Relationship of sonographic wall components of the brachial artery to hypertension and coronary atherosclerosis

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Abstract: The aim of this study was to determine whether sonographically assessed intimal (echodense, ED) or medial (echolucent, EL) thickening of the brachial artery is associated with coronary artery disease (CAD) and/or arterial hypertension (HT). In 201 patients the ED and EL wall components, as well as the total wall thickness of the brachial artery, were measured with high-resolution ultrasound (13 MHz). According to the presence or absence of CAD and HT, the patients were divided into four groups: no HT and no CAD ($n = 26$, group 1), CAD (≥30% diameter stenosis in ≥1 major branch) only ($n = 63$, group 2), HT only ($n = 34$, group 3), and HT and CAD ($n = 78$, group 4). EL ($p < 0.001$) and combined wall thickness ($p < 0.001$), but not the ED wall component, were significantly different between the groups, with the highest values occurring in group 4. On logistic regression analyses adjusting for age, coronary risk factors and body mass index, EL, but not ED, thickness correlated independently with the presence of CAD ($p = 0.04$) and HT ($p < 0.001$). High-resolution ultrasound examination of the brachial artery wall structure may contribute to the noninvasive assessment of early atherosclerosis.

Key words: atherosclerosis; brachial artery; coronary artery disease; hypertension; medial thickness; ultrasound

Introduction

With high-resolution ultrasound, the noninvasive assessment of early atherosclerotic changes in peripheral arteries has become possible.[1–6] Previous studies have revealed that sonographically measured wall thickness (WT; i.e. intima plus media thickness) of the carotid artery is increased in patients with coronary artery disease (CAD) compared with controls.[1,2] More importantly, carotid artery WT is also increased in patients with vascular risk factors but without symptomatic atherosclerotic disease.[1,3–6] Furthermore, patients with arterial hypertension (HT) in particular have been found to show increased WT.[4–6] Whether this reflects adaptation to a higher blood pressure or early atherosclerotic changes is unknown.[7]

In our previous studies we have shown that brachial artery (BA) WT is increased in patients with CAD.[8,9] It is interesting that, in particular, patients with HT but without CAD have been shown to have an increased WT.[8] Whether or not this is mainly due to medial hypertrophy, which has been suggested in experimental HT,[10,11] still needs to be clarified.

The use of 13 MHz high-resolution ultrasound gives the opportunity to visualize different wall components of superficially located peripheral arteries such as the BA. The aim of this study was therefore to investigate whether sonographically assessed echodense (ED; 'intimal') or echolucent (EL; 'medial') thickening of the BA is associated with HT and/or CAD.

Methods

Patients

Written informed consent was obtained from all participants. A total of 201 men (mean age 54 ± 10 years, range 19–73) in whom coronary angiography was performed because of chest pain were consecutively enrolled into the study. Patients with unstable angina pectoris (<7 days before inclusion), a left ventricular ejection fraction <40%, significant valvular disease and/or other severe disease such as cancer or infection were excluded from the study. According to the presence or absence of CAD (defined as a visually estimated diameter stenosis ≥30% in ≥1 major vessel) and/or HT (systolic blood pressure ≥140 mmHg

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and/or diastolic pressure ≥90 mmHg: i.e. hypertension stage I according to the definition in the fifth report of the Joint National Committee,[12] 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), the participants were divided into four groups: group 1 consisted of patients without either HT or CAD ($n = 26$); group 2 included CAD patients without HT ($n = 63$); 34 patients with HT but no CAD comprised group 3; and group 4 patients ($n = 78$) had both HT and CAD.

Vascular risk factors were assessed as follows: smokers were defined as people who had smoked at least one cigarette a day for ≥1 year within the previous 5 years; HT was defined as described above; patients with a plasma low-density lipoprotein cholesterol >130 mg/dl or who were currently receiving cholesterol lowering therapy were classified as being hypercholesterolemic;[13] patients were considered to be diabetic if they were receiving treatment with insulin or oral hypoglycemic agents, or if the fasting blood glucose level exceeded 140 mg/dl; and a family history of CAD was sought. In addition, fasting blood samples were obtained for the measurement of plasma total, high-density and low-density lipoprotein cholesterol. The investigations conformed to the principles outlined in the Declaration of Helsinki.

