Increasing Peripheral Artery Intima Thickness From Childhood to Seniority

Walter Osika, Frida Dangardt, Julia Grönros, Ulf Lundstam, Anna Myredal, Mats Johansson, Reinhard Volkmann, Tomas Gustavsson, Li Ming Gan, Peter Friberg

Background—Using new, very high-resolution ultrasound biomicroscopy, we examined the thickness of artificial layers of silicone and intima thickness (IT) of radial and anterior tibial arteries in healthy subjects and in patients with vascular disease.

Methods and Results—Silicone layers of varying thicknesses and mesenteric artery specimens obtained from 18 patients undergoing colectomy were measured by both ultrasound biomicroscopy (55 MHz) and morphometry. There was high correlation \((r>0.9; P<0.0001)\) between IT and intima area versus ultrasound biomicroscopy. In 90 healthy subjects (aged between 10 and 90 years), radial and anterior tibial arterial IT and intima-media thickness were measured, as was carotid intima-media thickness in 56 of these subjects. Age was strongly related with both media thickness and IT of both peripheral arteries. Correlations were found between carotid intima-media thickness and both radial and anterior tibial IT/intima-media thickness \((r=0.44 \text{ to } 0.53; P<0.0001)\). The IT-to-lumen diameter ratio increased with age and was larger at all ages in the anterior tibial artery \((0.067 \pm 0.034)\) versus the radial artery \((0.036 \pm 0.012; P<0.0001)\). A thicker radial intimal layer was found in patients with peripheral artery disease.

Conclusion—This study is the first to our knowledge in humans to show the feasibility of measuring IT of the radial and anterior tibial arteries using very high-resolution ultrasound. IT progresses with age, and the IT-to-lumen diameter ratio is largest in the arteries of the foot. Assessment of IT by ultrasound biomicroscopy may aid in detecting early peripheral vascular abnormalities. (Arterioscler Thromb Vasc Biol. 2007;27:671-676.)

Key Words: atherosclerosis • cardiovascular disease children • intima media thickness • ultrasound

Detection of early atherosclerosis and identifying subjects at high risk for cardiovascular disease are of major importance for prevention. For this purpose, a number of noninvasive techniques have been developed. Pignoli et al.\(^1\) demonstrated that the intima-media thickness (IMT) complex of the carotid artery vessel wall could be measured reliably in vitro or in situ by B-mode ultrasonography. IMT has been shown to convey important information about risk for future cardiovascular disease\(^2-4\); thus, IMT measurements of the carotid arteries are considered a valuable marker of atherosclerosis.\(^5\)

The arterial wall consists of several layers with different functional and pathophysiological roles, and noninvasive imaging of the IMT produces combined pictures of both the tunica intima and media. Given their different physiological functions, we believe that investigating the intima separately from the media might give more insight into the early stages of atherosclerosis. Moreover, examining intima thickness (IT) in relation to the media layer might provide information about developing atherosclerosis, which leads to thickening of the intima and thinning of the media.\(^6\)

Although the radial arteries are not prone to atherosclerosis, radial artery hypertrophy occurs in patients with coronary atherosclerosis awaiting coronary bypass surgery.\(^7\) However, a more detailed morphology of the radial artery with the separation of the intima from the underlying structures has not been visualized in vivo.

We present results on human superficial vessels by using a 55-MHz ultrasound system with very high resolution, the so-called ultrasound biomicroscopy (UBM) technique, which was originally developed for investigations of small animals, allowing noninvasive detection of structures \(\approx 30 \mu m\). IT was measured separately from the tunica media to unravel possible changes occurring within the respective layers of the vascular wall. To identify the UBMs true level of detection, we constructed silicone layers of varying thicknesses and tested in vitro the correlation between UBM measurements and these predetermined silicone layers.
Thus far, UBM has not been used in human vascular research, whereas invasive and noninvasive conventional vascular ultrasound methods have been applied to estimate IT in both animals and humans. In terms of IT, no data exist from smaller peripheral human arteries other than the common carotid artery. In a mouse model, Gan et al used UBM successfully to measure atherosclerosis-related lumen changes of the left coronary artery as a result of aortic atherosclerosis.

