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Diagnostic value of flow mediated dilatation measurement for coronary artery lesions in men under 45 years of age

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Abstract

Background: *In those without symptoms of coronary artery disease (CAD), the incidence of coronary events is still high. The aim of this study was to evaluate whether flow mediated dilatation (FMD) is a useful tool in identifying those with CAD in who are under 45 years of age.*

Methods and results: *Seventy five men below 45 years of age, hospitalized in order to perform elective coronary angiography, were enrolled into the study. Based on coronary angiography findings, they were divided into two groups: study group (Group A, n = 55) with obstructive coronary lesions and the control group (Group B, n = 20) without significant lesions in coronary arteries. In all subjects atherosclerosis risk factors were analyzed. Endothelial dysfunction was assessed in ultrasound via FMD. FMD was significantly lower in the study group than in the control group (3.92 ± 1.1* vs *6.51 ± 1.1, p < 0.001). FMD, as well as age, diabetes and positive family history, appeared to be statistically significant CAD risk factors. AUROC for FMD was 0.957 (p < 0.001), meaning this model had an almost complete ability to predict the presence of CAD. AUROC for CAD diagnosis on the basis of significant clinical parameters was 0.992 (p < 0.001), also representing almost complete ability of this model to identify asymptomatic subjects with CAD risk.*

Conclusions: *The evaluation of endothelial function by the use of FMD in the population of men below 45 years of age with diabetes and positive family history can help in identifying subjects at high risk of coronary artery disease.* (Cardiol J 2010; 17, 3: 288–292)

Key words: endothelial dysfunction, coronary artery disease, flow mediated dilatation

Introduction

Among those without coronary artery disease (CAD) symptoms, the incidence of coronary events is still high. This concerns also the population with early onset of CAD, when the symptoms occur before 45 years of age. According to many epidemiological studies, about 40% of all serious coronary events occur in 20% of the population, in subjects with three or more risk factors. This means that almost 60% of all serious coronary events occur in the larger population, in which classical atherosclerosis risk factors are less frequent or less intense. Therefore, in this group risk stratification is re-

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quired to define the risk of a coronary event more precisely. It has been proved that the risk of a coronary event correlates strongly with the presence of atherosclerotic lesions [1]. In many studies, a positive correlation between endothelial dysfunction and atherosclerotic lesions formation has been observed [2–4].

The aim of this study was to evaluate whether flow mediated dilatation (FMD) can be useful in diagnosing CAD in the population below 45 years of age.

Methods

Seventy five male patients below 45 years of age with a positive stress test result, admitted to our department in order to perform elective coronary angiography, were enrolled into the study. Based on coronary angiography findings, they were divided into two groups: the study group (Group A) with obstructive coronary lesions and the control group (Group B) without lesions in coronary arteries.

Angiographic criteria: patients with coronary lesions narrowing vessel lumen ≤ 10% of vessel cross-section were considered without lesions and included in the control group. Patients with coronary lesions narrowing vessel lumen ≥ 50% of vessel cross section were included in the study group. Patients with coronary lesions narrowing artery lumen 10–50% of vessel cross-section were excluded from the study.

The following atherosclerosis risk factors were analyzed: hypertension, hypercholesterolemia, diabetes, smoking, overweight or obesity, family history of CAD. For the purpose of this study, the following definitions were used: hypertension — arterial blood pressure equal to or exceeding 140/ /90 mm Hg and/or use of anti-hypertensive therapy; hypercholesterolemia — plasma cholesterol concentration exceeding 200 mg/dL at the time of the study or any time in the past; diabetes — diagnosis of diabetes during index hospitalization or the use of anti-diabetic agents and/or diet; obesity — body mass index (BMI) exceeding 30 kg/m^2; smoker — smoking at least one cigarette/day for at least six months; positive family history — myocardial infarction in parents or siblings before 55 years of age.

The study was approved by the Bioethics Committee of the Medical University of Silesia and all patients provided written informed consent.

Study protocol

All patients used vascular agents, such as nitrates, calcium blockers, beta-adrenolytics, ACE--inhibitors, and statins which were administered routinely, also before ultrasound examination and coronary angiography.

Ultrasound examination of FMD was performed after overnight fast in the morning (before morning medications — minimum 8–12 hours post evening medications), after 15 minutes rest in the horizontal position, by means of SONOS 5000 ultrasoud scanner (Hewlett Packard, USA) with the linear transducer 11 MHz.

The diameter of the right brachial artery was measured 3–5 cm above the antecubital space in the M-mode, at baseline. The measurement was performed in the end-diastolic phase, marking the diameter between anterior and posterior artery wall in the zone between media and adventitia ('m-line'). An average of three measurements was taken and further analyzed to calculate FMD. Subsequently, a pneumatic tourniquet was placed on the upper part of the right forearm and inflated for four minutes to a pressure of 200 mm Hg or 50 mm Hg above systemic arterial blood pressure. Sixty seconds after cuff release, the diameter of the right brachial artery was measured three times. FMD was calculated as an increase of vascular diameter (in percentage) from the difference between maximum and baseline brachial artery diameter.

