ASSOCIATION OF CORONARY MACROVASCULAR DYSFUNCTION AND BRACHIAL ARTERY FLOW-MEDIATED VASODILATION IN PATIENTS WITH NONOBSTRUCTIVE CORONARY DISEASE

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Purpose: Our purpose was testing the possibility for correlation between endothelium-independent coronary function and flow-mediated dilation of brachial artery (FMD) and evaluation of their prognostic significance in patients with non-obstructive coronary disease. **Material and methods:** The vasodilatory response of left anterior descending coronary artery (LAD) to intracoronary nitroglycerin (NTG) was assessed and matched with the results of the ultrasound evaluation of brachial artery FMD in a group of 153 patients with non-obstructive coronary atherosclerosis and recurrent ischaemia. **Results:** In the setting of non-obstructive disease the frequency of endothelium-independent coronary macrovascular dysfunction (MAVCD) was 32.9% (n = 46). The mean values of FMD in our group were 7.97± 5.71% and only insignificantly differ in relation to the presence of coronary atherosclerosis on angiography. The examined two methods for vascular function assessment did not correlate substantially (r = - 0.010; p = 0.925) and were not associated with the adverse events incidence during seven-year follow-up (6.58 ± 4.45% vs 8.77 ± 6.71%, p = 0.252 for FMD; 54.7% vs 45.4%, p = 0.992 for MAVCD). The impairment of FMD in the group with angiographic signs of coronary atherosclerosis showed borderline significant correlation with coronary flow delay following intracoronary injection of NTG (r = - 0.292, p = 0.057). **Conclusion:** In patients with angina and non-obstructive atherosclerosis the extent of coronary dilation in response to NTG does not correlate substantially with brachial artery FMD. The significance of peripheral vascular dysfunction as marker of impaired coronary flow in non-obstructive coronary disease needs evaluation in larger cohorts.

Key words: coronary dysfunction, nitroglycerin, coronary flow, flow-mediated vasodilation

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Backgroud

Many patients, who undergo selective coronary angiography because of recurrent symptoms of chest pain do not have significant obstructions in epicardial coronary arteries despite abnormal results of instrumental and clinical laboratory test indicative of myocardial ischaemia [13]. Observational studies demonstrate tin this patients' group, vasospastic macro- or microvascular disease may present as acute coronary syndrome, ventricular arrhythmia, sudden cardiac death [13]. By consensus, the patients should be considered for evaluation with additional diagnostic methods if the arteriogram is visually normal or showing minimal coronary atherosclerotic lesions. Provocative test with vasoactive drugs to assess macro- and microvascular coronary response are the reference method for diagnosis of coronary vascular dysfunction [13]. The routine usage of these invasive methods is restricted by absence of standardized protocols, need of prolonged catheterization and higher incidence of fatal complications compared to standard coronary arteriography [27].

Research data regarding correlation of noninvasive and invasive methods for vascular function assessment are controversial [1,25].

Purpose

We assessed the significance of correlation between two methods for evaluation of vascular function - endothelium-independent coronary macrovascular dilation and endothelium-dependent dilation of brachial artery (FMD). We tried to specify their prognostic value in the setting of non-obstructive coronary disease.

Material and methods

We conducted a retrospective analysis of available data of 153 patients with non-obstructive coronary atherosclerosis (without coronary stenosis >50% on angiography) and recurrent symptoms of ischemia admitted at University Hospital "Alexandrovska", Sofia in the period 2006-2008.

Selective coronary angiography was performed via femoral approach using Simens Coroscop Plus imaging system. During diagnostic angiography, 6Fr and 7Fr diagnostic catheters, 60 U/kg i.v. heparin bolus and nonionic contrast medium (Iopamidol 370, Bracco diagnostics Inc, Monroe Township, NJ, USA) were used. Left anterior descending artery (LAD) was evaluated using standard projections (mostly right anterior oblique projection with caudal angulation). Intracoronary nitroglycerin 100 – 200 μg as a single or repeated boluses were then given according standard protocol [10, 27]. The diameter and coronary flow velocity

(using corrected TIMI frame count method, cTFC method) in LAD along with parameters of hemodynamics (systolic arterial pressure and heart rate using indirect measurements) were recorded at baseline and following intracoronary NTG. Endothelium-independent coronary dysfunction was defined as vasodilation in LAD of less than 20% following intracoronary NTG [27].