Thus, by means of this new noninvasive, very high-resolution 2-dimensional ultrasound technique, we validated comparative ex vivo measurements on human mesenteric arteries using UBM and histopathology. We further pursued visualization of the IT separately from the medial layer of the superficial small arteries, comparing our results with the outcome of standardized carotid IMT measurements to provide data on method variability. In addition, we explored in 90 subjects aged 10 to 90 years whether IT is related to different hydrostatic pressures by examining the vessel wall and its lumen of both radial and tibial anterior arteries, and whether IT increases with aging and cardiovascular risk factors, such as high systolic blood pressure and body mass index (BMI).

To extend our knowledge to also include investigation of IT in clinical medicine, we studied a group of patients with peripheral artery disease using UBM.

Methods

Study Population

We recruited 90 normotensive healthy volunteers, 10 to 90 years of age. Twenty-five schoolchildren (17 females) aged 10 to 17 (mean±SD, 13.3±1.8) had BMI adjusted for age and gender, with (values presented as z-scores) BMI standard deviation score of 0.712±1.103, systolic blood pressure (SBP) of 107±9 mm Hg, and diastolic blood pressure (DBP) 66±6 mm Hg. Fourteen younger adults (7 females) aged 21 to 29 (25.5±2.3) had a BMI of 21.8±1.9 (range, 18 to 25), SBP 116±11, and DBP 68±6; 23 adults (7 females) aged 30 to 57 (41.4±8.2) had BMI 24.1±3.8 (19–34), SBP 116±12, and DBP 76±8; and 28 (15 females) elderly subjects aged 60 to 90 (73.6±8.2) had BMI 24.6±2.6 (21–31), SBP 139±21, and DBP 83±9.

The children were recruited from a school in the city of Göteborg and the adults by advertisements at primary health care facilities in the Göteborg and Varberg areas, the latter 70 km south of Göteborg. For participation in the study as healthy volunteers, the subjects had to be apparently healthy, nonsmoking, and without any known chronic disease such as hypertension, dyslipidemia, or diabetes mellitus, or taking any medication.

Twelve patients aged 64 to 83 (73.3±7.6; 5 female, 7 male) with peripheral artery disease (PAD) in the lower extremities and with angiographic verified stenosis were recruited from the outpatient clinic at the department of vascular surgery at Sahlgrenska University Hospital, Gothenburg. Six underwent operation with femoral bypass or percutaneous transluminal angioplasty, and the other 6 were awaiting operation. Seven were current smokers, 2 were former smokers, and 3 were nonsmokers. They were compared with 12 healthy age- and sex-matched controls (73.5±8.4; 5 female, 7 male).

In the PAD patients the SBP was 155±18 and DBP was 74±7 versus 137±19 and 83±10 in the healthy controls (P<0.05 for both SBP and DBP). The BMI in the PAD was 25.9 (16.6 to 32.3) versus 24.6 (21.7 to 28.9) in the healthy controls (P=not significant).

Written informed consent was obtained before entry into the study. The study was approved by the local ethics committee of the Sahlgrenska Academy.

High-resolution ultrasound biomicroscopy (UBM, 55 MHz) of peripheral arteries

Figure 1. High-resolution, 55 MHz, of radial (left panel) and anterior tibial (right panel) arteries of a 13-year-old child. Lumen diameter is indicated. Arrows point to the intimal layer (white). Immediately beneath is the medial layer, which is depicted as black.

Study Protocol

Carotid (n=56), radial (n=90), and anterior tibial (n=86) successful ultrasound examinations were performed in healthy subjects, and 12 radial and 7 anterior tibial valid examinations were obtained in patients between 8:00 AM and 4:00 PM in one session, after at least 15 minutes of rest. Weight was measured by an electronic balance and height by a stadiometer allowing calculations of BMI (kg/m²). Resting blood pressure levels were indirectly measured in the right arm with the cuff method. Three separate readings were taken 2 minutes apart, and the average of the second and third readings was taken. The DBP was recorded when the Korotkoff sounds disappeared (phase 5).

