Association of Wall Thickness of the Brachial Artery Measured With High-Resolution Ultrasound With Risk Factors and Coronary Artery Disease

Franz Weidinger, MD, Matthias Frick, MD, Hannes F. Alber, MD, Hanno Ulmer, PhD, Severin P. Schwarzacher, MD, and Otmar Pachinger, MD

Intima-media thickness of the carotid and femoral arteries has been associated with coronary atherosclerosis and its clinical sequelae. The brachial artery (BA) is widely used for the assessment of flow-mediated vasodilation. The aim of this study was to examine whether BA wall thickness (WT) is associated with coronary artery disease (CAD) and risk factors. High-resolution ultrasound (13 MHz) examination of the BA was performed in 179 patients undergoing coronary angiography for the evaluation of chest pain. CAD (≥30% diameter stenosis in ≥1 major branch) was found in 132 patients, whereas 47 patients had smooth coronary arteries. WT of the posterior BA wall (0.4 ± 0.05 vs 0.35 ± 0.06 mm, p <0.001) and wall index (WI) (WT/vessel diameter × 100; 16.1 ± 0.0 vs 13.8 ± 0.8, p <0.001) were greater in patients with than without CAD. On univariate analysis, WT and WI correlated with age, presence of CAD, systemic hypertension, maximum coronary diameter stenosis, and baseline diameter. On logistic regression analyses adjusting for age, cholesterol levels, systemic hypertension, smoking, and positive family history, WT (p <0.01) and WI (p = 0.02) remained significantly correlated with the presence of CAD. Thus, BA-WT is independently correlated with the presence of CAD. WT may provide a novel noninvasive marker of atherosclerosis that can be assessed together with flow-mediated vasodilation to yield functional and morphologic information in the same vessel. ©2002 by Excerpta Medica, Inc.

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The relation of wall thickness (WT) of the brachial artery (BA) to coronary artery disease (CAD) is largely unknown. Although the BA has not been widely examined for the prevalence of atherosclerosis, a recent autopsy study by Sorensen et al[1] showed that atherosclerosis in this artery is a frequent finding and that correlations between BA and coronary and carotid lesions are at least as strong as between the latter 2 arterial beds. These findings support the use of the BA as a surrogate vessel for coronary circulation, provided it can be measured with the use of ultrasound. Accordingly, we examined the feasibility of BA-WT measurement with high-resolution ultrasound and its relation to the angiographic evidence of CAD and to flow-mediated vasodilation (FMD).

METHODS

Patients: One hundred seventy-nine male patients (mean age 54 ± 10 years, range 27 to 78) in whom coronary angiography was performed were consecutively enrolled in the study. Exclusion criteria were congestive heart failure, left ventricular ejection fraction <40%, significant valvular disease, and female sex. Based on angiographic findings, patients were categorized in 2 groups: group 1, 132 patients with CAD defined as visually estimated percent diameter stenosis ≥30% in ≥1 major vessel; and group 2, 47 patients with smooth coronary arteries. In addition, 17 young healthy volunteers (21 to 32 years old) with no or only 1 vascular risk factor were examined (group 3). We assessed the maximum percent stenosis index as previously described.[2] The use of medication was defined as the continuous use of a drug for at least 1 month before entry into the study.

Assessment of cardiovascular risk factors: Fasting blood samples were obtained in all patients for the measurement of plasma total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein (LDL) cholesterol. Coronary risk factors were assessed as follows: smokers were defined as subjects who had smoked regularly during the previous 12 months.[3] Systemic hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg (hypertension stage I as defined by the Joint National Committee fifth report [4]) based on the average of ≥2 readings taken at each of ≥2 different days or as current use of antihypertensive drugs. With regard to hypercholesterolemia, for the purpose of this study, subjects with plasma LDL cholesterol >130 mg/dl or those taking current cholesterol-lowering therapy were classified as being at increased risk.[3] Patients were considered diabetic if they were receiving treatment with insulin or oral hypoglycemic agents or if fasting blood glucose was >140 mg/dl.[3] A family history of CAD and a history of diabetes were obtained.

