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THE ROLE OF CORONARY ARTERY PLAQUE IN PREDICTION OF CORONARY ARTERY DISEASE USING PHARMACOLOGICAL-STRESS ECHOCARDIOGRAPHY

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Abstract

It was confirmed that coronary artery plaque [CAP] and its larger burden may influence myocardial perfusion independent of presence of significant coronary artery stenosis.

The aim of our study was to examine the role of CAP as predictor of coronary artery disease [CAD] presence using pharmacological stress echocardiography [SE].

We prospectively assessed 61 consecutive patients with symptoms implying CAD who underwent dipyridamole or dobutamine SE and coronary angiography. Conventional 2D echocardiographic wall motion score index [WMSI] as well as global LV longitudinal strain using speckle tracking [GLS%] were measured at rest and peak stress.

Out of 61 patients, 25/41.0% had normal coronary arteries, 18/29.5% had obstructive CAD and 18/29.5% had nonobstructive CAD with CAP. In patients with CAP, GLS% at maximal SE showed worsening in comparison to those with and without CAD who showed insignificant lower GLS% or better function after SE [p=0.057]. Presence of CAP [OR=8.358; 95%CI 1.929-36.216;p=0.005] and worsening of WMSI at maximal SE [OR=190.5; 95%CI 2.517-14426.687;p=0.017] appeared as independent predictors of CAD presence, while worse values of GLS% at maximal SE [OR=1.155; 95%CI 0.999-1.334;p=0.051] as well change [increase] of the number of segments with LS< 12% at maximal SE [OR=0.755; 95%CI 0.602-0.946;p=0.015] appeared as independent predictors of CAP presence.

Coronary artery plaque presence appeared as independent predictor of CAD as well as worse values of GLS%

***Keywords*:** Coronary artery plaque, coronary artery disease, stress echocardiography, LV systolic longitudinal strain

Introduction

Patients with obstructive coronary artery disease [CAD] defined as ≥50% luminal stenosis have established diagnostic pathways, evidence-based treatment and well known prognosis. However, nowadays the main scientific interest is turned toward ischemia due to non-obstructive CAD on angiography and its multifactorial mechanism that may operate alone or in combination, given that risk analysis found that non-obstructive CAD conferred increased risk for unfavorable prognosis [1-3]. It was confirmed that coronary artery plaque [CAP] and its larger burden may influence myocardial perfusion independent of presence of significant coronary artery stenosis [2, 4-8]. Noninvasive assessment of effects of plaque burden may improve risk stratification enabling preventive therapy to be initiated earlier in more persons at risk. The purpose of our study was to examine the role of CAP as predictor of CAD presence using pharmacological stress echocardiography [SE].

Methods

Patients

We prospectively assessed 61 consecutive patients, who underwent dipyridamole or dobutamine stress echocardiography [SE] as well coronary angiography between January 2016 and May 2018 in a University Clinic of cardiology in Skopje. Before the study, patients' demographic characteristics were obtain along with history of CAD risk factors and/or presence of CAD disease. The inclusion criteria were as follows: chest pain or nonspecific symptoms, lack of ST-segment changes on ECG, negative troponins, LV ejection fraction ≥45% [LVEF] and wall motion score index up to a maximum of 1.2 at rest. The study excluded patients with: previous bypass surgery and/or significant valvular disease, increased troponin value during chest pain, markedly impaired cardiac rhythm and/or existence of conduction abnormalities, significant left ventricular hypertrophy, signs of heart failure and/or LVEF < 45%, uncontrolled arterial hypertension and associated illnesses that would affect the results and/or limit the duration of life [chronic obstructive pulmonary disease, renal

failure, neoplasms]. The study was approved by the Medical Ethics Committee of Medical School, University "St.Cyril&Methodius", Skopje, and all patients provided informed consent.

