Atherosclerosis

Prognostic Value of Brachial Artery Endothelial Function and Wall Thickness

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OBJECTIVES	We sought to examine the prognostic value of brachial artery (BA) flow-mediated vasodilation (FMD) and intima-media thickness (IMT) in patients admitted for invasive evaluation of chest pain.
BACKGROUND	Both FMD and IMT of the BA have been associated with coronary risk factors and the presence of coronary artery disease (CAD). Recent studies on the prognostic value of FMD have been conflicting.
METHODS	In 398 consecutive patients (age 54 ± 9 years) undergoing coronary angiography, FMD and IMT of the BA were measured using high-resolution ultrasound (13 MHz). Patients were divided into two groups according to the FMD median (7.6%). After a mean follow-up of 39 ± 12 months, cardiovascular events were documented.
RESULTS	No difference was found in the number of cardiovascular events between groups. On multivariate Cox regression analysis, including age, number of risk factors, BA diameter, presence of CAD, FMD, and IMT, only the presence of CAD and IMT remained significantly associated with cardiovascular events.
CONCLUSIONS	Intima-media thickness predicted late (up to 4 years) cardiovascular events in a large population admitted for evaluation of chest pain. In contrast, the long-term prognostic value of a single baseline measure of BA-FMD seems to be limited. (J Am Coll Cardiol 2005;46: 1006–10) © 2005 by the American College of Cardiology Foundation

Endothelial dysfunction is an early phenomenon in atherosclerosis and often precedes structural changes and clinical manifestations (1). Flow-mediated vasodilation (FMD) is a non-invasive test using high-resolution ultrasound for the assessment of endothelial function in the brachial artery (BA) (2). An improvement of BA-FMD after various therapeutic interventions has been demonstrated (3,4), suggesting that FMD may serve as a surrogate marker for long-term clinical benefit. Accordingly, some (5–7) but not all (8) recent studies have shown an association of FMD with cardiovascular events. Thus, the prognostic value of endothelial function testing is not yet established.

Intima-media thickness (IMT) is another sonographic parameter of atherosclerosis (9) and is usually measured in the carotid and/or femoral arteries (10,11). The IMT measurement of the BA is less well established, although atherosclerosis also occurs in this vessel (12). The sonographic assessment of the BA has the advantage of obtaining functional and morphologic information within the same artery.

The aim of this prospective study was to compare the prognostic importance of BA-FMD and IMT in a large group of patients admitted for invasive evaluation of chest pain.

METHODS

Study population. A total of 398 male patients (mean age 54 ± 9 years) in whom coronary angiography was performed due to chest pain, as well as a positive exercise stress test, were consecutively enrolled. Exclusion criteria were age >70 years, acute coronary syndrome, congestive heart failure, left ventricular ejection fraction <40%, and significant valvular disease. Coronary artery disease (CAD) was defined as ≥30% diameter stenosis in one or more major vessels. Written, informed consent was obtained from all patients.

Study protocol. At entry, fasting blood samples were obtained and coronary risk factors were assessed as previously described (13,14). On the day after angiography, high-resolution ultrasound (13 MHz, Acuson Sequoia C 256, Mountain View, California) was used for the assessment of FMD and IMT. After a mean follow-up of 39 ± 12 months, cardiovascular events were documented by phone calls to the patients, followed by a review of hospital records for verification. In the power analysis, we calculated that a sample size of 150 patients in each group would have 80% power to detect a 10% difference in events after 36 months (alpha = 0.05).

Ultrasound studies of the BA. The ultrasound examination was performed between 9 AM and 12 AM by an observer blinded to the patients' diagnoses, as previously described (3,13). After a resting period of at least 10 min in the supine position, the right BA was scanned. After recording of resting diameters (electrocardiographically triggered to the

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Abbreviations and Acronyms

BA	= brachial artery
CAD	= coronary artery disease
FMD	= flow-mediated vasodilation
IMT	= intima-media thickness
NMD	= nitroglycerin-mediated vasodilation

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peak of the T wave), a cuff was placed on the upper arm and inflated to suprasystolic levels for 5 min. For all 120 s after deflation of the cuff, serial post-hyperemia scans were stored on the hard disk. Finally, 0.8 mg nitroglycerin was given sublingually, and diameters within 10 min were recorded (nitroglycerin-mediated vasodilation [NMD]). The maximum diameter after cuff release and nitroglycerin application were used for calculation of FMD and NMD.

Intima-media thickness was assessed as previously described (13,14); the IMT at the far wall was measured directly as the distance between the lumen-intima and media-adventitia border by using a regional expansion system in addition to 13-MHz ultrasound. Measurements were made at two sites per image in four different images per patient. Interobserver variability of FMD and IMT measurements in our laboratory has been previously published (3,13).