Method introduced by Gibson et al. [9] was applied for coronary flow velocity assessment. It is based on estimation of the number of frames required by the contrast medium to opacify standard predetermined distal coronary landmark (the apical branching of LAD).

Measurement of the flow-mediated dilation of brachial artery was performed according guidelines for ultrasound assessment [4]. The patients fasted and restrained from drinking cofee, alchohol, smoking for at least twelve hours prior to vascular scan. The last intake of vasoactive drugs was also 12 h prior to test [4]. The brachial artery was imaged longitudinally with 3-11 MHz transducer using high-resolution ultrasound (Sonos 5500 HP imaging system) 2-10 cm over antecubital fossa. Two end-diastolic images of vessel diameters were acquired before and after (but within two minutes of) cuff release following 5-minute compression. Brachial artery was compressed with cuff which was inflated to pressure of 200 mmHg or 50 mmHg higher of the patient's systolic pressure (the higher value was attained and used). FMD was calculated as maximum change in the vessel diameter following cuff release from baseline diameter (expressed as percentage change).

The patients were followed after period of seven years. Data for ischemic adverse events as a combined endpoint (ischemic-driven hospitalizations, acute coronary syndromes, revascularizations, transient ischemic attacks - TIA and ischemic strokes) were collected from medical records, by standartised telephone interview and by clinical examination at the time of hospital visits and re-admissions during follow-up.

In the course of statistical analysis of data were employed the following methods: Kolmogorov-Smirnov and Shapiro-Wilk normality tests; Chi-square and Fischer's exact test; Student's T test for independent samples; Mann-Whitney U test; correlation and regression analyses. Statistical significance was considered for P values lower than 0.05. Data was processed with SPSS version 19.0 (Chicago, IL, USA) for Windows.

Results

Baseline characteristics of the examined group are presented on table 1. History of myocardial infarction with spontaneous fibrinolysis or treated with pharmacologic thrombolysis was found in 11.7 % (n=18) of patients. The assessment of coronary artery (LAD) vasodilation yielded 32.9% (n=46) incidence of endothelium-independent vascular dysfunction (MAVCD) (table 1).

Variable	n (%)
Age, years	58.8 ± 9.1
Gender – men/women	54 (34.8) /101 (65.2)
Hypertension	135 (90)
Diabetes mellitus	28 (18.8)
Dyslipidemia	44 (31.7)
Smoking	34 (29.3)
Prior myocardial infarction	18 (11.7)
Prior TIA/stroke	9 (6.1)
Anemia	6 (9.4)
LV hypertrophy > 14 mm	14 (9.4)
Atherosclerotic lesions	37 (23.7)
Adverse events	32 (43.8)
FMD, %	7.97 ± 5.71
ΔD_{LAD}, %	10.3 ± 11.3

Legend: LV hypertrophy - left ventricular hypertrophy; ΔD_{LAD} - change of LAD diameter following NTG

Significant drop in systolic pressure (SBP), increase of heart rate (HR) and considerable LAD dilation as well as insignificant acceleration of coronary flow velocity were observed after intracoronary NTG (table 2).

Table 2. Change of systolic pressure, heart rate, LAD diameter and coronary flow velocity after NTG

Variable	Baseline	After NTG	P value
SBP, mmHg	132.7 ± 17.7	122.3 ± 18.7	<0.0001
HR, bpm	69.4 ± 10	74.3 ± 11.8	<0.0001
D_{LAD}, mm	3.6 ± 0.7	3.9 ± 0.7	<0.0001
cTFC, frames	34.3 ± 17.2	32.8 ± 15.2	0.950

LAD diameter following intracoronary NTG did not correlate substantially with change of SBP, HR and coronary flow rate (table 3).

Table 3. Correlation of LAD diameter and systolic pressure, heart rate, coronary flow velocity following NTG

	Δ D $_{LAD, \%}$
SBP, mm after NTG	r= 0.112 ; p= 0.206
HR, bpm after NTG	r= - 0.040 ; p= 0.662
cTFC, frames after NTG	r= - 0.155 ; p= 0.071

No considerable difference in the values of endothelium-independent coronary and endothelium-dependent brachial artery dilation in relation to patient's gender and the presence of atherosclerosis (coronary plaques) could be found (table 4).