From the Division of Cardiology, Department of Medicine, and Institute for Biostatistics, University of Innsbruck, Innsbruck, Austria. Manuscript received October 27, 2001; revised manuscript received and accepted January 7, 2002.

Address for reprints: Franz Weidinger, MD, Cardiology Division, Department of Medicine, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. E-mail: F.Weidinger@uibk.ac.at.

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TABLE 1 Characteristics of Patients

Variable	Group 1 (CAD) (n = 132)	Group 2 (no CAD) (n = 47)	p Value
Age (yrs)	55 ± 10 (32–78)	51 ± 10 (27–68)	0.03
No. of risk factors	1.9 ± 0.8 (0–4)	1.5 ± 0.9 (0–3)	0.01
Systemic hypertension	71 (54%)	19 (40%)	NS
Smoker	47 (36%)	12 (26%)	NS
Hypercholesterolemia*	97 (74%)	29 (62%)	NS
Diabetes mellitus	13 (10%)	1 (2%)	NS
Positive family history of CAD	22 (17%)	5 (11%)	NS
Total cholesterol (mg/dl)	224 ± 47 (96–367)	211 ± 40 (119–296)	NS
LDL cholesterol (mg/dl)	147 ± 44 (31–279)	129 ± 38 (60–198)	0.02
HDL cholesterol (mg/dl)	48 ± 12 (27–84)	52 ± 19 (28–108)	NS
Body mass index (kg/m^2)	27 ± 4 (19–41)	26 ± 3 (19–37)	NS
Aspirin	65 (49%)	11 (23%)	0.01
Statin	25 (19%)	3 (6%)	0.06
Nitrate	27 (20%)	4 (9%)	0.07
β blocker	39 (30%)	10 (21%)	NS
Angiotensin-converting enzyme inhibitor	13 (10%)	4 (9%)	NS

*Patients with plasma LDL cholesterol >130 mg/dl or those taking current cholesterol-lowering therapy.
HDL = high-density lipoprotein.
Values are expressed as mean ± SD (range) or number (%).

Ultrasound studies of the BA: On the day after angiography, patients underwent sonographic assessment of functional and morphologic changes in the BA. Written informed consent was obtained from all patients. High-resolution ultrasound (13 MHz, Acuson Sequoia C 256) was used to measure WT and vasoreactivity. The ultrasound examination was performed between noon and 2 P.M. by 1 of 2 operators (MF, HA) blinded to the patients' diagnoses. All vasoactive drugs were withdrawn 18 to 24 hours before examination. Patients were instructed not to smoke and to remain fasting before the ultrasound examination. After a resting period of at least 10 minutes in the supine position, the right BA was scanned longitudinally above the antecubital fossa. After optimizing gain settings and the transducer position, yielding a clear image of the BA as a vessel arch, images were stored (electrocardiographically triggered to the peak of the T wave) on the hard disk for off-line measurements. Investigators were blinded to patient identity during off-line analysis of images.

Assessment of WT: WT was assessed in 2 ways on the peak of the vessel arch: First, the intima and media thickness at the far wall was measured directly as the distance between lumen-intima and media-adventitia border using electronic calipers. Measurements were obtained at 2 sites per image in 4 different images per patient. The 2 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. Care was taken to limit the distance between the 2 measurement sites to 3 to 5 mm. The mean of 8 measurements was defined as BA-WT. Second, diameters were measured as the distance between the anterior to the posterior media-adventitia border (diameter$_{media}$) and anterior to posterior lumen-intima border (diameter$_{intima}$) to obtain calculated BA-WT [(diameter$_{media}$ − diameter$_{intima}$)/2]. Finally, a wall index (WI) was derived to correct WT for vessel diameter: WI = [(diameter$_{media}$ − diameter$_{intima}$)/diameter$_{media}$] × 100.