After a 15 minute break, a nitroglycerine-mediated dilatation test (NTG-MD test) was performed using 0.4 mg of sublingual nitroglycerine (Nitromint 0.4 mg/dose, Egis Pharmaceuticals, Hungary). Before nitroglycerine administration, brachial artery diameter was measured three times as the baseline, and five minutes after nitroglycerine administration, it was measured another three times. NTG-MD was calculated as an increase of vascular diameter (in percentage) from the difference between maximum and baseline brachial artery diameter [5].

Coronary angiography was performed with the Judkins method from the right femoral artery access. After 6 F sheath insertion, angiography of both coronary arteries was done using contrast agent Visipaque 320 (Amersham Health, USA), showing right coronary artery in at least two opposite projections and left coronary artery in at least four different projections. Coronary artery narrowings were calculated digitally (QCA, Quantitative Coronary Angiography).

Statistical analysis

Qualitative variables were shown as absolute values and percentage and quantitative variables as mean and standard deviation (for normal distribution) and as median and interquartile range (for dis-

tribution different from normal). Type of distribution was assessed using the Shapiro-Wilk test. The differences between the groups were interpreted on the basis of Student's t-test (for normal distribution) and Mann-Whitney U test (for distribution different from normal), and for qualitative data on the basis of χ^2 test or the exact Fisher test. Additionally, in order to diminish the influence of confounding variables, multivariate analysis was performed in the model of logistic forward stepwise regression, where the dependent variable was angiographically verified presence of coronary artery disease, and the independent variables were age, BMI, the presence of coexisting diseases, LDL cholesterol and triglycerides concentrations, diabetes, positive family history and FMD value. The ability of FMD measurement, and of all clinical parameters together, to diagnose coronary artery disease was verified on the basis of ROC curve analysis (the accuracy of patients' assignment to study/control group in particular FMD cut-off points). For the model adjustment assessment, the value of the area under the ROC (AUROC) was calculated as was its statistical significance. P value < 0.05 was considered statistically significant.

Results

Seventy five males were enrolled into the study, 55 into the study group (Group A) and 20 into the control group (Group B). Patients in Group A more frequently had diabetes and were overweight, and had significantly higher triglyceride concentration in comparison to the control group. The characteristics of the groups are presented in Table 1.

Patients in the study group had a significantly lower FMD value compared to the control group (Table 2).

The analysis of coronary artery disease determinants is shown in Table 3. In this multivariate model, only the influence of FMD (logOR = 0.94, 95% CI 0.86–0.97), age (logOR = 0.3, 95% CI 0.04––0.71), diabetes (logOR = 0.92, 95% CI 0.81–0.98) and positive family history (logOR = 0.92, 95% CI 0.82–0.98) appeared to be statistically significant.

ROC curve for CAD diagnosis on the basis of FMD is presented in Figure 1. Each 1% increase in FMD value diminished the likelihood of CAD diagnosis almost nine times (logOR = 0.102, 95% CI 0.024–0.262, $p < 0.001$). The value of the AUROC was 0.957 ($p < 0.001$), which means there was an almost complete ability of this model to predict the presence of CAD.

ROC curve for CAD diagnosis on the basis of clinical parameters in the model of logistic regression is shown in Figure 2. After adjustment for statistically significant determinants of CAD prevalence,

Table 1. Characteristics of the groups.

Variables	Group A	Group B	p
Age (years)	38.1 ± 4.3	40.9 ± 4.8	0.006
BMI [kg/m^2]	27.7 ± 3.3	27.0 ± 1.9	0.5
Overweight (%)	100.0	83.6	0.05
Smoking (ever) (%)	85.4	100.0	0.07
Diabetes (%)	25.0	7.3	0.05
Arterial hypertension (%)	50.9	70.0	0.1
Positive family history of CAD (%)	45.0	30.0	0.2
Total cholesterol [mg/dL]	224.6 ± 48.6	216.8 ± 33.7	0.5
LDL cholesterol [mg/dL]	151.9 ± 43.5	139.8 ± 32.7	0.3
Triglycerides [mg/dL]	167.8 ± 68.4	131.0 ± 53.5	0.02

BMI — body mass index; CAD — coronary artery disease

Table 2. Flow mediated dilatation (FMD) value.

Variable	Group A	Group B	p
FMD (%)	3.92 ± 1.1	6.51 ± 1.1	< 0.001

Table 3. Determinants of coronary artery disease (CAD) prevalence in multivariate model.

