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Morphologic Rather Than Functional or Mechanical Sonographic Parameters of the Brachial Artery Are Related to Angiographically Evident Coronary Atherosclerosis

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OBJECTIVES The purpose of this study was to determine the relationship among coronary atherosclerosis and functional, morphologic, and mechanical parameters assessed noninvasively within the brachial artery (BA).

BACKGROUND Flow-mediated vasodilation (FMD) of the BA, intima-media thickness (IMT) of the carotid artery, and distensibility of the aorta have been correlated with the presence of coronary artery disease (CAD).

METHODS The BA was examined with high-resolution ultrasound (13 MHz) in 117 male patients, in whom coronary angiography was performed. Coronary artery disease (≥30% diameter stenosis in ≥1 major branch) was found in 84 patients, and 33 patients had smooth coronary arteries (non-CAD). Wall cross-sectional area (WCSA) was calculated from resting diameter and IMT.

RESULTS The BA-WCSA (5.3 ± 1.5 mm^2 vs. 4.4 ± 1.4 mm^2, $p = 0.002$) and IMT (0.37 ± 0.07 mm vs. 0.31 ± 0.07 mm, $p < 0.001$) were significantly greater in patients with CAD compared with non-CAD patients. Flow-mediated vasodilation and distensibility were similar among groups. Using logistic regression analyses adjusting for age, positive family history, hypertension, hypercholesterolemia, smoking, FMD, and distensibility, only WCSA ($p < 0.01$) and IMT ($p < 0.001$) correlated independently with the presence of CAD.

CONCLUSIONS Morphologic but not functional and mechanical parameters of the BA are associated with the presence of CAD. Among BA sonographic parameters, IMT and WCSA seem to be the most accurate ones for the estimation of coronary atherosclerotic risk. (J Am Coll Cardiol 2002;40:1825–30) © 2002 by the American College of Cardiology Foundation

Ultrasound examinations of peripheral arteries have been increasingly used for the noninvasive assessment of early atherosclerotic changes including functional, morphologic, and mechanical properties (1–10). The intention of these studies was to determine the association of sonographic parameters of peripheral arteries with coronary arteries in the search for appropriate surrogates. Indeed, morphologic changes such as increased intima-media thickness (IMT) of the carotid artery have been associated with coronary risk factors (1,2) and atherosclerotic disease (1,3,4). In addition, studies have shown that changes in mechanical properties (distensibility, compliance, or stiffness) of central arteries are associated with atherosclerotic risk or manifest disease (11–17). However, the latter measurements were inconclusive in peripheral arteries (5–7). Flow-mediated vasodilation (FMD) as a functional parameter of the brachial artery (BA) has shown correlation with risk factors (8,9) and coronary endothelial function (10).

The BA offers the opportunity to perform all of these non-invasive measurements during one single examination. Which of these parameters is the most useful and reliable for the detection of vessel dysfunction and/or atherosclerosis remains controversial. Therefore, the aim of this study was to determine the relationship between coronary atherosclerosis and functional, morphologic, and mechanical parameters noninvasively assessed within the BA.

METHODS

Patients. One hundred seventeen male patients (mean age 52 ± 11 years, range 19 to 73 years) in whom coronary angiography due to chest pain was performed were consecutively enrolled into the study. Exclusion criteria were congestive heart failure, left ventricular ejection fraction <40%, and significant valvular disease. Coronary artery disease (CAD) (defined as visually estimated percent diameter stenosis ≥30% in ≥1 major vessel) was found in 84 patients; 33 patients had smooth coronary arteries. Number of vessels diseased and maximum percent stenosis index were assessed as previously described (18). Written informed consent was obtained from all patients. Investigations were done in accordance with the Declaration of Helsinki.

