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ORIGINAL ARTICLE

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Endothelial functional and structural impairment in patients with different degrees of coronary artery disease development

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Abstract Flow-mediated dilatation (FMD) and intima-media thickness (IMT) are noninvasive methods for patient evaluation. In this study we aimed to estimate the correlation between FMD and IMT in patients with different degree of coronary artery disease (CAD) development, and to explore their prognostic significance for the presence of angiographically significant coronary artery stenosis. We included 198 patients divided into five groups according to the degree of CAD development. All patients had FMD and IMT measured, 105 (53.03%) performed a Treadmill test in our clinic, and 146 (73.7%) underwent coronary arteriography (CAG). Patients with significant (≥50%) coronary artery stenosis had lower FMD and higher IMT values compared to patients without significant CAD: FMD: 2.78% ± 2.71% vs 8.24% ± 5.16%, respectively, $P < 0.001$; IMT: 0.882 ± 0.17 mm vs 0.763 ± 0.16 mm, respectively, $P < 0.001$. There existed a weak negative correlation between FMD and IMT (correlation coefficient: –0.242, $P < 0.001$), which was lost in subgroups and after controlling for the presence of significant CAD, number of diseased coronary arteries, and percent coronary artery stenosis. Analyzing the receiver operating characteristic curves we found that FMD values ≤4.5% had 74% sensitivity, 77% specificity, positive predictive value (PPV) 81.8%, and negative predictive value (NPV) 68%, and IMT values ≥0.81 mm had sensitivity 71%, specificity 67%, PPV 76.1%, and NPV 63.1% for the presence of significant CAD. Patients with advanced CAD had lower FMD and higher IMT values compared to patients with minor changes. The correlation between FMD and IMT was weak and inconsistent. Both methods demonstrated an acceptable prognostic significance for the presence of significant CAD.

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Introduction

Coronary artery disease (CAD) is the main cause of morbidity and mortality in developed countries. The atherosclerotic process develops gradually in the course of several decades and affects different vascular territories.[1]

Flow-mediated endothelial dependent vasodilatation (FMD) of the brachial artery is a method capable of detecting changes in the endothelial function. The method was first described and implemented in clinical practice by Celermajer et al.[2] For over two decades the method has been used to evaluate the early atherosclerotic changes in patients with various risk factors for coronary atherosclerosis or with an already established CAD. The echographic measurement of intima-media thickness (IMT) of the common carotid artery using B-mode technique began in 1986. In that year Pignoli et al.[3] measured in vivo the echographic distance between the two echogenic lines, separated by a hypoechogenic space, in the wall of the common carotid artery. They found that this distance was significantly correlated to the in vitro determined histological thickness of the intimal and smooth muscle layers of the artery.

These two methods for noninvasive patient evaluation have the ability to detect changes in the inner layer of the arterial wall – functional for FMD, as well as structural for IMT. The correlation between the two methods and the clinical implementation of the measurements derived from them have been the subject of several investigations, and the results are rather contradictory.[4–6] The purpose of the present study is to estimate the correlation between FMD and IMT measurements in patients with different degrees of CAD development and to explore their prognostic significance for the presence of angiographically significant coronary artery stenosis.

Patients and methods

Study group

We studied 198 patients, admitted to the Clinic of Cardiology, University Hospital Alexandrovska, between April and October 2007. One hundred and five of the patients had a stress ECG test performed in our clinic. These were patients with angina pectoris as well as some of the patients (9) with multiple risk factors. We used a Treadmill Track Master (Schiller, Miami, FL, USA). The choice of the protocol was left to the discretion of the performing physician (most commonly Bruce protocol or modified Bruce for patients with limited exercise capacity). The test was considered positive (and inducible myocardial ischemia accepted) in the presence of ≥1 mm horizontal or downsloping ST depression or ST elevation, persisting at least 60–80 ms after the end of the QRS complex, or the occurrence of typical angina pectoris leading to test termination.

During diagnostic and therapeutic workup some of the patients underwent coronary arteriography (CAG) according to the results of noninvasive testing. The indication for an invasive study was evidence of inducible myocardial ischemia during the Treadmill test (or unequivocal results from an ambulatory performed stress ECG test – 46 patients) or during Dobutamine stress/Echocardiography test – 16 patients. We also included in the present study some ambulatory patients with risk factors for CAD development without angina pectoris. The demographic characteristics and risk factor distribution of the patients are presented in Table 1. The clinical characteristics with respect to CAD are presented in Table 2.

The study excluded patients with acute coronary syndrome, patients with hemodynamically significant valvular disease, and patients with previously performed coronary interventions or surgical revascularization. We also excluded from our final analysis patients with an atherosclerotic plaque of the common carotid artery (see below).

