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Case report

The diagnostic value of coronary flow reserve by transthoracic Doppler echocardiography in non-diagnostic or inconclusive stress echocardiography tests

Marija Kotevska, Srđan Dedić, Nikola Bosković, Vojislav Giga, Milorad Tešić, Srđan Aleksandrić, Milan Dobrić, Branko Beleslin, Ana Djordjevic Dikić

Cardiology Clinic, Clinical center of Serbia, Faculty of Medicine, University of Belgrade

Abstract

Background: An inconclusive or non-diagnostic stress echocardiography test (SET) implies a need for additional tests, which often results in unnecessary invasive examinations and higher health costs.
Aim: The aim of our study was to investigate the value of non-invasive transthoracic Doppler echocardiography (TTDE) derived coronary flow reserve (CFVR) in patients with non-diagnostic and inconclusive SET.
Methods: The study group consisted of 122 patients (73 male, 49 females: mean age 63±8 years) with non-diagnostic SET (target heart rate (HR) not reached, chest pain without electrocardiographic (ECG) and echocardiographic changes; and inconclusive SET (target HR reached, chest pain without ECG and echocardiographic changes). All patients were referred for TTDE assessment of CFVR in left anterior descending artery (LAD). CFVR was calculated as the ratio of maximal hyperemic and baseline coronary flow velocity. CFVR LAD ≤ 2 was considered abnormal. All patients were scheduled for invasive coronary angiography (CA).
Results: Mean CFVR LAD was 2.4±0.44. CFVR LAD was abnormal in 22 (18%) and preserved in 100 (82%) patients. Significant LAD stenosis was found in 15 (12.2%) out of 122 patients. Sensitivity of reduced CFVR LAD ≤ 2 was 88% for significant LAD stenosis, while preserved CFVR >2 had negative predictive value of 95%. Correlation analysis found significant correlation between invasive CA and CFVR LAD (r -0.356; p<0.0001).
Conclusions: Reduced CFVR LAD ≤ 2.0 has additive diagnostic value in detection of significant LAD stenosis in patients with non-diagnostic and inconclusive SET.

Key words coronary flow reserve, non-diagnostic stress ehocardiography test

Background

Stress echocardiography test (SET) is an established non-invasive method in clinical cardiology guidelines[1-5] that is routinely used for diagnosis, risk stratification and prognosis of patients with suspected or known coronary artery disease (CAD).
Diagnostic end-point for detection of myocardial ischemia during SET is an achievement of the target heart rate and/or electrocardiographic (ECG) changes and/or occurrence of the chest pain and/or echocardiographic regional wall motion abnormalities (RWMA)[2]. However, a number of patients have inconclusive or non-diagnostic results because they either do not reach target heart rate or fulfill ECG or echocardiographic diagnostic criteria for myocardial ischemia. An inconclusive or non-diagnostic exercise test results are in most cases followed by another provocation test in order to reach correct diagnosis[6].

Advancements in ultrasound technology have made noninvasive visualization of coronary arteries and assessment of coronary flow velocity reserve (CFVR) available technique in routine clinical practice[7,8]. Today, non-invasive assessment of CFVR during vasodilator SE has been endorsed by the European Society of Echocardiography for the diagnosis of microvascular angina[2], but there is a growing body of evidence that it could be used for detection of hemodynamically significant stenosis of the epicardial artery[9].
In our institution, non-invasive transthoracic Doppler echocardiography (TTDE) derived CFVR of left anterior desending (LAD) artery is often used as additional test following non-diagnostic or inconclusive SET, since it has been shown to have excellent diagnostic and prognostic value[10].
The aim of this prospective study was to investigate diagnostic value of TTDE CFVR in detecting significant stenosis in LAD in patients with known or suspected CAD and non-diagnostic and inconclusive SET results.

Methods

Study Population

Study population included 122 patients (73 male, 49 females: mean age 63±8 years) with suspected or known coronary artery disease prospectively enrolled from January 2016 to December 2017. All patients were referred for TTDE CFVR assessment of LAD after non-diagnostic or inconclusive SET. SET was considered **non-diagnostic** when target HR (85% the age-predicted maximum HR) was not reached, with chest pain without electrocardiographic (ECG) and/or echocardiographic changes, and **inconclusive** if the target HR was reached, with chest pain, without ECG and/or echocardiographic criteria for ischemia. Exclusion criteria were contraindications to stress testing (acute myocardial infarction, unstable angina, significant valvular heart disease, and primary hypertrophic or dilated cardiomyopathy) as well as contraindications to adenosine infusion, poor image quality of LAD, and refusal to participate in the study. All patients were scheduled for invasive coronary angiography. For the analysis, patients were divided into two groups: group 1: patients with reduced CFVR LAD (≤ 2) and group 2: patients with preserved CFVR LAD (>2). The study received institutional review board approval. Informed consent was obtained from all patients included in the study.

