Wall shear stress calculations using phase contrast MRI

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Wall Shear Stress Calculations Using Phase Contrast MRI

Wouter Vincent Potters
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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).
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.

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Chapter 2

Measuring wall shear stress using velocity-encoded MRI

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Measuring wall shear stress using velocity-encoded MRI
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![QR Code](Image)
2.1 Introduction

Wall shear stress (WSS) is the tangential force on the endothelial wall, exerted by flowing blood. WSS is calculated as the product of blood viscosity and the spatial gradient of velocity perpendicular to the vessel wall. Velocity-encoded magnetic resonance imaging (MRI), often referred to as phase contrast MRI (PC MRI), is a technique to measure the spatiotemporal velocity of blood or tissue. The velocity data from velocity-encoded MRI can be used to calculate WSS.

WSS magnitude and derived parameters like e.g. oscillatory shear index (OSI) have been directly associated with properties of the vessel wall [1], such as flow-mediated dilation [2, 3], endothelial function [4, 5] and vessel wall thickness [7]. In fact, low WSS may force the endothelium to switch to an atherogenic phenotype, commonly referred to as endothelial dysfunction. It has been shown for the thoracic aorta that low WSS modulates plaque progression, but not regression [8]. However, the exact mechanism for WSS-induced vascular remodeling is still largely unknown and is likely different for different anatomical arteries. Additionally the WSS magnitude differs in various human arteries [9] and between species with different body mass [10].

Due to continuous improvements in the quality of velocity-encoded MRI and WSS quantification methods, there is an increase in publications regarding WSS values in patient populations. However, numerous new methods exist to calculate WSS from velocity-encoded MRI. In 2007, Pantos et al. previously published a review on velocity-encoded MRI-based WSS [11]. Since then numerous methods and clinical studies have been published. The objectives of this review are (1) to identify existing WSS calculation methods based on velocity-encoded MRI, (2) to identify the current usage of the identified methods, and (3) to compare WSS assessments performed in in vivo studies of WSS.

2.2 Image acquisition of velocity-encoded MRI

This section provides a brief summary of velocity-encoded MRI. For more detailed information, we refer the reader to the book by Haacke et al. and several review papers on velocity-encoded MRI [12–16]. Velocity-encoded MRI is a technique to measure velocity of blood and tissue. For velocity-encoded MRI a symmetric bipolar magnetic gradient is applied with zero net magnetic moment. Application of this velocity-encoding gradient causes phase change (φ) of zero in voxels with static tissue, and a phase change linearly related to the velocity (v) in voxels in which blood or tissue moves [17], see Equation 2.1.

\[ \phi = \gamma G v \delta^2 \]  

(2.1)

The change in phase (\(\phi\)) depends on the strength of the gradient (\(G\)), the duration of the gradient (\(\delta\)) and the gyromagnetic ratio (\(\gamma\)) and ranges from \(-\pi\) to \(\pi\). As can be seen in the phase images (Figure 2.1 b,c,f,g), position dependent phase offsets do not only reflect tissue motion and may also occur due to main magnetic field (\(B0\)) inhomogeneities. These systematic phase offsets can be corrected by subtraction of two subsequent acquired phase images with toggled bipolar gradients (Figure 2.1 i,j). The toggling does not affect the \(B0\) inhomogeneity artifacts and inverts the phase accumulation related to motion. Subsequent subtraction will thus cancel out the time-independent artifacts, resulting in a phase difference image (Figure 2.1 d,h).
The amount of velocity encoding is defined by the venc value, which describes the velocity corresponding to a phase difference of $\pi$, see Equation 2.2:

$$venc = \frac{\pi}{(\gamma G \delta^2)}$$

(2.2)

When the measured velocity exceeds the predefined venc in an acquisition, the measured phase will wrap around. To prevent phase wraps in the phase difference image, usually a venc above the expected velocities is used to acquire data. In case of unexpected high velocities one could also ‘unwrap’ the errors in the phase difference data by addition or subtraction of $2\pi$.

Eddy currents and concomitant gradient errors are other sources of errors in velocity-encoded MRI are, which may induce local differences in the magnetic field between the two velocity-encoded acquisitions (18). These errors can introduce local phase-offset errors in the phase-difference image, which have to be corrected during post-processing (19). When looking at complex flow geometries, intra-voxel dephasing may occur (20). Due to the natural presence of multiple velocities with different magnitude within one voxel, there will be canceling of opposite phase directions (i.e. $\pi$ and $-\pi$) leading to decreased signal magnitude and incorrect velocity quantification. Lower venc values amplify this effect, as they increase the phase dispersion in a voxel. A smaller voxel size will decrease the physiological velocity variation within a voxel and thus render velocity-encoded MRI less prone to signal loss due to intravoxel dephasing. Saturation (decrease of longitudinal magnetization) is another source of signal voids, especially in case of 3D acquisitions, high flip
angles and regions with low velocity.

Velocity-encoded MRI is performed with three-directional velocity encoding by adding bipolar gradients along the other two orthogonal directions. At least four velocity-encoded acquisitions are required, which is commonly denoted by four-point encoding (18). This effectively doubles the scan time and decreases the temporal resolution by 50%, but provides directional velocity vectors. The tradeoff between spatial and temporal resolution is especially difficult in smaller vessel geometries (e.g., carotid artery), where the required spatial resolution restricts the temporal resolution due to gradient strength limitations of clinical MRI scanners. Considering the recent developments in 3D cine velocity-encoded MRI acquisition (21, 22), it is expected that the required scan times will decrease in the next years, thereby mitigating such limitations.

Both 2D and 3D (cine) velocity-encoded MRI data have been used for WSS quantification using either one or three velocity-encoding directions. In the current paper, 2D velocity-encoded MRI refers to single-slice acquisition with one velocity-encoding direction, whereas 3D velocity-encoded MRI refers to a 3D acquisition with 3 orthogonal velocity-encoding directions.

### 2.3 Identification of WSS methods

WSS is either derived from 2D or 3D cine velocity-encoded MRI measurements. The velocity-encoded MRI measurements provide wall segmentation as well as a spatial velocity profile. Both are used to determine the spatial velocity derivative on the vessel wall (wall shear rate). The viscosity of blood is generally assumed to be constant, although wall shear rate dependent models are sometimes used as well (23). Because the differences in WSS due to blood viscosity are negligible in patients without hematological disorders (24), generally a constant viscosity \( \eta \) is assumed (\( \eta = 0.004 \text{ Pa} \cdot \text{s} \)). Avril et al. suggested to determine in vivo viscosity from velocity-encoded MRI measurements (25).

#### 2.3.1 2D WSS calculation methods

WSS is often obtained using the Poiseuille formula (Equation 2.3), where \( \eta \) is the viscosity, \( Q \) the measured flow rate and \( r \) the radius (5).

\[
WSS = \frac{4\eta Q}{\pi r^3} \tag{2.3}
\]

This equation holds for fully developed parabolic flow in circular cross-sections of vessels. Similar equations for WSS calculations based on average velocity (\( v_{\text{avg}} \), Equation 2.4, Equation 2.5 (26, 27)) or maximal velocity (\( v_{\text{max}} \), Equation 2.6 (28)) exist.

\[
WSS = \frac{4\eta v_{\text{avg}}}{r} \tag{2.4}
\]

\[
WSS = \frac{8\eta v_{\text{avg}}}{d} \tag{2.5}
\]

\[
WSS = \eta v_{\text{max}} \sqrt{\frac{2\pi v_{\text{max}}}{Q}} \tag{2.6}
\]

Because only integrated velocity measurements and radius or diameter are used, this category of methods is straightforward and robust (28). They can be applied easily on 2D (cine) velocity-
Figure 2.2: Schematic representation of the linear and parabolic fitting method. **a** Simulated parabolic flow profile as measured by velocity-encoded MRI. **b** 3D representation of measured velocity values inside the vessel (red dots). **c** Velocities as function of the distance to the vessel wall and the corresponding linear fit of the data. **d** Velocities as function of the distance to the vessel wall and the corresponding parabolic fit of the data. Note the improved spatial derivative estimation at the wall compared with the linear curve fitting method in c.

encoded MRI data, which is available on most clinical scanners. For these reasons it has been widely adopted, especially in studies with large patient cohorts (23, 27, 29). Box et al. found that for the different Poiseuille methods, the maximal velocity Poiseuille method (Equation 2.6) provides the most reliable WSS values (28). The disadvantage of the Poiseuille based methods is that these methods do not take into account any asymmetries of the velocity profile.

Alternatively, methods based on curve fitting are able to account for asymmetries in the velocity profile and thereby provides a local rather than an average WSS value. Oshinski et al. were the first to directly calculate WSS in vivo from velocity-encoded MRI data using linear fitting (30). In their approach, a straight line is fitted through one wall point \(v_{\text{wall}} = 0 \text{ cm/s}\) and one or more velocity measurements \(v\) in the vessel (Equation 2.7 and Figure 2.2 a-c).

\[
WSS = \eta \frac{dv}{dx} = \eta \left( v_{\text{vessel}} - v_{\text{wall}} \right) \quad (2.7)
\]

The derivative \(a\) in this function is the shear rate; multiplication with viscosity yields the WSS (Equation 2.7). The distance \(dx\) between the vessel wall and the velocity measurements varies across studies (30–35).

The shape of the velocity profile near the edge of the vessel is parabolic rather than linear. As shown in Figure 2.2 d, parabolic fitting of the local velocity profile may therefore improve the estimated local shear rate (32). However, the parabolic shape estimation does not account for the bluntness of the velocity profile in the center of the vessel, caused by the oscillatory nature of in vivo velocity profiles (36). Hence it will likely cause an underestimation of the shear rate. To account for this blunted profile, Oyre et al. developed the 3D paraboloid modeling method (37, 38). Figure 2.3 shows the fitting procedure for the paraboloid method, a 1 mm band of pixels is selected, excluding voxels at the wall and in the center of the vessel. Subsequently a 3D paraboloid function (Equation 2.8) is fitted to these through-plane velocities.

\[
v(x, y) = a(x^2 + y^2) + bx + cy + d \quad (2.8)
\]

Transformation to a radial coordinate system enables fast calculation of WSS (39):

\[
WSS = \eta \frac{dv}{dr} \bigg|_{\text{wall}} \quad (2.9)
\]
Measuring wall shear stress using velocity-encoded MRI

Figure 2.3: Paraboloid fitting method of the entire vessel (top row) and paraboloid fitting method of 2 segments (bottom row). a, d Simulated parabolic flow profile as measured by velocity-encoded MRI. Only velocities in the colored bands are included for the fitting. b, e Visualization of the included velocities (red, green, and blue dots). c, f Velocities plotted as function of the distance to the vessel wall and the corresponding paraboloid fits of the (segments of the) data.

Depending on the acquisition resolution, vessel size and curve fitting parameters, a limited number of velocity measurements inside the vessel are available for local WSS curve fitting. By performing one curve fit for each segment of the vessel, multiple WSS values can be measured over the vessel contour. Depending on the required level of WSS resolution and robustness, the size of segments can be adapted (7, 39).

Curve fitting requires the definition of the location of the vessel wall, resulting from either manual or (semi-) automatic segmentation. The effect of errors in the segmentation is large: a small offset from the true vessel wall severely changes the calculated WSS (40). Also the distance to the measured velocity closest to the wall may hamper the WSS calculations (41), but correction methods are available to reduce these effects (30). Another source of error is the partial volume effect. Voxels partly including tissue may have arbitrary phase values. Exclusion of voxels on the vessel wall or partial volume correction solves part of the problem (31).

Although linear and parabolic curve fitting are frequently used in literature, the velocity profiles are frequently not linear or parabolic. With polynomial fitting both simple and complex velocity profiles can be fitted. For example, the method of Cheng et al. uses localized Lagrangian base functions to fit the local velocities and analytically derive the spatial derivative along the inward normal (Equation 2.10, Figure 2.4) (33).

\[
\text{WSS}(x, y) = \eta (\nabla v(x, y) \cdot n(x, y))
\]  

(2.10)
Figure 2.4: Localized Lagrangian fitting method. a In this method, a vessel segment (green line in a, b) is selected. b Velocities at locations outside the vessel are set to zero (blue dots), velocities inside the vessel are not set to zero (red dots). Then for 16 velocity points (orange) the velocity is interpolated from the surrounding measured and zero velocities. c Finally, these interpolated (orange) velocity points are used to create a 2D Lagrange polynomial.

Alternative methods are based on the spatial distribution of velocities within a voxel (standard deviation) and provide a surrogate WSS marker related to turbulence [42–44]. A related in vivo method using Fourier velocity-encoded MRI was presented by Carvalho et al. [45].

2.3.2 3D WSS calculation methods

Although the 2D methods work rather well in 2D (cine) velocity-encoded MR images and straight vessels, they are not directly applicable to 3D (cine) velocity-encoded MR images and complex flow geometries, such as curved vessels, bifurcations or aneurysms. Such vessel geometries have three-directional velocity patterns and nonparallel vessel walls and thus require 3D (cine) velocity-encoded MRI for WSS calculations.

Köhler et al. and Papathanasopoulou et al. applied 5th order polynomial fitting to fit the entire 3D velocity profile and to obtain volumetric WSS, but so far this was only applied to phantom data [46, 47].

Stalder et al. presented a method to analyze 3D velocity-encoded MRI data by reslicing the 3D geometry at predefined locations in the vessel, to calculate the local WSS from a fitted 2D piecewise polynomial function (B-spline surface) [48] (Equation 2.11 and Equation 2.12).

\[
WSS = 2\eta \dot{\varepsilon} \cdot n
\]

\[
\dot{\varepsilon}_{ij} = \frac{1}{2} \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)
\]

Although this method is useful and the reproducibility is good [49], this approach is limited to only cross sections of the vessel at interest. To obtain volumetric WSS without fitting the entire velocity field, segmentation of the entire lumen is required. With a complete vessel wall-lumen contour segmentation, the tangential and perpendicular velocity components close to the wall can be determined. These velocity components can subsequently be used in a curve fitting method to determine WSS (Equation 2.13):

\[
WSS = \eta \frac{dv}{dn}
\]

Linear fitting [50, 51] or smooth piecewise polynomial fitting [40, 52] is used to determine \( dv/dn \) along the normal, see Figure 2.5.
Figure 2.5: Volumetric WSS method to calculate 3D WSS. a For illustrative purposes a straight vessel is used here. First, the vessel is segmented (red surface). Then for each point on the vessel wall (green star) the inward normal vector is calculated (green arrow) and along the normal the velocity profile is interpolated at a fixed number of points at fixed distances (red arrows). b Finally, curve fitting (blue line) is used to determine the spatial velocity gradient at the vessel wall.

There are two differences between this volumetric approach and the 3D approaches using only cross sections by (46). First the 3D velocity vector field is fitted directly in the volumetric approach instead of interpolated. Second, the fitting functions for this volumetric approach uses only velocity measurements close to the analyzed vessel wall point rather then the entire velocity field in one cross section. An advantage of volumetric WSS is the ability of detecting small abnormal regions of WSS that could be missed by 2D or reslice-based WSS calculation methods. A disadvantage of 3D WSS measurement in general is the increased scan times associated with 3D velocity-encoded MRI, usually a limited resolution of velocity measurements is feasible. This translates to less available velocity measurements, leading to underestimation of WSS.

2.3.3 Accuracy and reproducibility of WSS measurements

One of the major challenges in WSS quantification is to further improve accuracy and the reproducibility of WSS measurements. Besides large physiological variation, it has been shown that resolution limitations and segmentation errors limit the accuracy of WSS (33, 40, 41, 48). Reproducibility of the different Poiseuille based methods was investigated by Box et al., they found that for diastolic, systolic and average WSS, the short- and long-term reproducibility is reasonable (1 week follow-up ICC 0.38 to 0.95 and 1 month follow-up ICC 0.50 to 0.87) (28). To further improve the reproducibility of flow and maximal velocity measurement one can use the average of multiple center voxels and multiple phases in the cardiac cycle (1 week follow-up ICC 0.65 to 0.95 and 1 month follow-up ICC 0.56 to 0.89). Stalder et al. showed that Gaussian smoothing to compensate for velocity noise as well as a decrease in resolution go at the expense of WSS accuracy (48). Despite the reported underestimation of 50%, the intraobserver variability of the reslicing method is good (variability 69% of WSS magnitude; bias 0.003 Pa, limits of agreement −0.149 to 0.155 Pa). The inter-observer variability was higher (variability 87% of WSS magnitude, bias 0.066 Pa, limits of agreement −0.125 to 0.257 Pa) (53). For the same method Hope et al. reported good intra-observer and inter-observer ICCs of 0.91 and 0.97 respectively (3 observers, n = 48) (54).

Duivenvoorden et al. reported measurement variability for a method similar to that of Oyre
et al. (7, 31): correlation (ICC) for between scan sessions was 0.79 (95% confidence interval (CI) 0.67 – 0.88), the interobserver ICC was 0.99 (CI 0.99 – 1.00) and the intraobserver ICC was 0.96 (CI 0.94 – 0.97).

Masaryk et al. showed that parabolic fitting is more accurate than linear fitting (32). Petersson et al. extended this work and showed that there are many more factors involved in the accuracy of WSS. Furthermore they emphasized that all methods will severely underestimate WSS, especially if an insufficient resolution for high WSS values is used (underestimation up to 30% of the actual WSS magnitude) (41). Strecker et al. showed that WSS estimates at higher field strengths are more reliable due to better image quality (55).

2.4 Clinical application of WSS methods

Many volunteer and patient studies have been performed to assess the feasibility of WSS methods and to compare different WSS methods. In Figure 2.6 we present an overview of WSS studies in humans published up to October 2013; for animal studies we refer the reader to some other papers (10, 56–59).

![Figure 2.6: Cumulative number of patient and volunteer studies that applied WSS calculation methods based on velocity-encoded MRI, sorted as Poiseuille, 2D fitting (including the paraboloid fitting), 3D reslicing, and 3D volumetric WSS methods.](image)

2.4.1 Aorta

For aortic WSS, 18 studies on volunteers and 15 studies on patient populations were found; see Figure 2.7 (8, 22, 30, 31, 33, 48, 51, 53–55, 60–68). Substantial variations in WSS values were reported for between the different studies. The average WSS over all studies is 0.43 ± 0.38 Pa, for volunteers it is 0.40 ± 0.33 Pa, for patients 0.48 ± 0.46 Pa. Due to low numbers of patients and the plethora of methods and MRI sequence parameters used we did not perform statistical comparisons. Nevertheless, there are some obvious outliers in the graph, e.g. Barker et al. is the only one to show the direction of the WSS, resulting in negative WSS values (65). One outlier of maximum WSS was found for the descending aorta in volunteers (31).

