Chapter 1

Introduction
1.1 Atherosclerosis

Heart attack and stroke are worldwide the number one causes of death. Both are caused by cardiovascular disease, which is a major field of research. Extensive progress has been made in the past decades in the understanding and treatment of cardiovascular diseases. Interventional procedures with vessel dilation and stent placement are now a matter of routine practice, particularly for coronary arteries. Many effective anticoagulants are available and large-scale campaigns are being organized in an attempt to convince people to a better and healthier life style by promoting more exercise and healthy dietary habits. As a result of improved imaging and analysis techniques, the diagnosis can be established at an earlier moment in time, which favors more effective treatments, thereby extending the age expectancy of people. Despite all these developments in prevention and treatment, cardiovascular disease is still the leading cause of death, especially in western societies.

Risk factors for cardiovascular disease include smoking, obesity, elevated cholesterol levels, diabetes mellitus, hypertension, kidney failure and polygenetic factors. Because death rates from atherosclerosis are so high, it is important that research aiming at better treatment and early diagnosis is performed. The screening of populations or individuals with one or more of the risk factors mentioned above can lead to early diagnosis.

Atherosclerosis occurs at damaged vessel walls of large elastic arteries, where plaques may subsequently develop following a more or less typical pattern. The American Heart Association has classified the atherosclerotic lesions in types I through VI (Fig 1). Type I and type II lesions are already found in children. Type I lesions consists only of an increased number of inflammatory cells (macrophages) and some macrophages filled with lipid droplets (foam cells). Type II lesion consists primarily of layers of macrophages and lipid droplets within smooth muscle cells. Type III lesions can be found from the third decade in life in progression prone regions. These are type II lesions plus an extracellular lipid pool. In type IV lesions the intimal structure is disrupted. These lesions consist of a core with extracellular lipid. Type IV lesions are frequently found from the third decade on. After the third decade type V and VI lesions can appear. Type V lesions consist of multiple layers of lipid formed at different moments in time; a thick fibrous cap covers the plaque. Finally, a type VI plaque is a complicated lesion with a disruption of the surface and/or hemorrhage. In types I to IV and sometimes also in type V the vascular lumen is kept intact and the plaque remodels the vessel mainly to the outside, without affecting the lumen. In type VI and mostly also in type V the plaque obstructs the blood flow [Stary1994, Stary1995, Glagov]. The process, that a plaque first develop inside the wall and at a much later point in time it starts comprising the lumen, is called the Glagov effect. An advanced plaque is a threat for health in two ways. First, the plaque obstructs the lumen and thereby reduces the necessary blood flow. Some of these plaques have a thin cap, and as a consequence have a high chance of rupture. If such an obstruction ruptures, thrombus formation occurs, leading to vessel occlusion or embolus formation. It has been demonstrated, that 76% of all fatal coronary thrombi are caused by vulnerable plaques [Falk].
Figure 1: Example of atherosclerotic lesions types I through VI [Stary 1995].

The process of atherosclerosis affects all arteries, but atherosclerosis in the coronary arteries, the aorta and the carotid arteries is particularly relevant in terms of morbidity and mortality. At locations where the blood flow is low, (for instance at the inside of curves and bends) or where the blood flow oscillates during the cardiac cycle (for instance near bifurcations), plaque is formed (Fig 2).

Figure 2a: Oscillation of the blood near the vessel wall during the cardiac cycle is caused by recirculation.

b: Plaque development is often observed at locations where the blood oscillates.

When the plaque extends into the vessel lumen and obstructs the lumen, recirculation in blood flow (which is equivalent to oscillating shear stress) and low shear stress will be present downstream of the plaque (Fig 3).
Figure 3a. Velocity vectors for simulation of blood flow in a straight vessel part with a 50% stenosis. The area with recirculation is clearly visible (in blue). Red indicates high velocity, via yellow and green to blue, which indicates low velocity.

