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.

It is well known that atherosclerotic risk factors such as a high cholesterol level, hypertension, cigarette smoking, and diabetes mellitus aggravate vascular alterations in aging; although these interactions are known, very few studies take them into consideration, which might be of interest to enable a better understanding of the relation of aging to the named arterial changes. Furthermore, only little data exist on the differences in the progression of these alterations.

It is well known that atherosclerotic risk factors such as a high cholesterol level, hypertension, cigarette smoking, and diabetes mellitus aggravate vascular alterations in aging; subjects who bear major atherosclerotic risk factors have stiffer arteries6,10,11 or thicker intima-media than 178 healthy subjects.12–16 To examine the alteration of structural, functional, and hemodynamic vascular parameters during aging and not the effect of overlying atherosclerotic risk factors, it was necessary to screen the study population for the absence of major atherosclerotic risk factors or existing cardiac disease.

Therefore, in this study we examined the relation of aging with alterations of the vascular dimensions, elastic wall properties, and the regional blood flow characteristics of the common carotid artery (CCA) in a population thoroughly screened for the absence of major cardiovascular risk factors over an age range from 16 to 75 years. All parameters were assessed with a noninvasive ultrasound system with high-resolution B- and M-mode for dimensional measurements, pulsed-wave Doppler for the evaluation of the regional blood flow characteristics, and tissue Doppler for the analysis of the elastic arterial wall properties.

For the analysis of the independent association of the assessed parameters, we took only directly measured param-
ers into consideration. Although calculated parameters such as wall shear rate\textsuperscript{17} or distensibility\textsuperscript{18} may sometimes allow a better understanding of certain pathophysiological observations, they usually comprise 2 or more of the directly measured parameters and therefore seem to be less suitable.

**Methods**

**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 (D\text{dia}) was measured shortly after the R wave of the ECG during the prejection phase. A region 2 to 3 cm proximal to the carotid bulb gave the best conditions for 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 (D\text{dia}) was measured shortly after the R wave of the ECG during the prejection 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.\textsuperscript{19} The maximum spatial resolution in M-mode was 0.1 mm. The error of this consecutive measurement was computed according to Sachs.\textsuperscript{20} 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 Doppler signals from blood with low backscattered energy. Basically, tissue Doppler imaging is an ultrasonic technique, where Doppler signals from tissue with low backscattered energy are eliminated by gain adjustment. In this way only Doppler signals from tissue are shown, which are \( \sim 40 \) 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 (W\text{n}) and the far (W\text{f}) 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 variation during the cardiac cycle. The peak velocity of the Wexp time profile was calculated to be Wexp\textsuperscript{max}, which 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\textsuperscript{max} is a parameter that characterizes arterial elasticity.\textsuperscript{21} The velocity time integral of the Wexp time profile is equivalent to a diameter change curve. Thus, the maximum value of the curve (max D\text{Ch}) represents the maximum systolic increase of the inner vascular diameter. Therefore, the maximum systolic diameter (D\text{sys}) was calculated to be D\text{sys}=D\text{dia}+max D\text{Ch}, because the accuracy of max D\text{Ch} is 0.02 mm and therefore considerably better than the precision of D\text{sys} 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 the text or in the figures. The correlation of different parameters was tested by Pearson’s correlation. Kolmogorov–Smirnov 1-sample test was applied to either peak blood flow velocity, IMT thickness, or local blood flow per heart beat, peak expansion velocity and absolute diastolic/systolic diameter change (Figure 5) and peak expansion velocity (Wexp,) (Figure 6) decreased highly significantly (r = −0.73, P < 0.001; and r = −0.62, P < 0.001, respectively) and continuously with age at a rate of 0.10 mm/10 y and 0.12 cm·s⁻¹·10⁻¹ y⁻¹, respectively.

