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The Value of Stress Echocardiography Imaging and Functional Parameters in Patients with aVR Lead ST-Segment Elevation during an Exercise Stress Test to Detect Significant Left Main Stenosis

Marija Petrovic[1, 2], Jelena Dotlic[3], Nikola Boskovic[1], Vojislav Giga[1], Srdjan Aleksandric[1], Srdjan Dedic[1], Branko Beleslin[1], Ana Djordjevic Dikic[1]

[1]Cardiology Clinic, Clinical Center of Serbia, School of Medicine University of Belgrade, Serbia, [2]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, US, [3]Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, School of Medicine University of Belgrade, Serbia

Correspondence: *petrovic_marija@yahoo.com*; Tel.: + 1 832 726 4486; Fax.: +1 718 519 3734

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Abstract

Objective. To evaluate the role of functional and imaging parameters during exercise stress echocardiography (SE) in the presence of ST-segment elevation (ST-E) in aVR leads to predict significant left main/left main equivalent/or ostial left anterior descending (LAD) stenosis (LM+). **Methods.** The study population included 548 patients with ECG and echo markers of myocardial ischemia, in whom diagnostic coronary angiography was performed. We analyzed the patients' clinical characteristics, ECG changes, wall motion score index (WMSI) by stress echocardiography (SE), as well as functional capacity during exercise (METs) and Duke treadmill score. **Results.** aVR ST-segment elevation was found in 60/548 (11%) patients, whereas aVR ST-E was found in 23/57 patients with left main LM stenosis (Sn 40%, Sp 92%, PPV 38%, NPV 93%). When aVR ST-E was combined with other functional/imaging parameters, patients with aVR ST-E and LM+ had significantly worse functional capacity in METs (5.0±2.2 vs. 6.7±2.3, P=0.005), lower Duke score (-6.8±6.8 vs. -3.6±4.1, P=0.049), and higher deterioration of WMSI (0.51±0.24 vs. 0.39±0.24, P=0.046). Significant multivariable predictors of the left main (LM) stenosis were aVR ST-E and positive SE in LAD territory in the whole group of patients, and Delta WMSI, Duke score and METs achieved in patients presented with aVR ST-E during exercise. **Conclusion.** The aVR ST-segment alone has intermediate sensitivity in detecting significant LM stenosis in patients referred to SE testing for chest pain. When combined with other functional and imaging parameters, including poor exercise functional capacity in METs, lower Duke score or greater WMA in the territory of LAD, its diagnostic power to detect LM significantly increases.

Key Words: aVR Lead ST-Segment Elevation ▪ Left Main Stenosis ▪ Stress Echocardiography.

Introduction

The augmented unipolar right arm (aVR) lead, also known as the orphan lead, was originally constructed to detect electrical changes from the right ventricular outflow tract and basal inter-ventricular ischemia (1-4). The aVR lead provides electrical information about the left ventricular basal septum as well as global ischemia. Many studies have shown that ST-segment elevation (ST-E) in the aVR lead is an important predictor of acute severe stenosis or obstruction of the left main (LM) or proximal left anterior descending (LAD) coronary artery. Due to the limited specificity of electrocardiographic (ECG) ST- segment changes in general, ST-E in the aVR lead during exercise tests was ignored for a long time by the practice guidelines (1, 5, 6). However, the latest recommendations on exercise testing again emphasize the importance of the aVR lead ST-E as a marker of significant inducible myocardial ischemia (7). The stress echocardiography (SE) testing that reveals regional wall motion abnormalities (WMA) is spe-

cific for coronary artery disease (CAD). The significance of ST-E in the aVR lead combined with wall motion abnormalities (WMA) during exercise treadmill SE in the prediction of significant LM or LM equivalent stenosis has not been fully evaluated. We hypothesized that exercise-induced aVR lead ST-E, combined with other functional parameters obtained during exercise, and imaging by SE, would improve the predictive value of aVR lead ST-E alone to detect significant and life-threatening LM stenosis.

