Structural, Functional, and Hemodynamic Changes of the Common Carotid Artery With Age in Male Subjects

Arno Schmidt-Trucksäss, Dominik Grathwohl, Andreas Schmid, Raffael Boragk, Christine Upmeier, Joseph Keul, Martin Huonker

Abstract—Aging of the common carotid artery (CCA) is associated with different principal structural, functional, and hemodynamic changes, which are often influenced by several atherosclerotic risk factors, so that it is difficult to estimate the exclusive effect of aging on this process. Studies dealing with vascular aging of the CCA usually assess only single, dimensional, or functional parameters, although it is likely that there are interactions and probably differences between them. Moreover, regional vascular blood flow characteristics are often not taken into consideration. Therefore, the aim of the study was to assess the age-related multiparametric changes of the CCA properties with ultrasound in 69 male subjects between the ages of 16 and 75 (42.4±16.5 years), who were screened for the absence of major atherosclerotic risk factors or existing vascular disease. As a result, the intima media thickness (0.052 mm/10 y) and diastolic diameter (0.17 mm/10 y) increased nearly linearly with age (r=0.60, P<0.001; and r=0.46, P<0.001, respectively). The absolute diastolic/systolic diameter change diminished by 0.10 mm/10 y (r=−0.73, P<0.001) and peak expansion velocity dropped by 0.12 cm/s per 10 years (r=−0.62, P<0.001) highly significantly with age. The peak blood flow velocity decreased continuously with age (r=−0.67, P<0.00) by 9.3 cm/s per 10 years. According to multiple regression analysis, peak blood flow velocity seems to reflect the changes of several structural and functional parameters in one; intima-media thickness was determined by diastolic arterial diameter and age as independent variables. The data indicate that a multiparametric assessment may contribute to a better understanding of vascular aging and might be the basis for further studies to evaluate the association of atherosclerotic risk factors and/or major vascular disease with local changes in the CCA. (Arterioscler Thromb Vasc Biol. 1999;19:1091-1097.)

Key Words: carotid artery ■ aging ■ arterial stiffness ■ ultrasound

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Carotid Artery Changes During Aging

Study Population
The study population initially consisted of 160 ambulatory male patients and athletes of the Department of Preventative, Rehabilitation and Sports Medicine at Freiburg University Hospital, Center for Internal Medicine. Sixty-nine of these subjects were free from major cardiovascular risk factors; ie, they had systolic blood pressure <160 mm Hg, pulse pressure <60 mm Hg, LDL cholesterol/HDL cholesterol ratio <3.5, triglycerides <200 mg/dL, a fasting serum glucose level <100 mg/dL, they were nonsmokers, and they had no diabetes or history of cardiac disease and thus were permitted to participate in the study. None of them took any antidiabetic or hypolipidemic medication. There was no plaque formation in the CCA, carotid bifurcation, and internal/external carotid artery detected by ultrasound screening. Regular physical activity was limited to 3 times per week and not more than 30 minutes per training session. All study subjects gave their written informed consent to the examinations after an explanation was given of the study design.

Carotid Ultrasonography
After at least 15 minutes of rest in the supine position, the ultrasonic examination of the right CCA was performed. A Toshiba SSA-380-A ultrasound scanner with a high-resolution and digital beam former was used with a linear 10-MHz transducer. The necks of the study subjects were turned slightly to the left side. The transducer was positioned at the lateral side of the neck without any compression of the inner jugular vein, which was located between the transducer and the CCA. The lumen was maximized in the longitudinal plane with an optimal image of the near and the far vessel wall of the CCA. Thus, typical double lines could be seen as the intima-media layer of the artery. The diastolic diameter of 3 consecutive beats was determined in M-mode at a speed of 25 mm/s with the cursor perpendicular to the vessel walls. The minimum luminal diastolic diameter (Ddia) was measured shortly after the R wave of the ECG during the preejecction phase. A region 2 to 3 cm proximal to the carotid bulb gave the best conditions for the measurements, because the diameter was not influenced by the area surrounding the bifurcation. The intima-media thickness (IMT) of the far carotid wall was measured in the same region. The average value of 3 consecutive measurements was taken for a statistical analysis. High-resolution B- and M-mode ultrasonography enabled the measurement of the IMT of the wall of superficial arteries with a high degree of accuracy and reproducibility. The maximum spatial resolution in M-mode was 0.1 mm. The error of this consecutive measurement was computed according to Sachs. For the diastolic diameter it was 0.16 mm and for the IMT 0.08 mm.