In recent years the first clinical studies on specific patients groups have been published, mostly using the reslicing method (48). Frydrychowicz et al. investigated WSS in relation with aortic coarctation (53, 69), whereas Barker et al. focused on bicuspid aortic valve disease (61, 65).
2.4.2 Carotid arteries

For WSS measurements in the carotid arteries, 16 volunteer and 11 patient groups were reported in 14 unique studies (Figure 2.8). Although the WSS variation between studies was less than the variation of the WSS found in the aorta, substantial variation between studies are reported. The average WSS is $0.87 \pm 0.24$ Pa, for volunteers $0.90 \pm 0.23$ Pa, and for patients $0.80 \pm 0.27$ Pa. Furthermore, the WSS values in the internal carotid artery (ICA) were generally reported to be lower than the WSS values in the common carotid artery (CCA). For the volunteers the WSS in the CCA was $0.81 \pm 0.33$ Pa and for patients $0.99 \pm 0.25$ Pa. The WSS in the ICA was $0.57 \pm 0.19$ Pa for the volunteers and $0.79 \pm 0.21$ Pa for the patients.

Several clinical studies highlighted the benefit of WSS measurement in the carotids. Van Es et al. showed that WSS, especially diastolic WSS, in the basilar and carotid artery strongly correlates with cognition in the context of Alzheimer disease (29). Mutsaerts et al. investigated the WSS in a population of 329 elderly patients (23) and as diastolic WSS correlated stronger with cognition it was concluded that diastolic WSS may be more clinically relevant than systolic or...
average WSS. Harloff et al. showed that carotid plaque removal leads to a significant decrease of systolic WSS in the internal carotid artery, but not in the external and common carotid artery (74). In their discussion WSS is suggested as future risk factor for stroke and restenosis in patients with atherosclerotic plaque.

2.4.3 Other anatomical locations

WSS has been suggested as the driving mechanism behind intracranial aneurysm growth and rupture. There is an ongoing discussion on whether high or low WSS are correlated with aneurysm initiation, progression or rupture (75). Recently, the first WSS estimations based on velocity-encoded MRI were presented (50, 52, 76–78). Comparison of velocity-encoded MRI data based WSS with patient-specific simulation-based (CFD) WSS values showed a fair correlation (50, 77), it was concluded that more research is needed to improve the accuracy of MRI-based WSS calculations. Van Ooij et al. also compared the direction of WSS with CFD simulations in a phantom and in MR data of one patient (52). However, until now no existing MRI-based WSS studies provide clinically relevant information on the pathophysiology of aneurysms, nor do they elaborate on the reproducibility of WSS quantification in such small-sized complex vessel geometries. More longitudinal research of untreated and treated aneurysm patients is required to clarify the effects of WSS on aneurysm initiation and rupture.

In young patients with Fontan circulation it was shown that WSS in Fontan patients was significantly lower than in controls (79). This may partly explain the different phenotype of the
Measuring wall shear stress using velocity-encoded MRI

endothelial wall of these patients.

Mano et al. describes velocity-encoded MRI-based WSS estimations in multiple abdominal arteries in the context of celiaco-mesenteric anastomosis. They found statistically significant WSS differences between patients and healthy volunteers in the gastroduodenal arteries as well as spatially varying WSS patterns around the abdominal aneurysm location (80).

2.4.4 Other WSS parameters

Next to WSS magnitude and direction, additional parameters exist to describe spatiotemporal WSS patterns. The most used parameter is the oscillatory shear index (OSI) parameter as proposed by Ku et al. (81). OSI has been shown to correlate directly with organization of cells on the endothelial layer (5). Gelfand et al. introduced a harmonious index (HI) to describe the frequency behavior of WSS. HI describes the relative contribution of non-static WSS intensity to net signal intensity using a frequency analysis (34). Finally, Barker et al. introduced the shear range index (SRI) to show asymmetries in the WSS patterns on the vessel wall (65).

2.5 Conclusion

Over the past decade, MRI-based WSS quantification was mainly performed using 2D velocity-encoded MRI. Recently, there is an increase in 3D volumetric WSS, providing comprehensive multidimensional information on WSS patterns.

The large variation of WSS values in literature (0.1 – 1.1 Pa for average aortic WSS), suggests that absolute WSS values cannot be compared between methods. Consequently, it is not yet possible to define reference WSS values for healthy and diseased states of a vessel. Considering the good reproducibility of some methods, it is however possible to compare WSS values between groups using the same WSS calculation method. In addition, one can pinpoint specific locations of altered WSS by comparing values within the same dataset.

More research is needed to lift WSS to the next level and establish its role in the clinical practice. Firstly, the application of new acceleration techniques to further decrease 3D cine velocity-encoded MRI scan times will increase the use of volumetric WSS to pinpoint specific locations of interest (21, 82). Secondly, more studies are needed to validate volumetric WSS as a clinical marker, for example by stimulus induced WSS changes in cross sectional studies or in longitudinal studies using WSS quantification as outcome parameter.

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Measuring wall shear stress using velocity-encoded MRI


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70. Wu S, Ringgaard S, Oyre S, Hansen MS, Rasmus S, and Pedersen EM. Wall shear rates differ between


Chapter 3

Volumetric arterial wall shear stress calculation based on cine phase contrast MRI

Volumetric arterial wall shear stress calculation based on cine phase contrast MRI

doi: 10.1002/jmri.24560
3.1 Introduction

The effect of blood flow on the vascular endothelium has been proposed to be a critical determinant of vascular disease progression in atherosclerosis and aneurysms (1, 2). This effect is suggested to primarily relate to the local wall shear stress (WSS), i.e. the tangential force per surface area acting on the endothelial cells (3). Both low and oscillating WSS patterns have been reported to correlate with atherosclerosis (4–7) and aortic dilatation (8, 9), whereas high WSS was found in aortas with bicuspid valves (9, 10). High WSS is believed to be a stimulus for physiological remodeling of the blood vessel wall and for maintaining an atheroprotective phenotype (4). In addition, spatial WSS gradients have been suggested to relate to intracranial aneurysm progression (2) and rupture risk (11), although an early warning sign for cardiovascular disease progression and acute events such as atherosclerotic plaque rupture and aneurysm rupture.

WSS can be estimated from temporal and spatial information on velocity direction and magnitude. Three-dimensional cine phase contrast magnetic resonance imaging (3D cine PC MRI), or 4D flow MRI, is currently the only method to noninvasively measure 3D velocity vector fields in a volume in vivo. WSS direction and magnitude can be obtained from spatial derivatives of these velocities on the vessel wall (12).

Stalder et al. presented a method for calculation of WSS magnitude and direction using in vivo 3D cine PC MRI data, in which b-splines (piecewise polynomial functions) were applied for velocity field fitting (13). However, their method was only applicable in 2D cross-sectional slices of the vessel geometry. Approaches in which the WSS vector is calculated at each wall position were presented by Bousset et al. in intracranial aneurysms (14) and Bieging et al. in the ascending aorta (15). These authors used the inward normal of each vessel wall position and respectively applied numerical differentiation and a linear least square method to obtain the spatial derivative. The availability of volumetric 3D WSS information is an improvement over existing 2D and slice-based WSS calculation methods (13, 16). These 3D methods could potentially benefit from the adaptation of smoothing splines, similar to the b-splines used by Stalder et al. for improving the robustness of the fitting procedure (13).

As was shown in simulations by Stalder et al. and later by Petersson et al., several factors hamper the calculation of WSS. Errors arise due to segmentation inaccuracies, low spatial resolution, SNR, spatial filtering and, to a lesser extent, the choice of encoding velocities (venc) (13, 17). Knowledge on these systematic errors is important for estimation of the reliability of these measurements. Simulations may help unraveling such errors. However, methods for calculating volumetric WSS at each wall position have so far not rigorously been validated by such simulations.

The goals of the current study are (1) to build on previously published algorithms (13, 16) for obtaining calculations of 3D WSS vectors and, more importantly, (2) to estimate the associated precision and accuracy in software phantoms by assessing the effects of algorithm parameters, spatial resolution and segmentation accuracy, (3) to verify these results in vivo using time-resolved PC MRI acquired in 2D slices (2D cine PC MRI) and finally (4) to show the applicability of the method by performing WSS quantification in the systolic cardiac phase of 3D cine PC MRI datasets of the carotid artery and the aorta.
3.2 Materials and methods

As detailed below, a volumetric 3D WSS method to calculate WSS was derived (3.2.1). We evaluated this method using software phantoms (3.2.2), and subsequently applied it to 2D and 3D cine PC MRI data acquired in the carotid arteries and aortas (3.2.3). All simulations and calculations were performed using in-house software developed in Matlab (version 2012b, The Mathworks, USA).

3.2.1 Wall shear stress algorithm

The input data for the algorithm consist of (i) a segmentation of the vessel lumen and (ii) the velocity vector field. Both inputs are either simulated using software phantoms or measured with time-resolved PC MRI. The output of the algorithm is a collection of WSS vectors on the vessel lumen boundary.

The segmentation of the vessel lumen boundary is represented by a surface consisting of connected triangles (3D cine PC MRI) or a polygon (2D cine PC MRI). Only velocity voxels with their midpoint inside the vessel lumen, as defined by the segmentation, are used for the volumetric 3D WSS calculations.

The edge points of these triangles and polygons are named wall points. WSS vectors ($\vec{\tau}$) were calculated on each wall point using the equation:

$$\vec{\tau} = 2\eta \hat{n} \cdot \vec{v}$$

where $\hat{n}$ the rate of deformation tensor, $\vec{v}$ the inward normal vector and the blood viscosity ($3.2 \times 10^{-3} \text{ Pa}$). Fully expanded, the WSS is given by:

$$\vec{\tau} = 2\eta \left[ \begin{array}{ccc} \frac{\partial v_x}{\partial x} + \frac{\partial v_y}{\partial y} & \frac{\partial v_x}{\partial y} & \frac{\partial v_x}{\partial z} \\ \frac{\partial v_y}{\partial x} + \frac{\partial v_z}{\partial z} & \frac{\partial v_y}{\partial y} & \frac{\partial v_y}{\partial z} \\ \frac{\partial v_z}{\partial x} + \frac{\partial v_y}{\partial y} & \frac{\partial v_z}{\partial y} & \frac{\partial v_z}{\partial z} \end{array} \right] \cdot \vec{n}$$

To simplify this equation, two steps were performed: (i) Selection of a local coordinate system for each point on the vessel wall such that the $z'$-axis aligns with the inward normal.

$$\vec{n}(x', y', z') = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$$

This is accomplished by rotating the original coordinate system with rotation $R$ determined using basic vector calculus:

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = R \begin{bmatrix} x \\ y \\ z \end{bmatrix}$$

(ii) Assumption of no flow through the vessel wall, i.e. $\vec{n} \cdot \vec{v} = 0$ at the vessel wall, which is valid for large, non-porous, vessels. This reduces most terms in the equation to zero and the WSS vector in the local coordinate system is defined by:

$$\vec{\tau} = \eta \begin{bmatrix} \frac{\partial v_x}{\partial x} \\ \frac{\partial v_y}{\partial y} \\ 0 \end{bmatrix}$$

For each wall point, at least two points along the inward normal were selected onto which the surrounding velocity vectors were interpolated (18). Velocity values of zero were imposed on the
wall points (zero forcing). A smoothing spline \(^{(19)}\) was subsequently fitted through the velocities \((v_x', v_y')\) of the selected points along the inward normal. In the spline fit, the weight for the manually forced zero velocity wall point was 10x lower than for the interpolated velocity points. The tolerance of the spline fit was set to 1% of the venc. The spatial derivatives \((\frac{\partial v_x'}{\partial z'} \text{ and } \frac{\partial v_y'}{\partial z'}\)) on the wall were analytically derived from the fitted splines. Multiplication of the spatial velocity derivatives (shear rates) with the viscosity resulted in the WSS vectors. As a last step, the WSS vector was transformed back to the original coordinate system \(\begin{bmatrix} x & y & z \end{bmatrix}\) using the inverse rotation matrix \(R^{-1}\).

### 3.2.2 Software phantom simulations

Software phantoms were created to assess the effect of spatial resolution and segmentation accuracy. The software phantoms were based on a high-resolution (0.05 mm isotropic) 2D parabolic flow profile (through-plane). In this high-resolution 2D image, partial volume effects in each voxel were simulated using the average velocity for each voxel. To avoid optimal positioning of the simulated vessel with respect to the voxel, all simulations were performed 100 times with the center of the vessel shifted to different positions within the voxels. The encoding velocity (venc) was set to 10 cm/s above the maximum (center) velocity to avoid aliasing.

The homogenous theoretical WSS magnitude for cylindrical vessels with parabolic flow was calculated using \((\text{20})\):

\[
WSS_{\text{theoretical}} = \eta \left. \frac{\partial v}{\partial n} \right|_{n=0} = 2\eta \frac{v_{\text{max}}}{\text{radius}}
\]  \(\text{(3.6)}\)

Details of the performed software phantom simulations are summarized in **Table 3.1**. The methods for the individual simulation experiments are described below. WSS values are reported as mean WSS magnitude ± standard deviation (SD). The accuracy and precision were defined as:

\[
\text{accuracy} = 100\% \frac{\text{mean calculated WSS} - \text{theoretical WSS}}{\text{theoretical WSS}}
\]  \(\text{(3.7)}\)

\[
\text{precision} = 100\% \frac{\text{SD calculated WSS}}{\text{theoretical WSS}}
\]  \(\text{(3.8)}\)

**Table 3.1:** Simulation parameters for phantom datasets. In all simulations both a calculation with and without velocity noise (10% of encoding velocity) was performed.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Experiment 1</th>
<th>Experiment 2</th>
<th>Experiment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel diameter (mm)</td>
<td>6.30</td>
<td>6.30</td>
<td>6.30</td>
</tr>
<tr>
<td>Center velocity (cm/s)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Viscosity (Pa · s)</td>
<td>3.2 · 10^{-3}</td>
<td>3.2 · 10^{-3}</td>
<td>3.2 · 10^{-3}</td>
</tr>
<tr>
<td>Theoretical WSS (Pa)</td>
<td>2.13, 0.43</td>
<td>2.13, 0.43</td>
<td>2.13, 0.43</td>
</tr>
<tr>
<td>Reference image resolution (mm, isotropic)</td>
<td>0.05, 0.10</td>
<td>0.05, 0.10</td>
<td>0.05, 0.10</td>
</tr>
<tr>
<td>Resolution (mm, isotropic)</td>
<td>0.5, 1.0</td>
<td>0.1 − 1.2, 0.15 − 3.0</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>Segmentation offset (mm)</td>
<td>0</td>
<td>0</td>
<td>−1.0 − 1.0, −1.5 − 1.5</td>
</tr>
<tr>
<td>Inward normal length (% diameter)</td>
<td>5 − 100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Number of points on inward normal</td>
<td>3 − 10</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Algorithm optimization - experiment 1

The algorithm has two customizable parameters: (i) length of the normal vector used for the spline fitting and the (ii) number of points on the inward normal. To investigate the accuracy and precision for the WSS calculations, multiple combinations of these parameters were tested (Table 3.1, experiment 1). The number of sample points on the normal was varied between 3 and 15. The length of the inward normal length was varied from 5% to 100% of the diameter. This experiment was performed both for a small 6 mm vessel (approximately the size of the common carotid artery) and a large 30 mm vessel (approximately the size of the ascending aorta). Their respective theoretical WSS values were 2.13 Pa and 0.43 Pa. The isotropic resolutions used for this experiment were respectively 0.5 mm and 1.0 mm. Additionally noise (normal distribution, the variance set to 10% of the venc) was added to investigate its effect on WSS estimates. The optimal parameter settings from this experiment were utilized in the remainder of this paper.

Resolution - experiment 2

In MRI, the physical resolution can be described using the point-spread function (PSF) (23):

\[
\text{PSF}(x, y) = (\Delta k \frac{\sin(\pi N \Delta k x)}{\sin(\pi \Delta k x)} e^{-i \pi \Delta k x}) \left(\Delta k \frac{\sin(\pi N \Delta k y)}{\sin(\pi \Delta k y)} e^{-i \pi \Delta k y}\right)
\]  

(3.9)

where \( N \) is the square matrix size, \( k \) the width of one k-line in k-space and \((x, y)\) the voxel coordinates. The PSF accounts for both sampling and truncation effects in k-space. Note that the PSF assumes Cartesian acquisition of k-space. We simulated the effects of variation in physical resolution by filtering a high-resolution (0.05 mm isotropic voxels) phantom using a 2D PSF, where \( N \) was changed while the distance between k-lines \( \Delta k \) and the other parameters were retained. This effectively resulted in a decreased k-space window with a decreased number of k-space samples. Although the physical resolution decreases after filtering with the PSF, the number of pixels remains equal. To decrease the number of pixels accordingly the PSF-filtered phantom data was down-sampled by averaging the high-resolution dataset and gridded to create pixel sizes matching the width of the PSF \( (\Delta k) \). Figure 3.1 visualizes the steps of this resolution reduction. The experiment was repeated after addition of noise (normally distributed, the variance set to 10% of the venc).

Segmentation - experiment 3

Effects of errors in the segmentation of the vessel wall lumen were induced by dilation and constriction of a perfect circular segmentation, while preserving the original velocity vectors in the software.
phantom. Segmentation offsets between $-1$ and $1$ mm and $-2$ and $2$ mm were used to mimic segmentation errors for the $6$ mm and $30$ mm vessel, respectively.

### 3.2.3 In vivo measurements

To be able to perform PC MRI with varying spatial resolution within a reasonable scan time, we chose to verify parameter dependency of WSS in in vivo 2D cine PC MRI datasets of the left and right common carotid arteries (healthy volunteer, male, 26y) and the ascending and descending part of the aorta in a healthy volunteer (healthy volunteer, male, 30y). 3D cine PC MRI datasets were acquired of the carotid bifurcation (3 healthy volunteers, 1 male, $26 \pm 1$y) and the aorta (3 healthy volunteers, 2 males, $27 \pm 2$y). Approval of the local ethical committee was obtained and informed consent was provided by all 8 volunteers.

The 2D cine PC MRI aorta and carotid datasets were acquired at multiple spatial resolutions using a symmetric velocity encoding in one direction and symmetric four-point velocity encoding in three directions, respectively. The 3D cine PC MRI datasets for the carotid bifurcation and aorta were acquired with symmetric four-point velocity encoding in three directions. The venc for the carotid artery was decreased in the left-right and anterior-posterior direction to increase velocity to noise ratio, see Table 3.2.

The data was acquired using a 3 T MR system (Ingenia, software version 4.1, Philips Healthcare, Best, The Netherlands) and various coils were used: the 2D cine PC MRI carotid artery measurements were performed with two surface coils positioned on both sides of the neck, the 3D cine PC MRI carotid artery measurements were performed with a dedicated eight channel carotid coil and both the 2D and 3D cine aorta measurements were done using two 16 channel phased-array coils at the posterior and anterior side of the volunteer. The carotid acquisitions were acquired with retrospective triggering with a peripheral pulse signal. The aorta acquisitions were performed with retrospective ECG triggering. The scan parameters are summarized in Table 3.2.

PC MRI datasets were corrected for systematic phase offset errors, by subtraction of phase offsets in static muscle tissue close to the vessel of interest. Aliasing artifacts were avoided by using a velocity encoding value exceeding the maximum expected velocity. Any remaining aliased voxels were corrected manually.