Assessment of FMD: Changes in vessel diameter after reactive hyperemia (flow-mediated, endothelium-dependent vasodilation, FMD) and after sublingual nitroglycerin (endothelium-independent vasodilation) were examined according to previously described methods.[2,5] In brief, the diameter at rest was defined as the mean of 3 measurements of diameter$_{intima}$. After suprasystolic compression of the right upper arm at 260 mm Hg for 4.5 minutes, the cuff was deflated and serial posthyperemia scans were stored on the hard disk. The mean of the 3 maximum diameters formed the posthyperemia diameter. When BA diameter had returned to baseline, 0.8 mg of nitroglycerin was given sublingually and the mean of the 3 maximum diameters within the following 10 minutes was recorded. Vasodilation (FMD and endothelium-independent vasodilation) was calculated as percent change in diameter compared with baseline.

Inter-/intraobserver variability: BA-WT: To evaluate interobserver variability, BA-WT was assessed in 11 patients by 2 observers independently of each other on the same occasion. Intraobserver variability was examined in 21 patients by 1 observer on 2 different occasions 1 week apart.

FMD: Interobserver variability was assessed in 10 patients. To exclude possible influences of repeated compression with the cuff, 1 operator did the ultrasound examination and 2 operators measured diameters off-line blinded to each other in a randomized fashion. Intraobserver variability was assessed by measuring FMD on 2 occasions, 2 weeks apart, in 18 patients with coronary risk factors but no clinical sign of cardiovascular disease.

Statistical analysis: Data are expressed as means ± SD (range) or as frequencies (percentages). Patient characteristics were compared using the unpaired *t* test or the Mann-Whitney U test for continuous variables (age, number of risk factors, total serum cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, BA diameter, and FMD) and the chi-square or Fisher's exact test for categorical variables (proportion of single risk factors) as appropriate. Pearson's or Spearman's correlation coefficients were determined to assess the association of WT and WI with clinical characteristics. One-way analysis of variance followed by Scheffé's test was used for comparison of WT and WI between groups. Two logistic regression analyses were performed to determine WT and WI as independent predictors of the presence of CAD, adjusting for major risk factors. The inter-/intraobserver variabilities are given as the mean differences (in mm) of

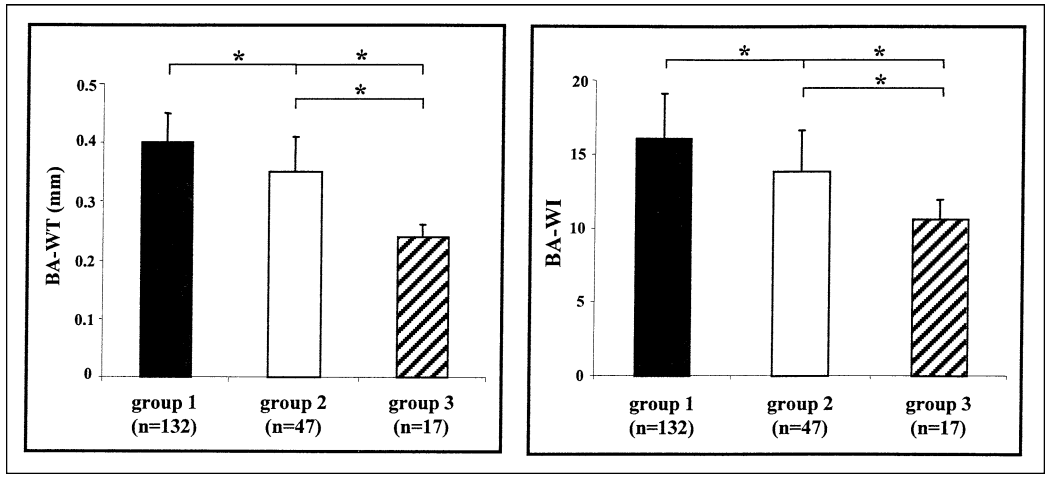

FIGURE 1. Bar graphs showing BA-WT (direct far wall measurements) and WI in CAD (group 1) and non-CAD patients (group 2), and young healthy controls (group 3). *p <0.001.

measurements and as their correlation assessed through linear regression. A p value <0.05 was considered statistically significant. All analyses were performed with the use of statistical software (SPSS for Windows, versions 7.5.2G and 9, SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics: The clinical characteristics of patients in groups 1 and 2 are summarized in Table 1.

