load, ATP, 140 μg/kg/min.
WMSI – wall motion stress index;
GLS, global longitudinal strain of left venticular.

Figure 2. Echocardiograms of patient B., 69 years old



A: rest; **B**: peak load, ATP, 140 μg/kg/min.
WMSI – wall motion stress index;
GLS, global longitudinal strain of left venticular.

Discussion

Russian Guidelines for stable CAD and ESC Guidelines for the management of CCS were revised in 2024 [2, 3]. Despite some differences in their names and classification of CAD, both groups of authors agreed that the cause of the CAD can be both organic and functional changes in the CA that lead to a discrepancy between the myocardial oxygen demand and delivery. Patients with LVEF <50%, hemodynamically significant CA stenoses, and the presence of extensive myocardial ischemia have the highest risk of developing CCEP.

Previously, international studies have shown that pre-test likelihood of obstructive atherosclerotic CAD allows the primary stratification of the CCEP risk and and selection of patients for specific noninvasive diagnosis of CCS. In our study, pre-test likelihood of obstructive atherosclerotic CAD and typical anginal pain at the peak load were independently associated with the CCEP. However, a high-quality prognostic model based on clinical indicators were added the data of SE.

Almost 40 years ago, the method of SE has been used to confirm and expansion of myocardial ischemia based on the detection of local RWMA [2–4, 11]. Until the 2010s, the appearance of new RWMA at the peak load was an unambiguous predictor of of cardiovascular death, a negative SE result associated with cardiovascular mortality less 1% per year [11]. However, at present, the evaluation only RWMA is insufficient both for diagnosis and prediction of overall mortality, cardiovascular mortality, and revascularization, especially in patients with diabetes mellitus [4, 6]. The decrease in the prognostic value of negative SE results by the RWMA criterion is due to the changes of clinical phenotype of patients, including an increased comorbidity, multicomponent cardioactive therapy and/or revascularization; earlier referral of patients for specific diagnostics; microvascular angina, etc. Scientists find new, more accurate and early prognostic markers, first of all, to exclude the disease [4]. Previously, LVCR demonstrated a predictive value on prognosis even in the absence of RWMA [6]. In our study, addition of LV CR significantly enhanced the prognostic characteristics of the model based on the pre-test likelihood of obstructive atherosclerotic CAD and typical anginal pain at the peak load. This model can be used for assessing the risk of the CCEP in case of difficulties in assessing RWMA.

In recent years, largest evidence base was accumulated for CFVR, which reflects the increase in coronary blood flow velocity in response to various types of stress, has been shown to have independent prognostic value in relation to the risk of death in addition and independent to RWMA [6, 12–14]. A negative result of SE by the RWMA and LAD CFVR is associated with a low risk of CCEP [6, 12–14]. In our earlier study, RWMA and CFVR were the strongest independent predictors of the CCEP [14]. However, the assessment of CFVR often has problems due to technical difficulties in visualizing the LAD, absence of specialists and/or the necessary equipment, especially at the outpatient practice and exersice SE. The updated European Consensus on Stress Echocardiography proposed to supplement the extended SE protocol to access of GLS LV due to its simplicity and the absence of need to additional equipment and software [4]. Previously, several stud-

ies demonstrated high intra- and inter- physician reproducibility and sensitivity of GLS LV in the diagnosis of obstructive and microvascular CAD [4]. We obtained comparable data on the possibility of assessing GLS: GLS LV in rest was correctly determined in all (100%) patients, at the peak load in 68.9%. GLS LV demonstrated higher sensitivity for detecting ischemia in early CCS compared to the visual assessment of RWMA in the meta-analysis by K. Gupta et al. [15] that included data from 13 studies (n=978) mainly with dobutamine SE. In patients with normal CA, a statistically significant increase in GLS (in absolute units) was found during exercise SE. Whereas GLS LV was significantly decreased at the peak load in CAD patients, especially with diabetes mellitus [16]. LV GLS absolute value of less than 16.9 is a predictor of hemodynamically significant coronary stenosis according to A. I. Stepanova et al. [16] in exercise SE (treadmill test).