The aim of our study was to evaluate the role of exercise-induced aVR lead ST-E as a predictor of significant LM or LM equivalent, or ostial LAD stenosis (LM+) in patients referred to exercise SE testing, in combination with other functional and imaging parameters obtained during SE.

Materials and Methods

This was a retrospective study including all the patients undergoing exercise SE at the Stress Echo Lab at the Clinical Center of Serbia, from 2012-2017. Out of 14,529 patients in whom SE was performed, 548 patients were included in the further analysis, who had both ECG signs and echo WMA suggestive of myocardial ischemia, and in whom diagnostic coronary angiography was also performed. Patients with non-interpretable ECG, such as those with pacemaker rhythm, left bundle branch block, baseline ECG ST-segment abnormalities, and patients with coronary artery bypass grafts (CABG) were not included in the analysis.

All patients underwent exercise tests on a Quinton 5500 treadmill (Quinton Cardiology, Inc. Bothell WA, USA), with standard Bruce protocol and continuous 12-lead ECG monitoring. The endpoints were: target heart rate (85% of maximum heart rate for age), severe chest pain requiring termination of exercise, and/or ST segment changes (ST-E of 1mm or more in any lead, without q wave, or ST-segment depression of at least 1 mm in at least two contiguous leads in three consecutive beats). We calculated the Duke treadmill score as an index combining treadmill exercise time using the standard Bruce protocol, maximum ST-segment deviation and exercise-induced angina, and presented metabolic equivalent (MET), describing the functional capacity or exercise tolerance of the patients during exercise testing. All patients provided informed consent for performing SE. Two-dimensional echocardiography monitoring was performed at baseline and immediately after treadmill exercise (peak stress), on a Vivid E9 ultrasound machine (General Electric Healthcare, Wauwatosa, USA). Regional wall-motion analysis was evaluated at baseline and at peak stress, with side by side analysis and semi-quantitative assessment of the Wall-Motion Score Index (WMSI). According to the Recommendations of the American Society of Echocardiography, a 17-segment model of the left ventricle (LV) was used (8-11). The WMSI was derived by dividing the sum of individual segment scores (ranging from 1-normal to 4 dyskinetic) by the number of interpretable segments. Left anterior descending artery (LAD) positivity was defined as the occurrence of new or the worsening of pre-existing WMA in at least 3 adjacent segments in the LAD-vessel territory. Two experienced observers independently reviewed the echo images, with inter-observer concordance of 95% (K=0.948). The extension and severity of induced ischemia was expressed as Delta WMSI (a difference between the resting WMSI and peak WMSI).

All 548 patients were referred for coronary angiography. Significant coronary artery stenosis was defined as ≥70% narrowing of the diameter stenosis of the coronary artery. As the left main equivalent disease, we considered significant ≥50% narrowing of the diameter stenosis of the ostial/proximal LAD artery and the ostial/proximal circumflex artery.

Statistical Analysis

Data were analyzed by descriptive and analytical statistics using SPSS statistical software (IBM SPSS statistics, Version 21.0, SPSS Inc. Chicago, IL), and expressed as mean ± standard deviation for normally distributed data, or as frequency and percentages for categorical data. The student's t-test and chi-square test were used to compare data

between the patients with and without significant LM stenosis (LM+). The Spearman correlation was applied to investigate the relationship between the SE parameters and aVR ST-E with LM stenosis. Calculations (classic reliability calculations) of sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were performed according to the standard definitions. Moreover we determined the positive likelihood ratio (LR+). ROC analyses and logistic regression analysis (uni and multivariate) were used to assess predictors of significant LM stenosis. A P value <0.05 was considered statistically significant.

Results

The study included 548 patients (mean age 61±9 years, 389 males and 159 females). aVR lead ST-E was present in 60/548 (11%) patients, whereas significant LM stenosis by angiography was found in 57 patients (10%). Both aVR ST-E and LM+ were present in 23 patients (Sn 40%, Sp 92%, PPV 38%, and NPV 93%). There was no significant difference between patients with or without aVR ST-E, except for body mass index that was higher in patients with aVR ST-E, and previous myocardial infarction, that was more prevalent in patients without aVR ST-E (Table 1).