Ultrasound Measurements

Images from both limb arteries were collected with a 55-MHz 2-dimensional UBM (Visualsonics, Toronto, Canada). The same transducer was used for the radial and tibial anterior artery measurements. Subjects were examined in a supine position. The radial artery was measured ~1 to 2 cm proximal to the skinfold separating the palma manus from regio antebrachii anterior, and the anterior tibial artery was measured above the proximal part of the first metatarsal bone in the foot. At the position of the thickest part of the far wall (visually judged), 4 consecutive beats were recorded in real time and saved. Analyses were then made offline. IT was defined as the total thickness measured with the caliper in a smaller window with higher resolution. In 18 subjects, three measurements of the IT and IMT were performed in systole, when the respective artery had its largest diameter. These measurements were averaged and the coefficient of variation calculated: 12% and 3% for radial arterial IT and IMT, and 9% and 5% for anterior tibial arterial IT and IMT, respectively. IT and IMT were thereafter measured once in each subject. We obtained high-quality UBM images from both arterial sites in all subjects, ensuring high-quality offline measurements with good accuracy (Figure 1). Measurements were analyzed by an investigator blinded to the study groups.

Furthermore, arterial IT and IMT were measured in a subgroup of another 23 subjects by 2 independent investigators blinded to the study protocol. Inter-observer variability, expressed as coefficient of variation, was 7% for radial arterial IT, 5% for radial IMT, and 8% and 7% for the anterior tibial arterial IT and IMT, respectively.

In another separate group of the healthy subjects (n=10), we investigated the reproducibility for radial and anterior tibial arterial IT and IMT measurements. Each subject was studied twice with a 4-week interval. Coefficients of variation for radial arterial IT and IMT were 15% and 4%, and for anterior tibial arterial IT and IMT 19% and 6%, respectively.

Media thickness (MT) was calculated as the difference between IMT and IT. IT was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media-
The adventitia interface. Lumen diameter was defined by the distance between the leading edges of the intima–lumen interface of the near wall and the lumen–intima interface of the far wall.13

B-mode real-time ultrasound with a linear high-resolution transducer (8 MHz Acuson Sequoia 512; Acuson, Mountainview, Calif) was used to evaluate arterial IMT in the common carotid artery of subjects in supine position. The IMT is defined as occurring from the lumen–intimal interface to the medial–adventitial border.13 ECG-triggered B-mode images from at least 3 consecutive cardiac cycles were stored and averaged.

In Vitro Validation of Silicone Layer Phantoms

To establish a relationship between high-resolution ultrasound images and true vascular wall biology characteristics, hardware phantoms were created. These phantoms were intended to test the actual axial resolution of the imaging system. The phantoms were produced by putting a small amount of silicone to a rotating disk. The thin layer of silicone that is created is proportional to rotation speed of the disk, the higher rotation speed the thinner the layer (Figure 2). As a convenient substrate for the silicone layers, plastic Petri bowls was used. Using this technique layers from 1 μm to ~200 μm were created. Silicone was selected because of its tissue mimicking properties. The phantoms were submerged in water and examined by the ultrasonic image system at a transponder frequency of 55 MHz. The silicone layers were later weighed with a precision scale to verify the actual average thickness. Circular shapes were stamped out of the silicone layers and weighed. Identity of the layer and its weight was recorded. The area and the density of the weighed samples are known, which gives the thickness of the layers. The densities were obtained from data sheets provided by the manufacturer of the silicone.

Histopathologic and Morphometric Analysis

For validation and verification purposes, specimens of the mesenteric artery were obtained from 18 patients with colon cancer undergoing total colectomy and evaluated with histopathology and in vitro UBM. Apart from their cancer diagnosis, they were healthy with no cardiovascular risk factors. The mesenteric artery was chosen because its lumen diameter is approximately the size of the radial artery diameter. A vessel segment ~1 cm long from the second or third mesenteric artery branch was free-dissected from the adjacent tissue and stored immediately in formalin. To validate the technical accuracy of the UBM, we chose to image the already fixated vessels ex vivo, to minimize artifact due to tissue shrinkage, and to perform comparisons with subsequent histological sections. The formalin-fixed arteries were placed in a Petri dish with physiological saline solution. UBM imaging was then performed using a 55-MHz ultrasound probe mounted on a 3-dimensional motor device connected to a holder. The vessel was scanned using the 3-dimensional software package from Visualsonics, generating a resolution of 30×30×30 μm.