Ethics

All patients signed an informed consent for FMD measurement. The investigation protocol was approved by the local ethical committee.

Coronary arteriography

We performed elective CAG using the Judkins–Gensini technique, femoral access. At least five projections were done to visualize the left coronary artery and at least two for the right coronary artery. The evaluation of the stenotic lesions was done with software for quantitative coronary angiography–Vessel analysis (Siemens, Erlangen, Germany). According to the degree of coronary artery stenosis, the patients were divided into groups without significant coronary stenosis (<50%) and such with one-, two-, and three-vessel disease.

Flow-mediated dilatation

Flow-mediated dilatation was accomplished according to the Guidelines for ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery.[7] The investigator has had experience of 100 supervised scans and measurements before claiming independency and then more than 100 scans per year to maintain competency. The inter- and intraobserver variability of the method was evaluated on a sample of 40 patients with a correlation coefficient $r > 0.92$, $P < 0.001$.[8]

We performed the FMD measurements in the morning hours between 07:00 and 09:00. After 20:00 on the day before, the patient refrained from eating, drinking alcoholic beverages or smoking. Long-acting nitrates were avoided for 24 h. On the morning of the study the patient was asked not to consume anything but water, not to smoke, to postpone taking the prescribed medication until after the study, and to refrain from vigorous physical activity.

After a 15-min rest in a quiet and temperate room the investigation started by taking the blood pressure on the dominant arm. We placed the cuff of the sphygmomanom-

Table 1. Demographic characteristics and risk factor distribution

Clinical variable	Distribution (n = 198)
Age, mean ± SD	60.73 ± 10.41
Female, n (%)	82 (41.4%)
BMI, mean ± SD	28.67 ± 4.24
Arterial hypertension[a], n (%)	178 (89.9%)
Diabetes mellitus[b], n (%)	46 (23.2%)
Dyslipidemia[c], n (%)	157 (79.3%)
Present smokers, n (%)	33 (16.7%)
Former smokers, n (%)	116 (58.6%)

BMI, body mass index
[a] Defined according to the Guidelines for the management of arterial hypertension[9]
[b] Defined according to the Guideline on diabetes, pre-diabetes and cardiovascular diseases[10]
[c] Defined according to the European guidelines on cardiovascular disease prevention in clinical practice[11]

Table 2. Clinical characteristics of the patients with respect to coronary artery disease (CAD)

Clinical variable	Distribution (n = 198)
Angina pectoris, n (%)	138 (69.7%)
History of myocardial infarction, n (%)	43 (21.7%)
Stress ECG performed, n (%)	105 (53.03%)
Positive stress test, n (%)	84 (80%)
CAG performed, n (%)	146 (73.7%)
Without stenosis, n (%)	61 (30.8%)
One-vessel disease, n (%)	32 (16.2%)
Two-vessel disease, n (%)	25 (12.6%)
Three-vessel disease, n (%)	28 (14.1%)
Significant CAD, n (%)[a]	85 (58.2%)

CAG, coronary arteriography
[a] ≥50% coronary artery stenosis

eter on the forearm of the same arm with the patient in a supine position and obtained a longitudinal image of the brachial artery with optimal visualization of the intima using a linear array transducer (3–11 MHz) and a Sonos 5500 echocardiograph (S&T, Bulgaria). We performed a 5- to 10-s recording on video cassette recorder (VCR) of the baseline state of the brachial artery. The cuff was inflated to a pressure of 200 mmHg or 50 mmHg above the systolic arterial pressure of the respective patient, whichever is higher, and maintained thus for 5 min. We executed a new recording on VCR during the last 30 s of the ischemic phase (cuff inflated) and then 120 s after cuff deflation. The whole image was ECG-gated.

Measurement

The analysis was made off-line. The diameter of the brachial artery at different occasions was measured manually. We considered two parameters: the baseline diameter of the brachial artery and the maximum postischemic diameter of the artery. All measurements were done in the end-diastole (the beginning of the R on ECG) from endothelial to endothelial surface along a line perpendicular to the artery's long axis. For the baseline diameter we used at least three heart beats and measured the distance between the intimal surfaces of the artery at three different locations along the vessel's axis. We then calculated the mean value for the baseline diameter. In the reactive hyperemia phase we measured the diameter of the brachial artery at 10-s intervals, beginning 30 s after cuff deflation and proceeding until the 120th second. For every measurement we estimated the diameter again at three different locations along the vessel's axis and calculated the mean value of these three measurements. The largest of the 10-s-interval measurements corresponded to the maximal response of the brachial artery during the reactive hyperemia phase.