Table 4. Coronary macrovascular dysfunction and FMD in brachial artery – difference in relation to gender and atherosclerosis

	Plaques (-)	**Non-obstructive plaques (+)**	**P value**
FMD, %	8.23 ± 6.12	6.85 ± 3.35	0.372
MAVCD, n (%)	84 (77.8)	29 (87.9)	0.318
	Men	**Women**	**P value**
FMD, %	6.61 ± 4.64	8.52 ± 6.04	0.152
MAVCD, n (%)	37 (78.7)	75 (80.6)	0.825

LAD dilation following NTG was not associated with brachial artery FMD. Subgroup analysis according to the presence of atherosclerosis confirmed lack of considerable correlation of both methods (table 5).

Table 5. Correlation analysis of dilation LAD in response to NTG and FMD in patients with non-obstructive CAD

	Δ D_{LAD}, %
FMD,%	
Nonobstructive CAD	r= - 0.010; p= 0.925
Plaques (-)	r= - 0.057; p= 0.646
Non-obstructive plaques (+)	r= 0.015; p= 0.955

FMD is not associated with LAD diameters and coronary flow rates at baseline and after NTG. Among the patients with visible atherosclerotic coronary lesions delayed coronary flow (higher cTFC) after NTG correspond with borderline significance with the degree of impaired FMD (lower FMD values) (r= - 0.292, p= 0.057). The relationships FMD and coronary flow velocity following NTG is nonsignificant in the subgroup without visible coronary plaques (r= - 0.071; p= 0.564).

During 7 year follow-up in 53 of patients occurred ischemic adverse events. Endothelium-independent coronary dysfunction (54.7% vs 45.4%, p=0.992) and FMD (6.58±4.45% vs 8.77±6.71%, p=0.252) were unrelated to the incidence of complications in the setting of non-obstructive coronary disease. The presence of minimal atherosclerotic lesions together with the impaired coronary macrovascular dilation as combined index remained insignificant prognostic marker for ischemic complications during long-term follow-up (75% vs 83.9%, p=0.398).

Discussion

The present study shows that there is no correlation in the results when vascular function is evaluated by two different methods – induced by NTG dilation of coronary artery and flow-mediated dilation of the brachial artery. This association remains statistically insignificant even in cases with visible atherosclerotic lesions.

Jost et al. describe that maximal dilation of epicardial coronary arteries can be easily achieved with intracoronary bolus administration of 100 μg nitroglycerin without considerable decrease in blood pressure. Additional doses of nitroglycerin cannot increase coronary dilation [10]. The degree in dilation using this protocol is unaffected by pretreatment with nonselective β-blockers [10]. In addition to

induction of vasodilation nitroglycerin reduced platelet thrombus formation eliminating the action of vasoconstrictor substances [5]. The angiographic investigation of macrovascular reactivity in the present study was done with intracoronary injection of total 100-200 μg nitroglycerin applied as a single or repeated (approximately every 10 minutes) boluses according to the protocol already described [10]. The dose applied was adapted to the patient's baseline blood pressure. In the study group the infusion of NTG produced drop of arterial pressure and tachycardia to degree inadequate to substantially influence the results of coronary vascular function tests. Prior data gives evidence that intravenous infusion of nitroglycerin in doses sufficient to produce a substantial drop in mean arterial pressure does not lead to any decrease in coronary blood flow [7].

On the average, flow resistance in severe lesions is reduced 38% by nitroglycerin [2]. Normal coronary reactivity testing in response to nitroglycerin is defined as a diameter increase >20% in patients with nonsignificant atherosclerotic lesions [27]. The frequency of abnormal non-endothelial dependent macrovascular function among our patients is lower compared to prior studies in the setting of nonobstructive coronary disease [27]. The number of patients in our cohort including women in whom vascular dysfunction typically prevails is lower compared to similar studies [8, 27].

Endothelium-dependent dilation of the brachial artery – correlation with coronary artery vascular function and prognostic significance

Previous studies have demonstrated a close relation of endothelium-dependent and endothelium-independent response of the brachial artery [12,19], of coronary artery endothelium-dependent function and flow-mediated vasomotor response in the brachial artery [1] and of flow-mediated coronary artery dilation and the change in coronary diameter induced by vasodilators [25].