Sonographic assessment of the brachial artery

High-resolution ultrasound (13 MHz, Acuson Sequoia C 256, Siemens, Mountain View, CA, USA) and a regional expansion system were used to evaluate BA WT, wall components (ED and EL) and BA endothelial function. The ultrasound examination was always performed between 10 a.m. and noon by an observer blinded to patients' diagnosis. All vasoactive drugs were withdrawn 18–24 hours before examination. The patients were instructed not to smoke and to remain fasting prior to the ultrasound examination. After a rest 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, thus yielding a clear image of the BA as a vessel arch, images were ECG-triggered to the peak of the T wave and stored on hard disk for offline measurement. The offline assessments of the combined wall thickness and the intimal and medial thicknesses were carried out on separate days several weeks apart.

Measurement of the combined wall thickness

Combined WT was assessed as described in previous publications.[8,9] Briefly, the combined intimal and medial thickness of the far wall was measured (using electronic calipers) as the distance between the lumen-intima and media-adventitia borders. Measurements were made at two sites per image on four different images per patient. The mean of the eight measurements was defined as the BA WT.

Assessment of wall components

In addition to the combined WT, the ED (intimal) and EL (medial) wall components were assessed at different times several weeks apart by an observer blinded to the diagnosis and the combined WT. The ED thickness was measured as the distance between the lumen-intima interface and the intima-media interface, and the EL thickness was assessed as the distance between the intima-media interface and the media-adventitia interface at the peak of the vessel arch on different days several weeks apart. Measurements were carried out at four sites per image on four different images per patient. The four sites per image were defined as being at or close to 1 mm of the 'peak' of the vessel arch over a length of approximately 10 mm. This peak is usually the location that gives the clearest image. The mean of the 16 measurements was defined as the ED (intimal) or the EL (medial) thickness, respectively.

Interobserver variability of brachial artery measurements

The interobserver variability in our laboratory was determined for 10 patients by two observers working independently of each other. The mean difference in ED thickness between the observers was 0.006 ± 0.01 mm ($r = 0.85$; $p = 0.02$), that for EL thickness was 0.009 ± 0.02 mm ($r = 0.98$; $p < 0.01$), and for the combined WT it was 0.005 ± 0.04 mm ($r = 0.91$; $p < 0.01$).

Evaluation of peripheral endothelial function

Changes in vessel diameter after reactive hyperemia (flow-mediated, endothelium-dependent vasodilation, FMD) and after sublingual nitroglycerine (endothelium-independent vasodilation, NMD) were examined according to previously described methods.[14,15] In brief, the resting diameter was defined as the mean of three lumen diameter measurements. After suprasystolic compression of the right upper arm at 260 mmHg for 4.5 minutes, the cuff was deflated and serial post-hyperemia scans were stored on the hard disk. The mean of the three widest diameters was taken as the post-hyperemia diameter. When the BA diameter had returned to baseline, 0.8 mg of nitroglycerine was given sublingually and the mean of the three widest diameters during the next 10 minutes was recorded. Vasodilation (FMD, NMD) was calculated as the percentage change in diameter compared with baseline.

Statistical analysis

The data are expressed as means ± standard deviations (range) or as frequencies (percentages). Patient characteristics were compared by an unpaired *t*-test or the Mann–Whitney U-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. Pearson's, Spearman's and eta correlation coefficients were determined to assess the association of the combined

WT and wall components with clinical characteristics. After log transformation, linear regression analyses for these parameters were performed. One-way analysis of variance followed by the least significant difference test or the Kruskal–Wallis-H test followed by the Mann–Whitney U-test was used for comparison of combined WT and wall components as well as FMD and NMD between groups, as appropriate. Logistic regression analyses were performed to determine wall components as independent predictors of the presence of HT or CAD, adjusting for major risk factors. *p*-values of <0.05 were considered to be statistically significant. All analyses were conducted using statistical software (SPSS for Windows, version 7.5.2G).