A 2D level set evolution algorithm (24) was used to segment the lumen for each transversal slice in the high resolution 2D cine PC MRI datasets during systole. The level set results at systole were subsequently utilized as an initial level set for the remaining cardiac phases, resulting in a time-resolved segmentation of the vessel lumen. To obtain equal temporal resolution, all lower resolution 2D cine PC MRI datasets were temporally resampled to the cardiac phases in the highest resolution dataset. Rigid spatial registration was performed to correct for patient motion in between the 2D cine PC MRI scans. The segmented vessel wall surface obtained from the highest resolution 2D cine PC MRI dataset was used in all lower-resolution datasets to avoid differences in the WSS calculation due to variations in the segmentation.

In order to check flow variations across measurements, flow was calculated by multiplication of the surface area of the segmentation and the time-averaged through-plane velocities in the segmented area. The effect of spatial resolution on calculated WSS was calculated for each cardiac phase and for the time-averaged WSS. For the 3D cine PC MRI datasets, we selected the systolic heart phase, because this cardiac phase provides the best contrast between the flowing blood and the vessel wall. The segmentations of 3D cine PC MRI data in systole (created using the active
Table 3.2: In vivo acquisition parameters of 2D cine PC MRI and 3D cine PC MRI performed in the common carotid artery and aortic arch.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carotis 2D cine PC MRI</th>
<th>Aorta 2D cine PC MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-interpolated spatial resolution* (mm)</td>
<td>0.4 × 0.4 0.48 × 0.48 0.56 × 0.56 0.72 × 0.72 1 × 1 1.12 × 1.12</td>
<td>1 × 1 1.5 × 1.5 2 × 2 2.5 × 2.5 3 × 3</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5 5 5 5 5 5</td>
<td>5 5 5 5 5 5</td>
</tr>
<tr>
<td>Number of slices (#)</td>
<td>1 1 1 1 1 1</td>
<td>1 1 1 1 1 1</td>
</tr>
<tr>
<td>Field of view* (mm)</td>
<td>80 × 160 80 × 160 80 × 160 80 × 160 80 × 160 80 × 160</td>
<td>130 × 252 130 × 254 130 × 251 200 × 360 200 × 365 200 × 365</td>
</tr>
<tr>
<td>Acquisition matrix (px)</td>
<td>200 × 400 168 × 336 144 × 286 112 × 221 80 × 160 72 × 143</td>
<td>132 × 252 88 × 168 64 × 120 80 × 144 68 × 122</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>10 10 10 10 10 10</td>
<td>20 20 20 20 20 20</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>9.3 8.1 7.2 6 4.8 4.5</td>
<td>3.5 2.7 2.4 2.3 2.3 2.3</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>20 20 20 20 20 20</td>
<td>5.6 4.2 3.9 3.6 3.5 3.5</td>
</tr>
<tr>
<td>Velocity encoding directions* (#)</td>
<td>3 3 3 3 3 3</td>
<td>1 (FH) 1 (FH) 1 (FH) 1 (FH) 1 (FH) 1 (FH)</td>
</tr>
<tr>
<td>Velocity encoding values* (cm/s)</td>
<td>60 × 60 × 100 60 × 60 × 100 60 × 60 × 100 60 × 60 × 100 60 × 60 × 100 60 × 60 × 100</td>
<td>200 200 200 200 200 200</td>
</tr>
<tr>
<td>Acceleration</td>
<td>n.a. n.a. n.a. n.a. n.a. n.a.</td>
<td>SENSE 2 SENSE 2 SENSE 2 SENSE 2 SENSE 2 SENSE 2</td>
</tr>
<tr>
<td>Heart phases</td>
<td>15 15 15 20 20 20</td>
<td>30 30 30 30 30 30</td>
</tr>
<tr>
<td>Non-interpolated temporal resolution (ms)</td>
<td>87 81 83 83 84 81</td>
<td>33 30 32 30 29 29</td>
</tr>
<tr>
<td>Average heart rate during scan (bpm)</td>
<td>55 59 58 58 57 59</td>
<td>61 66 62 66 66 68</td>
</tr>
<tr>
<td>Scan duration (s)</td>
<td>412 338 288 221 162 145</td>
<td>130 88 72 77 65 65</td>
</tr>
</tbody>
</table>

* AP × RL ( × FH); SENSE: sensitivity encoding reduction factor; TFE: transient field echo turbo factor
Table 3.2: (continued) In vivo acquisition parameters of 2D cine PC MRI and 3D cine PC MRI performed in the common carotid artery and aortic arch.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Aorta 3D cine PC MRI</th>
<th>Carotis 3D cine PC MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-interpolated spatial resolution* (mm)</td>
<td>2 × 2 × 2</td>
<td>0.63 × 0.63 × 0.65</td>
</tr>
<tr>
<td>Field of view* (mm)</td>
<td>217 × 80 × 217</td>
<td>135 × 135 × 30</td>
</tr>
<tr>
<td>Acquisition matrix (px)</td>
<td>108 × 40 × 108</td>
<td>216 × 216 × 46</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>Velocity encoding directions* (#)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Velocity encoding values* (cm/s)</td>
<td>183 × 183 × 183 (±29)</td>
<td>60 × 60 × 100</td>
</tr>
<tr>
<td>Acceleration</td>
<td>SENSE 2, TFE 2</td>
<td>SENSE 2, TFE 8</td>
</tr>
<tr>
<td>Heart phases</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Non-interpolated temporal resolution (ms)</td>
<td>81.5 ± 1.6</td>
<td>145.7 ± 22.3</td>
</tr>
<tr>
<td>Average heart rate during scan (bpm)</td>
<td>61.3 ± 1.2</td>
<td>60 ± 8.4</td>
</tr>
<tr>
<td>Scan duration (s)</td>
<td>1536 ± 68</td>
<td>434 ± 24</td>
</tr>
</tbody>
</table>

* AP × RL (× FH); SENSE: sensitivity encoding reduction factor; TFE: transient field echo turbo factor

contour evolution algorithm in ITK-SNAP (25) were filtered with a Laplacian filter (26) to reduce irregularities and discretization effects and the results were manually checked by overlaying them on all image types (velocity, magnitude images). The WSS was calculated and visualized using arrows and colored surfaces. Each arrow corresponds to a calculated WSS vector at that specific wall position on the vessel wall surface.

3.3 Results

Algorithm optimization - experiment 1

Figure 3.2 shows the results of variation of the algorithm parameters (Table 3.1, experiment 1). The effects on accuracy and precision are similar for both vessel sizes. Both the accuracy and precision improve when choosing fewer points on the inward normal or a large inward normal length, i.e. a long distance between fitted velocities. This was also the case when noise was added, although the precision decreased compared to the simulation without noise. Based on these data we decided to use an inward normal length of at least 50% of the diameter and 3 points, including the wall point ($v_{wall} = 0$ cm/s), on the inward normal to use as input for the smoothing spline fitting algorithm. These parameters correspond to the areas marked by the red boxes in Figure 3.2.

Resolution - experiment 2

Figure 3.3 a and Figure 3.3 b show the effects of varying resolution on the calculated WSS. Simulations at all resolutions on average underestimated the true WSS. However, both under- and overestimations were found on the individual wall points, likely depending on the distance between the vessel wall and the closest voxel. Overall, estimated WSS further decreased at lower resolution, resulting in increasingly impaired accuracy. Additionally, the precision of WSS calculation decreased with increasing voxel size. The precision for datasets with added noise was lower, but this effect was less pronounced for larger voxel sizes. At voxel sizes used in conventional protocols, the accuracy was 4.3 to 4.6% and the precision 19 to 22%, assuming an isotropic resolution of 0.7 mm for the carotid and 2.0 mm for the aorta protocol.

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Figure 3.2: Effect of inward normal vector length and number of points along the normal vector on the WSS calculation (experiment 1) on precision and accuracy for a 6 mm vessel and b for a 30 mm vessel with and without added noise. Noise is normally distributed, with the variance set to 11 cm/s (10% of the venc). The red rectangle shows the most optimal range of settings.

Segmentation - experiment 3

Figure 3.3 c and Figure 3.3 d show the effects of segmentation offsets on the calculated WSS in the phantom vessels. For wider segmentation (positive offset), the calculated WSS decreased, while the precision of the WSS calculation remained equal. For narrower segmentation, the calculated WSS increased rapidly. The algorithm performed similarly after addition of noise to the data. Assuming half the voxel size (respectively 0.25 and 1.0 mm) as segmentation accuracy, the accuracy of calculated WSS can be as low as 30% and 40% for the 6 mm and 30 mm vessels, respectively.

In vivo measurements - 2D cine PC MRI

The average flow rates for each resolution were found to deviate by less than 10% from the value obtained at 0.4 mm resolution. The level set segmentation in the left and right carotid artery for both the systolic (defined as highest flow rate) and diastolic (defined as lowest flow rate) time points are shown in Figure 3.4 a and Figure 3.4 b (diastole) and Figure 3.4 c and Figure 3.4 d (systole).
Volumetric arterial wall shear stress calculation based on cine phase contrast MRI

**Figure 3.3:** Results from the WSS calculations in multiple software phantoms. The theoretical WSS (blue line), the simulated WSS without noise (green line), and the simulated WSS with noise (red line) with the accompanying standard deviations (dashed lines) are displayed. Noise is normally distributed, with the variance set to \(11 \text{ cm/s} \) (10% of the venc). **a,b:** Resolution variation versus calculated WSS. **c,d:** Segmentation offsets versus simulated mean WSS at software phantom resolutions of 0.5 mm and 1 mm, respectively. Negative offsets represent a constricted (smaller) segmentation; positive offsets represent a dilated (larger) segmentation.

The results for the WSS calculations are shown in **Figure 3.4 e** and **Figure 3.4 f**. Overall the WSS magnitude increased in systole. Higher resolutions generally lead to a higher average WSS with a few exceptions. Investigation of these exceptions revealed a lower flow in those measurements (e.g. **Figure 3.4 e**, 0.4 mm resolution, at 582 ms). The spatially averaged WSS values in the common carotid artery ranged from 0.2 (diastole) to 6 Pa (systole). The spatiotemporal average WSS was 0.95 ± 0.78 Pa.

**Figure 3.5** shows similar data for the ascending and descending aorta. The absolute flow rates for each resolution were found to deviate by approximately 5% from the value obtained at 1 mm resolution. **Figure 3.5 a-d** show the level set segmentations of the ascending and descending aorta, for both diastole (**Figure 3.5 a,c**) and systole (**Figure 3.5 b,d**). As can be seen in **Figure 3.5 a-d**, the level set segmentation is based on intensity on the magnitude image with the highest resolution and is less accurate in diastole than systole. Despite some minimal automatic segmentation errors, the resulting resolution-dependent average WSS estimates, as shown in **Figure 3.5 e** and **Figure 3.5 f**, show a lower average WSS magnitude for lower resolution datasets. The average WSS magnitude in the ascending aorta was 0.05 to 6.9 Pa with a time-averaged WSS of 0.57 ± 0.70 Pa. In the
Figure 3.4: 2D cine PC MRI data in the left (left column) and right (right column) carotid artery of a healthy volunteer. a,b The first (diastole) and c,d second (systole) rows show the wall delineation for magnitude and velocity images at all acquired spatial resolutions. e,f The last row shows the calculated WSS values for the acquired spatial resolutions at each cardiac phase; the last graph in also shows the standard deviation due to physiological spatiotemporal WSS variation.

descending aorta the average WSS magnitude ranged from 0.09 to 11.9 Pa with a time-averaged WSS of 0.9 ± 1.10 Pa.

In vivo measurements - 3D cine PC MRI

Figure 3.6 a and Figure 3.6 b show the calculated WSS vectors at peak systole in the carotid bifurcation and aorta, respectively. The average WSS in the carotid bifurcations in systole was 1.34 ± 0.72 Pa, with values ranging from 0.03 to 4.82 Pa. The average WSS in the aortas in systole was 1.07 ± 0.42 Pa, with values ranging from 0 to 4.48 Pa. In both measurements we found a complex pattern of WSS, with substantial spatial gradients in both WSS magnitude and direction.

3.4 Discussion

We have presented and evaluated an approach to determine volumetric WSS in arteries. The volumetric WSS calculation method put forward here differs from existing methods in several aspects. Rather than presenting WSS in a manually placed slice perpendicular to the vessel wall...
Volumetric arterial wall shear stress calculation based on cine phase contrast MRI

Figure 3.5: 2D cine PC MRI data in the ascending (left column) and descending (right column) aorta of a healthy volunteer. a, b The first (diastole) and c, d second (systole) rows show the wall delineation for magnitude and velocity images at all acquired spatial resolutions. e, f The last row shows the calculated WSS values for the acquired spatial resolutions at each cardiac phase; the last graph in also shows the standard deviation due to natural spatiotemporal WSS variation on the vessel wall.

or a segment of the vessel wall (15), we quantify WSS at all points on the entire vessel wall. Thus, it is possible to detect abnormal regional variations that a slice or segmental based method would miss. This increase of spatial WSS resolution comes at the expense of the number of velocity measurements that is used for each fit at the wall. To minimize errors, we applied natural neighbor interpolation combined with a smoothing spline fit at each vessel wall point. Natural neighbor interpolation provides a continuous first derivative in contrast to methods using Lagrangian interpolation (27). As indicated by the accuracy results in this study, the smoothing spline provides better fits in the presence of noisy velocity data than linear or parabolic methods (17). Other methods combine the interpolation and fitting step by fifth-order polynomial fitting of the 3D cine PC MRI velocities (28, 29), but up to now, this approach has only been applied in phantom datasets. We showed that the accuracy of WSS is optimal when an inward normal length of 50% vessel diameter is used with 3 equidistant velocity points. This is relatively long compared to literature (6, 12, 14, 15, 30), which may be related to the parabolic velocity profiles that were used in our simulations. The use of only three points on the inward normal may smooth complex in vivo velocity profiles (31), resulting in WSS underestimations. More research is needed to further optimize the algorithm parameters in areas of complex velocity patterns.
Figure 3.6: Visualization of the WSS vectors as calculated directly from the 3D cine PC MRI datasets of six volunteers in a the carotid bifurcation and b the aorta in the systolic heart phase.

The effects of spatial resolution have been described previously (13, 27), but may differ significantly between fitting methods (17). A higher spatial resolution improves WSS calculations, but practical limitations exist, related to field strength and scan duration. Based on our software phantom experiments we conclude that spatial resolution of PC MRI data for WSS calculation should be such that at least 8 voxels are available across the diameter in order to obtain 5% accuracy. A guideline on resolution of flow quantification using PC MRI suggested at least 3 voxels across the diameter (32), and 16 isotropic voxels over the vessel lumen area (4.5 voxels across the diameter) (33). This difference results from WSS being related to the derivative of the velocity field as opposed to flow as an integration of this field. Our simulations show that the average
WSS is generally underestimated. The predictions are in contrast to analyses of Petersson et al., who found an overestimation of WSS at similar resolution and similar WSS magnitude. Other authors found an even larger underestimation at similar resolution. These differences are likely related to the used fitting methods (parabolic, linear vs. spline fitting).

The spatial resolution was also found to be critical for calculation of WSS in the in vivo 2D cine PC MRI data. Although we did not have a gold standard for the WSS magnitude in vivo, the 2D cine PC MRI data showed that the spatially averaged WSS converged towards higher values at higher spatial resolutions, similar to what was found for the phantom data. However, the spatial resolution effect in the in vivo 2D cine PC MRI data was larger than in the phantom data, suggesting the presence of steeper velocity gradients in vivo that are more prone to be underestimated.

The larger spatial variation of in vivo WSS at higher resolutions compared to the software phantoms may partly be due to noise, related to the MRI signal, and movement artifacts. However, there is also a contribution from the asymmetry of the flow profiles. WSS calculations based on low-resolution datasets may not be able to capture the variations occurring at a smaller spatial scale, and are thus biased towards a spatial average. Resolutions as high as 0.4 mm in the carotids seem therefore be mandatory when studying local changes in WSS, whereas lower resolutions may suffice if systemic disease and general patterns of WSS are studied.

Despite similar resolution-dependency of WSS estimates in 2D cine PC MRI datasets of carotid arteries and the aorta, we noticed that the aorta data were more consistent to the phantom experiments than those on the carotids. This can be attributed to a better velocity-to-noise ratio and a higher temporal resolution in the aorta scan, both of which improves the quality of the segmentations and the velocity measurements.

Our data show that segmentation is an important factor for determining the accuracy and precision of WSS calculations. Although the effect of segmentation errors is large, little quantitative information is available in literature. Studies have proposed to improve the segmentation by making use of the velocity profile. One recent study described the effect on WSS magnitude by changing the voxel location with respect to the wall. Given the large influence of segmentation errors, we advise (i) to always use a time-resolved segmentation to account for wall motion and (ii) to thoroughly check the segmentations for every slice and every heart phase on any of the available images (magnitude and velocity images).

Compared to other literature, our in vivo WSS values in the aorta are rather high. Publications using the method by Stalder et al. are consistent in reporting values up to 1.1 Pa. Other PC MRI-based methods report even lower values, while CFD-based WSS calculations report higher WSS values in the aorta. The larger WSS values compared with other PC MRI-based techniques may be due to the fact that the current volumetric approach does not use any spatial filtering before calculating the WSS values and is therefore less prone to spatial blurring that lowers the average WSS.

In the carotid artery, the WSS calculations in literature are mainly based on ultrasound velocity measurements and 2D cine PC MRI. For the carotid artery, our WSS calculations at the highest resolution of 0.4 mm match the WSS magnitude values reported in recent literature.

A limitation of the phantom study was the use of only parabolic velocity profiles in the simulations. Further research is needed to investigate the effect of complex flow on WSS calculation. A limitation of the in vivo 2D cine PC MRI measurements was that in the aorta the measurements were performed with unidirectional velocity encoding, whereas in the carotids the velocity measure-
ments were performed in three directions. The 3D cine PC MRI study acquisition of the carotid bifurcation was limited by a low temporal resolution, which has likely caused underestimation of the average and peak WSS. Another limitation can be the use of parallel imaging (SENSE), which may decrease the SNR \(41\). Because we used a relatively low acceleration factor, the effect of SENSE on the velocity measurements is expected to be limited \(42\).

In the future the method presented here may provide a WSS reference map of a vessel, which could be used in the (early) identification of pathologies. The next step towards clinical applicability will be to further validate the described method on complex geometries, where the estimates can be compared with CFD simulations, which are generally considered as the gold standard \(14\) \(43\) \(44\).

### 3.5 Conclusion

In conclusion, volumetric WSS calculation provides spatiotemporal information on WSS magnitude. Even with optimized algorithm parameters, the results of WSS calculations are strongly dependent on segmentation and resolution. To obtain reliable WSS estimates, we advise to first acquire of a high-resolution 3D cine PC MRI, including at least 8 voxels across the diameter of the targeted vessel, which is subsequently segmented using a time-dependent, manually checked method. Smoothing splines of velocity profiles over 50\% of the diameter and including 3 points along the inward normal should be applied to calculate the WSS.