Morphologic and functional changes in BA: Baseline BA diameters were similar in the 3 groups (4.2 ± 0.5 mm in group 1, 4.3 ± 0.6 mm in group 2, 4.1 ± 0.6 mm in group 3, p = NS). Directly measured and calculated BA-WT showed a close correlation (r = 0.90; $p < 0.001$). BA-WT ($p < 0.001$) and BA-WI ($p < 0.001$) were significantly greater in group 1 than in groups 2 and 3. BA-WT and WI were also greater in group 2 than in group 3 ($p < 0.001$) (Figure 1).

To evaluate the possible influence of systemic hypertension on BA-WT and WI, we subdivided patients in groups 1 and 2 according to the presence or absence of systemic hypertension. This subanalysis revealed the greatest WT and WI in CAD patients with systemic hypertension compared with the other groups ($p < 0.001$, Figure 2).

Correlations of BA-WT and WI with clinical characteristics and risk factors are shown in Table 2. On logistic regression analysis using age, LDL cholesterol, smoking, positive family history for CAD, and systemic hypertension as covariates, BA-WT and WI remained independently correlated with CAD (Table 3). Additional analyses subdividing the groups according to the use of statins did not change the results. Also, a regression analysis for the use of statins did not influence the results (data not shown).

FMD (8.5 ± 4.5% vs 7.9 ± 2.7%; p = NS) and endothelium-independent vasodilation (18.5 ± 4.5% vs 18.2 ± 5.8%; p = NS) were similar in groups 1 and 2. There was no significant correlation between FMD and BA-WT.

Inter-/intraobserver variability: BA-WT: The mean difference between 2 observers for measurements of BA-WT was 0.02 ± 0.02 mm (r = 0.89; $p < 0.001$). The intraobserver variability (21 patients, 1 week apart) was 0.03 ± 0.02 mm (r = 0.92; $p < 0.001$) for BA-WT. The mean difference in measurements of BA diameter from images (n = 136) stored on the hard disk between 2 observers was 0.04 ± 0.04 mm (r = 0.99; $p < 0.001$).

FMD: The interobserver variability of calculated FMD in 10 patients showed a mean difference of 0.9 ± 0.8% (r = 0.99; $p < 0.001$). In addition, variability of resting diameters, which were measured consecutively by 2 observers, was 0.06 ± 0.04 mm (r = 0.98; $p < 0.001$). The mean difference in FMD, assessed in 18 subjects on 2 different occasions by 1 observer at the same time of the day, 2 weeks apart (intraobserver, repeatability), was 1.8 ± 1.9%.

DISCUSSION

This study shows that BA-WT is significantly correlated with the angiographic evidence of CAD, independent of major cardiovascular risk factors. BA-WT measurement with high-resolution ultrasound appears to be feasible, reproducible, and shows interobserver variability values that are similar to published data obtained in other vascular beds such as the carotid artery.[6] The present findings are in accordance with histologic data from a recent postmortem study that found a close correlation between atherosclerotic changes in the brachial and coronary arteries.[1] Taken together, these studies support the use of the BA as a surrogate vessel for the noninvasive assessment of early atherosclerosis.