It has been found that distortions of friction force exerted by the flowing blood at the inner side of the vessel wall (the endothelium) are a key factor in the development of atherosclerosis. Healthy endothelium produces a constant amount of Nitric Oxide (NO). NO is, among others, an anti-atherogenetic molecule. Its anti-atherogenetic effects are achieved by a combination of vasodilation, inhibition of platelet aggregation, smooth muscle cell proliferation and effects on LDL-oxidation and leukocyte adhesion. The friction force of the flowing blood is one of the main factors for NO release [Monnink].

1.2 Historical Perspective of WSS

It has been hypothesized that a relation exists between the presence of atherosclerosis and Wall Shear Stress (WSS) in arteries. WSS is defined as the mechanical friction force per unit area exerted by flowing blood on vessel walls. WSS is determined by two terms: 1) the blood viscosity at the vessel wall ($\eta$), multiplied by: 2) the fluid velocity gradient with respect to the normal ($n$) at the wall. The gradient of the fluid velocity is called Wall Shear Rate (WSR). In other words, WSS is defined as:

$$WSS = \eta \frac{\partial v}{\partial n} = \eta \text{WSR}, \quad (1)$$

with $v$ being the fluid velocity [m/s], $n$ is the normal at the surface and $\eta$ the dynamic viscosity.
As early as in the 1960’s the first WSS measurements were carried out in the aorta by Ling et al. and Fry [Ling; Fry]. The conclusion was that WSS had to stay below a certain level (slightly above normal) to prevent damage of endothelium. For a long time it was suspected that fluid mechanical properties of blood were associated with development of atherosclerosis, but real evidence was lacking [Mitchel and Schwartz (1965), Patel and Vaishnav (1980)]. In the nineteen seventies and eighties first experiments were performed which proved the relation between low or oscillating WSS and the development of lesions [Caro 1971, Zarins et al 1983]. Ku et al. demonstrated this relation in the carotid artery in 1985 [Ku]. Friedman showed the relation between Intima Media Thickness (IMT) and shear stress for the coronaries in 1987 and Moore proved the relation between plaque and WSS for renal arteries in 1992 [Friedman, Moore]. Development of tools needed for a precise calculation of this parameter became a subject of significant research for engineers, mathematicians and physicists. Computing power in those days was too limited to calculate realistic time-dependent 3-dimensional flows and therefore simplifications in two dimensions had to be made [van de Vosse]. At the end of the eighties, computing power had improved to the extent that 4D flow field calculations could be carried out [Rindt]. The diameter of blood vessels, however, varies during the cardiac cycle in healthy young individuals by about 10%, which is known as distensibility. For elderly individuals and patients with increased blood pressure distensibility is decreased. Distensibility can only be taken into account when blood pressure variations during the cardiac cycle, which affect the vessel wall, are modeled as well; this field of research is called fluid-solid interaction. It was developed and applied by Reuderink in 1991 and Rutten in 1998 [Reuderink, Rutten]. Nowadays, some commercially available computational fluid dynamics software packages such as FIDAP® (Fluent, Nebanon USA) allow inclusion of fluid-solid interactions.

In 1991 Sharefkin et al. demonstrated that flow induced suppression of gene expression might influence the inverse relation between shear stress and the formation of neointimal hyperplasia [Sharefkin]. Since that time, gene expression modulated by WSS has become a subject of increasing scientific interest. Hierck et al. and Groenendijk et al. showed that the development of the heart in chick embryo’s depends on the distribution of shear stress of the embryonic chicken heart [Hierck,Groenendijk]. WSS regulates gene expression in physiological as well as in pathological conditions such as atherosclerosis. Moreover, WSS has been found to regulate endothelial phenotype on a time scale of hours to days. It controls the expression of all the known major functional product classes of the endothelial phenotype [Malek].

1.3 In vivo WSS assessment with Magnetic Resonance Imaging

Since shear stress is such an important parameter, it is important to develop methods to assess WSS in vivo in an accurate way. For such methods modeling of several parameters is a prerequisite. Blood viscosity is such a parameter. Although blood viscosity can be assumed to be a constant, in reality it is not. When viscosity is constant, it is called ‘Newtonian viscosity’. Blood, however, is a non-Newtonian fluid: it is shear-rate dependent. This means that viscosity is dependent on the local spatial steepness of velocity profiles (WSR). When WSR is high, viscosity is low and vice versa. Viscosity is also determined by blood constituents. For low WSR the amount of haematocrit (Hct) is important: a high percentage of haematocrit gives a high blood viscosity. When WSR
increases, blood viscosity becomes more related to the viscosity of blood plasma. Viscosity of blood plasma is assumed to be influenced by factors such as fibrinogen and cholesterol.