Stress echocardiography test

All patients performed symptom-limited treadmill exercise according to the standard Bruce protocol, with continuous ECG and blood pressure monitoring. Transthoracic stress echocardiographic studies were performed using commercially available ultrasound machine (Vivid System 9, GE) equipped with a multifrequency phased-array sector scan probe using second harmonic technology. Echocardiographic images were semiquantitatively assessed using a 17-segment, four-point scale model of the left ventricle at rest and immediately after exercise. Myocardial ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality[3,11].

TTDE evaluation of CFVR

TTDE CFVR measurements were performed using a commercially available ultrasound machine Vivid 9 (GE Healthcare) equipped with multifrequency transducer 4MHz using second harmonic technology. Coronary flow in the mid to distal LAD artery was searched in the low parasternal long axis section under the guidance of color Doppler flow mapping. Color Doppler flow mapping velocity range was set to 16 to 24 cm/sec. A sample volume (3–5 mm wide) was positioned on the color signal of the distal part of the LAD. Flow velocity recordings were performed at rest and maximal hyperemia, which was induced by administration of intravenous adenosine (140 mg/kg over 2 min) (2). All studies were digitally stored for offline analysis. CFVR was calculated as the ratio of hyperemic to basal peak diastolic coronary flow velocity. CFVR LAD ≤2 was considered abnormal.

Coronary angiography

Coronary angiography (CA) was performed in all patients using standard techniques. Significant LAD disease was defined by quantitatively coronary angiography as ≥50% diameter stenosis narrowing of coronary arteries in the view showing the most severe stenosis.

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation or as median (interquartile range) for data not normally distributed. Differences in quantitative variables were assessed with Student's t test. The chi square test was used for categorical variables. The differences of means of CFVR between 3 independent groups were analyzed using One way analysis of variance (ANOVA). We used Spearman´s correlation coefficient to measure the relationship between CFVR and percentage of LAD stenosis. Receiver operating characteristic (ROC) curve analysis was used to calculate sensitivity in detecting significant stenosis in the LAD and to determine the optimal cut-off value for CFVR, diagnostic for LAD disease. Negative predictive value and diagnostic accurancy were calculated according to standard formulas. Statistical significance was defined as $p < 0.05$. Data were analyzed with the statistical software package SPSS 25.

Results

Main clinical characteristics of the study population are presented in Table 1.

Table 1. Clinical characteristics of the study population

Variable	N / %
Gender (men/women)	73 (59.8%) / 49 (40.2%)
Age	62.5 ± 8.4
Non-diagnostic SET / Inconclusive SET	53 (43.4%) / 69 (56.6%)
CV risk factors	
HTA	106 (86.9%)
HLP	95 (77.9%)
Smoking	65 (63.3%)
Heredity	50 (41%)
Menopause	16 (13.1%)
DM type 2	30 (24.6%)
Angina pectoris	50 (41%)
LBBB	15 (12.3%)
AF	8 (6.6%)
Known CAD	75 (61,5%)
Prior MI	44 (36.1%)
Suspected CAD	47 (38.5%)
Anti-ischemic therapy	118 (96.7%)
Beta-blockers	101 (82.8%)
CCBs	36 (29.5%)
Nitrates	38 (31.1%)

SET, stress echocardiography test; CV, cardiovascular; HTA, arterial hypertension; HLP, hyperlipidemia; DM, diabetes melitus; LBBB, left bundle brunch block; AF, atrial fibrillation; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAB,= coronary artery bypass grafting; CCBs, calcium channel blockers

Table 2. Heart rate during stress echocardiography test and coronary flow velocity in patients with non-diagnostic and inconclusive stress echocardiography test

	Non-diagnostic SET (N=53)	Inconclusive SET (N=69)	P value
HR basal (beats/min)	64 ± 8.5	72 ± 11.7	**0.001**
HR maximal (beats/min)	118 ± 11	143 ±10	**0.001**
V max basal (cm/sec)	24.2 ± 9	24.3 ± 6	0.980
V max Adenozin (cm/sec)	57.3 ± 15	57.4 ± 16	0.976
CFVR LAD	2.4 ± 0.4	2.3 ± 0,4	0.421

SET, stress echocardiography test; HR, heart rate; CFVR LAD, coronary flow reserve of left anterior descending artery; V max, maximal velocity of coronary flow

Most of the patients were hypertensive and with hyperlipidemia, and 83% were on a chronic therapy with beta-blockers. Out of 122 patients, 75 had known CAD (previous myocardial infarction, and/or previous percutaneous coronary intervention or previous coronary artery bypass grafting), while 47 patients had suspected CAD.

