Chapter 8

Summary
Wall shear stress (WSS) exerted by flowing blood at the vessel wall, is defined as the velocity gradient at the vessel wall times the blood viscosity. Low WSS is related to atherosclerotic risk profiles and WSS is low or oscillating at locations where plaque development is observed. *In vivo* cross-sectional images of blood flow suffer from limited resolution and lack of info on local viscosity. However, WSS can be assessed by modeling of velocity profiles and blood viscosity. Already with a first approximation of velocity profiles by an imprecise model, such as a paraboloid, and under the assumption of a constant (average) human blood viscosity, correlations between various cardiovascular risk factors and WSS were found. Also the effect of treatment with pravastatin on WSS has been demonstrated with this model. The more detailed the model, the more accurate WSS can be assessed. An accurate 4D WSS assessment can be obtained by application of a so-called Finite Element Method (FEM) calculation. Blood velocity is then simulated for a certain vessel segment. The precision of this WSS calculation is among other things dependent on the precision of the so-called boundary conditions. Boundary conditions used for the FEM calculations are: no slip at the vessel wall, while for in- and outflow conditions the measured patient specific flow profiles must be used. This requires an accurate assessment of vessel morphology, blood flow velocity (both assessable with MRI) and blood viscosity. A model of the vessel geometry composed of bricks (a so called mesh) has to be created in order to simulate the blood flow.

In chapter 1 it is explained why atherosclerosis is an important topic and why WSS is a promising parameter for the study of the development of atherosclerosis. The discovery of WSS as an important factor influencing atherosclerosis is discussed. Also the aims and outline of this thesis are presented.

In chapter 2 an automatic method to assess blood flow in the carotid and vertebral arteries is discussed. When flow in the vertebrals and internal carotid arteries (ICA) is known, total cerebral blood flow (TCBF) is simply the sum of these four flow values. We developed an automatic method for assessment of blood flow, since conventional manual segmentation approach is tedious, time-consuming and leads to significant inter- and intra-observer variabilities. To assess blood flow from phase-contrast magnetic resonance (MR) imaging studies, accurate delineation of vessel contours in cross-sectional MR images is essential. The aim of this study was to verify whether automatic model-based segmentation, by fitting a model to actual blood velocity profiles could solve these problems. Two new semi- automatic methods (a static and a dynamic approach) were developed and compared with manual analyses using phantom and *in vivo* studies of the ICA and vertebral arteries in healthy volunteers. The automatic segmentation approaches were based on fitting a 3D parabolic velocity model to actual velocity profiles. In the static method, velocity profiles were averaged over the complete cardiac cycle, whereas the dynamic method fits a parabolic profile on velocity data of each cardiac time bin individually. The only user interaction required was the indication of the vessel of interest. Materials consisted of MRI data from three straight phantom tubes and blood velocity profiles of eight healthy young volunteers (age 24.9 ± 3.5 years). For phantom studies, the automatic dynamic approach performed significantly better than the manual analysis. Reproducibility was expressed by the intra-class correlation (ICC) coefficient. The ICC was 0.62-0.98 for the automatic dynamic approach and 0.30-0.86 for the manual method. For assessment of total cerebral blood flow (TCBF) in *in vivo* studies, the automatic static method performed significantly better than the manual one (ICC of 0.98-0.98 and 0.93-0.95, respectively). On the other hand, the automatic dynamic method was not significantly better than the manual one (ICC
= 0.92-0.96). It was concluded that blood flow in MR images of small vessels can be assessed accurately, rapidly, with an excellent reproducibility and without observer variability using model-based post-processing techniques based on fitting a first approximation of velocity profiles to actual flow data.

In **chapter 3** the method described to measure blood flow was extended to the assessment of the WSS. The calculation of the WSS requires data on flow volume and maximum flow velocity (Vmax) in the cross-section of a vessel. It was verified, whether WSS can be assessed in a reproducible manner using automatic model-based segmentation. The approach was based on fitting a 3D paraboloid to actual velocity profiles as was discussed in chapter 2 and on assessment of Vmax. WSS was measured in the ICA of two groups of healthy young volunteers. Reproducibility of rescanning and repositioning was studied in the first group. In the second group a one-week and a one-month interval was investigated. It was found that WSS in MR images of the ICA can be assessed semi-automatically with good to excellent reproducibility without inter- or intra-observer variability using model-based post-processing. Reproducibility can be increased by application of temporal and spatial averaging.