### Bibliography


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Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm

Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm

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4.1 Introduction

Intracranial aneurysms occur in 5 percent of the population and lead to high morbidity and mortality when ruptured or during surgical or endovascular repair (1). Since risk of complications during treatment may outweigh the risk of rupture of the aneurysm (2), the latter needs to be estimated as accurate as possible when making treatment decisions. Hemodynamic parameters can significantly contribute to the accuracy of rupture risk assessment of intracranial aneurysms (3).

It is widely believed that wall shear stress patterns strongly influence plaque and aneurysm formation, progression and rupture (4, 5). Wall shear stress is the tangential force that flowing blood exerts on the vessel wall. High wall shear stress is believed to promote atheroprotective endothelial gene expression, whereas low and oscillating wall shear stress in regions with disturbed flow induce atherogenic behaviour of endothelial cells (6). To derive wall shear stress, sufficiently detailed information on velocity gradients close to the vessel wall is needed, which up until recently could only be provided by computational fluid dynamics (CFD) (4, 7). However, mesh creation and prescription of boundary conditions can be strenuous and the complexity of CFD calculations poses high demands on CPU systems and requires long computational times. Moreover, the reliability of CFD depends on the accuracy of the geometry and inflow boundary conditions.

The last few years much effort has been put into quantifying wall shear stress on the basis of non-invasively measured velocity data acquired with phase contrast MRI (PC MRI) (8, 9), a technique that is becoming increasingly accurate with the recent technical advancements in MRI. As described in the literature, several methods for estimation of wall shear stress were developed and applied to a range of vessel structures.

Oshinski et al. were the first to estimate wall shear stress in the aorta with through-plane PC MRI data (10). Stokholm et al. estimated 1D wall shear stress and oscillatory shear index by parabolic fitting to through-plane velocity profiles in the carotid artery (11). Papathanasopoulou et al. accounted for secondary flow in the carotid artery and bifurcation by measuring velocities with three-dimensional PC MRI and estimated three-dimensional wall shear stress vectors (12). Stalder et al. and Markl et al. improved this method in the aorta by using b-splines for fitting purposes (13, 14). However, they needed to manually select slices perpendicular to the aorta, prior to their calculations. Bieging et al. used a similar method in ascending aorta dilation (15). Boussel et al. were the first to estimate wall shear stress magnitude in intracranial aneurysms based on PC MRI data acquired at a resolution of 1 mm$^3$, followed by Isoda et al. using a similar resolution (5, 16). Petersson et al. showed with the use of numerical simulations that wall shear stress calculation by parabolic fitting produced the most accurate results (17).

The purpose of the current study was to estimate and visualize wall shear stress magnitude and direction with a wall shear stress algorithm in intracranial aneurysms that allows for local wall

Figure 4.1: a The aneurysm phantom, b the flow loop setup and c the inflow pulse waveform.
shear stress estimation in complex flow geometries. The study consisted of three parts. First, wall shear stress in an intracranial aneurysm phantom under controlled steady and pulsatile flow was estimated and compared to CFD estimates. Second, the effect of spatial resolution of 3D PC MRI measurements on wall shear stress accuracy was studied. Third, wall shear stress estimates obtained from an in vivo 3D PC MRI measurement and CFD simulation were compared.

4.2 Materials and Methods

In the first experiment, WSS estimated from high-resolution 3D PC MRI was compared with WSS calculated by CFD. In order to compare the two modalities, the WSS was calculated with the use of velocity vectors obtained from 3D PC MRI and wall delineation obtained from 3D rotational angiography (3DRA), which was the modality used for the creation of the CFD mesh. In the second experiment, WSS estimated from 3D PC MRI acquired at multiple spatial resolutions was compared. The wall segmentation was based on the PC MRI magnitude data of the spatial resolution under consideration. In the third experiment, WSS was estimated from 3D PC MRI acquired in an in vivo aneurysm and compared with CFD. In this experiment the wall was segmented from the magnitude data of the PC MRI dataset. These experiments are summarized in Table 4.1. In the remainder of this article 3D PC MRI is abbreviated to PC MRI. Throughout the article the vessel and aneurysmal wall are considered as the outermost part of the segmentation of the lumen.

**Table 4.1:** Resolution and wall used for wall shear stress calculation in the three experiments.

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Experiment 2</th>
<th>Experiment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>PC MRI (mm)</td>
<td>0.2 × 0.33 × 0.2</td>
</tr>
<tr>
<td>Wall</td>
<td>3DRA</td>
<td>0.19–0.94 isotropic</td>
</tr>
<tr>
<td></td>
<td>PC MRI</td>
<td>0.78 × 0.78 × 0.80</td>
</tr>
</tbody>
</table>

4.2.1 Aneurysm phantom and flow loop set-up

A glass reproduction of an aneurysm located in the anterior communicating artery of a patient who supplied informed consent was hand-blown by a glass-blower based on a 3DRA dataset. The dimensions of the aneurysmal lumen were 6 × 4 × 9 mm in the x, y and z-directions (see Figure 4.1a) respectively. The phantom was submerged in agar gel and connected to a pump supplying constant flow and a computer-controlled piston pump supplying pulsatile flow. In Figure 4.1b the flow loop setup is displayed, in Figure 4.1c the velocity profile that served as input for the pulsatile measurement. For all scans and simulations water was used. Further details are described in (18).

Experiment 1. In vitro wall shear stress from steady and pulsatile PC MRI compared with CFD

**PC MRI**

All PC MRI measurements were performed on a 3 T MR system (Philips Healthcare, Best, the Netherlands) in a solenoid rat coil (Philips, Hamburg, Germany) with a diameter of 7 cm. Steady and retrospectively gated pulsatile flow measurements were performed at a spatial resolution of 0.2 × 0.33 × 0.2 mm and velocity encoding of 50 × 100 × 50 cm/s in x, y and z-direction respectively.
Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm

Table 4.2: Voxel size, TE, TR and scan time of the steady flow measurements.

<table>
<thead>
<tr>
<th>Voxel size (mm × mm × mm)</th>
<th>TE (ms)</th>
<th>TR (ms)</th>
<th>Scan time (min · s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94 × 0.94 × 1.0</td>
<td>2.8</td>
<td>4.6</td>
<td>0.19</td>
</tr>
<tr>
<td>0.75 × 0.75 × 0.8</td>
<td>2.95</td>
<td>4.9</td>
<td>0.29</td>
</tr>
<tr>
<td>0.62 × 0.62 × 0.7</td>
<td>3.0</td>
<td>5.2</td>
<td>0.41</td>
</tr>
<tr>
<td>0.54 × 0.54 × 0.6</td>
<td>3.2</td>
<td>5.7</td>
<td>1.06</td>
</tr>
<tr>
<td>0.47 × 0.47 × 0.5</td>
<td>3.4</td>
<td>6.3</td>
<td>2.07</td>
</tr>
<tr>
<td>0.38 × 0.38 × 0.4</td>
<td>3.7</td>
<td>7.1</td>
<td>4.20</td>
</tr>
<tr>
<td>0.27 × 0.27 × 0.3</td>
<td>4.3</td>
<td>8.7</td>
<td>11.35</td>
</tr>
<tr>
<td>0.19 × 0.19 × 0.2</td>
<td>5.4</td>
<td>11.7</td>
<td>36.33</td>
</tr>
</tbody>
</table>

(see Figure 8.1a). Other imaging parameters: field of view: 25 × 16.5 × 25 mm; flip angle: 15°; TE/TR: 3.9 / 11.1 ms. Scan time of the steady measurement was approximately 15 minutes. Due to different viscosity properties of fluids in a previous study, the temporal resolution of the pulsatile PC MRI measurement was 150 ms in a cardiac cycle of 3 s, resulting in 20 measured cardiac phases. Scan time was approximately 3 hours. More detail can be found in [18].

CFD

The geometric vascular model of the in vitro aneurysm phantom was obtained by filling the phantom with a contrast agent and performing 3D Rotational Angiography (3DRA). The 3DRA dataset was segmented and meshed in VMTK (19). The wall of this 3DRA mesh was used as wall delineation for experiment 1. The mesh consisted of 742,316 tetrahedral cells with a mesh density of 3119 elements per cubic millimeter. The simulations were performed in FLUENT (Ansys, Canonsburg, PA, USA) using boundary conditions derived from the PC MRI measurements for both constant and pulsatile flow. More detail can be found in [18].

Experiment 2. In vitro wall shear stress from steady PC MRI at increasing resolutions

The PC MRI measurements at varying spatial resolutions were performed in a different scanning session. The resolutions, TE/TR and scan times are listed in Table 4.2. Further imaging parameters were: field of view 60 × 21 × 60 mm and velocity encoding of 30 × 60 × 30 cm/s in x, y and z-direction respectively.

Experiment 3. In vivo wall shear stress from pulsatile PC MRI compared with CFD

PC MRI

The protocol consisted of two MRI sequences that were conducted on a 3 T scanner (Intera, Philips Healthcare, Best, The Netherlands) using an 8-channel head coil.

First, to acquire 2D PC MRI data that served as inflow boundary conditions for CFD, velocity was measured in three directions in a slice placed perpendicular to the vessel proximal to the aneurysm. Scan resolution was 0.64 × 0.65 × 3 mm. Further imaging parameters: TE / TR / FA: 5.7 ms / 5 ms / 10°; Field of view: 200 × 200 × 3 mm in one slice; parallel imaging factor: 2; venc: 100 cm/s in all directions. The number of measured cardiac phases was 36 cardiac phases, resulting
in a temporal resolution of 26 ms. Scan time was approximately 3 minutes and 30 seconds. The view sharing factor for the retrospective sorting of acquired k-lines was set to 1.8 \cite{20}.

Figure 4.2: a,c,e Wall shear stress as calculated from PC MRI data using 3DRA wall delineation and b,d,f wall shear stress as calculated by CFD. This was done for the steady a measurement and b simulation, c,d in peak systole (cardiac phase 5) and e,f end diastole (cardiac phase 20) for c,e the pulsatile measurement and d,f simulation.

Second, 3D PC MRI was acquired at a resolution of $0.8 \times 0.8 \times 0.8$ mm. Further imaging parameters were: TE / TR / FA: 3.0 ms / 5.8 ms / 15°; Field of view: 200 $\times$ 200 $\times$ 20 mm in 25 transversal slices; parallel imaging factor of 3; the velocity encoding was 100 cm/s in all directions; scan time was approximately 10 minutes and 20 seconds. The number of acquired cardiac phases was 10 resulting in a temporal resolution of 90 ms. The 2D and 3D PC MRI acquisition were retrospectively gated using PPU.

CFD
The geometric vascular model used for the CFD simulation, based on in vivo data, was created from 3DRA images. The mesh consisted of 1,422,476 tetrahedral elements with a mesh density of 5230 elements per cubic millimeter. The CFD simulations were performed in FLUENT 6.3 (Ansys, Canonsburg, PA, USA). Blood density was set to 1060 kg/m$^3$, dynamic viscosity to 0.004 kg/m$\cdot$s.
The 2D PC MRI data was positioned on the TOF data using rotation and translation matrices extracted from DICOM headers. A rigid registration of the TOF measurement on the CFD mesh was conducted in FLIRT [21]. The velocities measured with 2D PC MRI were rotated and translated likewise and interpolated onto the nodes of the CFD inflow boundary. These steps were performed with custom-built software in Matlab (Mathworks, Natick, MA, USA). CFD iterations were continued until the residual of the continuity equation was below 0.001. The CFD estimates were resolved at fixed time intervals equal to the measured RR interval divided by the number of cardiac phases used for the 2D PC MRI. Three heart cycles were simulated to eliminate transient effects. The third of these cycles was used to compare the calculated wall shear stress with the wall shear stress calculated from the 3D PC MRI results. Flow through the outflow vessels of the CFD model was prescribed according to flow velocity measurements at every cardiac phase of the 3D PC MRI data averaged over time. The simulation time was approximately 36 hours.

4.2.2 Postprocessing

PC MRI background correction for phase offset errors was performed for every slice and, in case of pulsatile measurements, for each individual cardiac phase by subtracting the mean velocity in the stationary agar gel or brain tissue (amygdala). Wall delineation of the phantom and in vivo aneurysm was defined by a level set evolution algorithm [22], applied to the magnitude images of the PC MRI measurements. SNR of the phase contrast magnitude images of the pulsatile in vitro and in vivo measurements were calculated according to Price et al. [23]. For these processes custom-built software was developed in Matlab (Mathworks, Natick, MA, USA).

In experiment 1, the rigid registration between the PC MRI data and 3DRA wall delineation was automatically performed in FLIRT (FMRIB’s Linear Image Registration Tool, FSL). After registration, PC MRI voxels located outside the 3DRA wall delineation were discarded. Since the wall delineation of CFD is used for the wall shear stress calculation using velocity values obtained from the PC MRI measurement, wall shear stress values are obtained at the same locations for CFD and PC MRI.

4.2.3 Wall shear stress calculation

Wall shear stress vectors can be calculated by:

\[
\vec{\tau} = 2\eta \dot{\epsilon} \cdot \vec{n}
\]  

(4.1)

where \(\vec{\tau}\) is the wall shear stress vector, \(\eta\) is the dynamic viscosity, \(\dot{\epsilon}\) is the rate of deformation tensor and \(\vec{n}\) is the normal vector. By rotating the coordinate system such that the z-axis aligns with the normal vector of the vessel wall it holds that: \(\vec{n} = (0, 0, 1)\). Combined with the assumption that no flow occurs through the wall, \(\vec{n} \cdot \vec{v} = 0\) at the wall, the inner product of the rate of deformation tensor and the normal vector is reduced to:

\[
2\epsilon \cdot \vec{n} = \left( \frac{\delta v_x}{\delta z'}, \frac{\delta v_y}{\delta z'}, 0 \right)
\]  

(4.2)
where the shear rates \( \frac{\delta v_x'}{\delta z'} \) and \( \frac{\delta v_y'}{\delta z'} \) are the spatial gradients at the wall in the rotated coordinate system. The rotated wall shear stress vector \( \vec{\tau}' \) is then defined as:

\[
\vec{\tau}'_x = \eta \frac{\delta v_x'}{\delta z'}, \quad \vec{\tau}'_y = \eta \frac{\delta v_y'}{\delta z'}, \quad \vec{\tau}'_z = 0
\]  

(4.3)

The shear rates are derived from 1D smoothing splines \(^{(24)}\) fitted through the rotated \( x' \)-, and \( y' \)-velocity values along the inward normal vector. Measured velocity values surrounding the inward normal were interpolated such that the spline was fitted through 3 velocity values over a distance of 0.6 mm. To obtain a smooth surface of the aneurysm wall, the segmentation obtained by postprocessing is smoothed using a Laplacian filter \(^{(25)}\).

### 4.2.4 Data quantification and visualization

In experiment 1, mean and standard deviation of the wall shear stress magnitude values are calculated and plotted. The mean and standard deviations of the paired differences are given. Furthermore, linear regression is performed on the PC MRI and CFD data and the Spearman correlation \( \rho \) is calculated. Statistical comparison was done for paired groups (Wilcoxon-signed rank test) as differences were not normally distributed. The difference in direction between wall shear stress vectors is quantified in terms of the angle between corresponding wall shear stress vectors and expressed as the median of the angle distribution. Statistical analysis was performed in the total phantom and in the in-, and outflow vessels and phantom aneurysm separately. In experiment 2 and 3, the wall shear stress magnitude values are expressed in terms of mean wall shear stress and the standard deviation. All postprocessing and visualization was performed with in-house built software in Matlab (Mathworks, Natick, MA, USA).

**Figure 4.3:** Mean and standard deviation of wall shear stress for the in vitro pulsatile PC MRI measurement and CFD simulation.

### 4.3 Results

Experiment 1. In vitro wall shear stress from steady and pulsatile 3D PC MRI compared with CFD The SNR of the pulsatile in vitro PC MRI measurements was 28. In **Figure 4.2** the wall shear stress patterns calculated from PC MRI with 3DRA wall delineation are shown for steady flow (**Figure 4.2 a**) and for systole (**Figure 4.2 c**) and diastole (**Figure 4.2 e**) under pulsatile flow.
Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm

Figure 4.4: Correlation and Bland-Altman plot of wall shear stress calculated from a, d the steady, b, e systolic and c, f diastolic PC MRI measurement with CFD delineation compared with wall shear stress calculated from the CFD simulation.

Figure 4.2 b, d, f show the corresponding estimates from CFD using the same wall segmentation. For both PC MRI and CFD, the wall shear stress patterns spreads upward and left and right (‘star-like’) in the region where the flow impacts the wall (arrow 1). Pronounced spatial wall shear stress gradients of PC MRI are visible, which are a result of using the wall shear stress algorithm on non-isotropic velocity data with high resolution isotropic wall delineation. The magnitude of the wall shear stress vectors in the dome and bleb of the phantom was approximately twice as low for PC MRI than CFD. In the inflow and outflow vessels the magnitude of the wall shear stress vectors was similar for PC MRI and CFD. Note that the small circular wall shear stress pattern in the tip of the aneurysm was resolved for both PC MRI and CFD (arrow 2).

In Figure 4.3 the spatially averaged wall shear stress and standard deviation over time of the PC MRI measurements and CFD simulations is shown. The mean and standard deviation of the wall shear stress are lower for the PC MRI measurement than for the CFD simulation, specifically in systole.

Differences between the wall shear stress obtained from PC MRI with 3DRA wall delineation and CFD are quantified and summarized in Table 4.3. Due to the complexity of flow in the aneurysm, for the steady and systolic wall shear stress, the estimation of wall shear stress in the aneurysm is worse than in the inflow and outflow vessels, i.e. the slope of the regression line is closer to 1 if only the inflow and outflow vessels are considered. Due to the lower wall shear stress for PC MRI compared to CFD, moderate quantitative agreement was found, as can be appreciated from the Spearman correlation in Table 4.3 and the correlation and Bland-Altman plots for the total phantom in Figure 4.4.

Experiment 2. In vitro wall shear stress from steady 3D PC MRI at increasing resolutions

In Figure 4.5 the wall shear stress vectors calculated for the steady PC MRI measurements at four different resolutions are shown. The wall delineation was obtained from the individual measure-
Table 4.3: Mean paired difference ± standard deviation of the paired difference of the wall shear stress magnitude as calculated from the steady and pulsatile PC MRI measurements and CFD simulations for the inlets and outlets, the aneurysm and the total phantom. The median angle describes the difference in wall shear stress direction and p1 and p2 represent the slope and intercept of the linear regression analysis. The Spearman correlation coefficient is given as well.