Fasting blood samples were obtained in all patients for the measurement of plasma total, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol as well as triglycerides. Coronary risk factors were assessed as follows:

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Abbreviations and Acronyms

BA = brachial artery
BP = blood pressure
CAD = coronary artery disease
CD = cross-sectional distensibility
E_{inc} = incremental elastic modulus
FMD = flow-mediated vasodilation
IMT = intima-media thickness
LDL = low-density lipoprotein
NMD = nitroglycerin-mediated vasodilation
WCSA = wall cross-sectional area

smokers were defined as subjects who had smoked regularly during the previous 12 months (19). Hypertension was defined as a systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg (which is hypertension stage I as defined in the fifth report of the Joint National Committee on detection, evaluation, and treatment of high BP [20]) based on the average of two or more readings taken on each of two or more different days or as current use of antihypertensive drugs. Subjects with plasma LDL cholesterol level >130 mg/dl or who were receiving cholesterol-lowering therapy were classified as hypercholesterolemic patients (19). Patients were considered as diabetic if they were under treatment with insulin or oral hypoglycemic agents or if fasting blood glucose exceeded 140 mg/dl (19). A family history of CAD and a history regarding diabetes were obtained.

Ultrasound studies of the BA. On the day after angiography, high-resolution ultrasound (13 MHz, Acuson Sequoia C 256, Mountain View, California) was used for the assessment of functional, morphologic, and mechanical properties of the BA. The ultrasound examination was performed between 9 AM and 12 AM by an observer blinded to patients' diagnoses. All vasoactive drugs were withdrawn 18 to 24 h before examination. Patients were instructed not to smoke and to remain fasting before the ultrasound examination. After a resting period of at least 10 min in supine position, BP was measured using a manual sphygmomanometer, and the right BA was scanned. Transducer position and gain settings were optimized, and electrocardiogram-triggered images were stored to the peak of the T-wave on the hard disk for off-line measurements. The off-line measurements for functional, morphologic, and mechanical parameters were done on different days several weeks apart.

Assessment of morphologic parameters. The IMT was assessed as follows using electronic calipers (21): the IMT at the far wall was measured directly as the distance between lumen-intima and media-adventitia border by using the regional expansion system in addition to 13-MHz ultrasound. Measurements were made at two sites per image in four different images per patient. The two sites per image were defined as being at or close to 1 mm of the "peak" of the vessel arch. Usually, this peak is the location that gives the clearest image. The mean of eight measurements was defined as BA-IMT. In addition, wall cross-sectional area (WCSA) was calculated (see the following text).

Assessment of mechanical properties. End-diastolic luminal diameter (D_{dia}) and peak systolic luminal diameter (D_{sys}) were carefully measured in M-mode-image with longitudinal B-mode guiding. Brachial artery mechanical properties were calculated according to the following formula:

$$\text{Cross-sectional distensibility (CD)} = (2\ \Delta D\ D_{dia} + \Delta D^2)/(\Delta P\ D_{dia}^2)$$

$$\text{Incremental elastic modulus } (E_{inc}) = 3/CD[1 - (1 - \gamma)^2]$$

$$WCSA = \pi[(IMT + (D_{dia}/2))^2 - (D_{dia}/2)^2]$$

where ΔD is the difference between D_{dia} and D_{sys}, ΔP is the difference between systolic pressure and diastolic pressure, and γ is $IMT/(D_{dia}/2)$ ratio (5,7,11).

Assessment of BA function. Changes in vessel diameter (intima to intima diameter) after reactive hyperemia (FMD) and after sublingual nitroglycerin (nitroglycerin-mediated vasodilation [NMD]) were examined according to previously described methods (18,22). In brief, after recording of resting diameters a cuff was placed on the upper arm and inflated to suprasystolic levels for 5 min. The cuff was deflated and serial post-hyperemia scans were stored on the hard disk. When BA diameter had returned to baseline, 0.8 mg of nitroglycerin was given sublingually and diameters within the following 10 min were recorded. Vasodilation (FMD, NMD) was calculated as percent change in diameter compared with baseline.

