Chapter 4

Differences in Blood Velocity Profiles between Young and Elderly Healthy Volunteers in the Internal Carotid Artery; a Study with MRI

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Abstract

Previous ultrasound studies have demonstrated that Wall Shear Stress (WSS) decreases with age. WSS however is heavily dependent on the velocity profile. We investigated blood velocity profiles from MRI data in the Internal Carotid Artery (ICA) of 20 healthy young volunteers (age 26.7 ± 7.1 years) and of 16 healthy elderly volunteers (age 73.9 ± 2.8 years). It was found that there was a significant difference in the spatial velocity profiles between the young and elderly individuals. The decay of flow volume in the ICA with age is 2 to 4 times faster with age than the maximum blood velocity measured in the cross section of the vessel. Due to these deviations in decay rate, it can be calculated that the actual decay of WSS with age is faster than was measured before. We conclude that spatial velocity profiles change in shape with age and that these changes may increase the decay rate of WSS with age.
4.1 Introduction

Wall Shear Stress (WSS) is defined as the mechanical frictional force per unit area exerted on the vessel wall by flowing blood. Low or oscillating arterial WSS is correlated with atherosclerosis.\(^1\) WSS (Pa) is defined as the product of the blood viscosity with the velocity gradient at the vessel wall. A relationship between WSS and age, blood pressure, body mass index, intima-media thickness, diabetes, kidney disease, smoking, history of myocardial infarction and history of hypertension has been found.\(^2-5\) For small to medium sized vessels outside of the thorax, a parabolic velocity profile is assumed to be a valid approximation of the velocity distribution in a vessel’s cross-section.\(^6\) Under this assumption, WSS assessment by paraboloid fitting has been used for the common carotid artery (CCA), the internal carotid artery (ICA), the brachial artery and the abdominal aorta for measurements by MRI and ultrasound.\(^2,3,5,7-11\) Although WSS has shown a decline with age the shape of the velocity profile has not been compared between young healthy and older healthy arteries. The goal of this study was to investigate whether differences in velocity profiles in the ICA exist between young and elderly healthy individuals, and whether this could affect WSS.

4.2 Materials and Methods

4.2.1 Subjects
The flow volume (Flow) and the maximum velocity in the vessels cross section (Vmax) were assessed in both ICA’s in 36 healthy volunteers. A first group consisted of 20 young volunteers, and a second group of 16 healthy elderly individuals. Clinical characteristics of the groups are presented in Table 1.

4.2.2 Acquisition procedures
MR examinations were performed on a 1.5 T MR system (Gyroscan NT; Philips Medical Systems, Best, the Netherlands) using a standard head coil. Flow measurements were performed using a radio frequency spoiled gradient echo phase contrast imaging sequence triggered by a vector ECG, resulting in 16 phases over the cardiac cycle. The imaging plane was positioned perpendicular to the ICA 4 cm distal from the carotid bifurcation. The imaging parameters were:

- echo time (TE) 9 ms, repetition time (TR) 16 ms, 7.5° flip angle, 5 mm slice thickness, 250 × 188 mm field of view, scan matrix 256 × 154 and a velocity sensitivity of 100 cm/s in the feet-head direction.\(^5,12\) The scan time was dependent on the heart rate, being 3 minutes at 60 beats/min.

4.2.3 Automatic fitting of a parabolic velocity profile
During a velocity-encoded MR study, phase difference and standard modulus images were acquired at multiple (in this study = 16) phases of the cardiac cycle. The analysis algorithm was developed to operate on phase images only. The basic steps in the quantitative analysis of the velocity encoded cine MR imaging studies were carried out with the analytical software package MRI-FLOW; details are described elsewhere.\(^13\)
Young volunteers, (n=20)  | Elderly volunteers, (n=16)
--- | ---
**Age, mean ± SD** | 26.7 ± 7.1  | 73.9 ± 2.8  
**Male sex (%)** | 10 (50 %)  | 8 (50 %)  
**Systolic blood pressure, mm Hg, mean ± SEM** | 122.6 ± 8.2  | 141.4 ± 16.4  
**Diastolic blood pressure, mm Hg, mean ± SEM** | 69.4 ± 8.1  | 79.1 ± 9.4  
**BMI, mean ± SEM** | 23.2 ± 3.5  | 23.9 ± 1.6  
**Intensive physical exercise, n (%)** | 17 (85 %)  | 13 (81 %)  
**Smokers, n (%)** | 3 (15 %)  | 0 (0 %)  