Schächinger et al. have suggested that a reduced coronary artery vasodilator reactivity to NTG might be related to early microscopic structural and functional changes (fibrosis or smooth muscle atrophy; decreased activity of intracellular guanylate cyclase with impaired cyclic GMP-dependent relaxation) and account for increased baseline diameter as a result of positive remodeling [20]. In summary, there is no available scientific data proving evidence for direct relation of endothelium-dependent and endothelium-independent macrovascular function in different vascular regions. We could suggest some reasons for this statistical insignificant result. Two different types of methods has been utilized (invasive and noninvasive) and two different vascular regions with diverse mechanisms of vascular tone regulation were objects of comparison. While coronary vasodilation

in response of NTG reflects only the coronary arteries' smooth muscle cell dysfunction, brachial artery FMD may serve as an index integrating several functions of endothelium dependent of its ability to produce nitric oxide (anti-inflammatory, antithrombotic, etc). Meanwhile, the mediated by shear-stress brachial artery dilation is very sensitive to the action of a number of intercurrent factors (viral illness, meal intake, vasoactive substances, ets). The influence of these factors cannot be predicted with certainty [3]. In contrast to the results of Schächinger et al. we could not demonstrate considerable association of LAD diameter and FMD in the subgroup of patients with atherosclerotic lesions. Nevertheless, the degree of FMD impairment correlates positively with another predictor of poor prognosis in the setting of coronary disease [6, 17] - the cTFC values following intracoronary NTG. A large number of studies have now been published evaluating endothelial function measurements in relation with the risk of cardiovascular events in general population [22] and among patients with coronary athersoclerosis [21]. In the present study FMD is not associated with the incidence of ischemic complications in non- obstructive coronary disease. It is possible that serial FMD measurements and structural changes in the brachial artery wall (increased brachial artery intima-media thickness) could indicate more accurately patients with atheroclerosis and predict the risk of cardiovascular events than FMD alone [24].

Endothelium-independent coronary macrovascular dysfunction – prognostic value

Prior research show that impaired endothelium-independent coronary vasoreactivity (response to nitroglycerin) is predictor independent of other vascular function tests of cardiovascular events (cardiovascular death, unstable angina, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass grafting, ischemic stroke, or peripheral artery revascularization) in 147 patients over a median follow-up period of 7.7 years [20]. We could not confirm these data possibly due to incomplete follow-up of our study's population

The results of the present study firmly establish that smooth muscle dilator function comprise only one side of various vascular functions most of which are endothelium-dependent (regulation of adhesion molecules, releasing of antithrombotic molecules, etc) [3]. Propensity to vasoconstriction rather than abnormality in vasodilator function is more important mechanism contributing to triggering of vascular events [16, 23]. A meta-analysis of studies shows that coronary arterial spasm could be provoked in 34% of patients with myocardial infarction and non-obstructive coronary atheroscelrosis [16]. It is not generally agreed that the prognosis of these patients is better compared to patients with MI and obstructive coronary disease [14, 16].

Endothelial dysfunction as well as the presence of atherosclerotic plaques are factors for the risk of vascular complications in coronary disease. Using sensitive coronary imaging techniques minimal atherosclerotic lesions and diffuse intimal thickening could be demonstrated in relation with focal coronary spasm [15, 18, 26]. Previous studies has demonstrated that the size and minimal lumen diameter in the region of plaque were less important cardiovascualr risk contributors compared to impaired coronary vasoreactivity [11, 26]. In the present study impairment in coronary smooth muscle dilator function and angiographic evidence of coronary atherosclerosis as integrated index remained poor predictors of outcome in the setting of non-obstructive coronary disease even during long-term follow-up. This result clearly underscores that demonstration of endothelial dysfunction and coronary spasm are more valuable tools in predicting clinical outcome of non-obstructive coronary disease.

Conclusion

Among patients with non-obstructive coronary disease induced by NTG dilation of coronary artery is not associated with flow-mediated dilation of the brachial artery. The significance of peripheral vascular dysfunction as marker of impaired coronary flow in the setting of non-obstructive disease needs evaluation in larger cohorts.

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