Variable		logOR	95% CI
Flow mediated dilatation (%)	Step 1	0.94	0.859–0.974
Age (years)	Step 2	0.3	0.04–0.71
Diabetes	Step 3	0.922	0.807–0.979
Positive family history of CAD	Step 4	0.925	0.817–0.98

$R^2 = 0.655$; $p < 0.001$; logOR — logistic odds ration value; 95% CI — 95% confidence interval of logistic odds ration

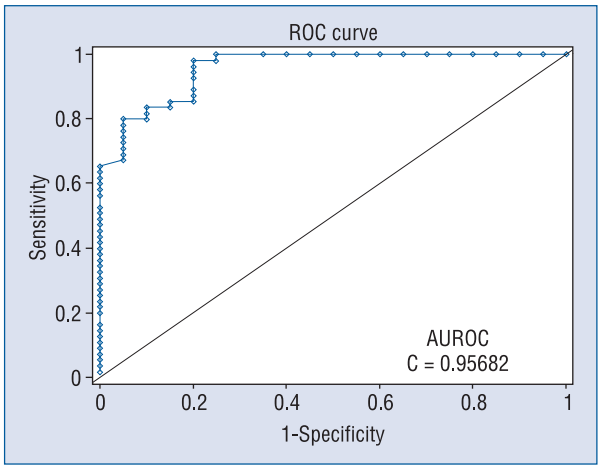

Figure 2. ROC curve for coronary artery disease diagnosis on the basis of flow mediated dilatation.

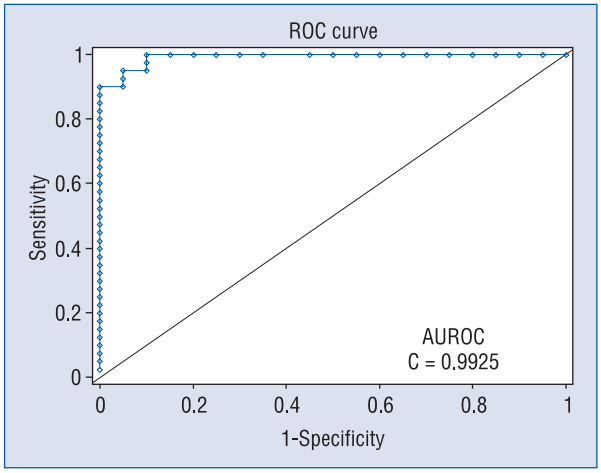

Figure 3. ROC curve for coronary artery disease diagnosis on the basis of clinical parameters in the model of logistic regression.

AUROC was 0.992 ($p < 0.001$), which represents an almost complete ability of this model to identify subjects at risk of CAD.

Discussion

Endothelium is the largest endocrine gland in the organism, which maintains circulatory system homeostasis using many biological transmitters [6]. As a non-invasive ultrasound technique which enables the evaluation of the brachial artery, FMD has been commonly recognized as a useful index of endothelial function [5]. The methodology described for the first time by Celermajer et al. [7] is based on evoking brachial artery ischemia and evaluating subsequent artery dilatation due to post-ischemic flow increase. Artery dilatation depends on the increase of shear stress, caused by blood pressure and blood flow velocity increase. Shear stress is defined as a force acting on the vascular wall area unit. As a response for the shear stress, endothelial nitric oxide is released and vascular smooth muscles are relaxed [8, 9]. Decreased FMD represents endothelial dysfunction, and can be observed in subjects with coronary artery risk factors and with symptomatic CAD [10–17].

Kirma et al. [18] investigated the relationship between FMD and CAD risk factors in 150 patients with stable angina, evaluating the following risk factors: age, diabetes, positive family history, smoking, hypertension, BMI and concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. In univariate analysis, FMD correlated negatively with age and BMI, and in patients with diabetes significantly lower FMD was observed. In stepwise multivariate analysis, estimating which risk factors have significant influence on endothelial function, this relationship was confirmed with regard to diabetes and age, but not to BMI. No correlation was shown between FMD and hypercholesterolemia, positive family history, hypertension or smoking [18].

In our study, the analysis of CAD prevalence determinants confirmed the results of Kirma et al. [18] concerning the influence of age and diabetes on FMD value. However, it has to be underlined that their study group was significantly older (57.0 ± ± 11.1 years) than ours. It has already been proved that FMD decreases as age increases [19]. Therefore, our findings concerning the evaluation of FMD in those below 45 years of age is even more significant.

One of our findings was that positive family history of early CAD onset has significant influence on FMD variability as a CAD risk factor, which was not confirmed by Kirma et al. [18]. Nevertheless, there are strong indications that positive family history is a significant risk factor of coronary artery disease, especially for young patients. Relative risk of CAD in siblings of patients with CAD is increased 2–12 times in comparison to the general population [20].

However, we are the first to report, on the basis of ROC curve analysis for CAD, that low FMD value can (with high probability) identify subjects with asymptomatic coronary artery disease.

Conclusions

The evaluation of endothelial function by the use of FMD in the population of men below 45 years of age with diabetes and a positive family history can help in identifying subjects at high risk of coronary artery disease.

Acknowledgements

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