Patients with aVR ST-E and LM had significantly worse functional and imaging parameters during stress echo, including worse Duke score and functional capacity as expressed in METs, as well as more severe echocardiographic signs for myocardial ischemia, particularly in LAD territory. Hemodynamic compromise and angina were more prevalent in patients with LM, but they did not reach statistical significance. Interestingly, the concomitant ST depression in contralateral leads was similar in patients with and without LM disease (Table 2). The coronary angiography findings in patients with and without aVR ST-E during SE testing are presented in Table 3. The aVR ST-E was significantly associated with stenosis in LM, with borderline significance for the proximal part of LAD (Table 3).

Out of general patients' data BMI was positively correlated with AVR STE findings (P=0.025)

Table 1. Baseline Clinical Parameters of Patients in Relation to aVR Lead ST-E during Exercise Testing

Variables	aVR ST-E +; (N=60)	aVR ST-E -; (N=488)	P*
Age (mean, yrs)	60.3±7.6	61.6±8.9	0.243
Sex male, N (%)	43 (72)	343 (70)	0.898
BMI (Mean ±SD)	29.6±3	26.7±3.8	0.039
Family history, N (%)	28 (46.7)	239 (48.9)	0.703
Smokers, N (%)	10 (16)	108 (22)	0.317
Diabetes mellitus type 2, N (%)	17 (28.3)	139 (28.4)	0.958
Diabetes mellitus insulin-dependent, N (%)	19 (31.6)	105 (21.5)	0.081
Hypertension, N (%)	50 (83.3)	399 (81.2)	0.813
Hyperlipidemia, N (%)	46 (76.7)	343 (70.2)	0.372
Previous myocardial infarction, N (%)	12 (20)	168 (34.4)	0.024
Beta-blockers, N (%)	48 (80)	364 (74.6)	0.627
ACE inhibitors, N (%)	40 (66.7)	308 (63)	0.880
Nitrates, N (%)	20 (33.3)	191 (39.1)	0.262
Aspirin, N (%)	45 (75)	372 (76.20	0.403
Clopidogrel, N (%)	11 (18.30)	136 (27.9)	0.080
Statins, N (%)	37 (61.7)	297 (60.9)	0.763

*Student's t-test and Chi-square test; BMI=Body mass index; ST-E=ST-segment elevation; aVR=Augmented unipolar right arm.

Table 2. SE Data in Patients with aVR ST-E in Relation to the Presence of Significant LM stenosis (LM+)

Variables	aVR ST-E+ and LM+; (N=23)	aVR ST-E+ and LM-; (N=37)	P*
Blood pressure drop, N (%)	6 (26)	4 (10.8)	0.123
Test angina, N (%)	10 (43.5)	11 (29.7)	0.278
Target SMF, N (%)	9 (39)	19 (51.3)	0.356
HRR, N (%)	15 (65)	28 (75.7)	0.290
ST-D D2, D3, Avf, N (%)	22 (95.7)	33 (89)	0.379
ST-D in V3/V4-V6, N (%)	20 (87)	30 (81)	0.553
ST-D diffuse, N (%)	20 (87)	27 (73)	0.201
MET (Mean ±SD)	4.95±2.2	6.7±2.3	0.005
Duke score (Mean ±SD)	-6.8±6.8	-3.6±4.1	0.049
Delta WMSI (Mean ±SD)	0.51±0.24	0.39±0.24	0.046
LAD positivity, N (%)	20 (87)	22 (59.5)	0.024

*Student's t-test and Chi-square test; LM=Left main coronary artery; ST-D=ST-segment depression; ST-E=ST-segment elevation; LAD=Left anterior descending coronary artery; WMSI=Wall motion score index; aVR=Augmented unipolar right arm; MET=Metabolic equivalent; HRR=Heart rate recovery: ST-D diffuse=ST segment depression in D2, D3, aVF, V3/4-6 segments.

