Reproducibility of Measurements of Intima–media Thickness and Distensibility in the Common Carotid Artery

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Objective: To assess reproducibility of ultrasonographic measurements of arterial distensibility and intima–media thickness (IMT) in the common carotid arteries.

Design: Prospective study.

Materials: Measurements of IMT and arterial distensibility were performed on-line in B-mode and M-mode, respectively. Blood pressure was assessed. From the measured variables stiffness indices were derived.

Methods: Twenty-five persons were included in the IMT study, both healthy subjects and patients with atherosclerotic disease. Distensibility was measured in a randomly selected subgroup of 10 persons. All subjects were examined by two different sonographers on the same day and were re-examined after 1 or 2 weeks.

Results: When data from both carotid arteries were combined, the interobserver coefficient of variation of IMT was on average 11.7%, of diastolic diameter 3.3%, of distension and relative distension 11.8%, of distensibility coefficient 12.3%, and of stiffness parameter β 19%. Intraobserver variability was slightly lower than interobserver variability. Variability for measurements in the right common carotid artery only was higher than for measurements of both carotid arteries combined.

Conclusions: Our study demonstrates that reproducibility of measurements of IMT and arterial distensibility of the common carotid artery, by B-mode and M-mode ultrasonography respectively, is acceptable when used in large studies.

Key Words: Carotid arteries; Ultrasonics; Observer variation.

Introduction

Characteristics of atherosclerosis include increased arterial wall thickness and stiffness.1,2 Gradual thickening of the arterial wall occurs in the slow process of atherosclerosis, in which localised atherosclerotic plaques may arise.2 Increasing arterial wall stiffness can be explained because of structural vascular changes with increasing diameter and wall thickness as well as calcification and fibrosis due to vascular risk factors like aging, diabetes and hypertension.3 Arterial wall stiffness can be expressed as the arterial distensibility, the relative increase in lumen diameter due to the rise in blood pressure during systole, which decreases when arterial wall stiffness increases.

Using high-resolution B-mode and M-mode ultrasonography, early stages of atherosclerosis can be quantified non-invasively in large superficial arteries, such as the carotids. Measurements of the combined thickness of the intima and media (the intima–media complex) and arterial distensibility give information about local atherosclerotic changes and are related to atherosclerosis in coronary, cerebral and peripheral arteries.4,5 Both measurements can therefore be used as intermediate outcome in clinical trials to determine the effects of risk factors for atherosclerosis.

B-mode and M-mode imaging provide simple methods for measuring intima–media thickness (IMT) and arterial distensibility respectively. Both techniques are widely available, cheap, easy to operate and therefore ideal for multicentre trials. Furthermore, both imaging modalities can be performed on-line on one ultrasound machine. Other techniques like automatic intima–media detection and phase-locked echo-tracking, developed for IMT and distensibility measurements, respectively, need specific equipment, which is only available in specialised centres.

Clinical and epidemiological studies often require several hundred participants to detect plausible treatment effects on IMT and distensibility. For efficiency unilateral examination is preferred to examination of
Table 1. Characteristics of the 25 participants, including healthy volunteers and patients with established atherosclerotic disease.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 ± 16.8*</td>
</tr>
<tr>
<td>Women (%)</td>
<td>48</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9 ± 3.7*</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>28</td>
</tr>
<tr>
<td>Past</td>
<td>28</td>
</tr>
<tr>
<td>Never</td>
<td>44</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>137 ± 20*</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>79 ± 10*</td>
</tr>
<tr>
<td>Known vascular disease (%)</td>
<td>56</td>
</tr>
<tr>
<td>Cerebral (%)</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral (%)</td>
<td>52</td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>12</td>
</tr>
<tr>
<td>Known diabetes mellitus (%)</td>
<td>16</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.

both carotid arteries, but variability may increase and larger sample sizes will be required.

To our knowledge, no studies on reproducibility of combined on-line measurements in B-mode and M-mode on one ultrasound machine have been reported. Furthermore, there is no consensus whether to use IMT and arterial distensibility measurements of only one carotid artery or to use the average of both carotid arteries. The purpose of the present study was to determine intra and interobserver variability of IMT and arterial distensibility measurements in the right carotid common artery as well as in both carotid arteries in a research-oriented vascular diagnostic laboratory setting.

Subjects and Methods

The IMT study was performed in 25 subjects, whose characteristics are shown in Table 1. In a random sample of ten of these, distensibility was measured. Both healthy subjects and patients with known atherosclerotic disease were included to obtain a wide range of IMTs and distensibilities. Subjects were examined by two different sonographers on the same day and were re-examined by the same sonographers after 1 or 2 weeks. Observers were unaware of the results of previous measurements.