**Table 1.** Clinical characteristics
Smokers were defined as: smoked during the last year; the three smokers smoked less than 10 cigarettes per day. Intensive physical exercise was defined as: clearly increased heart beating more than 5 times a week during at least half an hour per day.

In brief: MRI-FLOW yields the velocity profiles in cross-sectional images. Quantification of Flow from such MR examinations requires a post-processing step to differentiate the pixels within a vessel’s cross-section from the surrounding background tissue. The cross section of the vessel was assumed to be circular and the velocity profile parabolic. A typical example of a measured and a fitted velocity profile is presented in Figure 1. The fitting procedure is described in detail elsewhere. The time phase with the highest flow was taken as the systolic phase and the phase just before systole, with the lowest flow, was taken to assess information about the diastolic phase.

The diameter is difficult to determine directly from the MR image due to the relatively low image resolution. However for a parabolic flow profile, the diameter of the vessel can be calculated from the velocity data using the Hagen-Poiseuille formula.

\[
Diam = \sqrt{\frac{8 \text{Flow}}{\pi \text{Vmax}}}
\]  

It has been shown, that Flow can be assessed with an excellent reproducibility by paraboloid modeling. Vmax is the most reliable velocity parameter that can be obtained from MRI, since Vmax suffers less from noise and partial volume effects than other velocities.

**4.2.4 Validity of parabolic velocity profiles and statistical analysis**
Differences between young and elderly individuals were tested for: Flow, Vmax and Flow/Vmax averaged over the cardiac cycle (suffix M), during diastole (suffix D) and during systole (suffix S). The coefficient of variation was defined as SD/mean, where SD was defined by the inter-volunteer standard deviation of the measurements. The significance of the difference between the values in the young and elderly volunteers was calculated with a Student’s unpaired t-test.

According to the literature, a parabolic velocity profile is valid for small vessels outside of the thorax. Also the Womersley number \((\alpha=4.3)\) indicates that deviations from the parabolic shape are small for continuous forward flow. When the diameter is constant and the velocity profile is parabolic, the ratio between Flow and Vmax should be constant. For the analysis of the shape of the velocity profile, the 16 phases in the cardiac cycle were fitted separately. The deviations between the fitted velocity \(u(x,y)\) and the measured...
velocities were normalized to \( V_{\text{max}} \) (normalized deviation = \((u(x,y) - \text{measured velocity})/V_{\text{max}}\)). Normalized velocity profiles were averaged per age group for both the measured and the fitted profiles. After that the significance of the difference between the velocity profiles in the young and elderly was investigated. Therefore the measured profiles were divided by the fitted parabolic profiles both for the elderly and the young volunteers. An unpaired t-test was carried out for each pixel. The t-test was applied on the normalized deviations between the fitted paraboloid and the measurements. For each phase and pixel in the cardiac cycle a p-value was calculated. To exclude false positives caused by the number of t-tests, the number of pixels in the vessel was used to apply the Bonferroni correction.

\[ \text{Figure 1.} \quad \text{Cross sections of the average of measured (*) and fitted (line) velocity profiles for the young (left) and elderly (right) volunteers. Note that edge pixels with MRI are always unreliable due to slow flow, phase noise and partial volume effects.} \]