Results

Patient characteristics

As already noted, group 1 patients had neither HT nor CAD ($n = 26$), group 2 comprised CAD patients without HT ($n = 63$), group 3 patients had HT but no CAD ($n = 34$), and group 4 had both HT and CAD ($n = 78$). The clinical characteristics of the patients are shown in Table 1. Age, number of risk factors, total and low-density lipoprotein cholesterol, pulse pressure, body mass index, and prior statin and antihypertensive therapy showed differences between groups.

Wall components

The EL (medial) thickness was significantly greater in patients with CAD and/or HT compared with those without CAD and HT (Figure 1). In addition, a greater EL thickness was seen in groups 3 and 4 compared with group 2 (0.12 ± 0.04 versus 0.15 ± 0.05 versus 0.19 ± 0.08 versus 0.20 ± 0.06 mm; $p < 0.001$). Table 2 shows the univariate and multivariate associations of

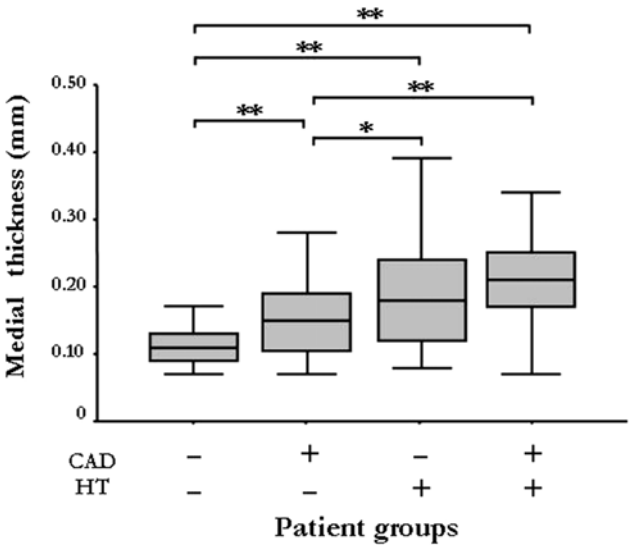

Figure 1 Box plots showing the influence of CAD and HT on brachial artery medial (EL) thickness. $^{*}p < 0.05$, $^{**}p < 0.001$; CAD, coronary artery disease; HT, arterial hypertension.

EL thickness with clinical characteristics. On linear regression analysis, age and HT were significantly correlated with EL thickness.

The ED (intimal) thickness revealed no significant differences between groups (0.15 ± 0.04 versus 0.15 ± 0.03 versus 0.16 ± 0.03 versus 0.16 ± 0.03 mm; NS). On multivariate analysis, ED thickness correlated only with age and BA diameter (Table 2).

On logistic regression analyses only EL thickness remained significantly associated with CAD or HT after adjustment for other factors (Table 3).

Combined wall thickness of the brachial artery

In groups 2, 3 and 4 the combined WT of the BA was significantly greater compared with group 1

Table 1 Patient characteristics (data expressed as mean ± standard deviation or as *n* (%)).