Subjects were examined in supine position after 5 min rest with their head turned 45 degrees opposite to the side being scanned. The carotid arteries were examined with an ATL Ultramark 9 or HDI 3000 ultrasound system (Advanced Technology Laboratories, Bothel, Washington, U.S.A.), equipped with a 5–10 MHz linear array transducer. Additionally, an electrocardiographic signal was recorded.

B-mode imaging

The left and right common carotid arteries were examined from anterolateral, posterolateral, and lateral positions respectively. In a two-dimensional image of the carotid artery and anterior wall, the lumen and the posterior wall can be distinguished. In the posterior wall, the interface between blood and intima gives rise to the upper demarcation line of an echogenic zone. The upper demarcation line of the second echogenic zone in this wall corresponds to the media-adventitia interface. There is agreement between histological and sonographic determination of combined intima-media thickness in the far wall.\(^6\) As a reference point we used the beginning of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave triggered optimal longitudinal image of the far wall was frozen. On this image the sonographer traced the leading edges corresponding to the transition zones between lumen-intima and media-adventitia, over a length of 1 cm proximal from the reference point (Fig. 1a). The total intima-media surface of this selected area was calculated instantly by the built-in software of the ultrasound system. The mean intima-media thickness was subsequently calculated and averaged for the three sites of each carotid artery.

M-mode imaging

Both common carotid arteries were examined in an anterolateral direction. The transducer was placed on the carotid bifurcation with the least possible pressure, not compressing the overlying jugular vein and allowing expansion of the carotid artery in all directions. Using B-mode a region 2 cm proximal to the origin of the carotid bulb was identified. An M-line perpendicular to the vessel walls was selected and an M-mode recording was made. The M-mode image was frozen after the recording of three consecutive pulsations to allow on-line measurements. The minimal and maximal lumen diameters were determined visually. Diameters were measured as the distance between two cursors, which were allowed to move only vertically, positioned on the leading edges (i.e. the upper demarcation line of the echogenic zones) of the lumen-intima interface of the anterior and posterior wall. Minimal and maximal diameters were measured at three consecutive pulsations in one frozen M-mode.
image (Fig. 1b). The entire procedure was performed three times resulting in nine minimal and nine maximal diameters for each common carotid artery.

Blood pressure measurements

Blood pressure was assessed non-invasively in the right brachial artery with a semi-automatic blood pressure device (Omega 1400, Invivo Research Laboratories Inc.) during each M-mode image acquisition. With the subject in supine position and the brachial artery at the same level as the carotid artery, this procedure gives an approximation of the blood pressure in the common carotid artery at the time of M-mode measurements.

The diastolic lumen diameter (Dd), the systolic lumen diameter minus the diastolic lumen diameter (AD), the systolic blood pressure (Ps), the diastolic blood pressure (Pd), and the systolic blood pressure minus the diastolic blood pressure (ΔP) were assessed. From these variables the following parameters were calculated:

1. distension (ΔD)
2. relative distension (ΔD/Dd)
3. distensibility coefficient (DC = [2*ΔD/Dd]/ΔP)
4. stiffness parameters β (β = ln(Ps/Pd)*Dd/ΔD)

The distensibility coefficient represents the relative increase in diameter normalised for pulse pressure (intrinsic wall property). The stiffness parameter β gives information about structural wall changes within the normal physiological blood pressure range where pressure-extension is assumed to be an exponential function.8

Intraobserver variability was determined for each parameter by comparing data of the same sonographer at two different measuring sessions; interobserver reproducibility by comparing data from both sonographers at one occasion. Thus two intraobserver and two interobserver variabilities could be derived for each parameter. Variability of measurements was assessed by means of the method described by Bland and Altman, including scatterplots showing the difference between two measurements (y-axis) against their mean (x-axis),9 and by calculating the coefficient of variation (CV) for each parameter. The coefficient of variation describes the difference as a percentage of the pooled mean values and is equal to the intra or interobserver error (standard deviation of the mean difference/√2) times 100 divided by the pooled mean values. Reproducibility-data are shown for both carotid arteries as well as for only the right carotid arteries.

Results

The mean values and the intra and interobserver coefficients of variation of IMT and arterial stiffness indices, for both carotid arteries combined and for only the right carotid arteries, are shown in Table 2. For both and for only the right carotid arteries, the interobserver variabilities in measurements of IMT were on average 11.7% and 11.9%, of diastolic diameter 3.3% and 6.3%, of distension 11.8% and 14.6%, of relative distension 11.8% and 15.7%, of distensibility coefficient 12.3% and 14.0%, and of stiffness parameter β 19.1% and 25.4%, respectively. Intraobserver variability was equal to or less than interobserver variability.