Statistical analysis. Data are expressed as means ± standard deviations (ranges) or as frequencies (percentages). Normal distribution of the variables was assessed using Kolmogorov-Smirnov test with Lilliefors correction. Patient characteristics between groups were compared using Student *t* test (age, lipid levels, BP, body mass index, BA diameter, FMD, NMD, IMT, WCSA) or Mann-Whitney *U* test (CD, E_{inc}, maximum percent stenosis index) for continuous variables and chi-square test or Fisher exact test for categorical variables (coronary risk factors, medication, vessels diseased), as appropriate. Pearson's (age, lipid levels, BP, body mass index, BA diameter, FMD, NMD, IMT, WCSA) or Spearman's (CD, E_{inc}, presence of CAD, vessels diseased, maximum percent stenosis index) correlation coefficients were determined to assess the association of vascular parameters with clinical characteristics. Multiple linear regression analyses were used to adjust for univariate associations of IMT and WCSA with clinical characteristics. For the presence of CAD, logistic regression analyses were performed. Values of $p < 0.05$ were considered statistically significant. All analyses were conducted using statistical software (SPSS for Windows, versions 7.5.2G and 9, SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics. The clinical characteristics of patients are summarized in Table 1. The number of risk

Table 1. Characteristics of Patients

	CAD (n = 84)	Non-CAD (n = 33)	p Values
Age (yrs)	53 ± 10 (31–73)	50 ± 12 (19–71)	0.21
Number of risk factors	2.2 ± 1.0 (0–5)	1.6 ± 1.1 (0–4)	0.01*
Hypertension	48 (57%)	16 (48%)	0.41
Smokers	31 (37%)	11 (33%)	0.83
Hypercholesterolemia	74 (88%)	25 (76%)	0.15
Diabetes mellitus	9 (11%)	0 (0%)	0.06
Positive family history for CAD	25 (30%)	4 (12%)	0.04*
Total cholesterol (mg/dl)	222 ± 46 (117–341)	220 ± 40 (120–298)	0.79
LDL cholesterol (mg/dl)	149 ± 41 (65–251)	148 ± 31 (59–213)	0.83
HDL cholesterol (mg/dl)	46 ± 12 (27–109)	49 ± 12 (32–72)	0.26
Triglycerides (mg/dl)	171 ± 88 (44–464)	160 ± 82 (38–329)	0.53
Body mass index (kg/m^2)	27 ± 4 (21–40)	27 ± 3 (19–35)	0.35
Ps (mm Hg)	133 ± 16 (90–180)	133 ± 17 (100–180)	0.95
Pd (mm Hg)	77 ± 10 (55–115)	75 ± 12 (40–90)	0.50
PP (mm Hg)	56 ± 15 (20–110)	58 ± 18 (30–110)	0.54
BA diameter (mm)	4.3 ± 0.6 (3.1–5.8)	4.2 ± 0.6 (2.8–5.3)	0.29

*p values are statistically significant.
BA = brachial artery; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Pd = diastolic blood pressure; PP = pulse pressure; Ps = systolic blood pressure.

factors, the proportion of patients with positive family history and of patients with non-insulin-dependent diabetes mellitus were significantly greater in patients with CAD. Angiotensin-converting enzyme inhibitor (15% vs. 14%; p = NS), statin (9% vs. 19%; p = NS), acetylsalicylic acid (42% vs. 39%; p = NS), and beta-blocker therapy (27% vs. 38%; p = NS) were not different between groups, whereas nitrate therapy was more often used in patients with CAD (14% vs. 0%; p = 0.02).

Morphologic changes. Patients with CAD revealed significantly greater BA-IMT ($p < 0.001$) and WCSA ($p < 0.01$) compared with non-CAD patients (Fig. 1). Univariate and multiple regression analyses of BA morphologic sonographic measurements are shown in Table 2.

Mechanical properties. The CD (1.40 ± 0.81 10^{-3}/kPa vs. 1.33 ± 0.85 10^{-3}/kPa, p = NS) and E_{inc} (935 ± 556 mm Hg vs. 938 ± 685 mm Hg, p = NS) were similar among groups. On univariate analyses E_{inc} was associated with IMT ($r = 0.34$, $p < 0.001$), WCSA ($r = 0.33$, $p < 0.001$), age ($r = 0.22$, $p = 0.02$), and hypertension ($r = 0.21$, $p = 0.03$).