The fixed vessels were thereafter embedded in paraffin and sectioned at 5 μm onto slides. The exact location of the sections was noted for comparison with the 3-dimensional image data. Three consecutive preparations from the middle part of the vessels were stained with hematoxylin for morphological analysis.

The 3-dimensional image of the vessel was analyzed using the imaging analysis tool provided by Visualsonics on an off-line workstation. Three consecutive cross-section vessel images from the middle section of the entire 3-dimensional setting were chosen for intima area measurements. The corresponding histological sites were measured on the specimen slides using Image-Pro software (Version 5.0; CyberMetrics Inc, Parameter AB, Sweden).

Statistics

Results are expressed as mean±SD. The vascular parameters IT, MT, and IMT were normally distributed. The relationship between the 2 variables was assessed from bivariate scatter plots and calculation of the Pearson correlation coefficient. Coefficient of variation=mean SD of differences between measurements divided by the mean of these measurements multiplied by 100. Two-way ANOVA and Student t test were used to examine differences between arterial sites among the 4 age groups.

Intima thickness, IMT, and IT-to-lumen diameter ratio demonstrated univariate associations (P<0.05) with age, BMI, and systolic blood pressure. A multiple, forward, stepwise linear regression analysis was performed using the aforementioned vascular measures as dependent variables, and age, BMI, and systolic blood pressure as independent variables.

Silicone layer thickness obtained from weighing is called W and thickness obtained from ultrasonic imaging (UBM) is called U. Bland-Altman plot was constructed according to the formula: X=(U+W)/2 and Y=(U–W).

All tests used were 2-sided, and P<0.05 was considered statistically significant.

Results

In Vitro Validation Experiments

There was good agreement between measurements by UBM and gold standard measurements of silicone layers by weighing showing correlation coefficient of 0.98. Moreover, Bland-Altman plot reveals no systematic error and a mean difference and standard deviation of 3.5±8.8 μm.

In human mesenteric vessels, we obtained sharp UBM images, which were subsequently analyzed morphologically; an example is shown in Figure 3, upper panels. The in vitro validation experiments performed on these arteries revealed high r values between UBM and gold standard histological measurements, in terms of both IT and intima area (Figure 3, lower panels).

In Vivo Experiments

There were positive correlations between carotid IMT and radial artery IT (r=0.53, P<0.0001) and carotid IMT and anterior tibial artery IT (r=0.44, P<0.0007) when healthy subjects were included, from children to old age. Figure 4 shows associations between carotid IMT and radial and anterior tibial artery IMT, respectively.

IT, MT, and IMT and Age

IT and MT increased with age (from 10 to 90 years), showing high correlation coefficients in both the radial (IT, r=0.74; MT, r=0.63; P<0.0001 for both) and the anterior tibial (IT, r=0.68; MT, r=0.51; P<0.0001 for both) arteries. Radial artery MT was slightly larger than anterior tibial artery MT.
when all subjects were compared (0.192±0.047 and 0.178±0.049 mm, respectively; P=0.04). In contrast, IT was larger in the anterior tibial artery (0.074±0.030 mm) versus the radial artery IT (0.064±0.019 mm; P=0.007), comparing all subjects. The most pronounced difference in terms of IT between artery sites was found in the oldest age group (Table). When IT and MT were combined, ie, the traditional way of measuring IMT, the IMT increased with age for both radial (r=0.74, P<0.0001) and anterior tibial (r=0.68, P<0.0001) arteries, and no difference could be detected between them.

Carotid IMT increased with age (r=0.70, n=56; P<0.0001) and was greater in adults (0.048±0.011 cm, n=33) compared with children (0.033±0.005 cm, n=25; P<0.0001). No gender differences in terms of any of the vascular measures could be detected.