The pattern of wall thickening seen in our patients is not one of localized or advanced plaque but rather mild diffuse intimal and/or medial thickening. In some patients, particularly those with systemic hypertension, an echolucent layer was prominent within the composite of intima-media thickness, consistent with adaptive medial hypertrophy[7,8] (Figure 3). Although such a distinction between intimal and medial layers

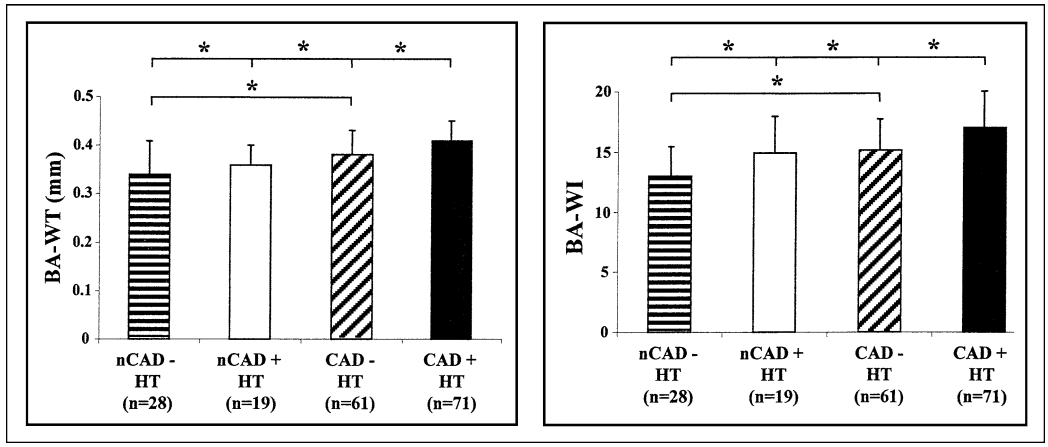

FIGURE 2. Bar graphs showing BA-WT and WI in 4 subgroups of patients according to the presence or absence of hypertension (HT) and CAD, respectively. nCAD = patients with smooth coronary arteries.

TABLE 2 Univariate Correlations of BA-WT and WI

Variables	WT r	WT p Value	WI R	WI p Value
Resting diameter	0.49	<0.01	−0.49	<0.01
Age	0.21	<0.01	0.47	<0.01
Systemic hypertension	0.30	<0.01	0.34	<0.01
No. of coronary arteries narrowed ≥30%	0.35	<0.01	0.34	<0.01
Maximum % diameter stenosis	0.27	<0.01	0.34	<0.01
Hypercholesterolemia*	0.27	<0.01	0.27	<0.01
LDL cholesterol	0.16	<0.05	0.27	<0.01
Total cholesterol	0.09	NS	0.18	<0.01

*Patients with plasma LDL cholesterol >130 mg/dl or those taking current cholesterol-lowering therapy.

could not be made in all patients, which is an inherent limitation of sonographic arterial imaging,[6] it seems likely that the media contributes importantly to overall BA-WT in some. Whether patients with systemic hypertension are more likely to have a prominent echolucent wall component has not been directly addressed in this study but deserves further investigation. Also, it would be interesting to determine whether hypercholesterolemia alters the appearance of BA wall thickening in favor of the intima, or if hypercholesterolemia is additive to the effect of systemic hypertension on WT. Indeed, in a recent epidemiologic study, close correlations were found between LDL cholesterol levels and carotid intima-media thickness in patients in the upper tertile of systolic blood pressure, but not in the lower tertiles, suggesting that arterial wall injury due to high systolic blood pressure increases susceptibility to cholesterol-mediated atherogenesis.[9]