Scatterplots of the difference between two measurements of IMT and distensibility coefficient in both
Table 2. Mean values and coefficients of variation of IMT and stiffness indices for the right and for both common carotid arteries.

<table>
<thead>
<tr>
<th></th>
<th>Interobserver variability (CV) using both common carotid arteries</th>
<th>Mean values (± S.D.)</th>
<th>Intraobserver variability (CV) using both common carotid arteries</th>
<th>Mean values (± S.D.)</th>
<th>Interobserver variability (CV) using the right common carotid artery</th>
<th>Mean values (± S.D.)</th>
<th>Intraobserver variability (CV) using the right common carotid artery</th>
<th>Mean values (± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>9.4%*</td>
<td>0.68±0.20</td>
<td>8.4%‡</td>
<td>0.67±0.23</td>
<td>10.4%</td>
<td>0.68±0.20</td>
<td>9.6%</td>
<td>0.66±0.22</td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>13.9%</td>
<td>0.71±0.20</td>
<td>6.9%§</td>
<td>0.72±0.18</td>
<td>13.3%</td>
<td>0.69±0.19</td>
<td>8.0%</td>
<td>0.71±0.17</td>
</tr>
<tr>
<td>AD (mm)</td>
<td>2.8%</td>
<td>6.3±0.7</td>
<td>2.9%</td>
<td>6.3±0.7</td>
<td>5.1%</td>
<td>6.4±0.7</td>
<td>3.5%</td>
<td>6.5±0.9</td>
</tr>
<tr>
<td>AD/Dd</td>
<td>3.8%</td>
<td>6.2±0.7</td>
<td>2.4%</td>
<td>6.1±0.6</td>
<td>7.4%</td>
<td>6.2±0.7</td>
<td>3.4%</td>
<td>6.1±0.6</td>
</tr>
<tr>
<td>DC I (10⁻³/mmHg)</td>
<td>10.4%</td>
<td>0.54±0.16</td>
<td>11.6%</td>
<td>0.55±0.14</td>
<td>12.8%</td>
<td>0.55±0.16</td>
<td>12.8%</td>
<td>0.55±0.13</td>
</tr>
<tr>
<td>AD/Tr</td>
<td>14.1%</td>
<td>1.54±0.14</td>
<td>12.0%</td>
<td>0.53±0.16</td>
<td>16.4%</td>
<td>0.56±0.14</td>
<td>12.6%</td>
<td>0.56±0.16</td>
</tr>
<tr>
<td>AD/Dd</td>
<td>7.8%</td>
<td>0.09±0.02</td>
<td>7.8%</td>
<td>0.09±0.02</td>
<td>15.7%</td>
<td>0.09±0.02</td>
<td>15.7%</td>
<td>0.09±0.02</td>
</tr>
<tr>
<td>DC (10⁻³/mmHg)</td>
<td>15.7%</td>
<td>0.09±0.02</td>
<td>7.8%</td>
<td>0.09±0.02</td>
<td>15.7%</td>
<td>0.09±0.02</td>
<td>15.7%</td>
<td>0.09±0.02</td>
</tr>
<tr>
<td>β</td>
<td>10.1%</td>
<td>2.7±1.0</td>
<td>9.9%</td>
<td>2.7±1.1</td>
<td>13.1%</td>
<td>2.7±1.0</td>
<td>10.3%</td>
<td>2.7±1.0</td>
</tr>
<tr>
<td></td>
<td>14.4%</td>
<td>2.7±0.9</td>
<td>12.8%</td>
<td>2.8±1.0</td>
<td>14.8%</td>
<td>2.7±0.8</td>
<td>14.6%</td>
<td>2.8±0.9</td>
</tr>
<tr>
<td></td>
<td>21.5%</td>
<td>9.1±3.7</td>
<td>10.0%</td>
<td>8.6±2.8</td>
<td>30.6%</td>
<td>8.9±5.0</td>
<td>23.4%</td>
<td>8.7±2.9</td>
</tr>
<tr>
<td></td>
<td>16.6%</td>
<td>8.6±2.8</td>
<td>18.5%</td>
<td>9.2±3.8</td>
<td>20.1%</td>
<td>8.6±2.6</td>
<td>30.8%</td>
<td>9.6±3.6</td>
</tr>
</tbody>
</table>

Abbreviations: IMT = intima-media thickness, Dd = diastolic lumen diameter, AD = distension, AD/Dd = relative distension, DC = distensibility coefficient, β = stiffness parameter, CV = coefficient of variation, S.D. = standard deviation.