**IT, MT, and IMT in PAD Patients**

The intimal layer of right radial artery was thicker in PAD patients compared with the healthy controls (0.089±0.017 versus 0.074±0.011; P<0.05) There was, however, no statistically significant difference in radial artery MT between groups (0.266±0.066 versus 0.223±0.039). When measuring

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**Figure 3.** Validation of an UBM image from human mesenteric artery (upper, left panel) and the same areas examined by histology (upper, right panel), clearly delineating IT and MT separate from each other. Validation experiments were performed on mesenteric artery specimens from 18 patients, and highly statistically significant correlations were found between ultrasound biomicroscopy and histology, both calculated as IMT (lower, right panel) and IMT area (lower left panel).

**Figure 4.** Relationships between radial (left panel) and anterior tibial (right panel) artery IMT and carotid IMT in healthy subjects across a wide age span.
the whole radial IMT, the PAD patients had thicker IMT versus controls (0.355±0.079 versus 0.298±0.042). The anterior tibial artery was visualized only in 7 of the PAD subjects, probably because of their disease, so further comparisons between the groups were not meaningful.

**IT Related to Vessel Size and Age**

Lumen diameter of the anterior tibial artery was smaller in each of the age groups compared with the radial artery. Average luminal diameter for the radial and anterior tibial arteries in all subjects was 1.84±0.47 and 1.20±0.40 mm for the former and latter, respectively (P<0.0001). The ratio of IT-to-lumen diameter for both radial and anterior tibial arteries increased with age (r=0.44 and 0.46, respectively; P<0.0001 for both). The latter demonstrated a larger ratio of 0.067±0.034 versus the former, which was 0.036±0.012 for all subjects grouped together (P<0.0001). A consistently larger ratio for the anterior tibial artery was evident within each of the separate age groups (Table).

**Multivariate Analyses**

BMI, systolic blood pressure, and age were related to IT, MT, IMT, and the ratio of IT to lumina in univariate analyses (P<0.05). Multiple regression analysis revealed age as the only independent factor for IT and MT of both the radial and anterior tibial arteries. Both BMI and systolic blood pressure lost their statistical influence on vascular wall structures when adjusting for age. Systolic blood pressure was of borderline statistical significance in the multivariate regression analysis (P=0.06) for both IMT and IT of the anterior tibial artery. Both systolic and diastolic pressure increased with age (P<0.0001).

**Discussion**

This study is the first to our knowledge in humans to demonstrate the feasibility of measuring IT of the radial and anterior tibial arteries separately from MT from childhood well into old age when using 2-dimensional, very high-resolution UBM imaging.

Our approach for validating UBM in vivo comprised both ex vivo and in vivo experiments. The former design involved human mesenteric arteries obtained at surgery, which demonstrated a range of IMT values similar to those of both the radial and anterior tibial arteries. Thus, we believe that this experimental validation procedure, together with the statistically significant correlation between carotid artery IMT and radial and anterior tibial artery IT and IMT, allows reliable measurements in human subjects. Although we found values of IT that were close to the level of detection of ~30 to 40 μm, particularly in young subjects, we are confident about the validity of these measurements given the relationship between IT/IMT of both radial and anterior tibial arteries and IMT of the carotid artery and the high magnitude of ultrasound discrimination capacity supported by the in vitro silicone layer thickness detection down to the level of 20 μm.

The measurements of the radial and anterior tibial arterial IT and IMT showed increasing values with ageing. IMT demonstrated similar values for these arterial sites, but when IT and MT were considered separately, it became clear that the anterior tibial artery showed thicker intima and thinner media compared with the radial artery, particularly in the oldest age group. Furthermore, it is also relevant to consider the different luminal size of radial and anterior tibial arteries in terms of IT. Thus, we calculated the IT-to-lumen ratio. The present study revealed not only increasing values for this ratio with ageing but also a consistently larger ratio for the anterior tibial artery across the presently investigated age span.

IT may represent the anatomic site of atherosclerotic structural changes, whereas MT augmentation might be a hypertrophic adaptive sign of increased blood pressure load. The more pronounced IT of the anterior tibial artery in all age groups may be related to higher blood pressures in upright positions as a sum of the hydrostatic and dynamic cardiac pressure inputs. The marked difference in radial IT but not MT between the PAD subjects and the healthy age- and sex-matched controls underscores this idea.