The FMD was measured in percentage terms and derived by the formula:

$$\text{FMD}\ (\%) = [(\text{post-ischemic diameter of the brachial artery} - \text{baseline diameter})/\text{baseline diameter}] \times 100$$

Intima-media thickness

We performed IMT measurement on the morning when FMD evaluation was done. In a quiet and temperate room with the patient in a supine position, we subsequently scanned the right and left carotid artery with the patient's head slightly elevated and turned on the contralateral side. We used a high-resolution ultrasound system, Sonos 5500 echocardiograph, with a high-frequency linear array transducer (3–11 MHz).

We acquired a longitudinal B-mode image of the common carotid artery in three different views, i.e., anterior-oblique, lateral, and posterior-oblique, with optimal visualization of the intimal layer of the vessel wall. We used the minimum gain necessary for clear visualization of lumen–intima and media–adventitia interfaces. The place where we measured IMT was the far wall of the common carotid artery, 10 mm proximal to the bifurcation of the artery. We excluded patients with focal atherosclerotic plaque in this area, defined as a clearly identified area of focal increased thickness (>1 mm). At a usual depth of 4 cm we acquired a several-second ECG-gated recording of the maximally zoomed image of the common carotid artery in every image projection, bilaterally.

Measurement

An end-diastolic image frozen on the beginning of the R wave of the ECG was transferred to a personal computer, where an automatic computerized edge detection algorithm IMT.LAB v 2.0 (MedicaSoft, Creteil, France) was used to measure IMT. For each image we performed a separate calibration and manually determined the region of interest (ROI), where IMT was to be measured. The dedicated software automatically recorded IMT to within 0.001 mm and gave the results as IMT Mean – the mean value of IMT, calculated as the mean of a normal distribution consisting of all the IMT values of all points along the ROI. Reported was also the 95% confidence interval (CI), the standard deviation (SD), and the quality index – the number of points in the ROI that qualified for the measurement. We included only images with a quality index ≥50%. The IMT of the patient was calculated as the mean of six measurements (IMT Mean) in each of the three different views for the right and the left common carotid arteries.

Statistics

We tested the distribution of continuous variables using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation ($\bar{X} \pm \text{SD}$), whereas non-normally distributed data were given as median and interquartile range (the difference between the 25th and 75th percentile). Categorical variables were presented in percentage terms. We evaluated the correlation between FMD and IMT with Pearson correlation coefficient for normally distributed data and with Spearman's rho correlation coefficient when the data were not normally distributed. We used partial correlation to test the relationship between the variables after controlling for demographic characteristics, risk factors, presence of angina pectoris, history of myocardial infarction, presence of angiographically significant CAD, number of diseased coronary arteries, percent coronary artery stenosis, and group membership. The sensitivity and specificity for FMD and IMT were assessed using the receiver operator characteristics (ROC) curves. We estimated the areas under the curves (AUC) with 95% CI under the nonparametric assumption. The sensitivity and specificity for exercise stress testing were assessed using risk estimation in a cross-tabulation procedure. The true and false negative results for exercise testing were estimated only considering patients who underwent CAG and were found not to have a significant CAD. We calculated the positive predictive value (PPV) of a diagnostic test using

the formula: PPV = (sensitivity × prevalence)/{sensitivity × prevalence + (1 − specificity) × (1 − prevalence)}. For the negative predictive value (NPV) we used: NPV = {specificity × (1 − prevalence)}/{specificity × (1 − prevalence) + (1 − sensitivity) × prevalence)}. The distribution of risk factors between groups was tested with ANOVA for continuous variables and with the Chi-square test for categorical variables. We compared the results for FMD and IMT between different groups using an independent samples *t*-test and ANOVA for multiple comparisons for normally distributed data, and the Mann–Whitney *U*-test for non-normally distributed data. A two-tailed *P* value of less than 0.05 was considered statistically significant. All tests were performed with SPSS 13.0 for Windows.

Results

Patients

We divided the patients in five groups as follows. Group 1: presence of atherosclerotic risk factors (not subjected to CAG) – 34 patients (17.2%); group 2: presence of angina pectoris in addition to the risk factors, negative stress test (only a minority of these patients underwent CAG) – 32 patients (16.2%); group 3: inducible myocardial ischemia, without coronary artery stenosis – 45 patients (22.7%); group 4: significant atherosclerotic involvement of coronary arteries (stenosis ≥50% in at least one epicardial vessel) – 38 (19.2%); group 5: history of major adverse cardiovascular events (MACE), myocardial infarction, or ischemic stroke – 49 patients (24.7%).