Aiming at WSS assessment also irregular vessel shapes, which occur in clinical practice, have to be modeled. Studies have shown that the shape of vessels is important for precise calculations of WSS [Perktold, Milner]. Vessels can be visualized with relatively high resolution with modern non-invasive techniques, such as Magnetic Resonance Imaging (MRI) or Multi-Slice Computed Tomography (MSCT). A post-processing procedure is then required to segment the vessel lumen. The geometry of a segmented lumen can be built with bricks or triangles using finite element techniques, so that a model of the lumen (a so-called mesh) can be used for subsequent fluid dynamic calculations. With these meshes blood velocity and blood pressure can be calculated. The geometry of blood vessels in vivo varies over a broad range. Triangles are easier to use than bricks when vessel geometries have to be built. Bricks have the advantage that fluid dynamic calculations are more precise. WSS is dependent on a precise calculation of the velocity field (especially at the lumen edge of the vessel) and thus it is best to achieve a vessel geometry built up by bricks. Vessel modeling by bricks and Finite Element Modeling (FEM) today still take a significant amount of time. As a result, it is feasible to carry out such WSS calculations in small groups of patients, but computer infrastructure permitting large scale studies or fast analysis in individual patients is not yet available.

Gnasso et al. showed that WSS can also be assessed with sufficient accuracy by using a first approximation of the velocity profile [Gnasso]. This velocity profile was described by a paraboloid and is matched with the true data based on the central blood velocity and the vessel’s diameter. It was applied in 21 subjects who underwent an echo-Doppler measurement of blood flow velocity in the common carotid artery. WSS assessed with this method was found to correlate with age, intima media thickness (IMT), systolic blood pressure (SBP) and body mass index (BMI) [Gnasso]. The fitting of a paraboloid on MRI velocity data has proven to be fast and robust and has a good to excellent reproducibility without inter or intraobserver variability. The advantage of MRI over echo-Doppler aiming at WSS is that all vessels in the body can be measured, with echo-Doppler only vessels at the surface of the body can be investigated. Palm-Meinders et al. demonstrated that WSS assessed with the paraboloid method on MRI velocity data correlates in a group of 379 elderly individuals (age 75 ± 3 years) with age, SBP and diastolic blood pressure (DBP), BMI, smoking, a history of hypertension, a history of myocardial infarction and with triglycerides [Palm-Meinders].

1.4 History of this thesis

1.4.1 Assessment of flow
A number of years ago, our department became involved in a large clinical trial (PROspective Study of Pravastatin in the Elderly at Risk; PROSPER) in which the benefits of pravastatin treatment were investigated in a group of individuals aged 70 to 82 years, with vascular disease or at risk of vascular disease [Shepherd]. A question was whether this statin ‘pravastatin’ would also affect the amount of blood supplying the brain in humans. Therefore, a method had to be developed which could assess the TCBF (Total Cerebral Blood Flow) from velocity encoded MRI images. The TCBF was defined by the summation of the flows through the two internal carotid arteries and the two vertebral arteries. The problem, however, was the low image resolution of 1 mm squared. The
internal carotid arteries (ICA) were about 15 pixels in cross-sectional area and the vertebrals about 5 pixels.

The idea developed to fit a parabolic velocity profile so that images could be segmented based on this fitted profile. The entire procedure was subsequently automated to a large extent. The user only had to indicate the vessel of interest within the image data with one click of the mouse; this spatial position (pixel) was saved. After having defined all these pixels, the calculations could be carried out in batch mode. The program automatically read all the data, read the connected vessels of interest, carried out the fitting procedure and saved the quantitative output. In the PROSPER study this automatic procedure was used by van Dam et al. [Dam]. The conclusion was that paravastatin does not affect TCBF.

