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
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.
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.
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 IMT but not FMD was related to cardiovascular events. In contrast to our observation, other studies have shown an independent prediction of cardiovascular events. 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.

**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.

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**REFERENCES**