* First session, † second session, ‡ first sonographer, § second sonographer.

Conversion from mmHg to kPa: multiply by 0.13.

carotid arteries (y-axis) against their means (x-axis) are shown in Fig. 2. Fig. 2a represents the difference in IMT measurements between both ultrasonographers at the first session against their mean. The mean difference was 0.06 mm. When only the right carotid arteries were examined the mean difference was the same. Fig. 2b depicts the same variables from the second measuring session, where the mean difference was 0.04 mm. When only the right carotid arteries were examined the mean difference was 0.05 mm. Figs 2c and d show the differences of IMT measurements against the mean of two measurements by each ultrasonographer at two measuring sessions. Mean differences were 0.03 mm and 0.01 mm, respectively. When only the right carotid arteries were examined these differences were 0.01 mm and 0.00 mm, respectively. Figs 2e to h show similar data for the distensibility coefficients. For only the right carotid arteries these mean differences for the distensibility coefficients were 0.3410⁻³/mmHg and 0.2210⁻²/mmHg for interobserver variability and 0.1910⁻³/mmHg and 0.3210⁻³/mmHg for intraobserver variability, respectively.

IMT reproducibility was essentially the same if calculated for the different sites of measurement (anterior, medial, posterior wall) separately (Table 3). Variability was less when using the mean of the measurements at three sites, instead of the measurement at a single site.

Discussion

The interobserver coefficient of variation for IMT measurements was almost 12%. The interobserver coefficient of variation of stiffness parameters and diastolic diameter was lowest for measurements of the diastolic diameter, higher for distension, distensibility coefficient or relative distension, and highest for stiffness parameter β. Intraobserver variability was slightly less than interobserver variability. The coefficient of variation of measurements in only the right common carotid arteries was higher for all parameters than when measurements in both carotid arteries were combined.

Our results for reproducibility of IMT measurements are in agreement with those reported in the literature using the same technique.

For arterial stiffness measured by M-mode, Gamle et al. found a coefficient of variation of 13–17% for the distensibility coefficient and about 6% for the diastolic lumen diameter. To our knowledge, our study is the first to report both the reproducibility of IMT measurements in B-mode and distensibility measurements in M-mode using the same ultrasound device. This combination of techniques is especially suitable for studying atherosclerosis in epidemiologic studies and clinical trials in centres without specialised equipment. Previous studies have used a variety of techniques for measurement of arterial...
Fig. 2. (a) Interobserver variability of intima-media thickness (IMT) of both common carotid arteries at the first measurement session. (b) Interobserver variability of intima-media thickness (IMT) of both common carotid arteries at the second measurement session. (c) Intraobserver variability of intima-media thickness (IMT) of both common carotid arteries for sonographer 1. (d) Intraobserver variability of intima-media thickness (IMT) of both common carotid arteries for sonographer 2. (e) Interobserver variability of the distensibility coefficient (DC) of both common carotid arteries at the first measurement session. (f) Interobserver variability of the distensibility coefficient (DC) of both common carotid arteries at the second measurement session. (g) Intraobserver variability of the distensibility coefficient (DC) of both common carotid arteries for sonographer 1. (h) Intraobserver variability of the distensibility coefficient (DC) of both common carotid arteries for sonographer 2.
compliance including phase-locked echo tracking, multi-gated pulsed doppler, magnetic resonance imaging, applanation tonometry, intravascular ultrasound and pulsed Doppler velocimetry. These measurement methods require equipment and training that is only available in a few centres.

In our research-oriented vascular diagnostic laboratory setting, all measurements were performed on-line, allowing instant handling of data. We preferred to use the mean IMT of measurements at three sites, because variability was less compared with measuring at only one site (anterior, medial or posterior wall). Moreover, measuring at several sites will give a better reliability in case of wall thickness eccentricity. IMT of the far wall of the distal part of the common carotid artery could be measured in 99.7% of subjects in ACAPS, a large study with 919 participants. Visualisation in this part of the carotid artery is good as plaques do not impede IMT measurements. For determination of distensibility, the common carotid arteries were examined three times in anterolateral direction without compression of the overlying jugular vein. This scanning procedure provides an optimal image of the leading edges of the lumen-intima interfaces in both vascular walls, without artifacts in the carotid lumen.