<table>
<thead>
<tr>
<th></th>
<th>Inlet/outlet</th>
<th>Aneurysm</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>Steady</td>
<td>Systole</td>
<td>Diastole</td>
<td>Steady</td>
</tr>
<tr>
<td>Mean ± SD WSS (Pa)</td>
<td>0.21 ± 0.30</td>
<td>0.28 ± 0.48</td>
<td>0.03 ± 0.11</td>
<td>0.38 ± 0.74</td>
</tr>
<tr>
<td>Median angle (°)</td>
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<td>11.1</td>
<td>9.1</td>
<td>24.0</td>
</tr>
<tr>
<td>p1/p2</td>
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<td>0.92/0.35</td>
<td>0.74/0.09</td>
<td>1.58/0.13</td>
</tr>
<tr>
<td>Spearman ρ</td>
<td>0.68</td>
<td>0.64</td>
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</table>

<table>
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<tr>
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<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Steady</td>
<td>Systole</td>
<td>Diastole</td>
</tr>
<tr>
<td>Mean ± SD WSS (Pa)</td>
<td>0.29 ± 0.56</td>
<td>0.45 ± 0.88</td>
<td>0.03 ± 0.14</td>
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<tr>
<td>Median angle (°)</td>
<td>16.5</td>
<td>15.8</td>
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<td>p1/p2</td>
<td>1.14/0.21</td>
<td>1.10/0.38</td>
<td>0.92/0.05</td>
</tr>
<tr>
<td>Spearman ρ</td>
<td>0.69</td>
<td>0.65</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Figure 4.5: Wall shear stress vectors calculated from steady velocity data measured with PC MRI at a 0.19 mm, b 0.47 mm, c 0.75 mm and d 0.94 mm. For visualization purposes, the vector length and colorbar scaling are different between plots. For 0.19 mm, only every second vector is displayed.
Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm

Figure 4.6: Mean and standard deviation of the WSS for steady measurements at increasing resolution averaged over the total phantom (Total WSS), averaged over a region of high WSS (High WSS) and averaged over a region of low WSS (Low WSS). Note that due to the inclusion of the inflow and outflow vessels, the WSS calculated over the total phantom is higher than the WSS calculated in the high WSS region.

ments, becoming increasingly coarse. The complexity of wall shear stress vectors diminished with coarser resolution in the region of impact of the flow with the wall, as pointed out by arrow 1. Furthermore, the maximum wall shear stress diminished with decreasing resolution. Note, however, that the circular wall shear stress patterns in the tip of the phantom could be resolved at all resolutions, even with decreased segmentation accuracy at lower resolutions. For regions of low wall shear stress, defined as lower wall shear stress than 25% of the maximum wall shear stress, for regions of high wall shear stress, defined as higher wall shear stress than 75% of the maximum wall shear stress, and for the wall shear stress over the entire geometry, the mean wall shear stress increased at higher spatial resolutions. This is graphically displayed in Figure 4.6. It can be seen that regions of high wall shear stress are more sensitive to spatial resolution than regions of low wall shear stress.

Experiment 3. In vivo wall shear stress from pulsatile PC MRI compared with CFD

The SNR of the in vivo PC MRI measurements was 15. Figure 4.7 depicts wall shear stress for the in vivo aneurysm. Arrow 1 indicates circular wall shear stress at the side of the aneurysms which was resolved for PC MRI as well as CFD. Elevated wall shear stress at the top of the aneurysms (arrow 2) was also seen in both methods. Wall shear stress was around two to three times lower for the PC MRI measurement than in the CFD simulation, while measured and simulated velocities were similar (34.7 ± 19.1 cm/s and 16.2 ± 9.5 cm/s at systole and diastole for PC MRI respectively versus 35.2 ± 25.0 cm/s and 15.5 ± 11.5 cm/s at systole and diastole for CFD respectively). Mean wall shear stress over time is displayed in Figure 4.8.

4.4 Discussion

In this study a wall shear stress calculation algorithm was applied to PC MRI data measured in an in vitro and an in vivo aneurysm. In this work we considered wall shear stress vectors, considering both direction and magnitude of the vectors. We demonstrated that in both the phantom and
Figure 4.7: Wall shear stress vectors calculated in a,c the in vivo PC MRI data and b,d CFD at a,b systole and c,d diastole.

Figure 4.8: Mean and standard deviation of wall shear stress for the in vivo PC MRI measurement and CFD simulation.
in vivo, wall shear stress patterns are qualitatively similar to their CFD predictions. It has been discussed in the literature (13, 26) that wall shear stress estimations improve with increasing spatial resolution. Furthermore, higher spatial resolution leads to more accurate wall delineation, thus further improving the accuracy of wall shear stress estimations. It was beyond the scope of this study to further investigate the influence of segmentation by artificially altering the position of the wall. This is the first study in an intracranial aneurysm that shows that wall shear stress estimations show higher values and more detail phantom by measuring velocity at increasing resolutions.

The wall shear stress magnitude estimated by PC MRI was lower than the CFD-based values, which can be attributed to the lower spatial resolution for PC MRI than CFD. This effect was most pronounced during systole, which can be a result of less accurate spline fitting when velocity gradients are higher. Increasing spatial resolution may help to overcome this issue. The difference in mean wall shear stress found for in vivo PC MRI and CFD was similar to the mean wall shear stress difference found between 0.75 mm and 0.19 mm for in vitro PC MRI. Imperfect registration of the high resolution 3DRA wall delineation to the lower and anisotropic resolution PC MRI grid may have introduced further discrepancies between wall shear stress profiles in experiment 1.

The quantitative agreement found in the in vivo aneurysm in this study was better than in Boussel et al., who remarkably found 6-12 fold higher maximum wall shear stress for PC MRI than CFD in three in vivo aneurysms (5). Apart from higher spatial resolution in our in vivo case, the spline-fitting nature of our wall shear stress algorithm may provide more robust results than their method. One other study comparing heavily interpolated PC MRI data with CFD (27) found a low to moderate degree of correlation. Neither visualized the wall shear stress vectors nor provided any information on the agreement in vector direction.

Disturbed and laminar flow provoke opposite biological reactions from endothelial cells (28). Wall shear stress patterns therefore play a possible role in rupture, forming the rationale for the current study. The exact link between spatial and temporal shear patterns and rupture remains subject of discussion. Identifying such a link in any case requires proper wall shear stress estimation. However, it is reassuring to see that presumably important wall shear stress patterns, such as elevated or circular wall shear stress, were similar for low and high resolution PC MRI and CFD. This hints to the possible clinical use of wall shear stress estimations from PC MRI data. Wall shear stress vectors calculated from PC MRI have been visualized in the aorta (13) and the carotid bifurcation (12). While those studies show complex spatial and temporal differences in direction, in the current intracranial aneurysm circular wall stress patterns are observed, resulting from ‘tornado-like’ vortices, i.e. with the vortex axis perpendicular to the wall. To our knowledge, this is the first study to show such circular wall shear stress behavior in the cardiovascular system. It remains to be addressed what the consequences are of such streaming for endothelial biology and rupture risk. These patterns can only be detected if WSS vectors are derived and will go undetected if merely WSS magnitudes are visualized.

Higher spatial resolution and SNR is beneficial for WSS estimations. With recent technical advances, scanners with higher field strengths are becoming rapidly available. The first studies that present PC MRI data with higher SNR and resolution are now being published (29). It is clear that this approach will be beneficial for the accuracy of WSS estimations from PC MRI. One recently presented new approach to improve measured PC MRI data is divergence reduction (30).

A requirement in WSS estimations is the accurate acquisition of the velocity close to the wall. Due to the nature of blood flow, this velocity is low. In PC MRI low velocities are difficult to resolve and noise on low velocity values will be more prominent. The divergence reduction technique
may therefore be able to improve WSS estimations, although velocities close to the wall remain troublesome to resolve.

4.5 Conclusion

In conclusion, this study evaluated the estimation of WSS vectors from PC MRI data in an in vitro and in vivo intracranial aneurysm. The direction of the WSS vectors was similar to the WSS vectors simulated with CFD, both in vitro and in vivo. Quantitative agreement between PC MRI and CFD was moderate. Furthermore, in order to increase the accuracy of estimated WSS values, the spatial resolution of PC MRI measurements must be as high as possible. However, important WSS vector patterns, such as circular WSS and elevated WSS near impingement zones, can be resolved at lower resolutions.

Bibliography

Wall shear stress estimated with phase contrast MRI in an in vitro and in vivo intracranial aneurysm


Chapter 5

Wall shear stress calculations based on 4D flow MRI and CFD: a comparison in healthy carotid bifurcations

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Wall shear stress calculations based on 3D cine phase contrast MRI and computational fluid dynamics: a comparison study in healthy carotid arteries

* shared first authorship

NMR in Biomedicine (2014)
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5.1 Introduction

Flow induced wall shear stress (WSS) is an important biomechanical parameter, widely accepted to influence the endothelial function in the vasculature and thereby involved in many pathophysiological processes related to cardiovascular diseases (1). The majority of studies have shown that, in the presence of risk factors, atherosclerotic plaques mainly form in the regions of low and oscillatory WSS (2–7). Other studies have also suggested that high WSS has a pathogenic effect on the initiation of aneurysm formation, while low WSS facilitates aneurysm growth (8). These findings suggest that knowledge of WSS may provide vital information about the initiation and progression of vascular diseases. Nevertheless, WSS assessment has not been integrated into clinical practice. This is mainly due to the difficulty of determining WSS in vivo.

WSS can be calculated by multiplying the blood viscosity with wall shear rate (WSR), the latter being the gradient of blood flow velocity in the normal direction of the vessel wall. The current gold standard method for determining 3D blood flow velocities and WSS is computational fluid dynamics (CFD). CFD has the advantage of solving velocities at a high spatial and temporal resolution. However, the disadvantage of CFD is that it requires non-clinical expertise and extensive computational power. Phase contrast (PC) MRI can also measure time resolved 3D velocities and several methods have been developed to quantify WSS using PC MRI velocities. In earlier studies, WSS calculation was based on parabolic fitting of the velocities measured by 2D PC MRI (9–16). This approach was improved by using b-splines for the fitting of velocities measured by 3D cine PC MRI in more recent studies (17–20). A drawback of these studies was that WSS calculations were limited to planar slices within an artery. Recently, a new algorithm for calculation of WSS throughout the 3D luminal surface using PC MRI velocities was introduced (21). In the current study, our objective was to compare WSS distributions on the entire 3D luminal surface of carotid arteries calculated using 3D cine PC MRI velocities with those calculated using CFD. To our knowledge, this is the first study that compares the WSS distributions based on PC MRI and CFD on the entire luminal surface of the carotid arteries.

Figure 5.1: a The luminal surface of the carotid artery was segmented on the magnitude images and subsequently inspected in phase images using ITK-SNAP. b The segmented surface was split into CCA, ICA and ECA using VMTK.
5.2 Methods

5.2.1 MRI scans

Six healthy volunteers (25 – 30 years old) were scanned on a 3 T MRI system (Intera with software version 3.2.1 for the first volunteers and Ingenia with software version 4.1.3 for the last volunteer, Philips Healthcare, The Netherlands) using a dedicated 8-channel bilateral carotid coil (Chenguang Medical Technologies, Shanghai, China). A retrospectively gated 3D transient field echo (TFE) sequence with RF spoiling, a TFE factor of 8 and a parallel imaging factor (SENSE) of 2 with symmetric four-point velocity encoding was obtained with an isotropic non-interpolated resolution of 0.625 mm and a temporal resolution of 138 ± 11 ms (8 timepoints / heart cycle) as part of a carotid scan protocol (FOV/ TR/ TE/ flip angle/ bandwidth/ venc RLxAPxFH, 140x140x30 mm/ 6.7 ms/ 3.1 ms/ 15°/ 299 Hz/px/ 60x60x100 cm/s). This 3D cine PC MRI sequence took ~20 minutes per volunteer, depending on the heart rate. No velocity aliasing was found in the images. We corrected the PC MRI datasets for possible phase-offset errors and visually checked for artifacts.

5.2.2 Segmentation and meshing

Three carotid arteries were excluded due to motion and pulsation artifacts and thus nine were found suitable for the analysis. We manually segmented the luminal surface of the carotid arteries on the magnitude images using ITK-SNAP (22). We excluded small scale side branches. The segmentations were inspected on the phase images and corrected if necessary (Figure 5.1 a). We smoothed the resulting surface with Taubin smoothing approach and split the carotid artery surface into three arteries (Figure 5.1 b), the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA) using the open-source Vascular Modeling Toolkit (VMTK version 1.0.0) (23). We performed the lumen segmentation only on the PC MR images acquired during diastole (t = 742 ms in Figure 5.2 a) because at this cardiac phase the blood flow fluctuations were minimal.

![Figure 5.2: a A representative flow waveform recorded at 8 time points. WSS_{MRI} was calculated using only the velocities recorded during diastole (t = 742 ms). b The generalized waveforms reported by Lee et al. (24). WSS_{CFD} was calculated using only the velocities recorded during diastole (t = 573 ms). The generalized and the recorded flow waveforms have equal mean flow rates.](image-url)
In the next step, we generated a tetrahedral volume mesh by using commercial mesh generation software package Gambit (Ansys). The element size was 0.12 mm at the vessel wall and increased inwardly. Each volume mesh contained approximately 1 million elements. For the computations of WSS based on PC MRI and CFD, we used the same volume mesh, enabling a one-to-one comparison between both WSS measures.

5.2.3 WSS calculations using 3D cine PC MRI velocities

WSS based on PC MRI (WSS$_{MRI}$) was calculated using the 3D cine PC MRI velocities and the volume mesh, as described before (21). In summary, we first determined the inward normal vector of each mesh node on the luminal surface. Along the normal direction, we interpolated the velocities at two inward equidistant points, which were at 1.5 and 3 mm on the inward normal. We imposed the velocity to zero on the vessel wall. We subsequently fitted a curve to the interpolated velocities using a smoothing spline. We derived the slope of this curve at the vessel wall which gives the WSR. We finally multiplied WSR with the shear dependent viscosity (Carreau-Yasuda model) resulting in WSS vectors for all mesh nodes on the vessel wall. We calculated only the diastolic WSS$_{MRI}$. This calculation took $\sim 15$ minutes for each carotid artery.

5.2.4 WSS calculations using CFD

We calculated the CCA, ICA and ECA flows using PC MRI velocities recorded at 8 time points (Figure 5.2 a) as inflow boundary condition. The sum of the ICA and ECA flows did not always match the CCA flow. We therefore corrected the ICA and ECA flows to match their sum with the CCA flow, while maintaining the ratio of the ICA and ECA flows constant. Due to the limited temporal resolution of the 3D cine PC MRI measurements, the recorded flow waveform was flattened (Figure 5.2 a). To account for the temporal flow changes in higher frequencies, we used the generalized flow waveforms of CCA and ICA reported by Lee et al. as substitute for the recorded flow waveforms (Figure 5.2 b) (24). We scaled the generalized flow waveforms so that they had mean flow rates equal to the measured mean flow rates.

As inflow profile, we used a single velocity profile, which was obtained by using both axial and in plane velocities and acquired during diastole ($t = 742$ ms in Figure 5.2 a). We scaled it at each time point in the cardiac cycle so that the flow was increased or decreased according to the flow waveform but the velocity profile shape did not change (Figure 5.3). ECA outlet was left as stress free. Fluid density was set at 1060 kg/m$^3$ and the Carreau-Yasuda model was used to mimic the non-Newtonian behavior of blood with the parameters used in (25).

We performed the CFD simulations on a standard desktop computer (Intel Xeon six core processor, 2.40 GHz CPU and 12 GB RAM) using the commercial finite element software FIDAP 8.7.4 (Ansys). We set the temporal resolution to 5 ms and performed the simulations for 2 cardiac cycles. The CFD simulations took $\sim 15$ hours for each carotid artery. Although CFD results were acquired for a complete cardiac cycle, we analyzed WSS$_{CFD}$ only in
diastole ($t = 573$ ms in Figure 5.2 b) where CCA flow was equal to the measured diastolic CCA flow ($t = 742$ ms in Figure 5.2 a).

### 5.2.5 Analysis of WSS\textsubscript{MRI} and WSS\textsubscript{CFD}

**WSS magnitudes**

As shown in the previous studies, the spatial resolution of the velocities may affect the calculated WSS\textsubscript{MRI} values \cite{17, 21, 26}. To study the effect of resolution, we down-sampled the CFD velocities into PC MRI resolution and calculated WSS (WSS\textsubscript{CFD,lowres}) based on the down-sampled velocity field. To down-sample the CFD velocity field, we first interpolated the CFD velocities to a cubic grid with an isotropic resolution of 0.1 mm. The isotropic PC MRI voxels of 0.625 mm contained $\sim 216$ of these 0.1 mm isotropic voxels. We averaged these $\sim 216$ velocity values and obtained a down-sampled CFD-based velocity field that mimicked the PC MRI velocity data. The down-sampling procedure is schematically depicted in Figure 5.4.

**Figure 5.4:** a CFD velocities interpolated to 0.1 mm cube grid. b The interpolated CFD velocities placed in PC MRI voxels. c Each voxel contained $\pm 216$ of 0.1 mm isotropic velocities that were averaged. d The down-sampled CFD velocities into PC MRI resolution of 0.625 mm.

We present the WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} magnitude maps of each artery. We report the mean of WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} per artery and also within CCA, ICA and ECA. To check whether a systematic relation exists between WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres}, we plotted mean WSS\textsubscript{CFD} versus the difference of mean WSS\textsubscript{MRI} and WSS\textsubscript{CFD}, and also mean WSS\textsubscript{CFD} versus the difference of mean WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} within CCA, ICA and ECA. For the same reason, Bland-Altman analysis, which contained all data points of all arteries, was performed between WSS\textsubscript{MRI} and WSS\textsubscript{CFD}, and between WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres}. Statistical significance was assessed using paired t-test.

We also compared the location of low, medium and high WSS regions. We labeled all WSS\textsubscript{MRI} and WSS\textsubscript{CFD} magnitudes according to three categories representing the low, medium and high tertiles. For each node, we compared the categorization of WSS\textsubscript{MRI} and WSS\textsubscript{CFD}. We report the percentage of the nodes having the WSS\textsubscript{MRI} and WSS\textsubscript{CFD} values labeled in the same tertile. Note
that the nodes on the luminal surface were uniformly distributed; each tertile therefore represented 33\% of the total lumen surface area.

**WSS directions**

We calculated the angles between WSS\textsubscript{MRI} and WSS\textsubscript{CFD} vectors for all mesh nodes on the luminal surface. We generated an angle map for all carotid arteries. We report the mean angle of the luminal surface and within the low, medium and high WSS tertiles. Histogram analysis was also performed for the angles that were sorted in three tertiles.

### 5.3 Results

**Figure 5.5:** Left: WSS\textsubscript{CFD}, middle: WSS\textsubscript{MRI}, right: WSS\textsubscript{CFD,lowres} magnitude [Pa] maps during diastole. The numbers 1 to 5 indicates the volunteers; while L and R represent left and right carotid arteries respectively.
Table 5.1: The mean WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} [Pa] within CCA, ICA and ECA.

<table>
<thead>
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<th>CCA</th>
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<th>ECA</th>
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<tr>
<td>CFD</td>
<td>0.81 ± 0.28 Pa</td>
<td>1.07 ± 0.52 Pa</td>
<td>1.09 ± 0.46 Pa</td>
</tr>
<tr>
<td>MRI</td>
<td>0.60 ± 0.17 Pa</td>
<td>0.73 ± 0.26 Pa</td>
<td>0.56 ± 0.18 Pa</td>
</tr>
<tr>
<td>CFD\textsubscript{lowres}</td>
<td>0.57 ± 0.19 Pa</td>
<td>0.59 ± 0.24 Pa</td>
<td>0.52 ± 0.20 Pa</td>
</tr>
</tbody>
</table>

Figure 5.6: Bland-Altman plots a between WSS\textsubscript{MRI} and WSS\textsubscript{CFD} and b between WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres}. The regression shown in black and the mean and the limits of agreement lines are shown in red. The colors indicate the density of the data points scaled with the colorbar on the right.