Stress echocardiography test and CFVR LAD assessment

SET was non-diagnostic in 53 patients (43.4%), and inconclusive in 69 (56.6%). Table 2 presents heart rate during SET and coronary flow recordings.

Average basal and maximal HR during SE test were significantly higher in patients with inconclusive results compared with patients with non-diagnostic results. Values of coronary flow did not differ between the two groups (Table 2). No complication occurred during both tests. Measured values of CFVR LAD were in the range 1.5–4.0 (2.4 ±0.44).

Coronary angiography and CFVR findings

Angiographic findings of LAD are presented in Table 3. Distribution of angiographic severity of coronary stenosis is presented in Table 3.

Table 3. Angiographic findings on LAD

LAD stenosis severity	
• LAD stenosis **0-50%**	91 (75%)
• LAD stenosis **50-70%**	16 (13%)
• LAD stenosis **≥70%**	15 (12%)

CAD, coronary artery disease; LAD, left anterior descending artery

CFVR LAD was reduced (≤ 2) in 22 (18%), and preserved in 100 (82%) patients. All patients (n=16) with angiographically intermediate LAD stenosis had preserved CVR.

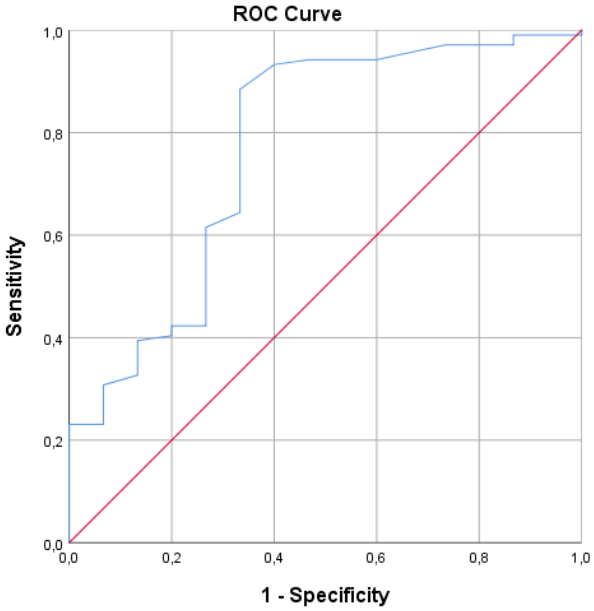

Figure 1. Sensitivity and specificity of CFVR LAD in detection of significant LAD stenosis CFVR LAD, coronary flow reserve of left anterior descending artery

In the subset of patients with LAD disease, CFVR was significantly lower in patients with stenosis ≥70% compared with those with intermediate (p =0.002) and non-significant LAD stenosis (p =0.002) (Table 4). The values of CFVR LAD were significantly lower in patients with intermediate compared with patients with non-significant stenosis. (2.38±0.35 vs 2.45±0.44; p=0.001)

According to receiver operating characteristic (ROC) analysis, a cut-off of CFVR LAD ≤ 2.02 has the best sensitivity of 88% and limited specificity of 36% in detection of significant epicardial coronary stenosis of LAD (Area 0.771 (95% CI 0.62 to 0.91) p=0.001) (Figure 1). Negative predictive value was very high (95%). Diagnostic accuracy was 85%.

Table 4. Relation of stenosis severity and CFVR

	CVFR LAD							
	N	Mean	Std. Dev.	95% CI Mean LowerBound	UpperBound	Minimum	Maximum	P value
0-50%	88	2.45	0.44	2.36	2.54	1.52	4.00	**0.001**
50-70%	16	2.38	0.35	2.19	2.57	2.05	3.00	**0.002**
≥70%	15	2.01	0.36	1.81	2.22	1.60	2.68	**0.002**