Table 3. Coronary Angiography Findings in Patients with and without aVR ST-E during SE Testing

Variables	aVR ST-E + (N=60)	aVR ST-E - (N=488)	P*
LM+ group N (%)	23 (38.3)	34 (6.96)	<0.001
LM – group			
One-vessel CAD N (%)	10 (16.7)	157 (32.2)	0.411
LAD, N (%)	7 (70)	61 (38.9)	0.052
LCx, N (%)	1 (10)	20 (12.7)	0.800
RCA, N (%)	2 (20)	76 (48.4)	0.081
Two-vessel CAD, N (%)	13 (21.7)	129 (26.4)	0.481
LAD, N (%)	7 (53.8)	92 (71.3)	0.061
Three-vessel CAD, N (%)	6 (10)	77 (15.8)	0.960
None, N (%)	8 (13.3)	85 (17.4)	0.943

*Chi-square test; CAD=Coronary artery disease; RCA=Right coronary artery: LCx=Left circumflex coronary artery; LAD=left anterior descending coronary artery; LM=Left main coronary artery; ST-E=ST-segment elevation; aVR=Augmented unipolar right arm.

as well as the findings of combined AVR STE and stenosis (P=0.019). Among the investigated cardiological parameters, only ST depression in leads V3 to V6 and V4 to V6 did not correlate with the findings of both stenosis (P=0.657) and AVR STE (P=0.205). Moreover, LAD positivity (P=0.291) and ST depression (P=0.137) were not significantly associated with AVR STE. After confirming the associations of the investigated parameters, we performed regression analysis.

In logistic regression, a significant equation (model) was obtained for prediction of significant LM stenosis (χ^2=79.038; P=0.001; B=2.103; Wald=208.840; Exp(B)=0.122; R^2 Nagelkerke=0.601; total classification %=90.8). Findings of univariate analysis were used to selected parameters to be tested in multivariate analysis. Significant predictors by multivariate analysis were aVR ST-E and LAD positivity in the whole group of patients. We also constructed an equation for prediction of significant LM stenosis in the group of patients with aVR ST-E (χ^2=76.055; P=0.001; B=3.051; Wald=195.537; Exp(B)=0.047; R^2 Nagelkerke=0.670; total classification %=96.5). Interestingly, in patients with aVR ST-E, the magnitude of ischemia presenting as Delta WMSI, together with the Duke score and MET categories (good >5, and poor <5) were predictors of significant LM stenosis (Table 4).

Table 4: Regression Analyses for Prediction of Significant LM Stenosis

Variables	OR	95% for CI	P	OR	95% for CI	P
	Univariate analysis			Multivariate analysis		
Whole sample						
Patients' sex	0.542	0.837-4.065	0.188	-	-	-
Patients' age	0.036	0.009-1.077	0.079	-	-	-
BMI	0.034	0.003-1.159	0.494	-	-	-
aVR ST-E	1.554	1.536-11.225	0.001	0.255	0.160-0.350	0.001
LAD positivity	1.333	1.030-4.231	0.001	0.054	0.001-0.106	0.045
Delta WMSI	1.240	0.485-29.765	0.242	-	-	-
ST-D diffuse	0.570	1.225-7.872	0.438	-	-	-
MET score	0.247	0.778-1.138	0.521	-	-	-
Duke score	-0.065	0.855-1.023	0.124	-	-	-
Constant	26.106	-	0.997	-	-	-
aVR ST-E						
Patients' sex	0.307	0.214-4.347	0.634	-	-	-
Patients' age	0.009	0.004-1.149	0.797	-	-	-
BMI	0.048	0.011-1.232	0.540	-	-	-
LAD positivity	0.195	0.251-4.637	0.754	-	-	-
Delta WMSI	5.303	0.367-97.527	0.001	0.420	0.228-0.612	0.001
ST-D diffuse	0.725	0.549-14.824	0.507	-	-	-
MET score	1.399	0.501-1.142	0.027	-	-	-
Duke score	0.174	0.834-1.127	0.014	-0.011	-0.0018-0.004	0.002
Constant	24.422	-	0.997	-	-	-