Functional changes. The FMD (7.7 ± 4.7% vs. 8.7 ± 4.7%, p = NS) and NMD (16.5 ± 8.0% vs. 18.2 ± 6.1%, p = NS) were similar among groups. On univariate analysis, FMD correlated with NMD ($r = 0.74$, $p < 0.001$) and inversely with resting diameter ($r = -0.63$, $p < 0.001$), WCSA ($r = -0.41$, $p < 0.001$), and age ($r = -0.21$, $p = 0.024$). The NMD correlated inversely with resting diam-

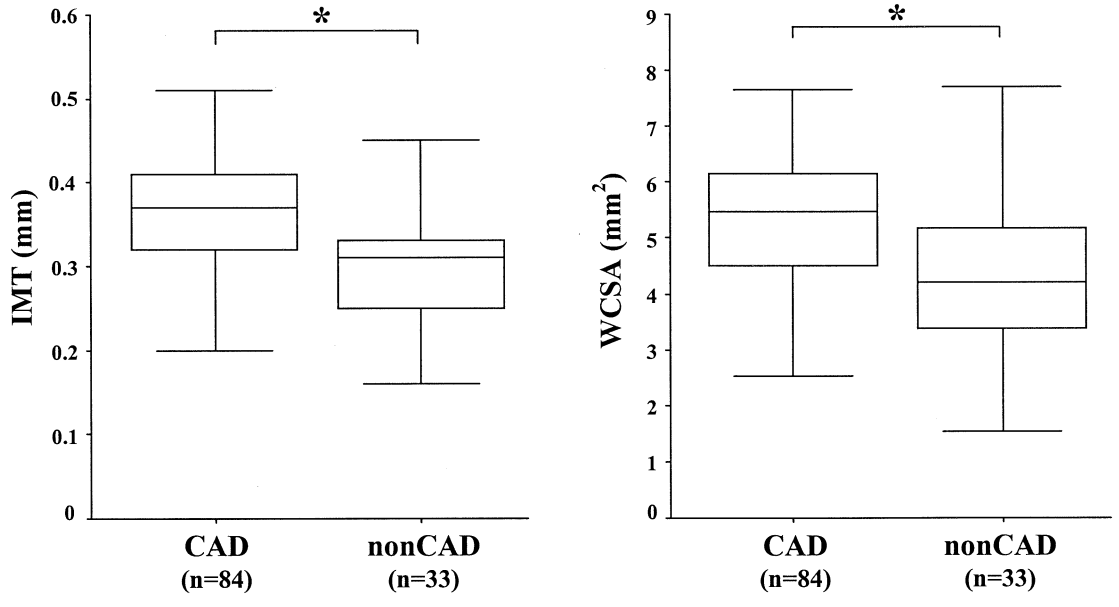

Figure 1. Box plots showing brachial artery morphologic parameters (intima-media thickness [IMT] on the **left panel**, wall cross-sectional area [WCSA] on the **right panel**) in coronary artery disease (CAD) and non-CAD patients. *$p < 0.01$.

Table 2. Univariate and Multivariate Associations Between Morphologic Parameters, Clinical Characteristics, and Different Functional and Mechanical Sonographic Parameters

	IMT			WCSA		
	r	p	Adjusted p	r	p	Adjusted p
CAD	0.36†	< 0.001	< 0.001*	0.31†	0.001	0.003*
VD	0.26†	0.006	n.i.	0.25†	0.008	n.i.
ST	0.30†	0.001	n.i.	0.22†	0.017	n.i.
HT	0.38†	< 0.001	0.013*	0.32†	0.001	0.005*
Age	0.37‡	< 0.001	0.056	0.41‡	< 0.001	0.952
D	0.24‡	0.010	0.120	0.56‡	< 0.001	< 0.001*
BMI	0.32‡	0.001	0.092	0.30‡	0.001	0.424
FMD	−0.16‡	0.090	n.i.	−0.41‡	< 0.001	0.771
NMD	−0.12‡	0.210	n.i.	−0.39‡	0.001	0.192
E_{inc}	0.34†	< 0.001	0.100	0.33†	< 0.001	0.022*

*Adjusted p values are statistically significant. †Spearman's correlation coefficient. ‡Pearson's correlation coefficient.