Stress echocardiography protocol

An accelerated high-dose dipyridamole protocol was used at a dose of 0.84 mg/kg body weight over 6 min. Aminophylline [up to 240 mg] was routinely administered to patients 5 min after the end of the test or immediately if there was obvious clinical and/or ECG signs of ischemia. A graded dobutamine infusion was administered intravenously beginning at a dose of 5μg/kg per minute and the dose was every 3 minutes to doses of 10, 20, 30, and 40 μg/kg per minute. Two-dimensional echocardiography and 12-lead electrocardiography [ECG] were used for continuous monitoring during the test and the recovery phase. Blood pressure measurements using a cuff were recorded every 3 minutes. Echocardiographic images were semi quantitatively assessed using a 17 segments, 4-point scale model of the left ventricle. Wall motion score index [WMSI] was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality [WMA], or biphasic response [i.e. low-dose improvement followed by high-dose deterioration]. A test was normal in case of no stress new or worsening WMA. A test was considered positive for ischemia when at least 2 adjacent segments of the same vascular territory showed an increment of WMSI [worsening or regional function] of at least 1 point at peak stress [9, 10,11,12].

Speckle Tracking Longitudinal Strain Analysis

Transthoracic echocardiography was performed using commercially available equipment [Vivid 7; GE, USA]. Global and regional peak systolic longitudinal strain was assessed from apical two-chamber, four-chamber, and long-axis views using speckle tracking analysis before and at the peak stress [13, 14]. The frame rate was set between 55 and 80 frames per second. Recordings were processed using acoustic-tracking software [Echo Pac; GE], allowing off-line semi-automated analysis of speckle-based strain. The LV was divided into 17 segments, and each segment was analyzed individually. Only myocardial segments considered to be of adequate quality by both the automatic system and the operator were included in the analysis. Global longitudinal strain [GLS%] for the LV was automatically provided as the average value of the regional peak systolic longitudinal strain of the three apical views by the software. Assessement and calculations of WMSI was done out of stress-echo protocol at rest and after stress. All measurements were made by a single experienced investigator.

Angiographic study

Within few days of the stress echocardiography tests coronary angiography was done. Angiographic assessments involved presence and quantification of coronary artery stenosis severity as well as calculation of Syntax score [15].

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as mean ±SD. Comparisons of prestress vs. post stress data were performed using a Wilcoxon Signed Rank test for related samples. Continuous variables were compared either using analysis of variance [ANOVA], and categorical parameters were compared using Pearson's chi square test. Assessment of correlations was done using Pearson's correlation analysis. Multivariant logistic regression analysis was performed in order to define the independent significant predictive variable of CAD presence. All data analysis was performed using SPSS version 25.0 [IBM SPSS, Inc., Chicago, Illinois] and p value ≤ 0.05 was considered significant.

Results

Of the 61 patients who underwent coronary angiography, presence of CAP was found in 33/54.1%. Patients had a mean age of 59±7.8 years, 32/52.5% were female with a range of cardiovascular risk factors [Table 1]. Of these patients, 25/41.0% had normal coronary arteries, 18/29.5% had obstructive CAD and 18/29.5% had nonobstructive CAD with CAP.

Table 1. Characteristics of study participants.

	All pts. [n=61]	**Without CAD [n=25]**	**With CAD [n=18]**	**With CAP [n=18]**	**p**
Age [years]	59.9±7.8	57.1±6.7	61.9±8.5	61.7±7.8	0.070
Female [n/%]	32/52.5	16/50	7/21.9	9/28.1	0.258
BMI [kg/m2]	28.8±4.2	27.4±4.2	29.5±4.1	29.9±4.1	0.070
Smoking [n/%]	22/36.1	11/50.0	5/22.7	6/22.3	0.527
Hypertension [n/%]	48/78.7	16/33.3	16/33.3	16/33.3	0.066
Diabetes [n/%]	29/47.5	8/27.6	13/44.8	8/27.6	0.105
Dyslipidemia [n/%]	47/77.0	18/38.3	16/34.0	13/27.7	0.368
Family history of CAD [n/%]	33/54.1	11/33.5	10/30.3	12/36.4	0.335
Typical angina [n/%]	13/21.3	2/15.4	4/30.8	7/53.8	0.051

BMI=body mass index; CAD=coronary artery disease; CAP=coronary artery plaque; pts= patients.
*p<0,05 for comparison among the groups

There was no difference in frequency of risk factors among study patients. However patients with CAD and CAP were with limited significance older and with higher body mass index. In addition, typical angina was significantly more present in patients with CAP.
Wall motion score index [WMSI] after SE increased with limited significance [p=0.075] in patients with CAD [Table 2], it was almost the same in patients without CAD while it insignificantly decreased in patients with CAP. Thus, the WMSI was significantly the highest [p=0.006] at maximal SE in patients with CAD in comparison to another two groups. However, comparison of WMSI change between patients didn't show any significant difference [p=0.418] among the three groups. In addition, the analysis of correlations showed that WMSI was significantly positively correlated with presence of CAD [r=0.328, p=0.010], value of Syntax score [r=0.269, p=0.036] and the number of coronary arteries with plaques [r=0.328, p=0.010, Figure 1].