Statistical analysis. Data are expressed as the mean value ± SD (ranges) or as frequencies (percentages). A normal distribution of variables was tested using a Kolmogorov-Smirnov test with Lilliefors' correction. Patient characteristics between groups were compared using the Student t test or Mann-Whitney U test for continuous variables and chi-square test or Fisher exact test for categorical variables, as appropriate. Cumulative event rates were calculated according to the Kaplan-Meier method and log-rank test. Cox regression analyses were performed to determine the variables independently associated with cardiovascular events. A p value <0.05 was considered statistically significant. All analyses were conducted with the use of statistical software (SPSS for Windows, version 10.1, SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics. The clinical characteristics are summarized in Table 1. Of the 315 CAD patients, 57% had at least one significant coronary lesion (≥70% diameter stenosis). Percutaneous coronary interventions were not significantly different between groups. Based on the median value of FMD (7.6%), patients were divided into two groups: patients below (group 1) and above the median value (group 2).

Flow-mediated vasodilation (8.2 ± 4.2% vs. 7.9 ± 3.8%, p = 0.61) and NMD (17.6 ± 7.3% vs. 17.8 ± 6.3%, p = 0.82) were not significantly different between CAD and non-CAD patients, whereas IMT was greater in CAD patients compared with non-CAD patients (0.37 ± 0.07 mm vs. 0.34 ± 0.08 mm, p < 0.01).

Follow-up. During a mean follow-up of 39 ± 12 months (range 21 to 78 months), 44 adverse events were documented: cardiac death (n = 4), myocardial infarction (n = 8), percutaneous coronary intervention as well as bypass surgery (at least six months after baseline evaluation) (n = 24), repeat coronary angiography with documented progression of coronary atherosclerosis (n = 3), or hospitalization for worsening angina and exclusion of instability (n = 5). The proportion of patients who stopped smoking, as well as changes in medication and body mass index, were not significantly different between groups.
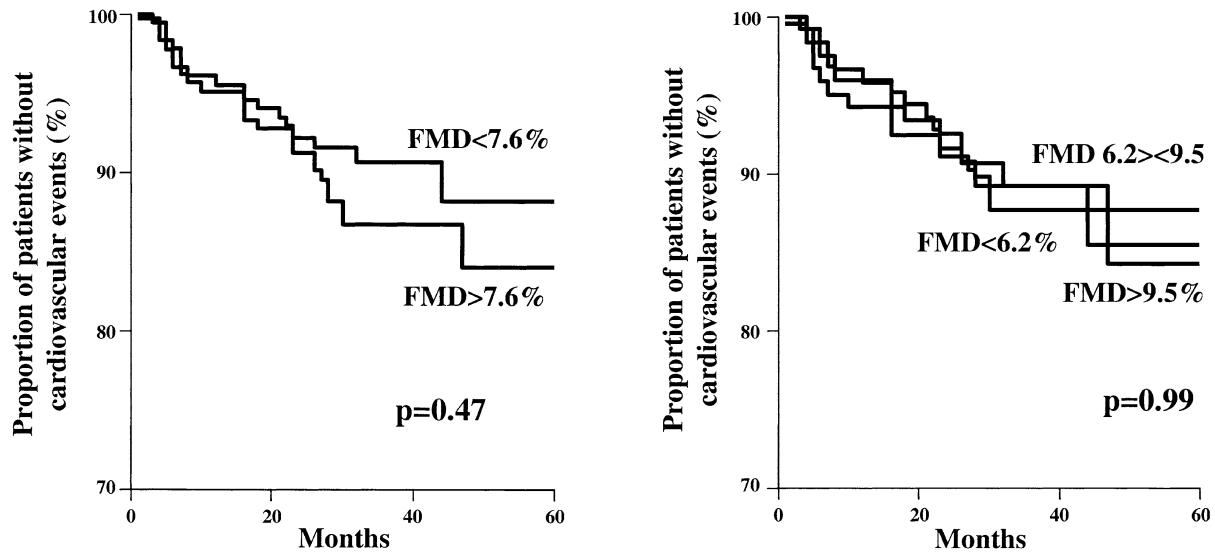
No significant difference in outcome was observed when patients were divided according to the median FMD value