Characteristic	Group 1 ($n = 26$)	Group 2 ($n = 63$)	Group 3 ($n = 34$)	Group 4 ($n = 78$)	*p*
Age (years)	50 ± 10	52 ± 10	55 ± 10	57 ± 8	<0.001
Number of risk factors	1.2 ± 0.8	1.7 ± 0.9	2.1 ± 0.7	2.4 ± 0.8	<0.001
Diabetes mellitus	0	3 (5)	2 (6)	7 (9)	0.371
Positive family history	5 (19)	20 (32)	5 (15)	22 (28)	0.233
Hypercholesterolemia	20 (77)	56 (89)	25 (74)	61 (78)	0.247
Smoker	7 (27)	30 (48)	9 (26)	19 (24)	0.022
Total cholesterol (mg/dl)	232 ± 36	230 ± 45	213 ± 43	210 ± 42	0.016
LDL-C (mg/dl)	164 ± 29	153 ± 42	140 ± 40	140 ± 37	0.018
HDL-C (mg/dl)	50 ± 12	45 ± 11	47 ± 12	44 ± 11	0.212
Triglyceride (mg/dl)	148 ± 71	184 ± 119	171 ± 74	165 ± 81	0.392
PP (mmHg)	52 ± 14	50 ± 12	59 ± 19	59 ± 16	0.001
BMI (kg/m^2)	26 ± 3	26 ± 3	28 ± 3	28 ± 3	0.003
Statins	1 (4)	10 (16)	8 (24)	24 (31)	0.018
Antihypertensive medication	0 (0)	0 (0)	19 (56)	43 (55)	<0.001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PP, pulse pressure; BMI, body mass index.

Table 2 Univariate and multivariate correlation of sonographic parameters.

	ED thickness			EL thickness			Wall thickness		
	r	*p*		*r*	*p*		*r*	*p*	
		Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate
Age	0.30	<0.01	<0.01	0.48	<0.01	<0.01	0.50	<0.01	<0.01
LDL-C	−0.14	0.05	0.32	−0.09	0.28	n.i.	−0.09	0.20	n.i.
BA diameter	0.31	<0.01	0.02	0.16	0.03	0.51	0.28	<0.01	0.08
FMD	−0.19	<0.01	0.91	−0.17	0.02	0.52	−0.22	0.02	0.41
NMD	−0.27	<0.01	0.88	−0.17	0.03	0.53	−0.23	0.02	0.45
HT	0.15	0.04	0.33	0.42	<0.01	<0.01	0.39	<0.01	<0.01
Diabetes	0.06	0.42	n.i.	0.17	0.02	0.22	0.18	0.01	0.11
CAD	0.08	0.26	n.i.	0.18	0.01	0.03	0.22	0.02	0.01
PP	0.25	<0.01	0.07	0.31	<0.01	0.07	0.22	<0.01	0.24
BMI	0.07	0.34	n.i.	0.23	<0.01	0.04	0.23	<0.01	0.07
ED	n.i.	n.i.	n.i.	0.15	0.04	0.39	0.48	<0.01	n.i.
EL	0.15	0.04	0.49	n.i.	n.i.	n.i.	0.81	<0.01	n.i.

ED, echodense; EL, echolucent; LDL-C, low-density lipoprotein cholesterol; n.i., not included; BA, brachial artery; FMD, flow-mediated vasodilation; NMD, nitroglycerine-mediated vasodilation; HT, arterial hypertension; CAD, coronary artery disease; PP, pulse pressure; BMI, body mass index.

Table 3 Logistic regression analyses for the presence of arterial hypertension or coronary artery disease.

	CAD			HT		
Covariate	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Age (per year)	1.02	(0.97−1.06)	0.49	1.03	(0.98−1.08)	0.25
Positive family history	2.04	(0.89−4.68)	0.09	1.34	(0.61−2.92)	0.47
Hypercholesterolemia	1.92	(0.85−4.32)	0.12	0.90	(0.36−2.23)	0.82
Hypertension	0.76	(0.36−1.58)	0.46	n.i.	n.i.	n.i.
Smoking	1.62	(0.74−3.53)	0.23	0.87	(0.40−1.87)	0.72
Diabetes mellitus	1.34	(0.25−7.23)	0.73	1.05	(0.20−5.39)	0.96
PP (per mmHg)	1.00	(0.98−1.02)	0.82	1.03	(1.01−1.05)	0.01
BMI (per kg/m^2)	0.97	(0.87−1.07)	0.51	1.14	(1.02−1.28)	0.02
ED thickness (per 0.01 mm)	2.24	(0.41−12.31)	0.35	1.84	(0.33−10.38)	0.49
EL thickness (per 0.01 mm)	2.72	(1.02−7.21)	0.04	5.26	(1.99−13.90)	<0.01

CAD, coronary artery disease; HT, arterial hypertension; OR, odds ratio; CI, confidence interval; n.i., not included; PP, pulse pressure; BMI, body mass index; ED, echodense; EL, echolucent.