Table 2. Changes of WMSI and LV strain pre- and post SE in patients divided according to the presence of CAD or CAP

	Without CAD [n=25]		**With CAD [n=18]**		**With CAP [n=18]**		**p**
	Rest	**Max. SE**	**Rest**	**Max. SE**	**Rest**	**Max. SE**	
WMSI	1.08±0.10	1.08±0.11	1.12±0.10	1.22±0.21	1.13±0.18	1.08±0.10	**0.006**
ΔWMSI	0.00±1.27		-0.09±0.21		0.05±0.17		0.418
p	0.860		0.075		0.384		
GLS%	-16.3±3.3	-16.8±3.9	-14.1±2.7	-14.2±3.7	-16.0±2.6	-15.6±3.9	**0.076**
ΔGLS%	0.50±2.79		0.00±3.02		-0.36±1.91		**0.057**
p	0.361		0.679		0.528		
No.seg. LS<12%	4.5±2.4	3.8±2.7	5.2±2.6	5.8±4.1	4.0±2.8	4.8±3.1	0.144
ΔLS<12%	0.72±2.54		-0.66±3.42		-0.77±2.10		0.418
p	0.138		0.583		0.120		

CAD= coronary artery disease; GLS=global longitudinal strain; LS=longitudinal strain; SE=stress echocardiography; WMSI= wall motion score index.
*p<0,05 for comparison pre- and post SE.

As for global LV systolic longitudinal strain [GLS%] at maximal SE, it showed the worst value [less negative] in patients with CAD, but also worse value in patients with CAP in comparison to those without CAD who had less deformation with limited significance [p=0.076], but steel less than reference normal limits. However, the most interesting thing that emerged was that in patients with CAP worsening of GLS% was detected at maximal SE in comparison to those with and without CAD who showed insignificant lesser GLS% or better function after SE [more negative] [p=0.057] [Table 2], but the change from the rest to maximal SE was steel insignificant for each group.

Regarding the number of segments with longitudinal strain [LS] of <12%, the results showed that patients with CAD and CAP showed insignificant increase in the number of segments while those without CAD showed decrease at maximal SE [Table 2]. In addition, the analysis of correlations showed that GLS% was significantly positively correlated with presence and extent of CAD [r=0.262, p=0.042; r=0.287, p=0.029; respectively] as well as with the value of Syntax score [r=0.306;p=0.016] along with the presence of CAP and the number of coronary arteries with plaques which were also significantly negatively correlated with the GLS% [r=-0.257, p=0.046;r=-0.296, p=0.021; respectively] [Figure 1].

The number of segments with LS< 12% was significantly correlated with the extent of CAD [r=0.273, p=0.033], the value of Syntax score [r=0.253;p=0.049] as well as with the number of coronary arteries with plaques [r=0.326;p=0.010]. In addition change of GLS% with SE was significantly correlated with the number of coronary arteries with plaques [r=-0.251;p=0.051] whilst change of the number of segments with LS< 12% was significantly negatively correlated with presence of CAP and the number of of coronary arteries with plaques [r=-0.331, p=0.009;r=-0.353, p=0.005; respectively].