1.4.2 Assessment of WSS

However, once the velocity profile is modeled more opportunities arise. It was decided to further explore the value and limitations of WSS. The aim was to demonstrate that velocity profiles and derived indices of WSS and Wall Shear Rate (WSR = the Wall Shear Stress divided by the blood viscosity) in carotid arteries can be obtained with small systematic and random errors from MRI acquisitions, and that differences in these parameters can be observed in groups of individuals with different risk profiles for atherosclerosis and stroke. Supported by a grant of the Netherlands Heart Foundation (2000B119) and with the support by of prof. F.N. van de Vosse and his coworkers at the Technical University Eindhoven, the Finite Element package SEPRAN was made applicable in year 2003 for in vivo circumstances. However, the robustness and speed turned out to be insufficient for application in a large clinical trial, such as the PROSPER study. A solution was found by combining the findings of Gnasso (paraboloid approximation of the flow velocity profile) with our automatic flow assessment (FLOW-MRI analytical approach). As a result, WSS calculations were carried out for the PROSPER trial by Box et al (this thesis Chapter 5), Palm-Meinders et al. [Palm-Meinders] and in relation to cognition [van Es].

1.5 Outline of this thesis

Velocity encoded MRI was applied to assess 4D velocity profiles. Velocity profiles in relatively small vessels outside the thorax can be approximated by a paraboloid. Chapter 2 describes how a parabolic velocity profile can be used to segment vessels and assess the flow. Flow was evaluated through a phantom connected to a pump and through the vertebrals and ICAs of eight healthy young volunteers. The systematic error and the reproducibility are derived.

In chapter 3 the paraboloid fitting method is extended to calculate WSS in the ICA. To assess reproducibility, a group of 20 volunteers (10 males, 10 females, age 26.7 ± 7.1 years) were scanned three times. The time between the first and second acquisition was one week, and between the first and third acquisition one month.

In previous studies it has been demonstrated that WSS decays with age. Since WSS is mainly determined by the shape of the velocity profiles, the difference in velocity profiles between healthy young and elderly individuals was investigated in chapter 4. For these purposes we used data from the group of healthy young individuals discussed in chapter 3 and performed measurements in 16 healthy elderly volunteers (8 males, 8 females, age 73.9 ± 2.8 years).
It has been suggested that the class of pharmaceutical agents known as statins increase NO synthesis, but it is not known whether WSS is responsible for this phenomenon [Endres]. In chapter 5 we present data on the influence of a statin (pravastatin) on the WSS. In the PROSPER study the effect of cholesterol-lowering therapy with 40 mg pravastatin on vascular events was examined in patients, aged 70 to 82 years, with vascular disease or at risk for vascular disease.

In chapter 6 it is explained how FEM and MRI can be combined to assess patient specific WSS calculations. By application of the technique presented in chapter 2 in- and outflow can be assessed. With velocity encoded MRI cross-sectional velocity profiles were assessed in a curved tube phantom. Since geometry was exactly known and easy to implement in the FEM software, the curved tube model was exactly meshed. Inflow measured with MRI was used as input for FEM calculations. Similarity between the measured and simulated velocity profiles was investigated. A good similarity for precisely modeled phantoms gives future possibilities for \textit{in vivo} assessed data. If that would be the case, MR measurements can probably be used to optimize boundary conditions or calculation methods for \textit{in vivo} assessed geometries and flows.

In chapter 7 the FEM method was applied to investigate the effect on WSS of realistic variations in geometry, flow, blood viscosity and diameter in young healthy individuals. For this purpose, viscosity measurements in a blood sample from the group discussed in chapter 3 were examined. Data from three volunteers was used. The volunteers with the highest, the lowest and an average blood viscosity were selected. The modeling of shear rate dependent viscosity was improved. Flow through the common carotid artery during 16 phases in the cardiac cycle was used as inflow to a mesh made from a segmented MR image of a carotid bifurcation phantom. Also, a diameter variation of 10% was modeled. Effects on WSS caused by variation in flow, viscosity and diameter, were investigated.

Following the summary of this thesis, conclusions and future directions are presented in chapter 8.

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