Multiple regression analysis showed that most of the increase in IT could be related to aging. The weak influence of blood pressure and weight in our group of 90 individuals is probably the result of the selection of our study subjects, who were mostly of normal weight and normotensive.

Measuring carotid IT separately from the media in 70-year-old subjects with different magnitudes of risk factors showed a thicker intimal layer in subjects with more cardiovascular risk factors compared with subjects with less cardiovascular risk; no difference could be seen by measuring the composite carotid IMT complex. Although this latter method did not allow high-resolution 2-dimensional vascular imaging with common offline measurements, it supports our proposal of measuring IT as a separate variable for atherosclerosis and as a complement to assessments of the whole IMT complex.

The thickness of the common carotid intima-media structure as measured by ultrasound imaging represents a composite surrogate marker of atherosclerosis, even in an early phase, and predicts cardiovascular events in various populations. The present results of age-dependent intimal thickening in peripheral arteries in parallel with carotid IMT changes, and the previously
shown inverse relationship between brachial flow-mediated vasodilatation and carotid IMT in the young.¹⁶ suggest that limited nitric oxide bioavailability may promote vessel wall thickening. Hence, as the endothelium/intima ages and is exposed to further damaging effects of environmental influence, it becomes thicker, as is shown in the present study, and loses some of its anti-atherogenic properties, such as nitric oxide release. One should bear in mind, however, that the correlation coefficient between carotid IMT and peripheral artery IT was only ≈0.5, which suggests that other factors are also involved in determining IT, and that there is no exact relation between these variables. However, by examining these superficial radial and anterior tibial arteries one gets a clearer picture of the intimal layer specifically, which may lead to detection of changes occurring earlier than what can be observed presently when measuring carotid IMT.

**Study Limitations**

Given that this new technique has an increased ultrasound frequency and consequently a 3-fold increase in resolution, there is a limitation of penetration depth. Hence, in terms of visualization of the carotid artery, the prevailing Visualsonic system does not allow analysis at such depth.

Risk factors like smoking, blood pressure, inflammation markers, and cholesterol correlate to the traditional carotid IMT. It would have been valuable to have information about inflammation markers and cholesterol concentrations in the present study and to relate these to our measurements of peripheral IT and MT, as well as IMT. We can state, however, that there was almost no smokers in our study, and SBP did not have any influence on peripheral IT and IMT, as tested in multivariate analysis. Thus, changes in peripheral IT, MT, and IMT merely reflect the aging process itself, somewhat free from any major risk influence. Because the present results are cross-sectional, we cannot conclude whether radial or anterior tibial artery IT is a more sensitive or better marker of risk than carotid IMT. To be able to give prognostic information, we would have needed a larger number of subjects for a follow-up. Our ongoing study and to relate these to our measurements of inflammation markers and cholesterol concentrations in the present study and to relate these to our measurements of peripheral IT and MT, as well as IMT. We can state, however, that there was almost no smokers in our study, and SBP did not have any influence on peripheral IT and IMT, as tested in multivariate analysis. Thus, changes in peripheral IT, MT, and IMT merely reflect the aging process itself, somewhat free from any major risk influence. Because the present results are cross-sectional, we cannot conclude whether radial or anterior tibial artery IT is a more sensitive or better marker of risk than carotid IMT. To be able to give prognostic information, we would have needed a larger number of subjects for a follow-up. Our ongoing studies in coronary patients will give more data on this topic.

In conclusion, we have validated and established in humans the use of a new, very high-resolution 2-dimensional ultrasound biomicroscopy with a frequency of 55 MHz and discrimination capacity down to 20 to 30 µm, as evidenced by in vitro silicone layer detection. Our results demonstrate the feasibility of measuring IT separately from the media in peripheral arteries, such as the right radial and right anterior tibial. Strong positive relationships were found between age and IT, from childhood to old age. The thicker intimal layer in the anterior tibial artery versus the radial artery suggests that blood pressure load, which is higher in the leg than in the foot, may contribute to this difference in IT. This novel UBM technology may aid in detecting early vascular changes and extend our knowledge about the early atherosclerotic process.

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**Disclosure**

None.

**References**


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