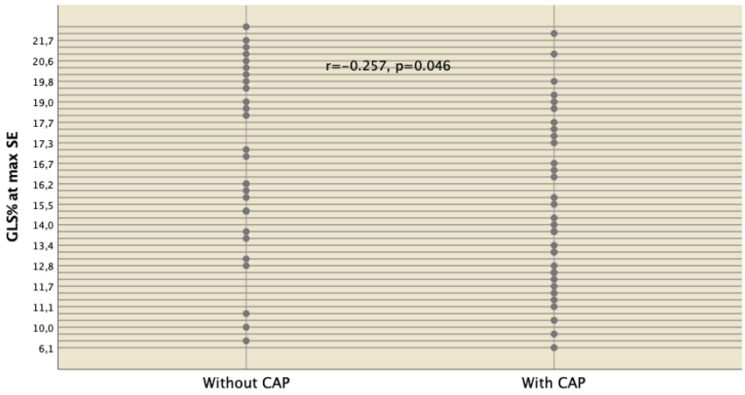

Figure 1. Correlation between the presence of CAP and GLS% at maximal SE.

Predictive factors of CAD presence

In order to determine the independent predictors of CAD presence among patients who were pharmacologically stressed, we performed multiple stepwise logistic regression analysis [Table 3] with echocardiographic covariates that showed significant relation to it. The results that were adjusted for age and gender, demonstrated that presence of CAP [OR=8.358; 95%CI 1.929-36.216;p=0.005] and worsening of WMSI at maximal SE [OR=190.5; 95%CI 2.517-14426.687;p=0.017] appeared as independent predictors of CAD presence.

Table 3. Stepwise logistic regression analysis of significant independent predictors of CAD presence.

								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	CAP	2,181	,703	9,615	1	,002	8,854	2,231	35,141
	Constant	-2,120)	,611	12,042	1	,001	,120		
Step 2[b]	CAP	2,123	,748	8,055	1	,005	8,358	1,929	36,216
	WMSI	5,250	2,208	5,656	1	,017	190,567	2,517	14426,687
	Constant	-8,064)	2,671	9,118	1	,003	,000		

a. Variable(s) entered on step 1: CAP.

b. Variable(s) entered on step 2: WMSI.

In addition we prepared multiple stepwise logistic regression analysis to determine the independent predictors of CAP presence [Table 4] with identical covariates as for CAD. The results demonstrated that increase [more positive] value of GLS% at maximal SE [OR=1.155; 95%CI 0.999-1.334;p=0.051] appeared as independent predictor of CAP presence whereas when we put into regression analysis also the difference between rest and maximal SE of GLS% and number of segments with LS< 12%, than the results demonstrated that change [increase] of the number of segments with LS< 12% at maximal SE [OR=0.755; 95%CI 0.602-0.946;p=0.015] appeared as independent predictor of CAP presence.

Table 4. Stepwise logistic regression analysis of significant independent predictors of CAP presence.

								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	GLS% at max SE	,144	,074	3,809	1	,051	1,155	,999	1,334
	Constant	2,440	1,203	4,110	1	,043	11,468		
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Delta-NbLS<12%	-,282)	,115	5,952	1	,015	,755	,602	,946
	Constant	,161	,273	,348	1	,555	1,175		

Discussion

The findings of our study demonstrate that WMSI, GLS% and the number of segments with LS< 12% at maximal SE were significantly correlated either with presence of CAP or with the number of coronary arteries with plaque. Patients with CAP showed worsening of the LV strain at maximal SE in comparison to those with and without CAD who showed insignificant lesser strain or better function after SE, but the change from the rest to maximal SE was steel insignificant for each group. In addition, our results demonstrated that the presence of CAP along with worsening of WMSI at maximal SE appeared as independent predictors of CAD presence while increase [more positive] value of GLS% or increased number of segments with LS< 12% at maximal SE appeared as independent predictors of CAP presence.

Extremely limited data exist in the literature regarding either the role of coronary artery plaque in prediction of CAD or with determinizing the independent predictors of CAP presence using

echocardiography. The rising clinical relevance of those findings are mainly explained by facts that in a lot of patients investigated for angina symptoms there is no evidence of obstructive CAD on angiography which may not be a guarantee of benign prognosis in this patient subgroup. Thus, in the obtainable data from the literature different invasive and/or noninvasive methods were used to assess the role of CAP and its burden [16]. To our knowledge, this is the first study to assess the relation between CAP and ischemia implying CAD presence during SE.