### 4.3 Results

In four scans of the elderly volunteers the major flow direction in one artery was not perpendicular to the imaging plane and these were excluded from analysis. For the young volunteers all scans could be positioned correctly. The fit quality was 0.02 ± 0.02 cm/s per pixel for both the young volunteers and the elderly individuals. The average shapes of the measured and fitted cross-sections of the velocity profiles for the young and elderly volunteers are presented in Figure 1. Flow, \( V_{\text{max}} \) and Flow/\( V_{\text{max}} \) are presented in Table 2. It shows that the Flow decreased faster with age than \( V_{\text{max}} \). In 5 decades Flow-M decreases 3.6 times faster than \( V_{\text{max}}\)-M, Flow-D decreases 2 times faster than \( V_{\text{max}}\)-D and Flow-S decreases 2.3 times faster than \( V_{\text{max}}\)-S. \( V_{\text{max}}\)-D and \( V_{\text{max}}\)-S were significantly lower for the elderly, while \( V_{\text{max}}\)-M was not.
Table 2. Measurements in ICA of healthy young and elderly volunteers

The presented results are: the ratio of the Flow (ml/min) and the maximum velocity (Vmax) (cm/s), in cm², WSS (Pa), Flow (ml/min) and Vmax (cm/s) with mean ± the SD and the coefficient of variation (CV) (%). The letters M, S and D refer to mean values over the cardiac cycle, those at systole and end-diastole, respectively. The difference in percent between young and elderly volunteers is given by Delta and the significance level is in given the last column, where * indicates a significant difference.

4.3.1 Validity of parabolic velocity profiles

The ratio Flow-M/Vmax-M was 0.15 ± 0.03 cm² and 0.11 ± 0.02 cm² for the young and elderly volunteers, respectively (p-value=1.3.10⁻⁷). For diastole the ratio’s were 0.12 ± 0.03 cm² and 0.08 ± 0.03 cm², respectively (p-value= 2.8.10⁻⁵), and for systole the ratios were 0.16 ± 0.04 cm² and 0.13 ± 0.03 cm², respectively (p-value=6.4.10⁻⁴). Thus for all ratio’s investigated, the Flow/Vmax was significantly higher for the young volunteers. In Figure 2 an impression is given of the structural differences between the fitted paraboloid and the measured velocity profile for both age groups. Therefore the deviations (mean measurement - mean fit) were made rotation-symmetric around the center, multiplied with 5 and added to the fitted profile. In Figure 2 can be observed that the profile of the young individuals is more blunted, while that of the elderly volunteers is more peaked than the fitted parabolic profile.

4.3.2 Significance of differences in velocity profile

The measured profiles were divided by the fitted paraboloids for the elderly (Figure 3A) and the young (Figure 3B) volunteers. From visual inspection it can be observed that the shapes are clearly different. This was confirmed by an unpaired t-test. The results of the t-test for the individual pixels are presented in Figure 4. It can be observed that for all phases in the cardiac cycle there is a significant difference between the deviations from the parabolic velocity profiles for the two groups. For each phase and pixel in the cardiac cycle a p-value was calculated. After applying the Bonferoni correction for all time phases in the cardiac cycle there is at least one pixel, which shows not only in the actual phase, but also in the previous and next phase a significant difference. This implies that there is a significant difference between the velocity profiles for young and elderly for all time phases in the cardiac cycle.
Figure 2. To illustrate the differences in shape, exaggerated differences between fit and velocity profiles for the young and elderly volunteers are presented. The solid lines represent the average of the fitted paraboloids; for the dashed line the deviations between the average fit and the average measurement was made rotation-symmetric around the center and enlarged by a factor of 5.

Figure 3. Deviation between measurement and parabolic fit for elderly (A) and young (B) volunteers. Presented is the average of ((fit-measurement)/Vmax) in the cross section of the ICA.
4.4 Discussion

The main finding of the study is that the velocity profiles in the ICA of healthy volunteers differ significantly between healthy young and elderly individuals for all 16 phases of the cardiac cycle. Flow and Vmax both decrease with age in the ICA. However, the decrease in Flow is more than two times faster than the decrease in Vmax. The ratio Flow/Vmax is significantly smaller for elderly volunteers as compared to young volunteers. The annual decrease in Flow we measured was 2.2 ml/min per ICA. The total cerebral blood flow (TCBF) is frequently defined as the flow volume through the two ICA’s together with the flow volume through the vertebrals.\(^{17}\) A fast decay in TCBF with age was also measured by Hendrikse et al. (3.1 ml/min per year) and by Buijs et al. (4.8 ml/min).\(^{18,19}\)