We did not find a statistically significant difference between the five groups regarding patients' age, BMI, serum levels of total cholesterol, HDL cholesterol, and triglycerides. The LDL level in group 5 was significantly lower compared to that in group 1 ($P = 0.018$). The percentage of women progressively decreased while increasing group number ($P < 0.001$ for comparison between groups). The percentage of patients with arterial hypertension, diabetes mellitus, dyslipidemia, and family history of premature CAD, as well as the number of present and former smokers did not differ significantly between the groups (Table 3).

Patients with ≥50% stenosis of a coronary artery were considered to have an angiographically significant CAD. We included all other patients in the group without angiographically significant CAD. In this group we considered also patients without CAG, i.e., patients without angina pectoris or inducible ischemia during exercise testing.

Comparison of FMD and IMT between groups

Patients with angiographically significant CAD had FMD values ($\overline{X} \pm$ SD) of 2.78% ± 2.71%. Compared to patients without angiographically significant CAD (FMD 8.24% ± 5.16%) there was a highly statistically significant difference in the FMD values between the groups: $P < 0.001$. The results for IMT were similar: ($\overline{X} \pm$ SD) for patients with and without angiographically significant CAD: 0.882 ± 0.17 and 0.763 ± 0.16 mm, respectively, $P < 0.001$.

The mean values with 95% CI for FMD and IMT in different patient groups are presented in Figs. 1 and 2, respectively. For the FMD values we did not find a statistically significant difference between groups 1, 2, and 3. There was not a statistically significant difference in the reactivity of the brachial artery between groups 4 and 5 as well. There was, however, a statistically significant difference for FMD values between groups: 1 and 4, 1 and 5, 2 and 4, 2 and 5, 3 and 4, and 3 and 5 ($P < 0.01$).

Intima-media thickness values did not differ significantly between groups 1, 2, and 3 and between groups 4 and 5 as well. We found a statistically significant difference for the thickness of the intimal and medial layer of the common carotid artery between groups: 1 and 4, 1 and 5, 2 and 4, 2 and 5, and 3 and 5 ($P < 0.05$). Here, however, groups 3 and 4 did not demonstrate a significant difference regarding the IMT values.

Flow-mediated dilatation and IMT values were not significantly different between patients with one-vessel disease, two-vessel disease, and three-vessel disease. The mean values with 95% CI in the different groups are presented in

Table 3. Distribution of risk factors between groups

Variable	Group 1 ($n = 34$)	Group 2 ($n = 32$)	Group 3 ($n = 45$)	Group 4 ($n = 38$)	Group 5 ($n = 49$)
Age[a]	62.4 (±12.5)	59.5 (±10.4)	60 (±9)	62.3 (±9.4)	59.5 (±10.8)
Female[b]	21 (61.8%)	18 (56.3%)	23 (51.1%)	10 (26.3%)	10 (20.4%)
Arterial hypertension[b]	31 (91.2%)	27 (84.4%)	39 (86.7%)	36 (94.7%)	45 (91.8%)
BMI[a]	27.8 (±4.7)	29.7 (±5.4)	28.4 (±3.8)	28.5 (±3.8)	28.9 (±3.8)
Diabetes mellitus[b]	6 (17.6%)	6 (18.8%)	29 (20%)	10 (26.3%)	15 (30.6%)
Total cholesterol[a]	5.01 (±0.84)	5.22 (±0.92)	5.06 (±1.18)	5.02 (±1.23)	4.61 (±0.98)
Triglycerides[a]	1.56 (±0.75)	1.65 (±0.76)	1.52 (±0.88)	1.54 (±0.67)	1.54 (±0.63)
HDL cholesterol[a]	1.35 (±0.3)	1.33 (±0.23)	1.33 (±0.25)	1.21 (±0.33)	1.27 (±0.39)
LDL cholesterol[a]	2.94 (±0.72)	3.17 (±0.89)	2.82 (±0.75)	2.92 (±1.08)	2.49 (±0.73)
Present smokers[b]	6 (17.6%)	9 (28.1%)	6 (13.3%)	5 (13.2%)	7 (14.3%)
Former smokers[b]	17 (50%)	17 (53.1%)	24 (53.3%)	24 (63.2%)	34 (69.4%)
Family history for CAD[b]	11 (32.4%)	14 (43.8%)	16 (35.6%)	12 (31.6%)	23 (46.9%)

HDL, high-density lipoprotein; LDL, low-density lipoprotein
[a] Mean (±SD)
[b] Number (%)