Blood Flow Measurements
Blood flow and velocity measurements were made by using pulsed-wave Doppler. The angle of incidence was uniformly 60° and the vessel area aligned parallel to the transducer. The area of measurement was 2 to 3 cm proximal to the bifurcation to avoid disturbance by turbulent flow in the region of the bifurcation. The range-gate length was adjusted to span the carotid artery and the ultrasound beamwidth was greater than the arterial diameter. The pulsed-wave Doppler was kept continuously in the correct position by monitoring the suitable position with the Duplex mode of the ultrasound system. This method is described in more detail elsewhere. The peak velocity of the systolic flow (Vs) was assessed for 3 to 4 consecutive heart cycles. The mean blood flow velocity (Vmean) over 1 heart cycle was calculated by the computer program of the ultrasound system and the regional blood flow over 1 heart cycle was calculated by multiplying the time velocity integral by the diastolic carotid lumen area. The average of 3 consecutive measurements was taken for statistical analysis. The error was computed to be 4.8 cm/s for Vmean and 1.8 cm/s for Vmax.

Arterial Wall Motion
Tissue Doppler imaging (TDI) was performed for the measurement of the wall motion velocity (W) of the near and the far CCA wall. Basically, tissue Doppler imaging is an ultrasonic technique, where Doppler signals from blood with low backscattered energy are eliminated by gain adjustment. In this way only Doppler signals from tissue are shown, which are ~40 dB greater in amplitude than those for blood flow. The pulse repetition frequency was 3.0 kHz and the images were also obtained with a 10-MHz linear transducer. Thirty-five to 45 wall motion measurements were made at opposing sides of the near (Wn) and the far (Wf) wall of 1 complete heart cycle of the CCA. All measurements were performed at the level of the intimal layer or at the adventitia, assuming that for an analysis of wall motion the compression of the arterial wall during systole is negligible. Simultaneous velocities of the far wall were subtracted from W of the near wall, resulting in a wall expansion velocity (Wexp). All measurements started at the top of the R wave of the simultaneously recorded ECG to minimize intersubject variability during the cardiac cycle. The peak velocity of the Wexp time profile (Wexp) was observed approximately in the middle of the CCA distension period. A representative Wexp time profile and distension curve of a 38-year-old man is shown in Figure 1. It has been proved that Wexp, a parameter that characterizes arterial elasticity, is a parameter that characterizes arterial elasticity. The velocity time integral of the Wexp time profile is equivalent to a diameter change curve. Thus, the maximum value of the curve (max DCh) represents the maximum systolic increase of the inner vascular diameter. Therefore, the maximum systolic diameter (Dsys) was calculated to be Dsys=max DCh, because the accuracy of max DCh is 0.02 mm and therefore considerably better than the precision of Dsys in the Doppler M-mode (0.16 mm). However, there was a strong correlation between the M-mode and the combined M-mode plus TDI measurement of the systolic arterial diameter (r=0.94, P<0.001) (Figure 2). All ultrasound measurements were performed while the subjects were breathing out slowly.

For the determination of the accuracy of TDI measurements, 1 complete heart cycle of each subject was measured twice. Then we...
plotted all associated values of diameter changes in a Cartesian coordinate system and tested the hypothesis that the regression line did not differ from the bisector of an angle (\( y = x \)). The regression line was evaluated according to Passing and Bablok. The hypothesis had to be confirmed and we used the dispersion of the residues to describe the accuracy of our measurements. The accuracy of the diameter change is 0.02 mm (68% percentile).

Blood pressure was measured oscillometrically, using a cuff applied to the upper right arm before and directly after the ultrasound examination.

Statistics

The arithmetic mean and the standard deviation were used for descriptive statistics. To describe the dependency of the variables on age, we used linear regression analysis. The equation for those variables with significant changes with age are presented in Table 1. The mean blood flow velocity decreased only tendentiously with age at a rate of 0.10 mm/10 y and 0.12 cm \( \cdot \) s\(^{-1} \) \( \cdot \) 10 y\(^{-1} \), respectively.

