Wall shear stress calculations using phase contrast MRI
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Chapter 1

Introduction and outline
1.1 Introduction

Cardiovascular disease is a major health problem in the world (1, 2). In the four-year timespan when this thesis was composed, an estimated number of 152,000 people in the Netherlands did not survive cardiovascular pathologies. Although this is a tremendous amount, the cardiovascular deaths count in the Netherlands declined more than 50% over the past three decades (3). Certainly improved health care and the reduction of smoking contributed to this. However, due to an aging population in the Netherlands, it is expected that the health burden due to cardiovascular disease will increase dramatically in the next decade.

Among cardiovascular diseases, atherosclerosis is one of the most prevalent diseases. According to a recent study, over 50% of the people between 40 and 54 years of age has atherosclerotic plaques, especially males (4). Depending on the location, stability and severity of atherosclerotic plaques, these can cause a stroke, heart attack or gangrene.

Early atherosclerosis already starts in childhood. It is a disease of the vessel wall involving inflammation and lipid metabolism within a complex pathophysiology, which develops over a prolonged period. During the development of atherosclerosis, several processes occur in the multiple vessel wall layers. At the outside of the vessel wall, smooth muscle cells migrate from the media layer and the adventitia layer towards a neointima layer, where these cells proliferate and produce extracellular matrix molecules, such as elastin and collagen. At the inside of the vessel, one of the factors contributing to the initiation of atherosclerosis is the disruption of the integrity of the endothelial layer. An intact and fully functional endothelial layer serves as an atheroprotective barrier for the surrounding vessel wall. In contrast, a damaged endothelial layer expresses leukocyte adhesion molecules, which promote migration of leukocytes from the vessel lumen to the intima. Blood-derived monocytes may mature into macrophages, leading to the inflammatory status of the tunica intima. Over time, macrophages can convert into foam cells, contributing to the inflammatory lesion in the vessel wall (5–9).

The formation of atherosclerotic lesions leads to outward remodeling of the vessel wall (10). The continued influx of inflammatory cells also changes the composition of the vessel wall. Calcifications, atherogenesis, and a thin fibrous cap may render a stable plaque unstable, i.e. prone to rupture. The rupture of a plaque, as well as advanced lumen area decrease, will transform a patient’s asymptomatic plaque into a symptomatic plaque, which is a turning point that should be prevented.

The flowing blood plays a role in the initiation and progression of atherosclerosis at the endothelial layer, where it exerts a frictional force on the endothelium. This tangential force is called the wall shear stress (WSS), or endothelial shear stress. WSS directly affects the expression of endothelium-derived factors, such as nitric oxide (NO). NO is a protective factor, involved in a myriad of vascular processes, including vasodilation, inhibition of platelets, and maintenance of a quiescent phenotype of smooth muscle cells. Several studies showed a correlation between WSS and remodeling of the vessel wall. Steady flow of blood at the endothelium promotes an atheroprotective phenotype, whereas a low or a pulsatile, nonsteady flow of blood at the vessel wall increases atheroprone conditions in the endothelial cells (11–20).

Although it is known that WSS plays a role in the initiation and progression of plaques, the role of WSS on plaque composition remains unknown. The complex WSS distribution around a plaque may have contributed to this, i.e. high WSS values at the proximal side and center of the plaque and low WSS values on the distal side of the plaque (21). Some literature, therefore, advises against WSS analysis for predictive models in stenosed vessels (18). However, a large study by Stone et
al. showed that low WSS provides independent and additive information to predict progression of coronary plaques (22). Also, many animal studies investigated the role of low and high WSS in stenosed vessels (23). With new volumetric WSS measurement and simulation techniques, we may improve our ability to measure the distribution of WSS, thereby adding information to the insights on the relation between WSS distribution and atherosclerosis (19).

Besides atherosclerosis, WSS is also thought to be involved in other vascular remodeling pathologies, such as aneurysms. As aneurysms are often detected after rupture or too small to be eligible for treatment, it is difficult to obtain WSS measurements for rupture risk assessment in aneurysms and even more challenging to obtain WSS measurements before aneurysm initiation. Previous work by van Ooij et al. and Schneiders et al. therefore used computational fluid dynamics to obtain WSS values in aneurysms. They, however, found a limited role for hemodynamics and WSS in rupture risk assessment compared to existing location and size parameters (24–27). Also in other literature, the exact role of WSS and other hemodynamic factors in aneurysms remains under active debate (28, 29).

### 1.2 Velocimetry

Direct WSS measurements have been used in in vitro experiments, but not in in vivo experiments. For example, Gijsen et al. measured WSS by analyzing the deformation of gel deformations within an in vitro flow chamber setup (30). Recently, Lobo et al. showed a method to measure WSS with nanosensors, attached to the endothelial cells (31).