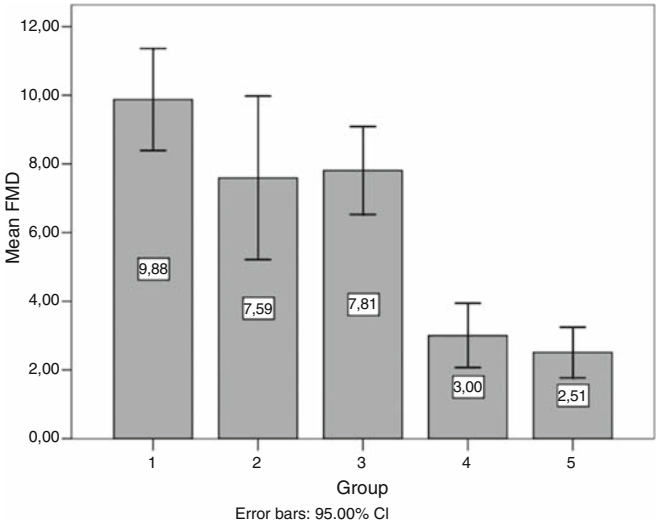

Fig. 1. Mean flow-mediated dilatation (FMD) values with 95% confidence interval (*CI*) for different patient groups

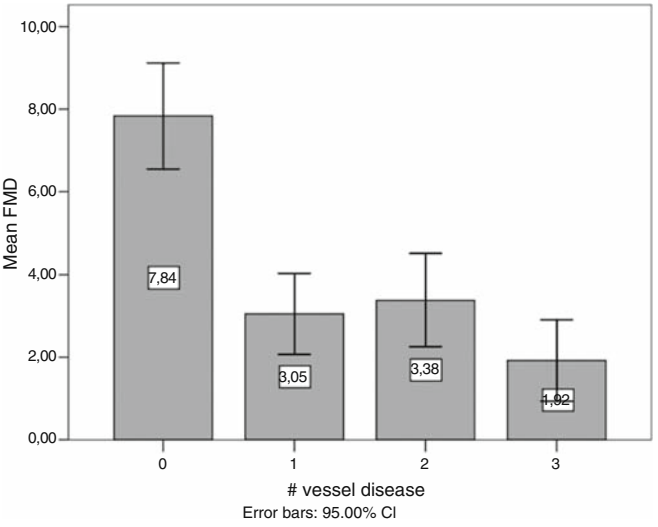

Fig. 3. Mean FMD values with 95% CI for patients without angiographically significant CAD and patients with one-, two- and three-vessel disease

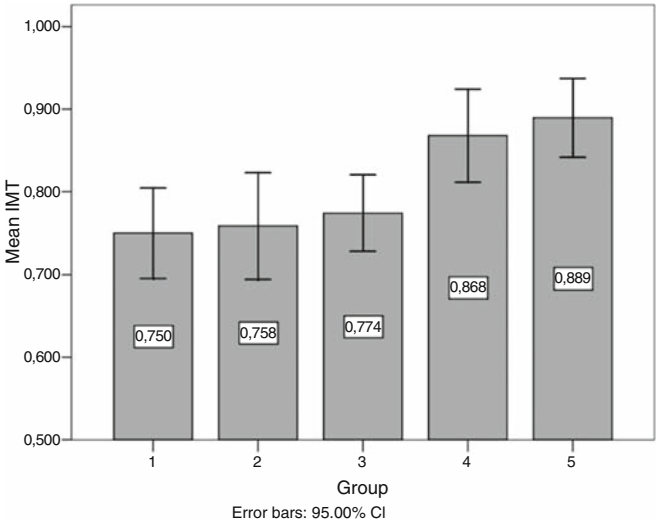

Fig. 2. Mean intima-media thickness (*IMT*) values with 95% confidence interval (*CI*) for different patient groups

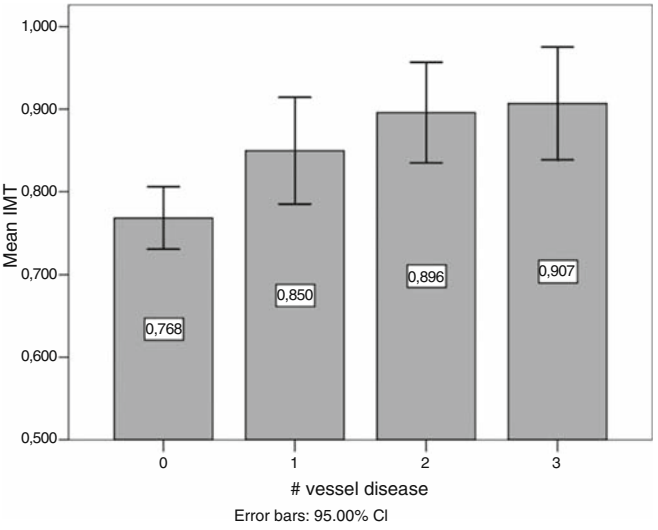

Fig. 4. Mean IMT values with 95% CI for patients without angiographically significant coronary artery disease (CAD) and patients with one-, two- and three-vessel disease