Table 1. Characteristics of Patients

	FMD <7.6% (n = 199)	FMD >7.6% (n = 199)	p Value
Age (yrs)	55 ± 9 (31–78)	53 ± 10 (27–74)	0.08
Prevalent CAD	155 (78%)	160 (80%)	0.62
Number of risk factors	2.0 ± 1.0 (0–5)	1.9 ± 0.9 (0–4)	0.44
Hypertension	107 (54%)	109 (55%)	0.92
Smokers	69 (35%)	63 (32%)	0.59
Hypercholesterolemia	151 (76%)	154 (77%)	0.55
Diabetes mellitus	24 (12%)	9 (5%)	**0.01**
Positive family history	49 (25%)	41 (21%)	0.40
Total cholesterol (mg/dl)	218 ± 54 (96–602)	218 ± 44 (104–367)	0.96
LDL cholesterol (mg/dl)	143 ± 41 (31–330)	143 ± 41 (32–279)	0.99
HDL cholesterol (mg/dl)	46 ± 14 (23–109)	47 ± 14 (20–123)	0.38
Triglycerides (mg/dl)	171 ± 148 (50–1,580)	172 ± 94 (41–736)	0.91
Body mass index (kg/m^2)	27 ± 4 (19–41)	27 ± 3 (19–40)	0.33
BA diameter (mm)	4.5 ± 0.5 (3.1–6.0)	4.0 ± 0.5 (2.9–5.4)	**<0.01**
BA-IMT (mm)	0.37 ± 0.06 (0.21–0.53)	0.36 ± 0.8 (0.16–0.53)	0.59
Statin	49 (25%)	46 (23%)	0.73
ACE inhibitor	52 (26%)	37 (19%)	0.07

Data are presented as the mean value ± SD or number (%) of subjects. Significant values (p < 0.05) are highlighted in **bold**.
ACE = angiotensin-converting enzyme; BA = brachial artery; CAD = coronary artery disease; FMD = flow-mediated vasodilation; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein.

Figure 1. Kaplan-Meier curves for flow-mediated vasodilation (FMD) median **(left)** and FMD tertiles **(right)**. The p value was calculated using the log-rank test.

or tertiles (Fig. 1). In a third analysis, groups were formed according to absolute changes in BA diameter during hyperemia compared with baseline, which did not reveal any association with cardiovascular events (19 vs. 25 events, p = 0.47). Neither NMD (22 vs. 22 events, p = 0.97) nor the FMD/NMD ratio (25 vs. 19 events, p = 0.46) was predictive of outcome.

When patients were classified according to their IMT, patients above the median value of 0.37 mm had significantly more events compared with patients whose value was <0.37 mm (Fig. 2). In addition, patients were divided into groups of IMT tertiles. Overall, we found a borderline significant difference with regard to cardiovascular events (Fig. 2).
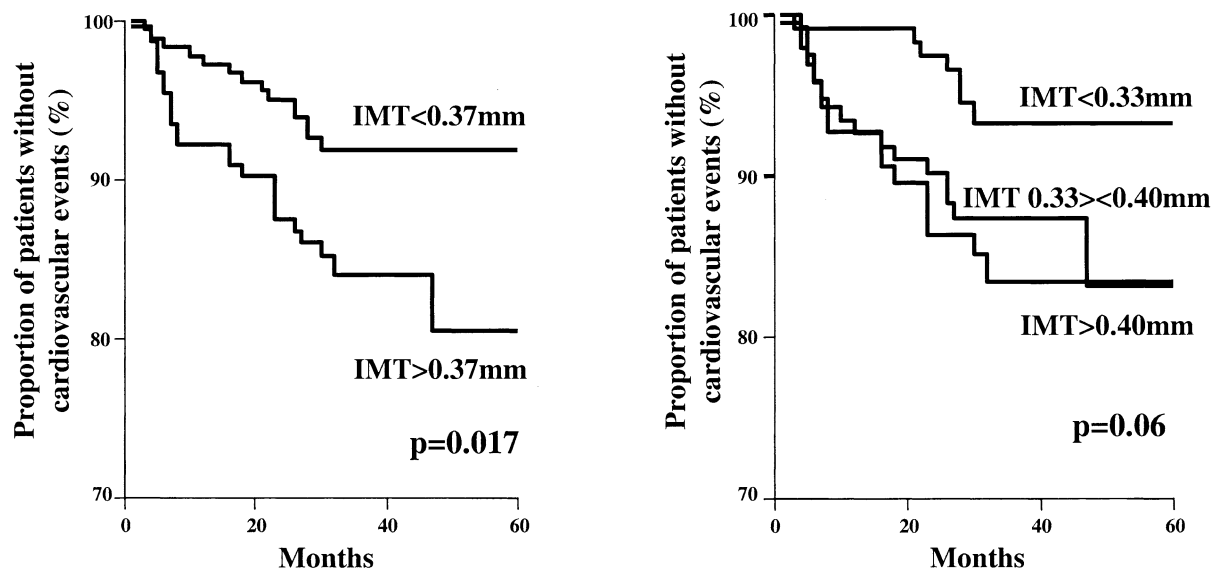
Finally, we calculated several Cox regression analyses

(Tables 2 and 3). Only the presence of CAD and BA-IMT remained significantly associated with cardiovascular events (Table 3).

DISCUSSION

In this prospective study of 398 patients undergoing coronary angiography, BA-IMT but not FMD was predictive of long-term cardiovascular events.