5.3.1 WSS magnitudes

WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} magnitude maps for nine carotid arteries are shown in Figure 5.5. The carotid bulb walls were mostly exposed to low WSS magnitude (blue) whereas the bifurcation apex and the inner walls of ICA and ECA had high WSS magnitude (red). Although these patterns were present in WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} maps, the magnitude of WSS was different in each map. WSS\textsubscript{MRI} was lower than WSS\textsubscript{CFD} (0.62 ± 0.18 Pa versus 0.88 ± 0.30 Pa, \(P < 0.01\)), but was only slightly higher than WSS\textsubscript{CFD,lowres} (0.56 ± 0.18 Pa, \(P < 0.01\)). The mean WSS\textsubscript{CFD}, WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} are presented in Table 5.1. For higher WSS magnitudes, the difference between the WSS\textsubscript{CFD} and WSS\textsubscript{MRI} was larger (\(r^2 = 0.4\)). Bland-Altman plot presented in Figure 5.6 a shows this trend. Such a trend was absent in the Bland-Altman comparison of WSS\textsubscript{MRI} and WSS\textsubscript{CFD,lowres} (\(r^2 = 0.01\)), which is shown in Figure 5.6 b.

Figure 5.7 shows WSS maps labeled according to the three categories where dark blue, light blue and yellow represent the regions of low, medium and high WSS. The percentage of the WSS\textsubscript{CFD} and WSS\textsubscript{MRI} values labeled in the same tertile is presented in Table 5.2 for each artery. On average, 68.7 ± 4.4% of the low and 69.0 ± 8.9% of the high WSS\textsubscript{CFD} and WSS\textsubscript{MRI} values matched.

5.3.2 WSS directions

The maps of the angles between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors are shown in Figure 5.8. The angles were small inside CCA and at the distal part of the ECA but larger around the carotid bulb and
Table 5.2: The $\text{WSS}_{\text{CFD}}$ and $\text{WSS}_{\text{MRI}}$ match [%] based on division of WSS values into three categories.

<table>
<thead>
<tr>
<th></th>
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<th>Medium WSS tertile</th>
<th>High WSS tertile</th>
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<tbody>
<tr>
<td>1L</td>
<td>65.3%</td>
<td>48.7%</td>
<td>69.5%</td>
</tr>
<tr>
<td>2L</td>
<td>64.1%</td>
<td>33.2%</td>
<td>57.9%</td>
</tr>
<tr>
<td>2R</td>
<td>66.5%</td>
<td>45.8%</td>
<td>70.9%</td>
</tr>
<tr>
<td>3L</td>
<td>67.9%</td>
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</tr>
<tr>
<td>3R</td>
<td>74.7%</td>
<td>63.0%</td>
<td>84.7%</td>
</tr>
<tr>
<td>4L</td>
<td>78.0%</td>
<td>51.3%</td>
<td>67.2%</td>
</tr>
<tr>
<td>4R</td>
<td>65.3%</td>
<td>50.0%</td>
<td>78.7%</td>
</tr>
<tr>
<td>5L</td>
<td>67.4%</td>
<td>37.0%</td>
<td>65.8%</td>
</tr>
<tr>
<td>5R</td>
<td>68.9%</td>
<td>51.7%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>68.7%</td>
<td>46.8%</td>
<td>69.0%</td>
</tr>
</tbody>
</table>

Figure 5.7: Maps of WSS in the nine carotid arteries where the WSS magnitudes are divided into three categories. Dark blue: low WSS, light blue: medium WSS, yellow: high WSS regions. $\text{WSS}_{\text{CFD}}$ (left) $\text{WSS}_{\text{MRI}}$ (right).
the apex. The mean angle was $65.6 \pm 17.4^\circ$ at low, $28.9 \pm 10.0^\circ$ at medium and $20.3 \pm 8.2^\circ$ at high WSS tertiles. The histograms of the angles that were sorted according to three tertiles are shown in Figure 5.9. The angle between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors was smaller than $30^\circ$ in 35% of nodes in the low WSS tertile, 67% of the nodes in the medium WSS tertile and 80% of the nodes in the high WSS tertile. Within the low WSS tertile, the angles were larger and varying. We found a particularly large angle of deviation in the proximal ICA of 1L. This seemed to be due to the helical flow pattern seen in the PC MRI data but not in the CFD model. Overall, the mean angle between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors was $38.2 \pm 9.0^\circ$.

Figure 5.8: The map of angles [$^\circ$] between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors throughout the luminal surface.

Figure 5.9: The histograms of the angles [$^\circ$] between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors within the low, medium and high WSS tertiles.
5.4 Discussion

In this study, the WSS vectors based on 3D cine PC MRI measurements and CFD simulations were compared in healthy carotid arteries. The strength of the current study with respect to the previous studies is that we calculated PC MRI-based WSS vectors on the entire 3D luminal surface instead of manually selected planar slices within an artery. Obtaining WSS vectors on the entire 3D luminal surface is essential, since WSS distributions in the arteries are heterogeneous and planar slices may not be representative for the entire luminal surface. In this respect, our study is the first to compare subject-specific WSS distributions based on 3D cine PC MRI velocities with those based on CFD on the 3D lumen surface of the carotid arteries. Our results showed that the spatial patterns of WSS\textsubscript{MRI} were in good agreement with those based on CFD. Regions of low WSS along the carotid bulb and regions of high WSS at the inner walls of ECA and ICA were found by both PC MRI- and CFD-based WSS calculations. However, WSS was lower when calculated using PC MRI velocities. By down-sampling the CFD velocity into PC MRI resolution, we were able to mimic the PC MRI velocity field, thereby demonstrating that this underestimation is caused by the limited resolution of PC MRI. We found that the difference between WSS\textsubscript{CFD} and WSS\textsubscript{MRI} increases in regions with higher WSS values. This finding indicates that PC MRI underestimates high WSS values more than low WSS values. This is because velocity gradients disappear within a voxel by the averaging effect of PC MRI, and the effect is more prominent for higher velocity gradients. Such a trend was not seen for the difference between WSS\textsubscript{CFD} and WSS\textsubscript{MRI,lowres}, demonstrating that the low resolution of the MRI was responsible for the large differences at high WSS.

The directions of the WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors were also compared. The angles were mainly small in the CCA and at the distal part of ECA because the flows within these segments were mainly in the axial direction of the vessel. We also found larger angles also in regions of low WSS and disturbed flows. The large deviation in direction of WSS\textsubscript{CFD} and WSS\textsubscript{MRI} vectors in these regions could be due to partial voluming effects and the low signal-to-noise ratio (SNR) of the PC MRI measurements.

The mean WSS values reported in the current study are in agreement with those reported previously. The mean diastolic WSS values reported in the literature were in the range of $0.58 - 0.61$ Pa for CCA \cite{10,11} and $0.55 - 0.70$ Pa for ICA \cite{12,13}, while we found the mean diastolic WSS values in the range of $0.60 \pm 0.17$ Pa for CCA and $0.73 \pm 0.26$ Pa for ICA. Although PC MRI- and CFD-based WSS calculations have never been compared for in vivo carotid arteries, such comparison studies were performed for realistic models of carotid arteries \cite{16,27}. These previous studies on carotid phantoms also reported a good qualitative agreement between PC MRI- and CFD-based WSS results. Kohler et al. showed that PC MRI measurements with an in-plane resolution of 0.7 mm resulted in 40\% lower mean WSS values than those predicted by CFD \cite{27}. Papathanasopoulos et al. obtained higher WSS values with PC MRI velocities, but they used different segmentations for PC MRI- and CFD-based calculations \cite{16}. Studies have also compared WSS\textsubscript{MRI} and WSS\textsubscript{CFD} for in vivo and in vitro intracranial aneurysms \cite{19,27,30} and found good qualitative agreement between them. Similar to our findings, WSS was underestimated for intracranial aneurysms when calculated using PC MRI, and this effect was more prominent for higher WSS values.

Our study showed the validity of the assessment of WSS distribution based on PC MRI by comparing it with CFD-based WSS. However, CFD results are also dependent on a number of assumptions and the chosen boundary conditions, which may not reflect the in vivo situation. In
that respect, by showing a good agreement between PC MRI-based WSS and WSS based on the
down-sampled CFD velocities, we can also interpret our results as the validation of subject-specific
CFD-based WSS calculation using PC MRI measurements. Thus, with the high correlation between
the two methods, it can safely be stated that the chosen boundary conditions and assumptions of
CFD result in in vivo WSS distribution at diastole.

There were three main limitations of our study design. First, we compared WSS$_{\text{CFD}}$ and WSS$_{\text{MRI}}$
values during diastole only. This is a direct result of the choice for increased spatial resolution of
the PC MRI measurements at the expense of temporal resolution. During our PC MRI scans, we
recorded the velocities with a temporal resolution of $138 \pm 11$ ms, which is low compared with
literature values $^{[20,31]}$. Due to the limited temporal resolution, we were unable to capture the
large fluctuations in flow that are known to occur particularly during systole. For this reason, we
decided not to compare the systolic data. Since the analysis was performed at a single time step,
time dependent hemodynamic parameters such as oscillatory shear index were not computed. To
analyze PC MRI-based WSS calculations during systole and to obtain time dependent parameters,
higher temporal resolution will be required in future studies. Second, by assuming rigid walls, we
neglected the pulsatility of carotid arterial walls in our CFD simulations. However, we segmented
the vessel walls on the diastolic images and we compared the WSS$_{\text{CFD}}$ and WSS$_{\text{MRI}}$ values only
during diastole. We assume that the use of rigid walls therefore had a limited impact on our
calculations. Finally, we used the diastolic spatial velocity profile shapes within the CCA and ICA
throughout the cardiac cycle. As a result, we were unable to capture the helical flow that we
observed in PC MRI data of carotid artery 1L in our CFD model. Acquisition of PC MRI data in
higher temporal resolution and applying time varying velocity profiles as boundary conditions in the
CFD simulations may prevent this limitation in future studies.

5.4.1 Clinical relevance

Spatial WSS patterns strongly affect endothelial cell signaling and early events in atherosclerosis $^{[1-7]}$. These patterns were estimated similarly by PC MRI- and CFD-based calculations. For
this reason, both WSS measures can be used when knowledge of low and high WSS patterns is
sufficient. WSS was however underestimated when calculated using PC MRI due to the limited
spatial resolution of PC MRI. Increasing the spatial resolution of PC MRI measurements may have
been a remedy for reducing underestimation of WSS. However, it would have also decreased SNR
and increased the scan duration dramatically. The future developments in MRI technology may
allow PC MRI measurements in higher spatial resolution within reasonable time frames and, as a
result of this, underestimation of PC MRI-based WSS may reduce in future studies. Despite this
limitation, PC MRI-based WSS calculations were completed within shorter time frames ($\sim 15$ min
versus $\sim 15$ h per artery) by using a simpler method that is easily applicable to the acquired MR
images. These advantages may make 3D cine PC MRI data an attractive candidate for calculating
WSS magnitudes in clinical practice in future. It should be noted that in the low WSS regions
we found large angles between the CFD- and PC MRI-based WSS vectors. In the carotid arteries,
particular locations such as the carotid bulb are exposed to low and also oscillatory WSS. Some studies
have suggested that oscillatory shear can induce proatherogenic effects on endothelial cells $^{[32]}$. It
may therefore also be necessary to obtain accurate WSS directions in the regions of low WSS, and
this may limit the use of PC MRI-based WSS calculations. The use of a variable encoding velocity over the heart cycle (33) or the use of a dual encoding velocity in combination with accelerated imaging (34) may also improve PC MRI measurements in regions of low velocity, such that the direction of WSS vectors is decently monitored and can also be used to estimate the degree of changes over the cardiac cycle.

5.5 Conclusion

We showed that PC MRI-based WSS magnitudes are lower than those based on CFD. This is mainly due to the limited spatial resolution of PC MRI measurements. However, we observed good agreement between high and low WSS\textsubscript{CFD} and WSS\textsubscript{MRI} patterns and also between the directions of the WSS vectors in the high WSS regions. Although the PC MRI-based WSS calculation method has some limitations, it has the potential to be applied in the clinical assessment of WSS in carotid arteries since it is simpler and easily applicable to the acquired images compared to the current reference standard CFD.

Bibliography


Chapter 6

The effect of temporal and spatial resolution of cine phase contrast MRI on wall shear stress and oscillatory shear index assessment

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The effect of temporal and spatial resolution of cine phase contrast MRI on wall shear stress and oscillatory shear index assessment

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6.1 Introduction

Atherosclerotic plaques develop at the sites of low wall shear stress (WSS) in the arteries (1, 2). Besides WSS magnitude, some studies show that oscillatory changes of the WSS direction may promote atherogenesis (3–5). Such oscillations within the cardiac cycle are quantified by the Oscillatory Shear Index (OSI) (6, 7). Although both WSS and OSI contribute to initiation and progression of atherosclerotic disease, most studies focus only on the WSS magnitude and exclude analysis of OSI due to the challenge of obtaining accurate WSS magnitude and OSI simultaneously (8–12).

WSS magnitude is calculated by multiplying blood viscosity with wall shear rate (WSR), the latter being the first radial derivative of blood velocity at the vessel wall. The velocity field in the artery that is necessary to calculate WSR is generally obtained with computational fluid dynamics (CFD). CFD is a powerful simulation tool that enables prediction of blood velocities and related hemodynamic parameters (13, 14). However, CFD requires accurate boundary conditions, non-clinical expertise and extensive computational resources and time. Alternatively, the velocities can be obtained by phase contrast MRI (PC MRI) measurements (15–18). However, the WSS values based on MRI depend on the spatial resolution of PC MRI (19–23). In a recent study, we showed that WSS estimates based on in vivo PC MRI data have a realistic representation of the spatial distribution but underestimate magnitude, due to the limited spatial resolution of PC MRI (19). Stalder et al. also investigated the effect of spatial resolution on flow and WSS using synthetic data (17) and showed that the WSS values calculated with the method they proposed were strongly affected by the spatial resolution. Petersson et al. showed that higher true WSS values were underestimated more by PC MRI and reducing the resolution enhanced the underestimation (20). These findings suggest that the spatial resolution of PC MRI measurements should be sufficiently high to obtain the magnitude of WSS accurately. OSI, on the other hand, is a measure of temporal changes of WSS. An accurate estimation of OSI might, therefore, only be possible with both sufficiently high spatial and temporal resolutions of PC MRI measurements.

The MRI settings such as the spatiotemporal resolution involve a trade-off between the measurement duration and the accuracy of the flow, WSS and the OSI estimations. To perform the measurement within clinically feasible scan time, the resolution is generally kept low and the accuracy of these parameters is given away. One can, however, argue that each estimated parameter is affected differently. To our knowledge, none of the previous studies has investigated the effect of spatial and temporal resolution together on these hemodynamic parameters extensively. Our objective was to evaluate the effect of resolution on the assessments of flow, WSS and OSI that we obtained from 2D cine PC MRI scans of a carotid artery phantom at different spatial and temporal resolutions.

6.2 Methods

6.2.1 Phantom and flow set-up

A silicone phantom was built based on the surface reconstruction of a healthy right carotid artery (age 25 years) acquired from a previous study (19) (Figure 6.1 a). The phantom was connected to a flow set-up (Figure 6.1 b). The set-up consisted of a computer, computer controlled pulse generator, an air pressure controller (LifeTec Group, Eindhoven, The Netherlands) and a closed flow
phantom circuit filled with water. The computer, the pulse generator, the air pressure controller, and the flow meter were placed outside the MRI room. The phantom circuit, including an MR compatible pump system, was placed on the MR table connected to the phantom. The pump system consisted of thin-walled silicone cylinders that were filled with water and embedded in a rigid air-filled enclosure. Air pressure in the rigid enclosure was varied to dilate and contract the water-filled cylinders. One-way valves ensured that this cyclic air pressure induced a pulsatile flow. The shape and the magnitude of the flow waveform were set by adjusting the shape and the amplitude of the cyclic air pressure wave. The shape of the waveform was then tuned by adjustment of resistors and capacitors within the closed fluid circuit. A real-time ultrasound flow probe was used to calibrate the PC MRI measured flow waveform before the MRI scans outside the MRI room while keeping all experimental conditions the same.

### 6.2.2 MRI acquisition

The carotid phantom was scanned with a 3 T MR system (Ingenia, software version 4.1.3, Philips Healthcare, The Netherlands) using a solenoid rat coil. 2D cine PC MRI scans were performed at two planes with velocity encoding in 3 directions using various temporal and spatial resolutions as shown in Figure 6.4 in red circles (venc: 100 cm/s, TR: 8.9 – 24.1 ms, TE: 4.67 – 6.57 ms, flip angle: 10°). We performed thirty measurements at different spatial and temporal resolutions at two planes, which took between 1.1 and 21.0 minutes per measurement depending on the spatiotemporal
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6.2 Flow waveforms at different spatial (sr) and temporal (tr) resolutions. Black lines show the PC MRI measurements and the red line shows the ultrasound probe measurement. Spatial resolution varied between 0.2 mm and 1 mm and the temporal resolution varied between 9.1 ms and 142.9 ms.

6.2.3 Segmentation

The vessels were automatically segmented on the MRI measurement planes by an in-house tool written in MATLAB. Initial segmentation was performed by k-means clustering, followed by an active contour segmentation using the method by Herment et al. (21). A separate segmentation was performed for each measurement. The segmentation performed on the images at the highest spatial resolution (0.2 mm) will be denoted as the ‘best segmentation’ in the rest of this article.

6.2.4 WSS calculations based on PC MRI

Since the workflow for WSS calculations based on PC MRI was discussed before in detail, we give a short overview only (22). Firstly, the inward normal was determined for each point on the surface. The velocities measured by PC MRI were interpolated along the inward normal direction at 2 points at a distance of 1.5 and 3 mm from the wall (22). The velocity at the surface was set to zero, and a spline curve was fitted through these two velocity vectors with inclusion of the zero velocity point at the wall. By taking the gradient of the curve at the point on the wall, wall shear rate (WSR)
was calculated. WSS was calculated by multiplying WSR with the dynamic viscosity of water which was assumed to be $1.0 \cdot 10^{-3}$ Pa · s. 

### 6.2.5 OSI Calculations

The commonly used definition of OSI was introduced by He and Ku (7) as follows:

$$\text{OSI}(\vec{s}) = 0.5 \left( 1 - \frac{\sum_0^T |\vec{WSS}(\vec{s}, t)| \delta t}{\sum_0^T |\vec{WSS}(\vec{s}, t)| \delta t} \right)$$  

(6.1)

where $\vec{s}$ is the position at the vessel wall, $t$ is the time point, $\delta t$ is time step, and $T$ is the number of time steps within the cardiac cycle. The OSI varies between 0 and 0.5 where higher OSI indicates larger changes in the WSS direction.