LM=Left Main; ST-E=ST-Segment elevation; ST-D=ST-Segment depression; ST-D Diffuse=ST segment depression in leads D2, D3, aVF, V3/4-6 segments; LAD=Left anterior descending coronary artery; LM=Left main stenosis; BMI=Body mass index; WMSI=Wall motion score index; MET=Metabolic equivalent; OR=Odds ratio.

A receiver operating characteristic curve (ROC) analysis (Table 5) identified cut-off values for Delta WMSI, MET and Duke score. Finally, when aVR ST-E was combined with other functional and imaging parameters, the predictive value for detection of significant LM stenosis increased significantly (Table 6). In particular, when aVR ST-E was combined with LAD positivity and low MET achieved during SE, its sensitivity to detect significant LM stenosis increased from 40% to 88%.

Table 5. ROC Analysis of Functional and Imaging Parameters in Prediction of Significant LM Stenosis

Variables		AUC (%)	P	Cut-off value	Sensitivity (%)	Specificity (%)	LR+
aVR ST-E +	Delta WMSI	87.5	0.001	0.31	81.8	76.1	3.42
	MET score	25.4	0.001	5.5	73.9	67.6	2.28
	Duke score	18.7	0.001	-4.750	60.9	62.2	1.61

LM=Left Main; WMSI=Wall motion score index; MET=Metabolic equivalent; ST-E=ST-Segment elevation; aVR=Augmented unipolar right arm; AUC=Area under the curve; LR+=Positive likelihood ratio.

Table 6. Reliability of Prediction of Significant LM Stenosis

Variables		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
Whole sample	aVR ST-E only	40.35	92.46	38.33	93.03	5.35
aVR ST-E +	MET categories	73.91	67.57	58.62	80.65	2.28
	LAD positivity	73.91	45.95	45.95	73.91	1.37
	ST-D diffuse + LAD positivity	70.01	44.44	48.28	66.67	1.26
	ST-D diffuse + MET cat	70.01	66.67	60.87	75.00	2.10
	ST-D diffuse + LAD positivity + MET cat	87.57	60.01	64.71	75.00	2.19

ST-D diffuse=ST segment depression in leads D2, D3, aVF, V3/4-6 segments; LAD=Left anterior descending coronary artery; MET cat=MET score<5; PPV=Positive predictive value; NPV=Negative predictive value; LR+=Positive likelihood ratio.

Discussion

Our results show that aVR ST-E during SE testing exercise has intermediate sensitivity for detection of significant LM stenosis in patients with chest pain who are referred for exercise stress testing. However, when combined with other functional and imaging parameters, including functional capacity in METs, Duke treadmill score, and particularly severe myocardial ischemia in the territory of LAD, as documented by SE, its diagnostic power significantly improves. In addition, aVR ST-E, if not predictive of significant LM stenosis, is associated in the majority of cases with proximal LAD/Cx stenosis and/or multivessel coronary artery disease.

ST-E in the aVR lead is not such a rare finding during treadmill stress testing, with incidence ranging from 10 to 25% (7), which corresponds to 11% of our patients with both ECG and echo markers of myocardial ischemia. ST-E in the aVR lead is thought to result from two possible mechanisms: diffuse sub-endocardial ischemia with ST-D in the lateral leads, producing reciprocal change in the aVR which could explain the extensive ischemia on ECG, or ischemia of the basal septum (12-14).