Figs. 3 and 4 for FMD and IMT, respectively. Flow-mediated dilatation values, however, were significantly higher and IMT significantly lower in patients with minor or no coronary artery stenosis compared to patients with one-, two-, or three-vessel disease ($P < 0.001$ for FMD and $P < 0.01$ for IMT). The only exception was that IMT values did not differ significantly between the group of patients without major coronary stenosis and the group with one-vessel disease ($P = 0.097$).

Correlation between FMD and IMT

For the whole group of patients we found a negative correlation between FMD and IMT values, which was highly statistically significant ($P < 0.001$). The Spearman correlation coefficient, however, was –0.242, indicating that although the two variables were linearly related to each other, the relation was a weak one (Fig. 5). In groups 1–5, however, the correlation between FMD and IMT was no longer significant.

When controlling for demographic characteristics and risk factors for the whole group we observed a significant negative correlation between FMD values and patients' age, sex (female patients had higher FMD values), and the presence of diabetes mellitus. Flow-mediated dilatation was not significantly correlated to BMI, the presence of arterial hypertension, dyslipidemia, or smoking status. The values of IMT were positively and significantly correlated to patients' age and sex (women had lower IMT values), the presence of arterial hypertension and present smoking, and not significantly correlated to BMI, the presence of diabetes

mellitus, or dyslipidemia and former smoking (Table 4). None of the demographic characteristics or risk factors had any influence on the correlation between FMD and IMT.

The presence of angina pectoris was negatively correlated with FMD values, and a history of myocardial infarction was negatively correlated with FMD and positively correlated with IMT values. None of these conditions influenced the relationship between FMD and IMT.

When controlling for the presence of significant CAD, the number of diseased coronary arteries, and percentage of coronary artery stenosis, we found a significant negative correlation for all of them with FMD and a positive correlation with IMT values. After controlling for these factors the correlation between FMD and IMT was no longer present.

Prognostic significance of FMD and IMT

We estimated the prognostic significance of FMD and IMT using their sensitivity, specificity, and positive and negative predictive values, derived from the ROC curves. In constructing the ROC curves we used only data from those patients who underwent CAG (146 patients).

Analyzing the ROC curve for FMD we found that values ≤4.5% had 74% sensitivity and 77% specificity with PPV 81.8% and NPV 68% for predicting angiographically significant CAD, whereas values ≤6% had 91% sensitivity and 62% specificity, resulting in a PPV of 76.9% and NPV of 83.2% (Fig. 6).

The ROC curve for IMT showed that values ≥0.81 mm had a sensitivity of 71%, specificity of 69%, PPV 76.1%, and NPV 63.1% for the presence of angiographically significant