### 6.2.6 Analysis

The flow waveforms measured in the CCA were compared with the ultrasound flow probe measurements. For different spatiotemporal resolutions, we analyzed cross-sectional area, mean flow, peak flow, WSS, and OSI at the CCA and ICA. The WSS values were firstly averaged over the cardiac cycle and subsequently over the circumference of the vessel wall. The OSI values were averaged over the circumference of the vessel wall. Furthermore, to study the local distribution of WSS and OSI over the circumference, WSS and OSI values were averaged separately over the quarters of the vessels. Finally, to investigate the effect of segmentation on the estimated hemodynamic parameters, the ‘best segmentation’ was applied to each dataset. The mean flow, WSS and OSI were obtained with the best segmentation and compared with those obtained with the segmentation per measurement.

### 6.2.7 Statistical analysis

The associations between spatiotemporal resolutions and the hemodynamic parameters and between the results based on the measurement-specific segmentations and best segmentation were tested by linear regression analysis. In statistical evaluations, the level of significance was chosen at $P < 0.05$. The results were represented as the mean ± standard deviation of the 30 measurements.

### 6.3 Results

The linear regression coefficients and the slopes of the linear regression lines (in %/mm and %/100ms) between the hemodynamic parameters and spatiotemporal resolution are summarized in Table 6.1.

### 6.3.1 Flow waveform at CCA

Flow waveforms obtained from PC MRI measurements at the highest and the lowest spatial and temporal resolutions are shown in Figure 6.2a. The red line shows the flow waveform based on the ultrasound probe measurement. At the highest spatial resolution (0.2 mm) and the highest
temporal resolution (24.4 ms, black dashed line), the shape of the flow waveform was similar to the one measured by the ultrasound probe. At the lowest spatial resolution (1.0 mm) and the highest temporal resolution (9.1 ms, light blue dashed line), the shape of the flow waveform was still captured although peak flow was underestimated (7.8 mL/s). At lowest temporal resolution (142.9 ms, red and orange dashed lines), the peak flow was shifted backward in the cardiac cycle and was underestimated. The ultrasound probe measurements were plotted against the PC MRI measured flows in Figure 6.2b which shows underestimation of flow at higher flows in all cases except for the measurement at the highest spatial and temporal resolution.

**6.3.2 Area, mean flow, and peak flow at CCA and ICA**

The cross-sectional area was 24.6 ± 0.6 mm² at the CCA and 29.0 ± 2.9 mm² at the ICA. The mean flow based on PC MRI measurements was 2.5 ± 0.2 mL/s at the CCA and 1.3 ± 0.2 mL/s at the ICA (Figure 6.4). The mean flow is plotted for the different spatial resolutions in Figure 6.3a and for the different temporal resolutions in Figure 6.3b. A significant association was found between mean flow and the spatial resolution (slope −13.0%/mm for the CCA and −49.0%/mm for the ICA). No correlation was observed between mean flow and temporal resolution. The mean flow based on the ultrasound flow probe measurement was 2.7 ± 0.02 mL/s at CCA; hence, the ratio of the mean flows based on PC MRI measurements and the ultrasound flow probe measurement was 95.1 ± 7.9%.

The peak flow was 7.6 ± 1.0 mL/s at CCA and 4.2 ± 0.6 mL/s at ICA (Figure 6.4). The peak flows at different spatiotemporal resolutions are shown in Figure 6.3c and Figure 6.3d. At the highest spatial resolution (0.2 mm) and the highest temporal resolution (24.4 ms), the peak flow was estimated accurately (9.1 mL/s) relative to ultrasound probe peak flow measurement (9.1 mL/s). At lower spatiotemporal resolutions, peak flow was underestimated. The estimated peak flow was significantly dependent on both spatial (−17.0%/100 ms for ICA) and temporal resolution (−19.0%/100 ms for CCA to −24.0%/100 ms for ICA).

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**Table 6.1:** The regression analysis for different spatiotemporal resolutions and the hemodynamic parameters (CCA: top, ICA: bottom). The slopes (in %/mm and %/100 ms) were calculated by dividing flow, WSS and OSI with their respective maxima. (∗) indicates P < 0.05, and (NS) indicates P ≥ 0.05.

<table>
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<th>CCA Spatial resolution</th>
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<td>OSI</td>
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<table>
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<th>Temporal resolution</th>
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</tr>
<tr>
<td>OSI</td>
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</tr>
</tbody>
</table>
6.3.3 Mean WSS at CCA and ICA

The WSS at different spatial and temporal resolutions are shown for CCA and ICA in Figure 6.6a and Figure 6.6b. The WSS was 0.12 ± 0.01 Pa at the CCA and 0.09 ± 0.02 Pa at the ICA (Figure 6.5). At the highest spatial resolution (0.2 mm) and the highest temporal resolution (24.4 ms), WSS was determined as 0.15 Pa at the CCA and 0.14 Pa at the ICA. At lower spatial resolutions, the estimated WSS was lower. We found a significant inverse relationship between the estimated WSS and the spatial resolution (−19.0 %/mm for the CCA and −33.0 %/mm for the ICA). No relationship was found between mean WSS and temporal resolution.

6.3.4 OSI at CCA and ICA

Figure 6.6c and Figure 6.6d show OSI at different spatial and temporal resolutions for the CCA and ICA. OSI was found 0.02 ± 0.02 at the CCA and 0.08 ± 0.05 at the ICA (Figure 6.5). The highest OSI values were found at the highest spatial resolution (0.2 mm) and the highest temporal resolution (24.4 ms), which were 0.08 for the CCA and 0.27 for the ICA. The OSI was underestimated at lower spatiotemporal resolutions. We found a significant association between OSI and spatial resolution in the CCA (−26.0 %/mm), but the association between OSI and temporal resolution was not significant in the CCA. In the ICA, we only found a significant association between OSI and temporal resolution (−16.0 %/100ms).
Figure 6.4: Mean flow of a CCA and b ICA at different spatial and temporal resolutions. Red circles show the measurement points. Peak flow of c CCA and d ICA at different spatial and temporal resolutions. Red circles show the measurement points. White lines show the measurement durations of 18, 6 and 2 minutes (left to right).

6.3.5 Local WSS distribution

The mean WSS of each quarter for four measurements in the CCA and the ICA is shown in Figure 6.7. For the CCA, the highest WSS quarter was the bottom right quarter (0.14 ± 0.01 Pa) and the lowest WSS quarter was the top left quarter (0.07 ± 0.02 Pa). These highest and the lowest of WSS regions were found in all measurements for the CCA regardless of spatial and temporal resolution. For the ICA, the highest WSS quarter was the bottom right quarter (0.13 ± 0.02 Pa) which was found in all measurements. The lowest WSS quarter for the ICA was the top left quarter (0.04 ± 0.02 Pa) which was found in 28/30 measurements (93%).

6.3.6 Local OSI distribution

The mean OSI of each quarter for four measurements is shown in Figure 6.8. OSI was generally low in all quarters of the CCA. The highest OSI quarter in the CCA was the top left quarter (0.04 ± 0.02) which was found in 23/30 measurements (77%). The lowest OSI quarter was bottom right quarter, (0 ± 0.01) and found in 29/30 (97%) measurements. For ICA, the highest OSI quarter was top left quarter (0.20 ± 0.08) and the lowest OSI quarter was the bottom right quarter (0.01 ± 0.01) which was found in all measurements regardless of spatial and temporal resolution.
6.3.7 Calculations using fixed segmentation at CCA

The best segmentation resulted in the cross-sectional area of 24.7 mm$^2$ for the CCA. The results based on the best segmentation were very similar to those based on the segmentations per measurement. The flow obtained with the best segmentation was $2.7 \pm 0.2$ mL/s which was in agreement with the ultrasound probe flow measurements and 8.0% higher than that obtained with the measurement specific segmentations ($2.5 \pm 0.2$ mL/s, $r^2 = 0.85$, $P < 0.001$). We found no significant correlation between the the mean flow and spatial resolution after switching to the best segmentation ($r = -0.09$, $P = 0.62$). The WSS with the best segmentation showed good agreement with that based on the measurement specific segmentations ($r^2 = 0.99$), which were on average only 2% lower in magnitude ($0.11 \pm 0.01$ Pa, $P < 0.001$). The mean OSI based on the best segmentation was $0.02 \pm 0.02$ which was also in good agreement with that based on the measurement specific segmentations ($r^2 = 0.99$).

6.4 Discussion

In this study, we investigated the influence of spatial and temporal resolution on the estimation of mean flow, peak flow, WSS and OSI in a realistic phantom of a carotid bifurcation. Our results show that not all parameters are affected to the same extent by spatial and temporal resolution. For example, mean flow was not dependent on the temporal resolution; but it was influenced by
The effect of spatiotemporal resolution of cine PC MRI on WSS and OSI assessment

Figure 6.6: a WSS [Pa] vs spatial resolution [mm], b WSS [Pa] vs temporal resolution [ms], c OSI vs spatial resolution and d OSI vs temporal resolution at CCA and at ICA.

Figure 6.7: The mean WSS [Pa] of each quarter at different spatial and temporal resolutions in CCA and in ICA. * shows the highest WSS quarter and + shows the lowest WSS quarter.
Figure 6.8: The mean OSI of each quarter at 4 different spatial and temporal resolutions in CCA and in ICA. * shows the highest OSI quarter and + shows the lowest OSI quarter.

the spatial resolution. This was caused mainly by the difference in segmentation. At lower spatial resolutions, delineating the borders of the cross-sectional area was more difficult with larger voxels around the vessel wall. In fact, applying the best segmentation improved the estimation of mean flow for all resolutions. Nevertheless, mean flow was estimated accurately with less than 10% error regardless of the segmentation, the spatial and the temporal resolution. These observations correspond well with previous literature that also showed correct flow rates for lower resolution scans (17). Please note that correct flow quantification requires a minimum number of 3-4.5 voxels/diameter (24, 25).

The estimated flow waveform and the peak flow were mainly dependent on temporal resolution. To obtain the peak systolic time point within the cardiac cycle and the peak systolic flow accurately, it was necessary to perform the acquisition at a high temporal resolution. The higher temporal resolution also reduced flattening of the flow waveform. At a temporal resolution lower than 50 ms, the error in the estimated peak flow was still more than 10%.

The WSS values were specifically relying on high spatial resolution. The observed effects of spatial resolution on average WSS magnitude are in correspondence with existing literature. The typical underestimation of WSS, when quantified by PC MRI, has been described extensively (17, 20, 22, 26, 27). For a parabolic flow with a flow rate equal to the measured CCA mean flow, the theoretical WSS value is approximately 0.15 Pa. Since the velocity profile at CCA was close to a parabolic shape, the WSS was expected to have a value close to the theoretical WSS value. Only at a spatial resolution of 0.2 mm, the WSS based on PC MRI was close to the theoretical value and underestimated at lower resolutions. However, the changes in the spatial resolution at lower spatial resolutions had only a marginal impact in the estimated WSS value, e.g. a decrease of 0.1 mm in spatial resolution only decreases the WSS by 2 – 3%. Note that the duration of our 2D PC MRI measurements at spatial resolution of 0.2 mm and temporal resolution of 24 ms was 21 minutes at only one plane which is not feasible in the clinic. Furthermore, the noise level increases with the increase of spatial resolution, even more if a standard receive coil is used. Nevertheless, recent developments in MRI acceleration technologies will lead to shorter scan times and/or decreased
The effect of spatiotemporal resolution of cine PC MRI on WSS and OSI assessment

noise levels at high resolutions (28, 29), which, in time, will allow faster and more accurate WSS based on PC MRI.

The effects of temporal resolution on time-resolved WSS parameters have not been investigated previously. We found that the WSS values averaged over the cardiac cycle were not dependent on the temporal resolution. For the CCA, OSI was dependent on spatial resolution, but not on temporal resolution. For the ICA, OSI was dependent on temporal resolution, but not on spatial resolution. This is likely due to the low OSI in the CCA and the high OSI in the ICA. OSI values were higher at high spatial and temporal resolutions. However, at lower spatiotemporal resolutions, the changes in the spatiotemporal resolutions affect the estimated OSI values only to a limited extent.

Despite underestimation of the WSS and the OSI magnitude, the locations of low and high WSS and OSI regions showed a good agreement in most of the measurements, regardless of spatiotemporal resolution. This result together with the limited dependency of WSS and OSI values on the chosen spatiotemporal resolutions indicates that WSS and OSI can be compared between studies with similar PC MRI protocols.

Although the segmentation had an influence on the estimated flow, the effect of segmentation on WSS and OSI was found to be small. This may be related to the fact that choosing zero velocity at the wall improves the robustness of WSS estimations, as shown by Petersson et al. (20).

In this study, we used a carotid flow profile of the CCA and the ICA, which represents two typical velocity profiles inside carotid arteries. We therefore expect that our results on the effect of spatiotemporal resolutions are representative for other areas of the carotid arteries and other vessels with similar velocity profiles.

This study had three main limitations. Firstly, we limited the study to only 2D PC MRI measurements (with 3D velocity encoding) within the carotid artery. We chose to perform 2D acquisition to keep the MRI scans within clinically acceptable scan times since high-resolution 4D PC MRI measurements would result in unacceptable long scan times. To overcome this limitation, we chose two MRI measurement planes, one at CCA, and one at ICA, representing the relevant two velocity profiles. Secondly, we performed only in vitro measurements, which do not necessarily represent in vivo situation. However, the long scan times would again be the limitation to perform measurements at very high spatial and temporal resolutions. Finally, we used water as the medium instead of a blood representing fluid. However, the effect of blood viscosity on the estimated WSS values was beyond the scope of this study.

6.5 Conclusion

In this study, we showed that the hemodynamic parameters such as mean flow, peak flow, flow waveform, WSS and OSI are influenced by spatial and temporal resolution of PC MRI measurements but to different extents. The mean flow is dependent on the spatial resolution which is caused by the segmentation errors. However, the effect of spatial resolution on the mean flow is small. We show that both mean flow and mean WSS are independent of temporal resolution. WSS is more sensitive to spatial resolution, while OSI is sensitive to both spatial and temporal resolution. Nevertheless, this study shows that the magnitude of mean and peak flow, WSS and OSI as well as the location of low and high WSS did not exhibit a strong dependency on the spatiotemporal resolution of the measurement.


The effect of spatiotemporal resolution of cine PC MRI on WSS and OSI assessment


Chapter 7

A methodology to detect abnormal relative wall shear stress on the full surface of the thoracic aorta using 4D flow MRI

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A methodology to detect abnormal relative wall shear stress on the full surface of the thoracic aorta using four-dimensional flow MRI

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7.1 Introduction

Clinical management of aortopathy employs anatomical and hemodynamic measurements, such as aortic diameter and peak transvalvular blood velocity. In the presence of aortic dilation or aortic valve disease, these parameters are simple to acquire, yet have limited predictive ability to identify subjects who may experience progressive aortic enlargement, dissection, or rupture (1-3). Current guidelines focus on consensus-based thresholds for aortic diameter (4, 5) and are known to lead to divergent outcomes in similarly classified patients in terms of symptom status, cardiovascular events, or aortic valve replacement (6-8). Furthermore, changes in aortic geometry are often detected late in the disease process, and management does not consider the underlying markers suspected to drive wall remodeling and progressive aortic dilatation. This is an important consideration given recent longitudinal studies finding independent associations between hemodynamic markers and aortopathy (9, 10). In this context, wall shear stress (WSS), the tangential force exerted by blood flow on the vessel wall (11), may be a promising prognostic marker associated with the expression of transcriptional factors responsible for extracellular matrix degradation and vascular smooth muscle cell apoptosis (12-14).

In the last decade, considerable progress has been made regarding the estimation of WSS. The development of four-dimensional (4D) flow MRI (time-resolved three-dimensional [3D] phase contrast MRI with three-directional velocity encoding) (15-17) with full volumetric coverage of the thoracic aorta has made the assessment of in vivo WSS a reality (18-27). Nonetheless, a number of challenges remain to determine whether abnormal WSS presents a definitive risk for adverse aortic remodeling in a large, well-controlled population-based study. The current challenges include the complexity of measuring WSS along the entire aortic surface, a lack of established baseline WSS values (for healthy individuals), spatial resolution effects, and the ability to consistently identify and describe aortic locations with abnormal WSS. As a consequence, there is currently no standardized method for comparing 3D aortic WSS between individuals and patient cohorts.

In this study, we present a novel methodology capable of quantifying 3D WSS over the entire aorta lumen surface and thereby provide a method to derive cohort-averaged 3D WSS vector maps. The technique allows for compact visualization of 3D WSS assessed across multiple subjects and enables a quantitative comparison of the 3D WSS environment on the surface of the vessel between cohort groups. The goal of this study was to present the methodology and test the hypothesis that the technique can statistically compare regional 3D WSS differences as expressed on the entire vessel surface between patient groups according to the nature of the aortic disease.

7.2 Methods

7.2.1 Study cohort

Thirty subjects were retrospectively enrolled according to the following subgroup criteria: (1) 10 age-appropriate healthy control subjects (59 ± 10 years) with no history of cardiovascular disease, normal aortic valve function, and normal thoracic aortic geometry; (2) 10 patients with normal aortic valve function and aortic dilation (59 ± 12 years); and (3) 10 patients determined to have moderate to severe aortic stenosis and concomitant aortic dilation (65 ± 14 years, referred to as the stenosis cohort). Patients were excluded if Marfan syndrome or Ehlers-Danlos syndrome was
Figure 7.1: A schematic overview of the data analysis workflow. 

**a** For all subjects (s1-s10) of each cohort, 4D flow MRI data were used to calculate the 3D WSS distribution along the aorta surface, resulting in 10 individual 3D WSS maps for each cohort. 

**b** For each cohort, the 10 WSS maps were coregistered to create a cohort-averaged 3D WSS map. 

**c** WSS estimation was projected onto the control aorta geometry allowing for statistical comparison between groups.

present. All subjects had trileaflet aortic valve morphology. Aortic dilation was defined as a sinus of Valsalva or midascending aorta diameter > 4.0 cm. Aortic stenosis was graded according to the absolute systolic peak velocities at the level of the aortic valve, as is recommended for continuous wave Doppler ultrasound guidelines (moderate stenosis: 3 – 4 m/s; severe stenosis: ≥ 4 m/s) [4]. Aortic insufficiency was graded as mild, moderate, or severe according to a regurgitant fraction of < 30%, 30% – 49%, or > 50%, respectively [4].

The demographics of the study subjects are summarized in Table 7.1. The study was approved by the local institutional review board. Nine controls, two patients with aortic dilation, and two patients with aortic valve stenosis provided informed consent. The tenth control presented normal findings on a clinical scan. The remaining subjects were enrolled using an institutional review
A methodology to detect abnormal relative WSS on the thoracic aorta using 4D flow MRI

Table 7.1: Demographics of the study population (N = 10).