Samijo et al. found that Vmax-M in the CCA decreases about 10% in 5 decades but that this decrease does not reach the level of significance. This is in good agreement with our measurements which demonstrate a decrease of 8.7 %, with \(p=0.14\). Other studies showed that pulse pressure increases with age.\(^{20,21}\). It can indeed be observed in Table 2 that the systolic blood flow in the carotid artery does not decay as fast as diastolic blood flow with age, which indicates an increase in pulse pressure.

The WSS (Pa) is defined as the velocity gradient with respect to the normal \(n\) at the wall multiplied by the blood viscosity \(\mu\) (Pa.s); or in other words

\[
WSS = \mu \frac{\partial v}{\partial n}, \quad (2)
\]
with \( v \) being the fluid velocity [m/s]. By assuming a parabolic flow profile, the WSS can be calculated as follows:\(^2\)

\[
WSS = 4\mu V_{\text{max}}/\text{Diam} \quad (3)
\]

, where the diameter is indicated by Diam, blood was assumed to be a Newtonian fluid and \( V_{\text{max}} = 2*V_{\text{mean}} \). Gnasso et al. measured \( V_{\text{max}} \) and Diam with regular echo-Doppler. They calculated WSS with Eq 3 and showed a decline in WSS with increasing age.\(^2\) Diameter determination with MRI is difficult because of the relatively low image resolution. Measurement of the whole velocity profile, however, shows that \( \text{Flow} \) (which is by definition \( V_{\text{mean}} \times \text{vessel area} \)) decreases much faster with age than \( V_{\text{max}} \).

Samijo et al. used a sophisticated ultrasound device and measured a whole velocity profile with a high resolution.\(^{22}\) They quantified WSS decay in 5 decades and observed values of 18.6% for females and 17.9% for males. With respect to WSS decay with age, the following observations are relevant: 1) age does not affect blood viscosity;\(^{23}\) 2) \( \text{Flow} \) decreases 30% for systole and more than 40% for diastole over the measured age range in this study, and 3) blood vessel diameter increases with age.\(^{22,24,25}\) Since \( V_{\text{mean}} = \text{Flow}/\pi \times \text{radius}^{2} \), \( V_{\text{mean}} \) will decrease more with age than \( \text{Flow} \). Furthermore since \( WSS = 8\mu V_{\text{mean}}/\text{Diam} \), WSS will decrease more than \( V_{\text{mean}} \). Therefore, compared to our measurements, it can be expected that also the technique of Samijo is underestimating the decline in WSS with age.

The central velocity in the elderly is relatively higher than the fitted paraboloid. When fitting a model to measured data, part of the flow profile will be above and a part will be below the measured data. Because, for the elderly, the central velocity is somewhat larger than the parabolic fit, the actual velocity in the region of the wall will probably be smaller than the fitted velocity. If the velocity near the wall is smaller than the parabolic fit this means that the WSR and thus the WSS is underestimated. Note that edge velocities are less reliable with MRI due to artifacts.\(^{26}\)