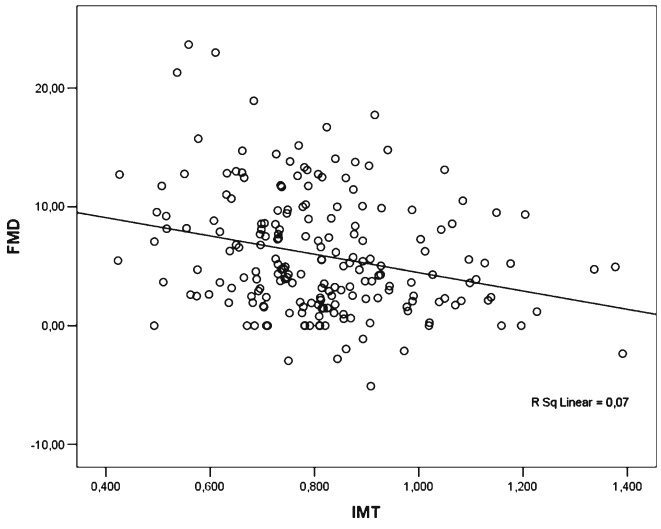

Fig. 5. Scatter-dot plot of FMD and IMT values with a fit line

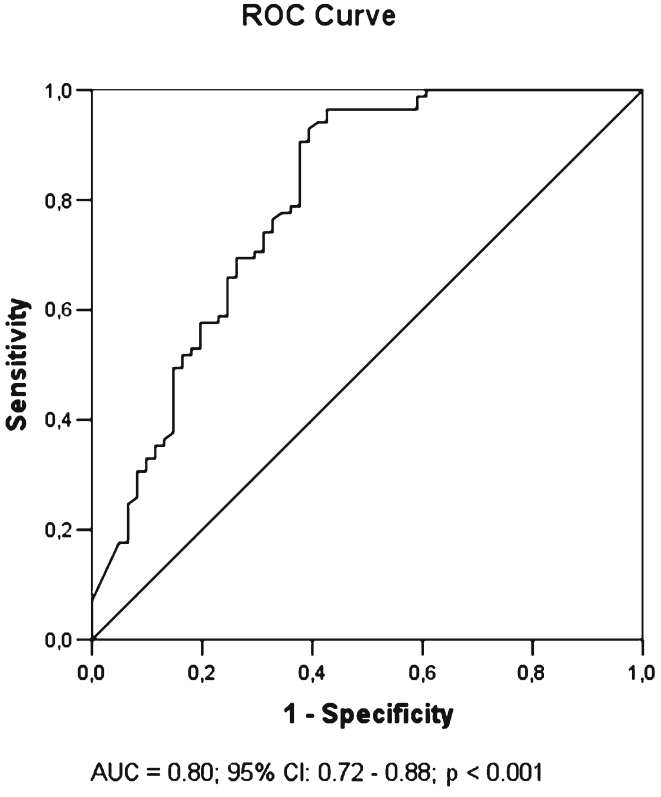

Fig. 6. Receiver operator characteristic (*ROC*) curve for FMD values with area under the curve (AUC) and 95% CI for AUC under the nonparametric assumption

Table 4. Correlations of flow-mediated dilatation (FMD) and intima-media thickness (IMT) with risk factors for atherosclerosis and clinical conditions, correlation coefficients, and significance

Variable	FMD		IMT	
	Corr. coefficient	*P*	Corr. coefficient	*P*
Age	–0.142	0.046*	0.357	<0.001*
Sex	–0.272	<0.001*	0.287	<0.001*
BMI	–0.032	0.653	–0.112	0.115
Arterial hypertension	–0.02	0.778	0.157	0.027*
Diabetes mellitus	–0.264	<0.001*	0.091	0.202
Dyslipidemia	0.02	0.784	0.021	0.774
Present smoking	–0.005	0.942	0.219	0.002*
Former smoking	–0.119	0.094	0.064	0.369
Presence of angina pectoris	–0.174	0.014*	0.117	0.102
History of myocardial infarction	–0.367	<0.001*	0.201	0.004*

*Significant correlation

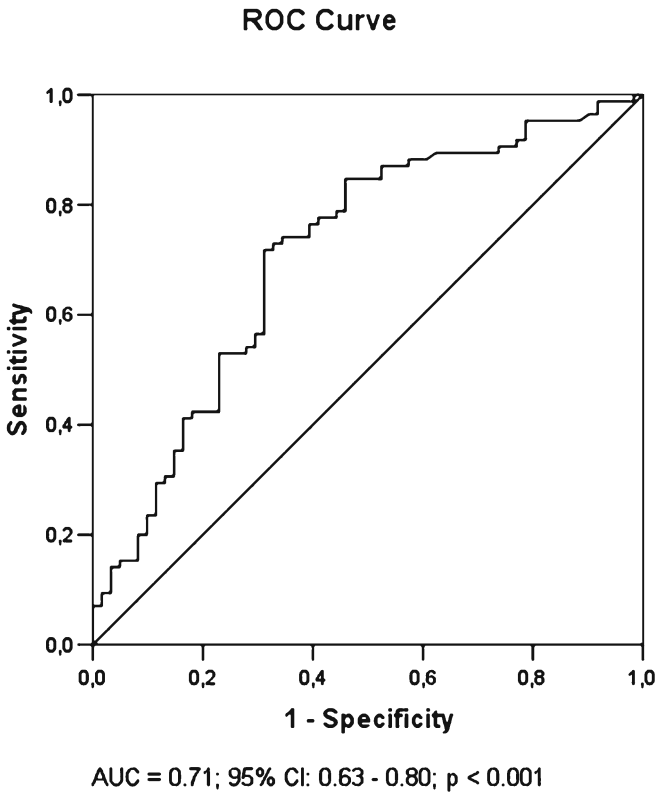

Fig. 7. Receiver operator characteristic curve for IMT values with AUC and 95% CI for AUC under the nonparametric assumption

CAD, and values ≥0.75 mm had 85% sensitivity and 54% specificity, with PPV 72% and NPV 72.1% (Fig. 7).