The peak blood flow velocity decreased continuously with age (r = −0.67, P < 0.00) by 9.3 cm·s⁻¹·10⁻¹ y⁻¹ (Figure 7). The mean blood flow velocity decreased only tendentially with age, but the differences did not reach significance (r = −0.13, P = 0.14). The local blood flow per heart beat did not significantly alter with age (r = 0.01, P = 0.45).

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 probably the most interesting variables for the change in the arterial structure and hemodynamics with age, multiple stepwise regression analysis were performed with the parameters in Tables 1 and 2. As a result, the peak blood flow velocity was predicted independently by age, local blood flow per heart beat, peak expansion velocity, and diastolic diameter with a multiple R² of 0.64 (Table 3). None of the remaining parameters improved the regression model. A second multiple stepwise regression analysis was performed to examine the independent contribution of the same parameters with IMT as the dependent variable. Diastolic

Blood pressure increased with age highly significantly (r = 0.52, P < 0.001; r = 0.46, P < 0.001, respectively). The body mass index (r = 0.24, P = 0.26), heart rate (r = −0.16, P = 0.45), and blood pressure difference (r = 0.15, P = 0.17) did not significantly increase with age.

Arterial Dimensions, Elastic Properties, and Hemodynamic Parameters
The arithmetic mean and standard deviation of carotid dimensions, elastic properties, and hemodynamic parameters are presented in Table 2. There was a close correlation between IMT and age (r = 0.60, P < 0.001) (Figure 3). The mean thickness of the IMT increased nearly linearly with age at a rate of 0.052 mm/10 y. The carotid diastolic diameter increased significantly (r = 0.46, P < 0.001) increased at a rate of 0.17 mm/10 y (Figure 4). The absolute diastolic/systolic diameter change (Figure 5) and peak expansion velocity (Wexp,) (Figure 6) decreased highly significantly (r = −0.73, P < 0.001; and r = −0.62, P < 0.001, respectively) and continuously with age at a rate of 0.10 mm/10 y and 0.12 cm·s⁻¹·10⁻¹ y⁻¹, respectively.

The peak blood flow velocity decreased continuously with age (r = −0.67, P < 0.00) by 9.3 cm·s⁻¹·10⁻¹ y⁻¹ (Figure 7). The mean blood flow velocity decreased only tendentially with age, but the differences did not reach significance (r = −0.13, P = 0.14). The local blood flow per heart beat did not significantly alter with age (r = 0.01, P = 0.45).

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 probably the most interesting variables for the change in the arterial structure and hemodynamics with age, multiple stepwise regression analysis were performed with the parameters in Tables 1 and 2. As a result, the peak blood flow velocity was predicted independently by age, local blood flow per heart beat, peak expansion velocity, and diastolic diameter with a multiple R² of 0.64 (Table 3). None of the remaining parameters improved the regression model. A second multiple stepwise regression analysis was performed to examine the independent contribution of the same parameters with IMT as the dependent variable. Diastolic

STUDY POPULATION
Sixty-nine males were included in the study. Anthropometric data are shown in Table 1. The mean systolic
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) or functional parameters (eg, arterial elasticity) 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 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, and in the ultrasound study of Persson et al\(^2\) the disease-free group had a mean IMT of 0.73±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±10 years)\(^24\) or untreated familial hypercholesterolemia (FH) (56.9±12.0 years)\(^25\) was markedly higher (0.83±0.20 and 0.81±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 may 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 in 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 been 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 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>0.416</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic diameter</td>
<td>0.101</td>
<td>0.404</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>

### 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>0.504</td>
<td>0.000</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>

Figure 7. Decrease of peak blood flow velocity with age in 69 male subjects.
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

This study was supported by a research grant from the Center for Clinical Research at the Freiburg University Hospital (Project C 3, ZKF II). We appreciate the support of Prof Schulte-Mönting, Institute for Biomedical Statistics, Freiburg University, in the statistical analysis.

References


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 and Martin Huonker

doi: 10.1161/01.ATV.19.4.1091

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/19/4/1091

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/