Eskerud et al. [4] demonstrates that global CAP area determined by quantitative angiography is an important determinant of the severity of myocardial hypoperfusion assessed by contrast echocardiography, independent of presence of significant coronary artery stenosis. They found that larger CAP area was associated with a 35% higher risk for having severe myocardial hypoperfusion. Bauer et al. [17] found lack of significant relation between calcified CAP and perfusion defects, while relation between noncalcified plaque volume and perfusion defects were highly significant. In multiple stepwise regression analysis they performed noncalcified plaque volume appeared as the single significant predictor of ischemia at stress MPI. Stolzmann et al. [18] in the study of 52 patients with suspected CAD performed coronary arteriography as well as computed tomography angiography [CTA] and cardiac magnetic resonance [CMR], showed that number of total CAP according to CTA appeared as independent predictor of myocardial ischemia and CAD presence. Thus, there is hypothesis that noncalcified plaque components are a more active, less stable, and therefore more relevant factor in the pathogenesis of CAD [17, 19, 20] and that tears can develop in the fibrous cap of noncalcified plaques, which may or may not be hemodynamically significant, and precipitate thrombus formation and acute stenosis or occlusion as well as microembolus formation; thus, repeated microruptures and consecutive microembolizations in small vessels may lead to myocardial ischemia [21-23]. In addition, it was found that plaque ruptures frequently appeared in more voluminous plaques with large plaque burden and positive remodeling [24]. It is important to stress that almost all patients with symptoms of angina and/or signs suggestive of myocardial ischemia and non-obstructed coronary arteries [INOCA] studied by intravascular ultrasound [IVUS] to date have some coronary atherosclerosis which is considered as a key mediator of its occurrence [25,26] whether it is CAP presence and characteristics and/or endothelial dysfunction [27].

Initial reports from The Women's Ischemia Syndrome Evaluation [WISE] study showed that women who presented with signs and symptoms of myocardial ischemia, and who were confirmed to have no obstructive CAD, had an increased risk of major adverse cardiovascular events [28] which was also confirmed in another studies where measurements of plaque burden and composition determined by coronary CTA have been proven to predict outcome beyond conventional anatomic coronary CTA readings [29-31]. In a brand new post hoc analysis of the SCOT-HEART study by Williams et al. [32] using coronary CTA in 1769 patients followed-up for 5 years, the data revealed that adverse plaque characteristics [positive remodeling or low attenuation plaque] and overall calcified plaque burden possessed an increased risk for CAD death or nonfatal myocardial infarction [coronary artery calcium score ≥1000 AU had 13-fold increase in CAD death].

Given that patients with CAP and nonobstructive CAD represent the heterogeneous population group which possessed substantial risk for unfavorable prognosis, it should be made any effort to use contemporary diagnostic tools to confirm CAD presence and especially its physiologically significant consequences [1,33]. It is well known that the presence of a non-occlusive stenosis by visual assessment is also known to have only moderate agreement with physiologically significant impairment of fractional flow reserve [34, 35]. Low level myocardial stunning may be occurring as well in the presence of non-occlusive disease. Non-obstructive coronary disease may also predispose to intermittent coronary spasm especially when CAP is irregular with complex structure, which can also induce myocardial stunning [36,37].

Study limitation

Our study is a single-center study. Angiographies read by clinicians were not blinded to the patient condition. We didn't use any other technique to confirm the presence of coronary artery plaque like computed tomography angiography [CTA] and/or cardiac magnetic resonance [CMR] as well we didn't performed assessment of coronary fractional flow reserve in order to confirm physiological significance of CAP presence. And at last, although stress echocardiography is well established and robust method with relatively low intra and interobserver variability in assessment of wall motion and

LV strain changes, there is objective possibilities for false-positive or false-negative findings that have to be considered as possible sources of error in our study.

Conclusion

Our study showed a positive correlation between CAP presence or the number of coronary arteries with plaque and the finding of ischemia at SE. Patients with CAP showed worsening of the GLS% after SE in comparison to those with and without CAD who showed insignificant lesser strain or better function after SE. Presence of CAP along with worsening of WMSI at maximal SE appeared as independent predictors of CAD presence while increase [more positive] value of GLS% or increased number of segments with LS< 12% at maximal SE appeared as independent predictors of CAP presence. More studies are needed to define the clinical relevance of this observation in order to establish risk stratification, implement combination of functional and morphologic imaging and to optimize the therapy.

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