Adjusted p = p values calculated from linear regression analyses; BMI = body mass index; CAD = coronary artery disease; D = resting diameter; E_{inc} = incremental elastic modulus; FMD = flow-mediated vasodilation; HT = hypertension; IMT = intima-media thickness; n.i. = not included; NMD = nitroglycerin-mediated vasodilation; p = univariate p value; r = simple correlation coefficients; ST = maximum % stenosis index; VD = number of vessels diseased; WCSA = wall cross-sectional area.

eter ($r = -0.71$, $p < 0.001$), WCSA ($r = -0.39$, $p < 0.001$), and number of diseased vessels ($r = -0.20$, $p = 0.03$).

On logistic regression analyses after adjusting for age, positive family history, hypertension, hypercholesterolemia, smoking, FMD, and distensibility, only WCSA ($p < 0.01$) and IMT ($p < 0.001$) correlated independently with the presence of CAD (Table 3).

DISCUSSION

This study shows that among sonographically measured parameters of the BA, only morphologic (IMT, WCSA), but not functional or mechanical parameters are associated with the presence of CAD.

Morphologic parameters. The association between wall thickening of the carotid artery and angiographic and/or histologic changes of the coronary artery has been examined by several previous studies (1–4). In the Atherosclerosis Risk In Communities (ARIC) study, an increased carotid artery wall thickness in patients with prevalent CAD, cerebrovascular disease, and peripheral vascular disease was demonstrated (3). Lekakis et al. (23) showed that the femoral and carotid artery IMT are independent predictors of the CAD extent. In contrast, another study revealed only a weak correlation between carotid IMT and the extent of coronary atherosclerosis (24). In our study, IMT and WCSA were significantly greater in CAD compared with non-CAD patients. Both parameters revealed an association with the extent and severity of coronary atherosclerosis, but only WCSA showed a correlation with functional parameters. This difference is most likely due to two important variables. First, the vessel size is included in the WCSA calculation, but not when IMT alone is measured. Second, the functional parameters did not significantly differ between groups. Consequently, a lack of correlation between morphologic and functional parameters is not unexpected. Third, a discrepancy between functional and morphologic signs of atherosclerosis has been observed by several authors. Hashimoto et al. showed an inverse correlation between carotid IMT and BA endothelial function when CAD and non-CAD patients were included into the calculation, but not in the CAD patients alone (25). Another study using intravascular ultrasound showed no relation of coronary endothelial function with the presence of mild (<30%) coronary atherosclerosis (26). Likewise, Barenbrock et al. (27) found no association between FMD of the BA and IMT of the carotid artery in hypertensive patients. Although there is growing evidence that endothelial dysfunc-

Table 3. Logistic Regression Analyses for the Presence of Coronary Artery Disease

Covariates	OR (95% CI)	p	OR (95% CI)	p
Age (per yrs)	0.99 (0.94–1.05)	0.76	1.00 (0.95–1.05)	0.97
Positive family history for CAD	2.32 (0.66–8.09)	0.19	3.13 (0.88–11.22)	0.08
Hypercholesterolemia	3.71 (0.99–13.90)	0.05*	2.96 (0.85–10.33)	0.09
Hypertension	0.67 (0.24–1.88)	0.45	0.84 (0.32–2.24)	0.73
Smokers	0.88 (0.31–2.49)	0.81	0.91 (0.33–2.48)	0.85
FMD (per %)	0.97 (0.88–1.08)	0.62	1.01 (0.91–1.12)	0.87
Distensibility (per kPa^{-1})	1.01 (0.95–1.07)	0.78	1.02 (0.97–1.08)	0.43
BA-IMT (per 0.01 mm)	1.15* (1.06–1.25)	< 0.001*		
BA-WCSA (per mm^2)			1.77* (1.16–2.70)	< 0.01*

*Values are statistically significant.

BA = brachial artery; CAD = coronary artery disease; CI = confidence interval; FMD = flow-mediated vasodilation; IMT = intima-media thickness; OR = odds ratio; WCSA = wall cross-sectional area.

tion is involved in the pathogenesis of atherosclerosis, it may not necessarily be associated with the morphologic extent of the disease.