(Figure 2). In addition, groups 3 and 4 revealed a greater WT than group 2 (Figure 2).

Univariate analysis demonstrated a close correlation between the combined WT and the summation of ED plus EL thickness ($r = 0.90$; $p < 0.001$).

Flow-mediated and nitroglycerine-mediated vasodilation

Patients without HT and/or CAD showed greater FMD values compared with the other three groups ($p = 0.028$; Figure 3). In contrast, NMD revealed no significant differences between groups (19.6 ± 6.1 versus 17.6 ± 7.6 versus 17.9 ± 6.6 versus 15.8 ± 7.1%; NS).

Discussion

This study shows that assessment of the specific wall components of the BA is feasible. Assuming that the ED layer largely represents the intima and the EL layer the media,[16] the medial, but not the intimal, thickness of the BA is associated with HT and coronary atherosclerosis.

In our previous studies we have shown that the BA WT is increased in CAD patients compared with non-CAD patients.[8,9] In addition, we have seen that the pattern of BA wall thickening in CAD patients, in accordance with the low prevalence of advanced atherosclerosis in this vessel,[17] is diffuse rather than localized.[8] As atherosclerosis is thought preferentially to affect the intima, we hypothesized that the sonographic ED (intimal) thickness may be increased in patients with CAD compared with hypertensive patients and controls. It is interesting that ED thickness was not significantly different between the groups. One possible explanation could be the small dimensions of the intimal layer and the inability to

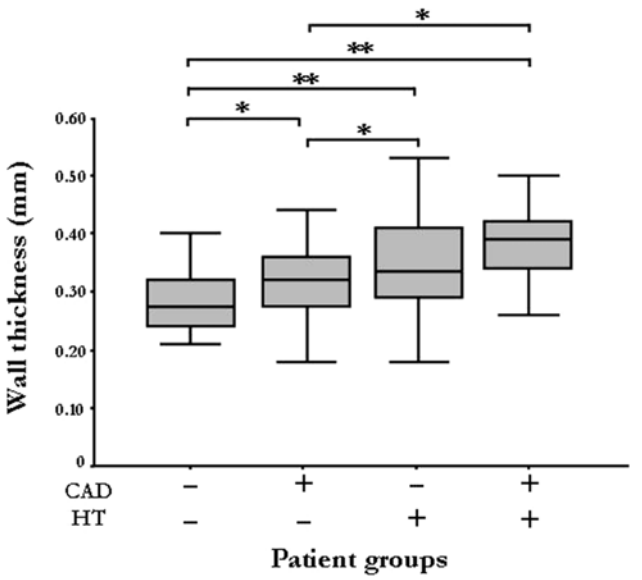

Figure 2 Box plots showing the influence of HT and CAD on combined brachial artery wall thickness (abbreviations as Figure 1).

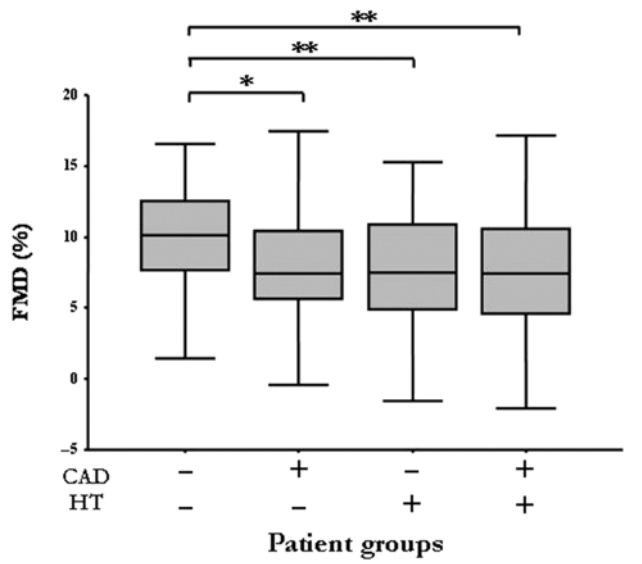

Figure 3 Box plots showing FMD between the different groups (abbreviations as Figure 1; FMD, flow-mediated vasodilation).