The clinical usefulness of non-invasive tests largely depends on their reproducibility and proof of predictive value. The role of FMD in this regard is still debated. Neunteufl et al. (15) followed 73 patients with chest pain for five years and showed that patients with FMD >10% had significantly less events than did patients below this threshold.

Figure 2. Kaplan-Meier curves for intima-media thickness (IMT) median **(left)** and IMT tertiles **(right)**. The p value was calculated using the log-rank test.

Table 2. Cox Regression Analyses for Cardiovascular Events Including FMD or NMD

Covariates	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (per yr)	0.99 (0.96–1.03)	0.69	0.99 (0.96–1.03)	0.64
No. of risk factors	1.30 (0.94–1.79)	0.12	1.27 (0.92–1.76)	0.14
BA diameter	0.81 (0.43–1.53)	0.52	0.76 (0.39–1.47)	0.41
Presence of CAD	6.61 (1.57–27.8)	**0.01**	6.86 (1.63–28.8)	**0.01**
BA-FMD <7.6%	1.10 (0.57–2.11)	0.79		
BA-NMD <17.9%			0.90 (0.45–1.81)	0.77

Significant values (p < 0.05) are highlighted in **bold**.
    CI = confidence interval; NMD = nitroglycerin-mediated vasodilation; HR = hazard ratio; other abbreviations as in Table 1.

After correction for the presence of CAD, this association no longer remained significant. In another study of 152 patients with CAD, only the FMD/NMD ratio but not FMD was independently predictive of cardiovascular events after a mean follow-up of 34 months (16). More recently, Fathi et al. (8) reported data on 444 patients with a high cardiovascular risk profile and demonstrated that carotid IMT but not FMD was related to cardiovascular events.

Our study is in accordance with the latter observation in that morphologic rather than functional arterial changes are associated with outcome. Furthermore, it is the first study to include both functional and morphologic information within the same artery in a multivariate model for the prediction of cardiovascular events. In contrast to our observation, other studies have shown an independent association of FMD with prognosis. Gokce et al. (5) showed that patients in the highest FMD tertile had a better short-term and long-term clinical outcome after vascular surgery (7). Recently, Brevetti et al. (6) demonstrated that BA-FMD had an additive prognostic value to the ankle-brachial pressure index in 131 patients with peripheral arterial disease. Several factors may explain the discrepancy between our data and the latter three studies. First, there are important differences among study populations. Second, angiographic documentation of CAD was not performed in all patients of previous studies. Third, disparate results on the prognostic value of FMD also relate to the interindividual variability and the lack of standardization, which still precludes its recommendation as a screening test in clinical practice (17,18).

From our observation, long-term cardiovascular outcome may not be predicted by a *single* baseline FMD measure. We cannot exclude, however, that improvement in FMD, which has been shown for a variety of therapeutic interventions, has a prognostic impact. Indeed, Chan et al. (16) showed

that serial measurements of FMD may improve the prognostic value of this test. Therefore, *serial* rather than single measurements of BA-FMD may be more useful in the assessment of cardiovascular risk. Therapeutic improvement in endothelial function, however, has not always translated into better clinical outcomes (18).

The finding that BA-IMT was predictive of cardiovascular outcome is in line with studies using carotid or femoral artery IMT (10,11). Therefore, morphologic examination of different vascular beds, perhaps in combination with serial assessment of endothelial function, may improve the management of high-risk patients, a concept that deserves further investigation.

Study limitations. We found no univariate or multivariate correlation between coronary risk factors and FMD. This may be due to the homogeneous risk profile of our population, as two-thirds of the patients had one or two coronary risk factors. In accordance with this interpretation, a recent publication in 1,154 male patients did not find a significant association between FMD and Framingham risk scores (19). All patients had coronary angiography, which may introduce selection bias toward symptomatic patients.

Conclusions. Intima-media thickness of the BA, but not FMD, predicted long-term (up to four years) cardiovascular events in a population with chest pain with or without underlying CAD. Whether morphologic examination of different vascular beds in combination with serial measurements of FMD may improve the identification of high-risk patients remains to be established.

Table 3. Cox Regression Analysis for Cardiovascular Events Including FMD and IMT

Covariates	HR (95% CI)	p Value
Age (per yr)	0.98 (0.94–1.02)	0.29
No. of risk factors	1.22 (0.86–1.73)	0.28
BA diameter	0.96 (0.48–1.90)	0.91
Presence of CAD	9.18 (1.24–68.0)	**0.03**
BA-FMD median	1.52 (0.75–3.08)	0.24
BA-IMT median	2.20 (1.08–4.47)	**0.03**

Significant values (p < 0.05) are highlighted in **bold**.
    Abbreviations as in Tables 1 and 2.

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