Functional parameters. At variance with previous studies (10,18,28), our data show that FMD was similar between CAD and non-CAD patients. There are several explanations for this disparity. First, differences in the study population could explain these results. In our study, the risk factor profile was very similar between CAD and non-CAD patients. As FMD most likely reflects "initial" risk and the earliest stage of the disease, showing an impairment even in children with vascular risk factors (8), it is not surprising that FMD is reduced in adult patients with vascular risk factors but smooth coronary arteries. Second, there is only one study published which clearly observed an inverse correlation between FMD and the extent and severity of CAD, and in that study the risk factor profiles showed greater differences between patients and control subjects (18). Another study failed to show an association between BA endothelial function and the extent of CAD but revealed a trend toward correlation between carotid IMT and coronary atherosclerotic severity (28).

Another possible explanation for similar FMD values between CAD and non-CAD patients may be the influence of medication. For example, statins and angiotensin-converting enzyme inhibitors have been shown to improve endothelial function (29). As these medications have only little effect on the measurable extent of atherosclerosis, they may have perturbed any existing relationship between BA endothelial function and coronary atherosclerosis. However, in this study the therapy (except nitrates) was not different between groups. We also performed additional analyses excluding patients with statin or angiotensin-converting enzyme inhibitor therapy, which did not change the results (data not shown). Consequently, the influence of medication does not explain the similar endothelial function in CAD and non-CAD patients in our study.

Based on these findings, FMD, despite reflecting endothelial dysfunction, seems not to be a reliable surrogate for the detection of prevalent coronary atherosclerosis. We propose that FMD may be more suitable as a tool for the detection of risk factor exposure and the earliest functional stage of atherosclerosis, whereas morphologic measurements, being independent of hemodynamic variables, are more closely related to the advanced stage of disease.

Brachial artery diameter. Holubkov et al. (30) have recently demonstrated that BA diameter is independently associated with the presence of CAD in women. Another study has shown similar results in male patients (31). However, the present and previous studies did not find a relation of BA diameter with coronary atherosclerosis (18,21,32). In addition, vessel size is an important independent predictor of FMD in the BA (18,33). Therefore, similar BA diameters are a prerequisite for comparison of FMD values between groups (33).

Mechanical parameters. The rationale for the assessment of arterial mechanical properties in clinical studies is mainly based on experimental data which collectively revealed increased arterial stiffness after the induction of an atherogenic diet and reversibility when these diets were withdrawn (34–36). In addition, most of the clinical studies assessing central artery mechanical properties showed an association of enhanced aortic stiffness with coronary atherosclerosis (15–17,37). However, our data and others indicate that this seems not to be true for peripheral arteries. Laurent et al. observed unchanged radial artery distensibility and greater IMT in hypertensive compared with normotensive patients. They argued that a greater wall thickness in response to increased wall stress may function as a means to maintain vascular distensibility similar to a normotensive patient (5). Our data demonstrated that mechanical properties of the BA are unchanged in patients with CAD compared with non-CAD patients despite intimal thickening. This suggests that at least in the BA mechanical properties are not a useful means for the assessment of overt atherosclerosis.

Study limitations. We did not measure BP continuously. However, there were no differences between the BP at the beginning and the end of the ultrasound examination (data not shown). The definition of CAD in our study was ≥30% stenosis in ≥1 major branch, which includes very early stages of the disease. Only patients in whom coronary angiography had been performed were studied, which creates a possible selection bias toward symptomatic patients.

The dimension of BA-IMT is between 0.2 and 0.6 mm, which is only a small fraction of the IMT seen in the carotid artery. A prerequisite for the assessment of BA wall thickness is therefore the use of 13-MHz high-resolution ultrasound. This technical requirement is a potential limitation for the widespread use of this method.

In conclusion, only morphologic sonographic parameters of the BA are associated with the presence of CAD. These data suggest that IMT and WCSA are the most reliable sonographic parameters of the BA for the assessment of coronary atherosclerotic risk.

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