measure the differences with this ultrasound technique. This hypothesis is supported by a postmortem study made by Sorensen et al,[17] who demonstrated that fatty streaks and intimal thickening, but not advanced lesions, are common in the BA and are significantly correlated with atherosclerotic changes in the coronary arteries. Thus, the pattern of atherosclerosis of the BA is likely to be different to that in the coronary arteries. However, the BA as an easily accessible vessel may contribute to the noninvasive estimation of atherosclerosis. Another possible explanation for the lack of difference in the ED layer between groups may be the ultrasound frequency. It is known that the ED thickness is dependent on the longitudinal resolution of the ultrasound system and may therefore not be related to the anatomical intima. To our knowledge, however, no study has so far investigated the association of sonographic measurements performed with 13 MHz and a regional expansion system with histologic data.

In the present study, the EL (medial) thickness was significantly greater in patients with HT compared with both control patients and those with CAD (Figure 1). Although HT seems to be a stronger stimulus for medial thickening compared with CAD (Figure 1; group 2 versus 3), the greatest EL thickness was seen in patients who had both HT and CAD, suggesting an additive effect of both conditions on wall changes in the BA. In addition, logistic regression analyses revealed that EL, but not ED, thickness was significantly associated with the presence of HT and/or CAD. Whether this increased EL thickness in patients with HT indicates early atherosclerosis or an adaptive change due to increased vascular pressure remains to be elucidated. Models of hypertension[10,11] have demonstrated that medial thickness increases as compensation for rising intravasal pressure, suggesting an adaptive mechanism. A recent study[18] has revealed that medial thickening is a component of atheromatous arteries and is associated with age as a cardiovascular risk factor.

It is interesting to note that endothelial function was also decreased in patients with HT, similar to patients with CAD. This result supports previous studies[19,20] showing endothelial dysfunction in hypertensive patients. Assuming endothelial dysfunction to be an early marker of atherosclerosis,[21] our data suggest that increased medial and combined WT in patients with HT may be an early marker of atherosclerosis. We did not find a significant difference in FMD between patients with hypertension or CAD only. These data support the hypothesis that BA endothelial function more closely reflects risk factor burden than the presence of CAD.[22] Regarding the prognostic value, some[23,24] but not all[25] previous studies have suggested that FMD may be associated with future cardiovascular events. In addition, we have shown that BA WT also predicts clinical outcome.[26] One could therefore speculate that, by using a combined assessment of endothelial function, WT and perhaps even arterial wall substructures, patients at high risk could be identified more accurately.

Limitations

From our data we cannot conclude that the EL layer corresponds to the media and the ED layer to the intima. This issue deserves experimental work. Although the media thickness is probably underestimated and the intima overestimated when using our method, the error is likely to be very small as

evidenced by the close correlation of WT versus ED plus EL thickness. Pending a histologic correlation of sonographic and anatomic vessel wall components, the combined measurement of intima and media thickness remains the only validated method for the in vivo assessment of human arterial wall structure. We included only patients who had undergone coronary angiography. This may have introduced a selection bias towards those with more advanced disease. Finally, the number of patients studied is insufficient to draw definite conclusions regarding the clinical utility of BA scanning.

Conclusion

This study demonstrates that EL, but not ED, thickness of the BA is independently correlated with the presence of CAD and HT. High-resolution ultrasound examination of the BA wall, in combination with the assessment of endothelial function, may contribute to the noninvasive assessment of early atherosclerosis. Further studies are required to confirm these results in larger patient groups.

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