CFVR LAD= coronary flow reserve of left anterior descending artery

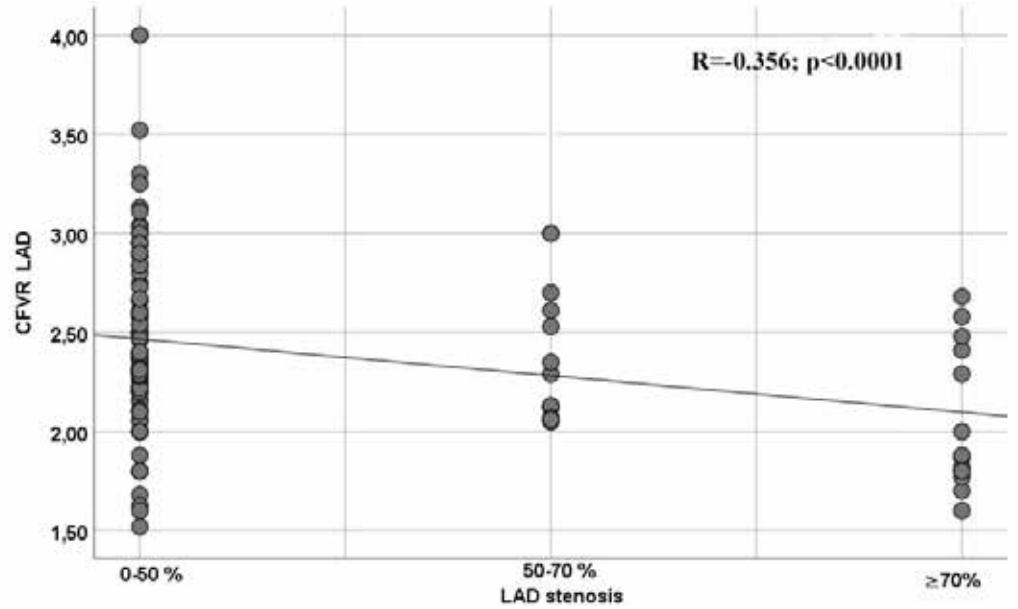

Figure 2. Correlation between invasive coronarography and TTDE CFVR LAD;

TTDE, transthoracic Doppler echocardiography; CFVR LAD, coronary flow reserve of left anterior descending artery

Correlation analysis found statistically significant correlation but with large overlap between invasive coronary angiography defined severity of stenosis and TTDE CFVR LAD (r = - 0.356; p<0.0001) shown in Figure 2.

Discussion

According to our results, reduced CFVR LAD ≤ 2 identifies patients with significant stenosis in the LAD with high sensitivity (88%) and diagnostic accuracy of 85%, while preserved CFVR >2 has high negative predictive value (95%). Moreover, we have shown that noninvasive CFVR could be used as additional test to non-diagnostic and inconclusive SET.

CFVR is an important functional parameter in pathophysiology of coronary circulation. It can be used to examine the integrity of microvascular circulation as suggested in a recent guidelines for chronic coronary syndromes[1] and to evaluate coronary stenosis[7,11]. Reduced CFVR ≤2[7,12] is not specific for epicardial coronary stenosis, because coronary flow and reserve depend on microvascular function and integrity[13]. However, in case of normal microvasculature it may indicate physiologically significant epicardial coronary stenosis[7].

A number of patients undergoing treadmill exercise stress test have non-diagnostic or inconclusive test from various reasons: low exercise capacity, beta-blocker therapy[14], atypical chest pain or failure to achieve target HR[2,5]. Failure to reach target HR is present in 15–25% of SET, and even higher among those on chronic beta-blocker therapy 30-50%[14]. In our study beta-blocker therapy was present in 83% of the patients and almost half of them, 47 (46.5 %) did not reach the target HR. Also, SET are often inconclusive in patients with left bundle brunch block (LBBB)[15], and atrial fibrillation (AF)[16].

Moreover, combine evaluation of RWMA and Doppler derived CFVR of LAD during vasodilatory SET known as „dual" imaging protocol is recommended by European guidelines for cardiovascular imaging[2]. Our results confirm usefulness of this approach in non-diagnostic/inconclusive tests.

Comparison with previous studies

Results of our study are in concordance with previous data in patients with suspected or known coronary artery disease. Matsumura et al.[11] reported similar results to our group for CFVR LAD ≤ 2 in detection of significant LAD stenosis, with sensitivity of 90%, specificity of 93%, a positive predictive value of 77%, and a negative predictive value of 97%[11]. Rigo et al.[10] reported sensitivity of stress echocardiography in detection of LAD stenosis to be 74%, while sensitivity of CFVR LAD <1.9 was 81%. When both criteria are considered, the sensitivity improves to 93%, with modest lost in specificity of 81%. When CFVR of LAD was added to wall motion abnormality analysis, the diagnostic accuracy for the detection of coronary artery disease has increased from 75% to 85%[20]. Overall, reduced CFVR LAD ≤ 2 have shown sensitivity from 85-94 % and specificity from 57-92%[20-22] in detection of significant LAD stenosis. Important findings refer also to preserved CFVR LAD > 2 that have very high negative predictive value 94-97%, allowing safe deferral from invasive procedures[11,22-24].