In Pearson’s correlation analysis with the parameters in Tables 1 and 2, most of the parameters correlated significantly with each other. To find out the variables independently predicting either peak blood flow velocity, IMT, or diastolic diameter as the dependent variable. Criterion for entry was a probability of \( F < 0.05 \). \( R^2 \), the probability of the \( F \) test between regression and residuals, a parameter (\( \beta = \text{beta weight} \)) of the model and the including constant were used to characterize the model. The \( \beta \) weights were used to estimate the influence of the dependent variables.

SPSS version 7.5.2 for Windows was used for analysis of the data.

TABLE 2. Arithmetic Mean (Mean), Standard Deviation (SD), Minimum (Min), and Maximum (Max) of the Dimensional, Functional, and Hemodynamic Parameters of the CCA in 69 Male Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima media thickness (mm)</td>
<td>0.64</td>
<td>0.14</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Carotid diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{D}_{\text{dia}} )</td>
<td>6.17</td>
<td>0.59</td>
<td>4.83</td>
<td>7.53</td>
</tr>
<tr>
<td>( \text{D}_{\text{sys}} )</td>
<td>6.88</td>
<td>0.56</td>
<td>5.63</td>
<td>8.40</td>
</tr>
<tr>
<td>Absolute diameter change (mm)</td>
<td>0.56</td>
<td>0.23</td>
<td>0.02</td>
<td>1.20</td>
</tr>
<tr>
<td>Peak expansion velocity (cm/s)</td>
<td>0.84</td>
<td>0.33</td>
<td>0.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Blood flow velocity (cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>95.3</td>
<td>23.0</td>
<td>38.5</td>
<td>136.5</td>
</tr>
<tr>
<td>Mean</td>
<td>22.0</td>
<td>4.8</td>
<td>8.6</td>
<td>36.2</td>
</tr>
<tr>
<td>Regional blood flow per heart beat (mL)</td>
<td>7.1</td>
<td>1.8</td>
<td>2.6</td>
<td>11.1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.
diameter and age predicted IMT with an $R^2$ of 0.50. None of the other parameters improved the regression model (Table 4). Finally, in the third multiple stepwise regression analysis with diastolic diameter as the dependent variable only IMT and diastolic blood pressure were independent predictors of the diastolic diameter with an $R^2$ of 0.44 (Table 5).

**Discussion**

The purposes of the study were, first, to examine the relation of structural, functional, and local hemodynamic changes in the CCA to the process of aging. This was done because several changes of the named parameters are correlated with the aging process, but the degree to which these changes are associated predominantly with aging and not with cardiovascular risk factors or atherosclerotic diseases like cerebral stroke or myocardial infarction has not yet been studied in any great detail. Second, in contrast to several other studies, which mainly focused on single aspects such as the change in structural (eg, IMT)$^{2-23}$ or functional parameters (eg, arterial elasticity)$^{6,16}$ with age, we observed structural and functional arterial properties, together with blood flow parameters, in all study subjects. This was done because probably all of them might have an effect to a different degree on the process of vascular aging and, thus, the analysis of their association might contribute to its understanding.

A total of 160 male subjects from our Department of Preventative, Rehabilitation and Sports Medicine, considered to have a better general state of health than that of the general population, were thoroughly screened for the absence of significant cardiovascular risk factors, no manifestation of atherosclerotic plaques in the area of the carotid tree on both sides, and no history of cardiac disease. Furthermore, the

Figure 3. Increase of IMT with age in 69 male subjects.

Figure 5. Decrease of absolute diastolic/systolic diameter change with age in 69 male subjects.

Figure 4. Diastolic arterial dilation of the CCA with age in 69 male subjects.

Figure 6. Reduction of peak wall expansion velocity with age in 69 male subjects.

Subjects were not allowed to perform more than 30 minutes of endurance exercise twice per week. Finally, only 69 subjects older than 16 to 75 years met these strict criteria.