The coefficient of variation for the diastolic lumen diameter was less than for the stiffness indices: distension, relative distension, distensibility coefficient and stiffness parameter $\beta$. The reproducibility of the indices reflects the cumulation of the variability of its constituents, which can be expected to be greater than the variability of only the diastolic lumen diameter. The stiffness parameter $\beta$ should give the best estimate (without pressure dependence) of the real deformation behaviour of the vascular wall within the physiological pressure range. However, we found only a moderate level of reproducibility of measurements of this parameter. This may be explained by the large influence of blood pressure, which cannot be assessed non-invasively at the same place and precisely the same time as the M-mode measurements. When reproducibility is taken into consideration, the stiffness parameter $\beta$ becomes unattractive.

In four large studies, no systematic differences in IMT between the right and left common carotid artery could be found. Bots et al. reported a better reproducibility when measuring IMT in both carotid arteries compared with measuring in only one. In our study, measurements of IMT and distensibility in both carotid arteries took about half-an-hour per person, whereas scanning of only one carotid artery took about 20 min. Therefore, the examination of only one carotid artery might be attractive in a clinical trial. On the other hand, with larger variability of the outcome measurement, a larger sample size is needed.

Reproducibility of measurements in the carotid artery may be better than in other arteries, as a result of its superficial and well-fixed position. However, it is uncertain whether carotid arterial wall measurements are fully representative of the overall atherosclerotic burden in individuals. There may be a difference in atherosclerotic progression between elastic arteries like the carotid artery, and muscular arteries like the femoral artery. In one study, carotid IMT was found to lack specificity and sensitivity for identification of patients with or without significant coronary artery disease. In another study, carotid IMT was consistently greater in persons with clinical evidence of cardiovascular disease than in disease-free subjects. The overall differences between persons with and without disease were 0.07 mm for a history of myocardial infarction, 0.04 mm for angina, 0.05 mm for cerebrovascular disease, 0.15 mm for peripheral vascular disease and 0.06 mm for diabetes. Similarly, the prevalence of cardiovascular disease was consistently higher in subjects with progressively thicker intima–media of the carotid artery. Hirai et al. investigated carotid artery stiffness in 19 normal subjects and 49 patients with myocardial infarction with a phase-locked echo-tracking system. Stiffness was significantly higher in patients with angiographically

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**Table 3. Coefficients of variation of IMT for the right and for both common carotid arteries, calculated for the different sites of measurement.**

<table>
<thead>
<tr>
<th></th>
<th>Interobserver variability (CV) using both common carotid arteries</th>
<th>Intraobserver variability (CV) using both common carotid arteries</th>
<th>Interobserver variability (CV) using the right common carotid artery</th>
<th>Intraobserver variability (CV) using the right common carotid artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior wall</td>
<td>14.1%*</td>
<td>11.0%§</td>
<td>17.7%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td>16.1%†</td>
<td>10.1%§</td>
<td>17.7%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Medial wall</td>
<td>11.5%</td>
<td>12.7%</td>
<td>14.7%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td>13.8%</td>
<td>8.6%</td>
<td>13.8%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>12.6%</td>
<td>15.7%</td>
<td>11.9%</td>
<td>18.1%</td>
</tr>
<tr>
<td></td>
<td>15.0%</td>
<td>9.0%</td>
<td>17.5%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

* First session, † second session, § first sonographer, § second sonographer.
proven coronary artery disease than in normal persons and was also higher with increasing number of diseased vessels. With respect to these discrepancies emerging from the literature, it seems prudent to gather more information on the relative importance of IMT and arterial distensibility measurements in different arteries in predicting overall atherosclerotic burden.

Nowadays, IMT measurements are being used as intermediate endpoints in clinical trials. Mean population values for IMT are between 0.4 and 1.0 mm and progression rates of 0.005–0.3 mm/year have been reported, depending on the cardiovascular risk status of the persons included in the study. Longitudinal studies on progression rates of distensibility parameters have not yet been performed. For a 3-year randomised clinical trial on risk factor intervention in persons at high risk for atherosclerosis, using IMT as an endpoint, the sample size can be calculated from the following assumptions: standard deviation of IMT 0.20 mm, progression rate in control group 0.10 mm/year, treatment effect 30%, power (1-β) 80% and significance level α<0.05. The 3-year progression in the control group and in the intervention group would be 0.30 mm and 0.21 mm, respectively. The estimated sample size for such a clinical trial would be 156 patients.

In conclusion, reproducibility of ultrasonographic measurements of IMT and distensibility of the common carotid artery, in the setting of a research-oriented vascular diagnostic laboratory, is acceptable when used in large epidemiologic or clinical studies.

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References

Reproducibility of Carotid Artery Measurements


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