L. S. Atabaeva et al. [17] showed that the supplement assessment of GLS LV at exercise contrast-enhanced SE increases the sensitivity for detecting borderline coronary stenoses and lesions of the right CA. GLS LV statistically significantly correlated with LAD CFVR [18]. Furthermore, both GLS LV and LAD CFVR were more sensitive for detecting subclinical ischemia in nonobstructive coronary atherosclerosis even in the absence of RWMA and with a normal LVCR. This allowed us to suggest the determination of LAD CFVR to change access GLS LV in multicomponent SE protocol for prediction of prognosis in patients. However, the prognostic value of GLS LV and ΔGLS independent and in addition to RWMA practically has not been previously studied, especially in exercise SE.

S. Romano et al. [19] using dipyridamole stress cardiac magnetic resonance imaging established an association between GLS LV and the prognosis of patients. The ultrasound study was performed only by D. M. Lowenstein et al. (2022) using dipyridamole SE in CAD patients. In that study, LV apical longitudinal strain had an independent and stronger than RWMA association with the CAE and myocardial revascularization during 36 months [20].

In our study, in group with all types of stress agents, including the exercise SE, and in the ATP group, the risk of the CCEP was associated not only with the appearance of new RWMA at the peak load, but with ΔGLS. Addition the assessment of ΔGLS to RWMA models improved its quality. In the ATP subgroup, the model had better statistical parameters than in the total group, despite a smaller number of patients. Probably it was due to the higher image quality in the test with a vasodilator than in the exercise test or dobutamine. The higher image quality was a result of lower target HR values, and the absence of hyperventilation and muscle movements. It is well known that the quality of the GLS LV assessment depends on the frame rate and is optimal at a HR below 100–110 bpm, which occurs precisely during the vasodilator test [4]. Also, especially vasodilators are recommended for assessing LAD CFVR as a sensitive marker of ischemia associated with microvascular dysfunction. We used GLS LV as a potential replacement for LAD CFVR in the multicomponent SE test.

LVCR, HR reserve, B-lines, GLS LV, or complaints not exceeded the WMSI and RWMA (+) in the prognostic significance, but were only to supplement it in our study. Replace RWMA with a GLS LV was possible only using the multifactorial models taking clinical factors, including pre-test likelihood of obstructive atherosclerotic CAD and chest pain characteristics.

Thus, assessment of GLS LV or its dynamics is important component of SE with an independent and supplementary to RWMA prognostic significance. This technology seems promising as an alternative to LAD CFVR in prediction prognosis. It is necessary to further refine and validate clean criteria for the GLS LV in SE as diagnostic and prognostic markers in large multicenter prospective studies.

Study limitations

Our study has several limitations. There was an uneven distribution of patients undergoing stress echocardiography with different stressors. This limitation was overcome by using for the analysis not the absolute values of CFR, LVCR, RWMA, and other indices, but their categorization into normal and pathological responses according to thresholds that have been previously defined in numerous studies and that differ for different stressors. In our study, GLS LV was determined in 68.9% of patients at the peak load due to the frequent use of exercise SE, which decreased the image quality. HR reserve and B-lines did not exert an independent or additional effect on the prognosis in the multivariate analysis. It was probably due to the small sample of patients, the use of different stress agents, and performing the study during the period of widespread coronavirus infection, which increases the prevalence of B-lines in the population due to extracardiac causes. We did not use an echo contrast agent in SE as recommended by the Consensus on Stress Echocardiography, because it is not available in the Russian Federation now.

Conclusion

The ΔGLS (difference between GLS LV at the peak load and at rest) obtained by stress echo is an indepen-

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dent from RWMA and additional to RWMA predictor of the CCEP, including cardiovascular death, ACS, stroke/TIA and myocardial revascularization in patients with suspected or known CCS. The ΔGLS demonstrates the best results when using a vasodilator (ATP) as a stress agent. An absolute ΔGLS value of <1.2 in the total group and <0.2 in the ATP subgroup indicates an unfavorable cardiovascular prognosis over the next 1.5 years.

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