Nevertheless, the usefulness of aVR in detection of severe LM stenosis is still debatable in the published literature. In our group of patients, 38% of our patients with aVR ST-E during stress echo testing and a positive echo for myocardial ischemia, had angiographically proven significant LM/LM equivalent, or ostial LAD stenosis on coronary angiography. Thus, the presence of exercise-induced aVR ST-E did not always indicate the presence of significant LM stenosis, but also proximal LAD or Cx lesions, or multi-vessel disease, as demonstrated by our study. In comparison to earlier data (1, 15), the sensitivity of aVR ST-E to detect LM in our study was lower than in previous literature, demonstrating high sensitivity, of more than 80%, but low specificity. However, the results of previous studies may be compromised by the methodology where exercise testing follows angiography, not as per routine and a rationale practice, with invasive evaluation of coronary artery disease indicated when the stress test is positive and suggestive of myocardial ischemia.

Previous data regarding the role of myocardial perfusion imaging (MPI) studies in addition to ECG (aVR lead ST-E), as markers of myocardial ischemia during exercise testing, failed to provide incremental information for detection of significant LM stenosis (5, 16). These investigators showed that in some patients aVR ST-E could detect LM or ostial LAD disease when SPECT was negative, although multivariate analysis showed that stress LVEF and the percentage of reversible LAD ischemia were significant predictors of LM/ostial LAD stenosis. In contrast, our study demonstrated that the amount and not only the site of myocardial ischemia, as detected by stress echocardiography, may suggest significant left main stenosis.

The role of ST-depression in prediction of LM stenosis other than aVR ST-E is not consistent in the literature. In a study of 200 patients undergoing ECG exercise testing (16), it was shown that patients would most likely have LM stenosis in the presence of ST depression in at least 5 leads on ECG, but not combined with aVR ST-E. It has been also shown that ST-E in V1 is more indicative of proximal LAD stenosis if accompanied by aVR lead ST-E (16, 17). In addition, in our study there was no specific and incremental role of ST-D accompanying ST-E to predict LM stenosis – the rate of concomitant ST depression was similar in patients with and without LM. Nevertheless, our study did show that aVR ST-E and inferolateral ST-D, present on ECG during SE, may indicate significant LM, especially if exercise is terminated with less than 5 METs achieved. However, even in the absence of imaging, poor functional parameters, including METs and particularly the Duke score during exercise, have an incremental role in detecting significant LM stenosis in the presence of aVR ST-E.

Limitations of the Study

This study only included patients with both positive ECG and echocardiographic signs of myocardial ischemia followed by angiography, so a number of patients with possible LM stenosis without both ECG and echo evidence of myocardial ischemia were not included. However, a larger group would further decrease the sensitivity and positive predictive value of aVR ST-E but not the other exercise functional parameters or imaging signs of myocardial ischemia. Also, during angiography we did not perform invasive evaluation of LM by fractional flow reserve to prove myocardial ischemia, as suggested by the guidelines (18). In the presence of documented ischemia by noninvasive testing, evaluation of LM by FFR is not recommended.

Conclusion

The aVR lead ST-E has intermediate sensitivity to detect LM stenosis, but can also disclose significant stenosis in a high proximal segment of LAD, or multivessel disease. However, when combined with functional parameters during exercise, including MET and Duke score, and particularly imaging parameters during SE testing, including the site and myocardial area at risk, its diagnostic power to detect significant LM coronary stenosis significantly improves, and may help to stratify patients for early coronary angiography and revascularization.

What Is Already Known on This Topic:

ST-segment elevation in the EKG lead aVR is an important predictor of acute obstruction of the left main coronary artery during acute coronary syndrome. To date, its use in predicting significant left main stenosis or the left main equivalent during the treadmill stress test is unclear in the literature. Despite its availability and simplicity for detecting inducible myocardial ischemia, the limited sensitivity and specificity of aVR lead ST-segment elevation suggest the need to combine ECG findings with imaging during the exercise test in order to improve it.

What This Study Adds:

Stress echocardiography testing showed potential to improve the diagnostic power of lead aVR in detection of significant LM stenosis. When we combined lead aVR ST-segment elevation with functional and imaging parameters, including poor exercise functional capacity in METs, lower Duke score or greater wall motion abnormalities in the territory of the left anterior descending artery, its diagnostic power to detect left main stenosis significantly increased.

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