Association of WT with endothelial function: An unexpected finding was the lack of a correlation of WT with FMD, and that FMD was similar in patients with and without CAD. This disagrees with other studies performed in patients undergoing coronary angiography.[2,10,11] Possible explanations for this discrepancy include differences in the degree and duration of risk factors, differences in lifestyle, and differences perhaps in the stage of atherosclerotic disease. In addition, FMD measurements were obtained at a different time of the day in this study compared with the previous study.[2] With regard to the risk factor profile, patients with CAD in the present study had lower total cholesterol levels (224 ± 7 vs 271 ± 04 mg/dl) and fewer patients smoked (36% vs 59%) than patients in the study of Neunteufl et al,[2] which could explain the higher FMD values in our patients with CAD than in patients in the study of Neunteufl et al (8.5 ± 0.5% vs 5.7 ± 0.8). Other factors such as different lifestyle habits, more vigorous exercise, and/or dietary habits, which have not been graded in most studies of FMD, cannot be excluded. However, not all studies have found a difference in FMD between patients with and without CAD,[12] and even in those studies reporting a difference, the overlap between patients and controls was considerable, leading most investigators as well as expert panels to conclude that FMD is not a suitable screening method for CAD.[13] Regardless of the factors involved, our data suggest that WT is a better discriminator between CAD and smooth coronary arteries than FMD.

Potential advantages of BA sonographic measurements: Assessment of an artery that is less prone to symptomatic obstructive disease than other arterial beds (carotid, iliofemoral) may have some potential advantages. First, functional and morphologic changes can be detected in the same vessel. Second, in contrast to advanced lesions more frequently seen in the carotid artery, changes in the BA are diffuse and may be a more sensitive indicator of long-term systemic exposure to risk factors. Third, because of its superficial location, measurements of the BA may be less variable than those of the carotid artery. However, no direct comparisons between the 2 vessels have been performed.

Study limitations: We included only patients undergoing coronary angiography, which may create a selection bias for more advanced stages of the disease, given that all patients were referred for symptoms of

TABLE 3 Logistic Regression Analyses for the Presence of CAD

Covariates	OR	(95% CI)	p Value	OR	(95% CI)	p Value
Systemic hypertension	1.04	(0.42–2.57)	NS	1.25	(0.53–2.94)	NS
Smoking	2.13	(0.82–5.54)	NS	2.58	(0.99–6.69)	NS
Positive family history of CAD	2.63	(0.75–9.22)	NS	1.91	(0.60–6.06)	NS
LDL cholesterol (per mg/dl)	1.01	(1.00–1.02)	NS	1.01	(1.00–1.02)	NS
Age (per year)	1.01	(0.95–1.06)	NS	1.02	(0.97–1.07)	NS
BA-WT (per 0.01 mm)	1.20	(1.08–1.33)	<0.01			
BA-WI (per unit)				1.28	(1.06–1.56)	<0.02

CI = confidence interval; OR = odds ratio.

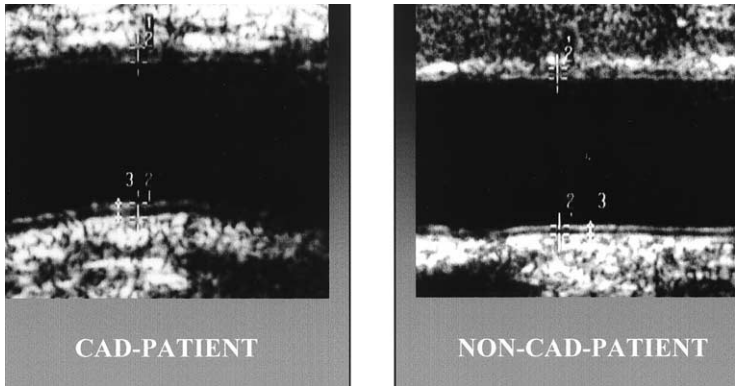

FIGURE 3. High-resolution ultrasound images (13 MHz) of the BA of a patient with CAD *(left panel)* and a patient with smooth coronary arteries *(right panel)*.

chest pain. Because the differences between patients with CAD and symptomatic (atypical chest pain), but angiographically verified non-CAD patients significant, one can speculate that even a greater difference would have been detected in a totally asymptomatic population. We did not use automated edge-detection software for measuring WT. Because the measurements at the 2 sites per image did not vary substantially, it is unlikely that the automated measurements would have revealed dissimilar results.

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