Discussion

In the present study we investigated 198 patients with a different degree of CAD development and found significantly lower FMD values and higher IMT values only in the presence of advanced coronary atherosclerosis. Flow-mediated dilatation and IMT were negatively correlated to each other for the whole group of patients, although the relationship was a weak one. In the subgroup analysis the relationship between those variables was lost. Flow-mediated dilatation was negatively correlated with age, sex, presence of diabetes mellitus, presence of angina pectoris, history of myocardial infarction, presence of significant CAD, number of diseased coronary arteries, and percent coronary artery stenosis. Intima-media thickness values were positively correlated with age, sex, presence of arterial hypertension, active smoking, history of myocardial infarction, presence of significant CAD, number of diseased coronary arteries, and percent coronary artery stenosis. When controlling for the presence of significant CAD, number of diseased coronary arteries, and percent coronary artery stenosis for the whole group of patients the correlation between FMD and IMT was no longer present.

Flow-mediated dilatation values ≤4.5% had 74% sensitivity and 75% specificity with PPV 81.8% and NPV 68%, and IMT values ≥0.81 mm showed a sensitivity of 71%, specificity of 69%, with PPV 76.1% and NPV 63.1% for predicting angiographically significant CAD.

Both methods we use, FMD and IMT measurement, are noninvasive, relatively easy to perform, and cost-effective. Nonetheless some studies have questioned the reproducibility and reliability of FMD.[12] Because of this we have tested the inter- and intraobserver variability for FMD, as already mentioned.[8] The automatic edge detection computer software methods for IMT measurement have considerably increased the reliability of the method.[13] Therefore we have not tested the inter- and intraobserver variability for IMT measurement and rely on following the exact protocol for image acquisition.

The correlation between FMD and IMT as well as their prognostic significance has been a subject of several investigations. A significant negative correlation has been found in a considerable group (2109) of young adults (24–39 years) without cardiovascular disease,[14] in 122 patients with angina pectoris with or without significant CAD,[6] in patients with advanced coronary atherosclerosis,[4] as well as in 41 young post-myocardial infarction patients.[15] Another two studies,[5,16] however, did not find a statistically significant correlation between FMD and IMT in over 1600 patients without cardiovascular disease, which is in concordance with our findings.

Comparing FMD and IMT values in patients with different degree of coronary artery stenosis, Furumoto et al.[17] find significantly lower FMD values in the presence of ≥50% coronary artery stenosis, while IMT values were significantly higher only in patients with a stenosis of ≥90%. Another group of investigators have demonstrated that patients with coronary artery stenosis ≥50% have significantly lower FMD values and significantly higher IMT values compared to patients with minor coronary atherosclerosis.[6] The authors found that FMD values ≤4.5% have 71% sensitivity and 81% specificity for the presence of angiographically significant CAD, which is very close to our findings. For IMT no such clear cut-off point could be defined. Finally, Matsushima et al.[4] proved a similar or even better prognostic accuracy for FMD and IMT values compared to stress ECG test for the presence of significant coronary atherosclerosis.

The controversy in these studies is considerable, and we have tried to elucidate the role of FMD and IMT measurement in patients with different degrees of CAD development. The weak and inconsistent correlation between them indicates that both of these methods have their individual value in the patient evaluation process. This is also confirmed by the finding of cutoff values for both of them (≤4.4% for FMD and ≥0.8 mm for IMT) which demonstrate an acceptable sensitivity, specificity, PPV, and NPV for the presence of angiographically significant CAD.

One possible limitation of the present study is that in the analysis of the ROC curves we have assumed that patients with risk factors without angina pectoris and patients with angina pectoris and negative treadmill test do not have significant CAD. As already mentioned these patients have not undergone CAG. There exists a real, although rare,

possibility that some of them have more than minor coronary artery stenoses. We believe, however, that even if such cases existed, they would not significantly influence the shape of the ROC curves and change the prognostic significance of FMD and IMT.

Conclusion

The results of the present study can be summarized as follows. (1) Patients with advanced coronary atherosclerosis have lower FMD values and higher IMT values compared to patients with risk factors, patients with angina pectoris and negative treadmill test, and patients with positive stress ECG test and minor coronary artery changes. (2). Flow-mediated dilatation and IMT show a weak correlation with each other, which is lost in the subgroup analysis and when controlling for the presence of significant CAD, number of diseased coronary arteries, percent coronary artery stenosis, and group membership. (3) Flow-mediated dilatation values ≤4.5% and IMT values ≥0.81 mm have to some extent the ability to predict the presence of angiographically significant CAD.

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