In our study CFVR LAD had high sensitivity (88%) in detection of significant coronary stenosis of LAD, and high negative predictive value (94%).

Study limitations

Almost all patients (96%) were studied under anti-ischemic therapy, mostly beta-blocker therapy, which may affect performance of stress test and may be responsible for non-diagnostic tests.

We only assessed CFVR in the LAD - from a practical viewpoint it is less technically demanding, and has higher feasibility than assessment of RCA or Cx. Thus, any significant coronary lesions in RCA and/or Cx myocar-

dial territories were not included in the analysis, but "dual" nature of combined CFVR and stress echocardiography imaging may compensate for absence of RCA and/or Cx coronary flow imaging. In addition and from prognostic viewpoint, LAD is stronger predictor of adverse cardiovascular events than RCA or Cx[21].

Clinical implications

Our results support aassessment of CFVR LAD into clinical non-invasive decision making before further invasive diagnostic in patients with non-diagnostic and inconclusive SET. Patients with reduced CFVR on LAD (or RCA), or both, despite absence of RWMA should be referred to invasive angiography[23]. On the other hand, preserved CFVR LAD > 2 have high negative predictive value in detection of significant coronary stenosis of LAD as previously demonstrated in many studies[11,22-24] Due to the excellent negative predictive value of preserved CFVR[23,24], unnecessary further invasive treatment and investigation may be avoided and save health care costs.

Conclusion

Our results have shown that TTDE assessment of CFVR in LAD could be used as additional test in detection of hemodynamic significant stenosis of LAD in patients with non-diagnostic and inconclusive SET. High negative predictive value of TTDE derived CFVR allows safely deferral from invasive diagnostic procedures.

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Sažetak

Diagnostički značaj neinvazivne procene koronarne rezerve protoka transtorakalnom dopler ehokardiografijom kod nedijagnostičkih i inkonkluzivnih stres ehokardiografskih testova

Marija Kotevska, Srđan Dedić, Nikola Bosković, Vojislav Giga, Milorad Tešić, Srđan Aleksandrić, Milan Dobrić, Branko Beleslin, Ana Djordjevic Dikić

Klinika za kardiologiju, Klinički Centar Srbije, Medicinski Fakultet u Beogradu

Uvod: *Nedijagnostički ili inkonkluzivni stres ehokardiografski test (SET) često vodi ka dopunskim ispitivanjima, što rezultuje nepotrebnim invazivnim procedurama i povećanom zdravstvenom trošku.*
Cilj *rada je bio da se utvrdi dijagnostički značaj koronarne rezerve protoka (CFVR) merene putem transtorakalne Dopler ehokardiografije (TTDE) kao dopunske metode, kod nedijagnostičkih i inkonkluzivnih SET.*
Metode*: Studija je obuhvatila 122 pacijenata (73 muškarca, 49 ženae: srednje godine 63±8 godina) sa nedijagnostičkim SET (ciljana srčana frekvenca (SF) nije dostignuta; anginozni bol bez elektrokardiografskih (EKG) i ehokardiografskih promena) i inkonkluzivnim SET (ciljana SF dostignuta, sa anginoznim bolom, bez EKG i ehokardiografskih promena). Svim pacijentima je procenjena CFVR na prednjoj descendetnoj arteriji (LAD) TTDE sa adenozinom. CFVR je bila izračunata kao odnos između maksimalne brzine koronarnog protoka u hiperemiji i maksimalne brzine koronarnog protoka u bazalnim uslovima. CFVR ≤2 je posmatrana kao redukovana vrednost. Kod svih pacijenata je urađena koronarna angiografija..*
Rezultati: *Prosečna vrednost CFVR LAD je bila 2.4 ±0.44. CFVR LAD je bila redukovana kod 22 (18%) i normalna kod 100 (82%) pacijenta. Invazivna koronarografija je detektovala značajne stenoze LAD kod 15 (12.2%) od ukupno 122 pacijenta. Redukovana CFVR LAD ≤ 2.0 je imala senzitivnosti 88%, dok je normalna CFVR LAD imala negativnu prediktivnu vrednost od 95%. Korelaciona analiza je ukazala na značajnu povezanost između nalaza koronarografije i CFVR LAD (r = -0.356; p<0.0001).*
Zaključak: *Redukovana CFVR LAD ≤ 2.0 ima dodatni dijagnostički značaj kod nedijagnostičkih i inkonkluzivnih SET u otkrivanju značajnih stenoza na LAD.*

Ključne reči: *koronarna rezerva protoka, nedijagnostički stres ehokardiografski test*