For in vivo WSS quantification, it is common to determine the 3D velocity field first and then calculate the WSS. There are several methods to determine the velocity field in vivo; below we describe both the approaches based on simulations and measurements.

#### 1.2.1 Simulations

Simulation-based velocity quantifications use mathematical equations to calculate the theoretical velocity field. This technique to estimate blood velocity vector fields is called computational fluid dynamics (CFD). The simulations are based on the Navier-Stokes equation. To make reasonable calculations that mimic an in vivo situation, we need to define boundary conditions. These conditions can include the location and dimensions of the vessel wall, the velocity profile, the flow ratios and pressure. CFD is widely applied to estimate blood velocity vector fields in all kinds of vessels (22, 32–38).

The biggest advantage of CFD is that we can obtain a very high spatiotemporal resolution in all complex geometries. Depending on the simulation complexity, a typical CFD simulation can take between one hour and multiple days. The inclusion of more complex boundary conditions, such as cyclic wall motion, is also feasible, but would increase the complexity and computational time.

#### 1.2.2 Measurements

To the best of our knowledge, in vivo velocity measurements can be achieved with three methods. The first method uses the Doppler effect to quantify velocity-induced shifts in the ultrasound or optical signal resulting in velocity. It is usually limited to one-dimensional velocity, although the combination of multiple acquisitions may enable a multi-directional velocity scan (39).
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The second method, particle image velocimetry (PIV), uses tracking techniques to follow particles in subsequent images of the flowing fluid. The images can be obtained by either ultrasound (40), X-ray (41) or optical techniques (42). The division of the distance and the time between two images results in the velocity vectors. PIV is, however, limited to measurements in transparent media (for fast optical techniques) and requires complex post-processing on very large datasets to calculate WSS.

The third technique is phase contrast magnetic resonance imaging (PC MRI). PC MRI is currently the only in vivo technique to measure 3D blood velocity accurately in three directions within a large volume. A common name for the measurement of cardiac-resolved, three-directional velocities within a 3D volume with MRI is ‘4D flow MRI’ (43, 44). 4D flow MRI has been shown to measure blood velocity accurately compared to ultrasound (45) or PIV measurements (24).

1.3 Aim of this thesis

As discussed above, atherosclerosis and aneurysms, in addition to other factors, are associated with altered WSS. The location of these pathologies strongly correlates with the presence of altered WSS. Vascular diseases, however, do not limit themselves to 2D planes. In fact, we see complex volumetric WSS patterns across the vascular tree, which may evolve over the cardiac cycle.

Until recently, the WSS was mostly calculated in 2D planes, using either 2D PC MRI (15, 46) or 4D flow MRI to obtain the velocity vectors (47). Bieging et al. showed a method to calculate in vivo WSS in separate parts of the ascending aorta (48), thereby improving the 3D coverage. However, a volumetric WSS quantification method, applied to and validated in multiple complex geometries was not available.

The aims of this thesis are to quantify volumetric WSS in any complex vessel geometry, using the velocity vector field data acquired by 4D flow MR measurements, and to validate this method with CFD simulations. Such volumetric WSS calculations will facilitate robust and reproducible WSS calculations in large patient populations. Additionally, volumetric WSS will be pivotal in longitudinal studies to follow up on the change of WSS over time to unravel further the role of WSS in vascular disease. Additionally, volumetric WSS might be useful to follow up on disease progression or to assess the effect of applied medication.

1.4 Outline of this thesis

First, in Chapter 2 we present an overview of existing methods for the calculation of WSS based on PC MR images of human arteries.

Following and combining the approach of several existing WSS calculation techniques, in Chapter 3 we present a new method to calculate WSS from in vivo 4D flow MR measurements. This method enabled us to calculate volumetric WSS on the entire vessel wall, including more complex vessel geometries. We performed further validation of this method, in vitro and in vivo, using a comparison with CFD, in aneurysms (Chapter 4) and in in vivo healthy carotid arteries (Chapter 5). We assessed the effects of spatiotemporal resolution using a realistic in vitro phantom of the carotid artery (Chapter 6).

In Chapter 7 we developed a method for the creation of WSS maps, which can be used to combine and compare volumetric WSS quantifications between different groups of patients and
healthy volunteers.

In Chapter 8, we shortly deviate from the wall and used the shear stress within the aneurysmal lumen to assess the vorticity of velocity patterns. In aneurysms, this parameter can be used for automatic aneurysmal flow pattern classification as part of rupture risk assessments.

In Chapter 9, we investigated the effect of velocity quantification accuracy on WSS calculations by application of a new 4D flow MR sequence with variable (cardiac-resolved) velocity-encoding.

Finally, in Chapter 10, the current limitations and future promises of 4D flow MRI and WSS calculations are discussed, and we take a sneak peek into the future of clinical WSS applications.

Bibliography


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