In this study we investigated IMT with high-resolution ultrasound. IMT increased nearly continuously with age. Based on the equation of the linear regression with age, the difference between 20 (0.52 mm) and 60 (0.73 mm) years was 40.4%. In the Atherosclerosis Risk in Communities (ARIC) database the mean IMT in the distal CCA was $\approx 0.73$ mm for healthy 60-year-old men,$^1$ and in the ultrasound study of Persson et al$^1$ the disease-free group had a mean IMT of $0.73 \pm 0.13$ mm, ie, at the same level as in our study. In contrast, the mean IMT of subjects with coronary artery disease (CAD) ($60 \pm 10$ years)$^{24}$ or untreated familial hypercholesterolemia (FH) ($56.9 \pm 12.0$ years)$^{25}$ was markedly higher ($0.83 \pm 0.20$ and $0.81 \pm 0.19$ mm, respectively). Taking the estimated IMT at the age of 20 years (0.52 mm) as a baseline for young and healthy men, the difference from the IMT of the CAD$^{24}$ or FH$^{25}$ subjects at the age of $\approx 60$ years is $\approx 57.7\%$, thus only an additional 17.2% compared with the difference between the age of 20 and 60 years in our study group and within the standard deviation of the CAD and FH subjects. This indicates that intima-media thickening is mainly determined by the aging process itself and therefore might not be a single suitable noninvasive parameter for the assessment of CAD, as demonstrated in the study by Adams et al.$^{24}$ They found a highly significant, yet only weak correlation between the IMT of the CCA and CAD ($r=0.26$). Similar results have been published by several other authors concerning atherosclerotic risk factors, plaque formation, and IMT.$^{26-28}$ However, the increase in IMT with age, even in
subjects without risk factors or clinical evidence of atherosclerosis, does not exclude the possibility that subclinical atherosclerosis was present and may be an explanation for the low difference between the IMT of our study subjects and those with CAD or FH. In addition, an age-adjusted IMT might be a more reliable measurement in determining the presence or absence of an abnormal IMT related to atherosclerosis.

In a multiple regression analysis with IMT as the dependent variable, age was the strongest independent predictor. Furthermore, only the diastolic diameter remained to be independently related to IMT. This may be considered as an indicator that the increase of wall stress in dilating arteries may be the main structural component for intima-media thickening, which supports the concept proposed by Glagov et al that intima-media thickening occurs in response to an increase in wall stress. The increase in the diastolic arterial diameter was 14.3% between the age of 20 and 70 years, which is similar to the results of other authors. Diastolic dilation of large arteries is known to accompany aging. It occurs predominantly in proximal arteries, like the CCA. The reason for the dilation has been partially ascribed to a reduction of peak expansion velocity with age in a similar way, thus probably indicating a parallel consequence of lifelong cyclic stress, has still not been fully clarified.

The absolute systolic/diastolic diameter change and peak expansion velocity decreased and IMT increased nearly linearly with age. However, the increase in IMT does not necessarily mean an increase in stiffness, which was found in cholesterol-fed monkeys with early-stage atherosclerosis. The latest results of the ARIC study show an increase in the arterial elasticity with increasing IMT in a human population 45 to 60 years old, with the exception of subjects with an IMT>0.8 mm. However, our data demonstrate a progressive decrease of arterial compliance and elasticity with age. Until now we have not been able to offer a conclusive explanation for these findings because noninvasive high-resolution ultrasound has not able to analyze the interior composition of the arterial wall. Measurement of the peak expansion velocity may be 1 step in the direction of a differentiated analysis of arterial wall properties. In contrast to the absolute systolic/diastolic diameter change, which probably reflects the overall arterial compliance, the peak expansion velocity is measured in the early systolic expansion phase and thus might mainly give information about the elastin fibers of the arterial wall, which are dominantly weight bearing during this period. As Sonesson et al were able to show a flattening of the pressure-distension curve with increasing age in the aorta as an elastic type artery in response to a similar tensile stress, the reduction of peak expansion velocity is probably due to a reduction in arterial compliance, and not a shift on the compliance curve. However, peak expansion velocity and absolute systolic/diastolic diameter change are associated with age in a similar way, thus probably indicating a parallel loss of elastin fibers and alteration of the collagen wall structure.