It is known that blood velocity increases in the presence of a stenosis.\(^{27}\) A thicker wall is common for a higher age and it is likely that the elderly volunteers have more stenoses.\(^{28}\) Due to the Glagov effect it is not expected that the lumen will decrease for small plaques.\(^{29}\) However if minor lumen decrease might be present this will probably cause a more peaked velocity profile. Therefore it might be that the relative increase in \( V_{\text{max}} \) in elderly volunteers is reflecting the presence of stenoses or a thicker wall in the neighborhood of the investigated cross section.\(^{30,31}\) Since statins have found to decrease plaque and wall thickness this would be in agreement with the fact that paravastatin decreases \( V_{\text{max}} \).\(^{32}\) Velocity profiles are parabolic when the flow is steady, the tube is circular in shape and the wall is fixed.\(^{14}\) However, in the ICA the flow is pulsatile and the wall is distensible so that during the cardiac cycle the diameter varies up to 10%. The distortions caused by distensibility are beyond the scope of this paper, but are expected to be small.\(^{22,33,34}\) Under pulsatile flow conditions, the amount of flow can alter the velocity profile since inertia starts to play a role. Inertia effects are affected by diameter, viscosity, amount of flow and frequency of the pulsation. This was modeled by Womersley.\(^{16}\) We applied Womersley’s theory on the data of this study and investigated whether inertia effects could explain the change in the velocity profile. Therefore, the velocity profile was simulated for a viscosity of 4.3 mPas as was measured by Gnasso et al. and a diameter of 6 mm.\(^{2}\) The flow as measured by MRI during 16 phases in the cardiac cycle gave two average flow curves, one for the young and one for the elderly group. The cardiac frequency was in both cases assumed to be 60 beats per minute. When a blood density of 1.4.10^3 kg.m^-3, and frequency
of 1 Hz, is assumed, $\alpha = 3.4$. To investigate the influence of inertia, Flow/Vmax was calculated for a simulated velocity profile where Womersley theory was applied, giving Flow/SimVmax. Flow-M/SimVmax-M was 0.18 cm² both for the young and elderly volunteers. For Flow-D/SimVmax-D these values were 0.20 cm² and for Flow-S/SimVmax-S the ratios were both 0.17 cm². The ratios are somewhat larger than the ratios found in the fitted measurements however, the ratio between Flow/SimVmax was not different for the young and the elderly volunteers. It can be concluded that changes in the velocity profile are not caused by inertia.

Changes in the velocity profile are probably not caused by blood viscosity, because it has been shown that differences in blood viscosity between young and elderly individuals are not significant. On the other hand, it has been shown that deformability of red blood cells does decline with age and it can be argued that this will affect the velocity profile. In general, MRI has a limited spatial and temporal resolution. Diameter measurements cannot be assessed directly and therefore have to be derived using a model. This limitation could partly be overcome by using an additional high-resolution MR acquisition at the expense of additional scan time. Conventional echo-Doppler has the advantage of a high precision in diameter measurements and a high temporal resolution. A drawback is that it can only be applied in vessels located close to the body surface and that it measures only one velocity. MRI has the advantage that it can measure a whole velocity profile in all vessels beyond approximately 1 mm in diameter at any position in the body. In this study group wall thickness and plaques were only measured in the elderly individuals. Most of the elderly volunteers had some thickening of the vessel wall but none of the volunteers had plaque. A drawback of the study was that we did not measure wall thickness in the young volunteers. However since all the volunteers were healthy it can be assumed that the vessel wall was thin in the carotids of these individuals.

A drawback for comparison between age groups is that the blood pressure between the groups is different because blood pressure increases with age. However this is a common age related increase and our healthy volunteers show an average human blood pressure rise. We have shown that both conventional echo-Doppler in combination with parabolic modeling and sophisticated echo-Doppler will probably underestimate WSS decline with age. In the future a better approximation of the real decrease of WSS with age can be assessed when echo-Doppler is combined with MRI. Conventional echo-Doppler is capable to assess high-resolution images in time and space. MRI is capable to measure 4D velocity profiles and vessel geometries. Also extended ultrasound devices capable to measure 4D velocity profiles with a higher resolution compared to MRI, would be an interesting extension. Another approach with promising prospects is the Finite Element Method (FEM). Modelling with this method is far more precise, but also much more time consuming. At present the calculation of WSS with FEM takes very much manual interaction and computing power. Therefore this method is not yet applicable in large clinical trials.

In summary, we have demonstrated that the velocity profile in the ICA changes significantly with age, both in shape and magnitude and that these changes may increase the decay rate of WSS with age.

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References