Based on a parabolic assumption of the velocity profile, ultrasound studies have demonstrated that WSS decreases with age. However, with a standard echo-Doppler device only one (central) blood velocity can be measured. With MRI a whole 3D velocity profile in a selected cross section can be obtained. The aim of the study described in **chapter 4** was to investigate whether differences in velocity profiles exist in the ICA between young and elderly healthy individuals, and whether these effects influence WSS. The blood velocity profiles in the ICA of 20 healthy young volunteers (age 26.7 ± 7.1 years) and of 16 healthy elderly volunteers (age 73.9 ± 2.8 years) were assessed; time resolution was 16 phases per cardiac cycle. The parameters Flow, Vmax and the ratio between Flow and Vmax were assessed after averaging over the cardiac cycle (indicated by the suffix M), for diastole (indicated by D) and for systole (indicated by S). Flow, Vmax-S and Vmax-D were found to be significantly lower for elderly volunteers. In all 16 subsequent phases of the cardiac cycle there was a significant difference in velocity profiles between young and elderly individuals. It is shown that the velocity profiles of young individuals were more blunted and that those of elderly were more peaked than the assumed paraboloid profile. Flow-M/Vmax-M was 26.4 % (p=1.3.10^{-7}) smaller for elderly individuals (0.15 ± 0.03 cm² versus 0.11 ± 0.02 cm²). Flow in the ICA seems to decay faster with age than Vmax. Due to these deviations in decay rate, it can be expected that the actual decay of WSS with age is faster than can be measured by paraboloid modeling. In summary, the study data demonstrated that velocity profiles in the ICA change significantly with age, and the data suggest that this decay is faster than was assumed so far.

Statins are a class of medications, which aim at lowering cholesterol levels. It is known that statins improve plaque stability; and even plaque regression has been demonstrated. However, it is still not exactly known if and how statins affect WSS. The aim of the study described in **chapter 5** was to assess whether pravastatin affects WSS in a double-blind randomized, placebo-controlled trial. **In vivo** WSS was assessed as described in chapter 3. The ICA of 355 participants was measured with MRI. WSS and mean and diastolic blood velocities decreased significantly both in the pravastatin group and in the placebo group. However, WSS and blood velocity decreased significantly faster in the pravastatin group.
(p<0.04, p<0.02) than in the placebo group. Blood volume flow did not differ significantly between the groups.

Plaque development is observed in particular at places where WSS is low or oscillating. Modern non-invasive MRI techniques combined with FEM can provide objective information about the presence, extent and severity of WSS distortions in 3D-visualizations of major vessels. With FEM the 4D blood velocity profiles and blood pressure can be simulated. For assessment of local WSS, the FEM method requires boundary conditions. The boundary conditions are formed by the 3D geometry of the vessel wall (where the blood velocity is zero) and blood flow at in- and outflow locations of a simulated vessel part. Geometry of vessels, blood flow and blood viscosity differ widely between individuals. Therefore, a method to achieve reliable patient specific data is necessary. A software package (MRA-CMS) has been developed for automated segmentation and visualization of arteries from 3D MR angiographic data. These 3D data sets, representing the surface of the lumen can be used to form the vessel wall boundary condition for FEM. The other necessary boundary conditions, in- and outflow, can be assessed with the procedure described in chapter 2. In previous chapters it was assumed that blood viscosity is a constant. Blood, however, is a non-Newtonian fluid, and viscosity is shear-rate dependent. When shear rate is high, blood viscosity is low and vice versa. In chapter 6 an overview of the current technology is given. Aiming at future possibilities to improve precision of several input parameters, a comparison between measured and calculated flow and velocity profiles is presented.

Plaque development particularly occurs in regions with recirculation, i.e. where WSS oscillates. In the study described in chapter 7 we investigated effects of non-Newtonian blood viscosity, variations in flow rate and vessel diameter on wall phenomena in a carotid bifurcation model. Flow through a model of a carotid artery bifurcation was simulated by means of the FEM. Whole blood viscosity is a function of shear rate, and was modeled by the Carreau –Yasuda (CY) model. Flow rate and vessel morphology were assessed with MRI. Flow rate, blood viscosity and haematocrit levels (Hct) were measured in 49 healthy volunteers. An adaptation of the CY model was proposed in order to incorporate differences in haematocrit levels; furthermore, plasma viscosity was varied in the CY-model. The data from our model indicate that flow increases have a larger effect on WSS than predicted with a paraboloid model. Hct has more influence on WSS when plasma viscosity is low. Low plasma viscosity is associated with a low WSS, which implies a contradiction, because both high WSS and low plasma viscosity are thought to be indicators for a healthy system. Maximum WSS oscillations are found at the edges of the recirculation region, and flow and diameter change have significant influence on WSS values. The same is true for viscosity, but to a lesser extent.

In conclusion, WSS has proven to be an interesting parameter, which can be used to study atherosclerosis and effects of therapeutic interventions. A practical and fast approach to assess WSS in large clinical trials, has been developed by fitting a paraboloid to MRI-derived flow velocity data; this approach requires little user interaction and computer power. With FEM, WSS and WSS oscillations in 4D can be investigated in 4D.