### TABLE 3. Multiple Linear Regression Model With Peak Blood Flow Velocity as the Dependent Variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardized Coefficients (b)</th>
<th>Standardized Coefficients (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>146.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.6571</td>
<td>-0.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic diameter</td>
<td>10.22</td>
<td>-0.26</td>
<td>0.004</td>
</tr>
<tr>
<td>Regional blood flow per heart beat</td>
<td>4.62</td>
<td>0.36</td>
<td>0.000</td>
</tr>
<tr>
<td>Peak expansion velocity</td>
<td>8.91</td>
<td>0.13</td>
<td>0.009</td>
</tr>
</tbody>
</table>

### TABLE 4. Multiple Linear Regression Model With IMT as the Dependent Variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardized Coefficients (b)</th>
<th>Standardized Coefficients (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic diameter</td>
<td>0.101</td>
<td>0.416</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.0035</td>
<td>0.404</td>
<td>0.000</td>
</tr>
</tbody>
</table>

and diastolic blood pressure as an independent variable. The observed increase of the lumen diameter in the ARIC cohort may thus be likewise attributed to an increase in diastolic blood pressure with age, but these data are not presented in the study. Whether the dilation of the CCA associated with aging is a physiological adaptation to an increased stiffness, which permits the heart to discharge the stroke volume in the large arteries without an excessive rise in afterload or a consequence of lifelong cyclic stress, has still not been fully clarified.

![Figure 7. Decrease of peak blood flow velocity with age in 69 male subjects.](http://atvb.ahajournals.org/)

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**TABLE 5. Multiple Linear Regression Model With Diastolic Diameter as the Dependent Variable**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardized Coefficients (b)</th>
<th>Standardized Coefficients (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>3.392</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intima media thickness</td>
<td>2.075</td>
<td>0.504</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.018</td>
<td>0.278</td>
<td>0.007</td>
</tr>
</tbody>
</table>
As a hemodynamic parameter, which is likely to be influenced by nearly all of the above-mentioned parameters such as arterial diameter, wall elasticity and structure, blood pressure, and local blood flow, we also measured the peak blood flow velocity. Although the peak blood flow velocity is easy to measure and most of its measurement variability can be eliminated, when the resting time of the subjects in supine position is at least 10 minutes before examination only very few studies took this parameter into consideration with the intention of characterizing its association with age and atherosclerotic risk factors. We found a marked reduction in peak blood flow velocity across the total age range. In a multiple regression analysis with peak blood flow velocity as the dependent variable, age was the strongest predictor of the reduction of peak blood flow velocity, followed by diastolic diameter, local blood flow per heart beat, and peak expansion velocity. This suggests that peak blood flow velocity is a parameter associated with structural, functional, and blood flow parameters and may reflect the status of the aging artery in 1 parameter set above the others. Thus, it may be a suitable parameter to evaluate the influence of age or atherosclerotic risk factors on arterial structure and function.

In the literature, the restoration of blood flow velocity by intimal thickening and consecutive reduction of the lumen is discussed as being a compensating mechanism in aging arteries.\(^{29,37}\) The observed reduction of peak blood flow velocity indicates incomplete success in this respect. An important reason for the reduction in blood flow velocity during aging may be a reduced cardiac output.\(^{38}\) However, the almost unchanged regional blood flow of the CCA in our study subjects challenges this.

The assessment of the different vascular parameters shows that the alteration of arterial properties in aging comprise structural, functional, and hemodynamic parameters. The observed parameters showed a predominantly continuous change within the examined age range. Even in our study subjects, considered to have a better general state of health than that of the general population, the observed changes may not be completely attributed to the aging process, but, at least in part, to the slight increase in diastolic blood pressure or subclinical atherosclerosis. It should be examined further whether the presence of atherosclerotic risk factors or manifest vascular diseases such as CAD will alter these parameters in a way that might be specific for a certain disease. The assessment of a single parameter such as the IMT in patients with CAD does not seem to be sufficient for the differentiation between disease and “healthy” state. However, the arterial tree is characterized by a great inhomogeneity.\(^{39}\) One vessel section, of course, cannot be representative for the changes of the complete arterial tree; but to get an idea of the multifactorial interaction of several structural and functional parameters in the process of aging, the CCA might be the suitable region.

Acknowledgments

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References


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