<table>
<thead>
<tr>
<th></th>
<th>Normal Controls</th>
<th>Patients with Aortic Dilation</th>
<th>Patients with Aortic Stenosis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean±SD (y)</td>
<td>59 ± 10</td>
<td>59 ± 12</td>
<td>65 ± 14</td>
<td>0.41</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SOV diameter mean±SD (cm)</td>
<td>3.1 ± 0.4</td>
<td>4.1 ± 0.6</td>
<td>4.0 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAA diameter mean±SD (cm)</td>
<td>3.2 ± 0.2</td>
<td>3.9 ± 0.5</td>
<td>4.2 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spatial resolution mean±SD (mm³)</td>
<td>16.6 ± 4.1</td>
<td>18.7 ± 1.3</td>
<td>18.9 ± 3.27</td>
<td>0.25</td>
</tr>
<tr>
<td>venc mean±SD (cm/s)</td>
<td>150 ± 0</td>
<td>170 ± 42</td>
<td>265 ± 118</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Aortic stenosis, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>NA</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>NA</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>NA</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>NA</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>NA</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>NA</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Differences across cohorts were evaluated using the Kruskal-Wallis test. Abbreviations: MAA, midascending aorta; NA, not applicable; SOV, sinus of Valsalva; venc, velocity encoding.

7.2.2 MRI

4D flow MRI measurements were performed on 1.5 T and 3 T scanners (Espree, Avanto, Skyra, Aera, Siemens, Erlangen, Germany). All patients underwent a standard-of-care thoracic cardiovascular MRI including electrocardiography-gated time-resolved cardiac MRI for the evaluation of cardiac function and valve morphology as well as contrast-enhanced MR angiography for the quantification of aortic dimensions. For valve imaging, a two-dimensional (2D) imaging plane was carefully positioned orthogonal to the aortic root at the level of the aortic valve. In addition, 4D flow MRI of the thoracic aorta was performed in a sagittal oblique volume using prospective electrocardiography gating and free-breathing with a respiratory navigator placed on the lung-liver interface (28). 4D flow pulse sequence parameters were as follows: spatial resolution: 1.7 – 3.6 × 1.8 – 2.4 × 2.2 – 3.0 mm³; temporal resolution: 37 – 42 ms (14 – 25 cardiac time frames); echo time/repetition time: 2.2 – 2.8/4.6 – 5.3 ms; flip angle: 7° – 15°; field of view: 144 – 380 × 120 – 285 × 67 – 116 mm³; velocity sensitivity: 150 cm/s, 150 – 250 cm/s, 150 – 450 cm/s for the healthy controls, patients with aortic dilation, and patients with aortic stenosis, respectively (manually specified by the technologist to minimize velocity aliasing).

7.2.3 Data analysis
Figure 7.2: Schematic display of WSS estimation in the aorta. **a,b** The original coordinate system was rotated (indicated by the green arrow) to an alternate coordinate system such that the z-axis aligned with the original normal vector. No flow occurs through the vessel wall ($\vec{n} \cdot \vec{v} = 0$), thus the equation in **a** can be approximated by the equation in **b**. **c,d** A spline was fitted through the three velocity values (one green dot, two blue dots) on the inward normal with a length of 1.5 cm (red arrow). **d,e** The derivative of the spline fit at the vessel wall is proportional to WSS in $x'$ direction. **f** Inverse rotation (green arrow) resulted in the WSS vector of interest.

4D flow MRI measurements were corrected for eddy currents, Maxwell terms, and velocity aliasing using custom-built software programmed in MATLAB (Mathworks, Natick, Massachusetts, USA) as described previously [29]. Voxel-wise multiplication of the magnitude data with absolute velocities averaged over all cardiac time frames [29]. The 3D phase contrast MR angiography images were semi-automatically segmented using a commercial software package (MIMICS, Materialise, Leuven, Belgium). To obtain a smooth surface of the aortic wall, the segmentation was smoothed using a Laplacian filter [30]. Peak systole was defined as the cardiac time frame with the highest average aortic velocity.

### 7.2.4 Cohort specific aortic geometry and WSS map

The data analysis workflow for 3D WSS estimation, calculation of cohort-specific aortic geometry and WSS maps, and quantification of intercohort differences is shown in Figure 7.1. All analyses were performed in MATLAB. Visualization of the results was partially performed using commercial software (Ensight, CEI Inc, Apex, North Carolina, USA).

#### 3D WSS estimation for individual aortas

As summarized in Figure 7.2, WSS vectors were calculated by:

$$\vec{\tau} = 2\eta \dot{\epsilon} \cdot \vec{n} \quad (7.1)$$

where $\vec{\tau}$ is the WSS vector, $\eta$ is the dynamic viscosity ($3.2 \cdot 10^{-3}$ Pa·s), $\dot{\epsilon}$ is the rate of deformation tensor, and $\vec{n}$ is the normal vector orthogonal to the vessel wall (Figure 7.2 **a**).

By rotating the coordinate system such that the z-axis aligns with the normal vector of the vessel wall (Figure 7.2 **b**), it holds that: $\vec{n} = (0, 0, 1)$. Since no flow occurs through the wall ($\vec{n} \cdot \vec{v} = 0$) at the wall, the inner product of the rate of deformation tensor and the normal vector is reduced to:

$$2\dot{\epsilon} \cdot \vec{n} = \left( \frac{\delta V_{x'}}{\delta z'}, \frac{\delta V_{y'}}{\delta z'}, 0 \right) \quad (7.2)$$

where the shear rates $\frac{\delta V_{x'}}{\delta z'}$ and $\frac{\delta V_{y'}}{\delta z'}$ are the spatial velocity gradients at the wall in the rotated
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Figure 7.3: Step-wise rigid coregistration and calculation of overlap. Top row: Coregistration of two aortic geometries (aorta 1 and aorta 2). The resulting overlap map is visualized as a maximum intensity projection (MIP). Bottom row: A third aorta (aorta 3) is coregistered, and the overlap map is updated. After inclusion of all 10 subjects, a final overlap map is created with values ranging from 1 to 10.

coordinate system. The rotated WSS vector \( \vec{\tau}' \) is then defined as:

\[
\vec{\tau}'_x = \eta \frac{\delta v'_x}{\delta z'}, \quad \vec{\tau}'_y = \eta \frac{\delta v'_y}{\delta z'}, \quad \vec{\tau}'_z = 0
\]

(7.3)

The shear rates were derived from one-dimensional smoothing splines \(^{31}\) fitted through the rotated x- and y-velocity values along the inward normal vector \(^{32}\). Figure 7.2 c, d. The WSS vector was transformed to the original coordinate system by inverse rotation; Figure 7.2 e, f. WSS was averaged over five cardiac time frames centered at peak systole to reduce noise. Systole was considered as it is the most hemodynamically active portion of the cardiac cycle. A previous study showed that important differences in hemodynamic behavior were diluted when the diastolic period was included \(^{33}\).

7.2.5 Cohort-averaged WSS map

A cohort-specific aorta WSS map was created using the following three-step process: (1) the individual aorta 3D segmentations from each cohort were rigidly coregistered, and a map quantifying the amount of shared geometry was generated (i.e. an ‘overlap’ map); (2) the maximal overlap was used to create a cohort-specific, idealized aorta geometry; and (3) the individual 3D WSS vectors were projected onto the cohort-specific aorta geometry and a 3D WSS map representative of the entire cohort was calculated.
Rigid coregistration and generation of the overlap map

As shown in Figure 7.3 (top row), two aortic 3D segmentations were rigidly coregistered (six degrees of freedom) using FMRIB’s Linear Image Registration Tool (FLIRT). To create the initial overlap map, two aortic segmentations were summed in a voxel-wise fashion, and volume containing either a 1 (no overlap) or 2 (both aortas overlapping) was created. Next, a third aorta was coregistered, as shown in Figure 7.3 (bottom row), and the overlap map was calculated to yield values ranging from 1 to 3 (1: no overlap, 2: two aortas overlapping, and 3: three aortas overlapping). This process was continued for all 10 subjects in each cohort such that the final map included values representing the amount of geometry shared by each segment, ranging from an overlap value of 1 to 10. Two sequence orders for aorta registration were used to test for reproducibility of the overlap map creation. This process can be expressed as:

Consecutive registration: \[
\sum_{n=1}^{10} A_n
\] (7.4)

Random registration: \[
\sum_{m} A_n \text{ with } m = [5, 9, 6, 4, 2, 10, 1, 8, 3, 7]
\] (7.5)

Identification of the cohort-specific, idealized aorta geometry

For each subject, the original aorta 3D segmentation was coregistered to multiple potential cohort-specific aorta geometries as defined by overlap thresholds \(O_{\text{thresh}}\) with a range of \(1 \leq O_{\text{thresh}} < 10\). Each \(O_{\text{thresh}}\) defined a potential cohort-specific aorta geometry with at least \(n = O_{\text{thresh}}\) overlapping aorta regions \(O_{\text{thresh}}\) map). Each aorta in the cohort was then rigidly coregistered to the threshold \(O_{\text{thresh}}\) map, and an individual registration error (RE, relative number of voxels not shared by the aorta and \(O_{\text{thresh}}\) map) was calculated as:

\[
RE = \frac{N_{|O_{\text{thresh}}-\text{Aorta}|}}{(N_{O_{\text{thresh}}} + N_{\text{Aorta}})/2} \times 100
\] (7.6)

where \(N_{|O_{\text{thresh}}-\text{Aorta}|}\) is the number of voxels not shared between the overlap map and the individual aorta, \(O_{\text{thresh}}\) the number of voxels of the \(O_{\text{thresh}}\) map and \(N_{\text{Aorta}}\) the number of voxels of the individual aorta. Finally, the \(O_{\text{thresh}}\) map with the lowest RE averaged over all aortas in the cohort was chosen as the cohort-specific aorta geometry. Figure 7.4 illustrates the optimization process for examples with \(O_{\text{thresh}} \geq 4\) and \(O_{\text{thresh}} \geq 6\).

Cohort-specific 3D WSS maps

To project the 3D WSS vectors onto the final cohort-specific aortic geometry, affine registration (FLIRT, 12 degrees of freedom) was used, followed by nearest-neighbor interpolation of the 3D WSS vectors (Figure 7.5). To investigate the influence of the interpolation process, each individual aorta and the cohort-specific aorta geometry were separated into three regions: ascending aorta (AAo), aortic arch (Arch), and descending aorta (DAo), as shown in Figure 7.5. The interpolation error (IE) was defined as the relative difference between the mean WSS of the cohort-averaged aorta geometry and the individual aorta:

\[
IE = \left(\frac{|\text{mean WSS geometry} - \text{mean WSS aorta}|}{(\text{mean WSS geometry} + \text{mean WSS aorta})/2}\right) \times 100
\] (7.7)
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Figure 7.4: Identification of the optimal cohort-specific aorta geometry. For the different overlap thresholds $O_{\text{thresh}} \geq 4$ (top row) and $O_{\text{thresh}} \geq 6$ (lower row), aorta 1 was registered to the $O_{\text{thresh}}$ mask to determine the RE. The RE for $O_{\text{thresh}} \geq 4$ was lower than the RE for $O_{\text{thresh}} \geq 6$ and was therefore preferred. This step was repeated for all aortas in each cohort.

Averaging over cohort

Finally, cohort-averaged 3D WSS vector maps as well as standard deviation (SD) maps reflecting interindividual differences in WSS were calculated for each of the three cohorts.

### 7.2.6 Analysis of WSS differences between cohorts

To enable comparison between cohorts, the 3D WSS vectors of the dilation and stenosis cohort were interpolated (nearest neighbor interpolation; see Figure 7.5) to the aorta geometry of the control cohort. For this process, the registration error and interpolation error were calculated.

To test the dependence of the comparison between cohorts on the choice of aorta geometry for comparison between cohorts, the subjects in the control cohort were registered and interpolated to the aorta geometry of the dilations.

### 7.2.7 Statistical analysis

A Kruskal-Wallis test was used to evaluate differences in age, aortic diameter, and interpolation error between cohorts. A Wilcoxon rank sum test was used to assess whether differences existed due to the sequence of the aorta registration for the overlap map creation. To identify regional differences in WSS between two cohorts, a Wilcoxon rank sum test was performed for each location on the control aorta geometry, resulting in a P-value map. Differences were considered statistically significant if $P < 0.05$. The resulting P-values were mapped onto the aorta geometry of the control cohort to create aorta P-value maps in order to visualize significant regional differences of WSS between cohorts. To test for reproducibility, a P-value map was created of the individual controls registered and interpolated to the aorta geometry of the dilations.

A Wilcoxon rank sum test was performed to investigate differences between the sinus of Valsalva and midascending aorta diameter of the dilation and stenosis cohort.
Figure 7.5: WSS projection. Aorta 1 was registered to the cohort-specific aorta geometry. The WSS vectors on aorta 1 were subsequently interpolated to the aorta geometry, and the interpolation error was calculated in the ascending aorta (AAo), aortic arch (Arch), and descending aorta (DAo). This step was repeated for each aorta in the cohort.

7.3 Results

7.3.1 3D WSS estimation for individual aortas

In Figure 7.6, examples of measured systolic blood flow velocities and derived 3D WSS maps for an individual aorta from each cohort are shown. The velocities along the outer curvature of the ascending aorta of the patient with valve stenosis (Figure 7.6 c) were higher compared with both the control (Figure 7.6 a) and the dilated aorta (Figure 7.6 b). As a result, differences in regional velocity profiles (e.g., in the distal ascending aorta in Figure 7.6 d-f resulted in altered velocity gradients at the wall in patients with aortic valve stenosis. This elevated velocity gradient resulted in regionally increased WSS for the aorta with valve stenosis (Figure 7.6 i) compared with the control (Figure 7.6 g) and dilated aorta (Figure 7.6 h).

7.3.2 Cohort-averaged WSS map

Cohort-specific aorta geometry

For all three cohorts, aorta geometries were successfully created and an overlap threshold, $O_{\text{thresh}} \geq 4$ (i.e., an overlap of four or more aorta regions), showed a minimum RE of $23\% \pm 3.0\%$, $20\% \pm 4.7\%$, and $23\% \pm 9.3\%$ for the control, dilation, and stenosis cohorts, respectively. For the creation of the cohort-specific aorta geometries, a consecutive registration sequence starting at 1 to 10 aortas was used. When the random sequence was applied, a minimum RE of $23\% \pm 4.0\%$, $20\% \pm 4.8\%$, and $23\% \pm 8.9\%$ was seen for the control, dilation, and stenosis cohorts, respectively. The differences between the consecutive and random registration errors were not significant for all cohorts ($P = 0.70$, $P = 0.94$, and $P = 0.91$ for the control, dilation and stenosis cohorts, respectively).

Cohort-specific 3D WSS maps

The mean interpolation error in the control cohort was $3.2\% \pm 3.0\%$, $2.2\% \pm 1.3\%$, and $4.7\% \pm 6.4\%$ for the AAo, Arch, and DAo, respectively. For patients with aortic dilation, the IE was $1.8\% \pm 1.2\%$, $2.9\% \pm 1.8\%$, and $4.7\% \pm 4.2\%$ for the AAo, Arch, and DAo, respectively. For the stenosis cohort,
Figure 7.6: Right-anterior oblique views of velocity vectors in a typical control aorta, b dilated aorta and c aorta with severe valve stenosis. Black lines indicate the location of the planes for which the velocity profiles are shown in d–f. Note that for visualization purposes, the velocity color bar for the aorta with valve stenosis is two times higher than for the other two aortas. g–i 3D WSS patterns in the right-anterior oblique view for g the control, h dilated aorta, and i aorta with valve stenosis. Also note that for visualization purposes, the WSS color bar for the aorta with valve stenosis is two times higher than for the other two aortas. A, anterior; H, head; R, right.
The IE was $4.1 \pm 2.8\%$, $3.6 \pm 4.2\%$, and $1.4 \pm 0.8\%$. The difference in IE between cohorts was not statistically significant (Kruskal-Wallis test).

Figure 7.7 a-c display a right-anterior oblique and posterior view of the cohort-averaged 3D WSS maps for healthy controls, patients with dilated aortas, and aortic valve stenosis. The SD maps show that WSS values varied substantially between subjects in the AAo of the stenosis cohort, compared with the SD maps of the controls and patients with aortic dilation, which showed smaller intersubject WSS variability.

![Figure 7.7](image)

**Figure 7.7**: Right-anterior oblique and posterior view of the cohort-specific 3D WSS map for a healthy controls, b dilated aortas, and c aortas with valve stenosis. Insets show the SD maps. The average regional WSS direction on the inner curvature of the AAo is shown by white arrows. The black arrow in c indicates elevated WSS at the outer curvature of the AAo. A, anterior; H, head; R, right; P, posterior.

### 7.3.3 Analysis of WSS differences between cohorts

The cumulative results of the intergroup comparison of aortic WSS are summarized in Figure 7.8 and Table 7.2. P-value maps for the intergroup comparisons in Figure 7.8 a show that WSS in patients with aortic dilation was significantly reduced in the distal outer curvature (arrow 1) and proximal inner curvature (arrow 2) of the ascending aorta compared with controls (significantly lower WSS in 7% of all AAo voxels; see Table 7.2). For registration and interpolation to the dilation geometry, the location and extent of regions with significant differences in WSS between cohorts were similar when compared with interpolation on the control geometry (see Figure 7.8 a and Figure 7.8 b).

**Table 7.2**: Percentage of the area where the difference was significant.

<table>
<thead>
<tr>
<th>Region</th>
<th>Dilations versus Controls</th>
<th>Stenosis versus Controls</th>
<th>Stenosis versus Dilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAo (%)</td>
<td>$+/-$</td>
<td>2/7</td>
<td>34/2</td>
</tr>
<tr>
<td>Arch (%)</td>
<td>$+/-$</td>
<td>1/2</td>
<td>18/0</td>
</tr>
<tr>
<td>DAo (%)</td>
<td>$+/-$</td>
<td>0/0</td>
<td>3/0</td>
</tr>
</tbody>
</table>

$+/-$: higher/lower than controls (columns 1 and 2) or dilation (column 3).

In contrast, WSS was significantly elevated in almost the entire outer AAo curvature and a fraction of the inner AAo (34% of AAo voxels; see Table 7.2) for patients with aortic stenosis...
compared with controls (Figure 7.8c, arrow 3). In similar regions, WSS was significantly elevated for patients with aortic stenosis compared with the aortic dilatation subjects (41% and 20% of AAo and arch voxels, respectively Figure 7.8d and Table 7.2).

The registration errors for the affine registration to the aorta geometry of the control cohort were similar in scale to the registration errors for the cohort-specific idealized geometry: 18% ± 1% for controls, 19%±5% for dilations, and 22%±4.7% for the stenosis cohort. The interpolation errors for the interpolation of the dilation cohort to the aorta geometry of the control cohort were similar to the interpolation error to the cohort-specific dilation geometry: 2.7% ± 2.6%, 2.4%±1.6%, and 4.0% ± 4.9% for the AAo, Arch, and DAo, respectively. For the stenosis cohort, the interpolation errors were similar for the AAo and Arch (4.2% ± 2.0%, 3.1% ± 3.0%) but higher for the DAo (8.4% ± 6.8%).

Figure 7.8: P-value maps of regional WSS differences in a patients with aortic dilation versus controls on the control geometry, b patients with aortic dilation versus controls on the dilation geometry, c patients with aortic stenosis versus controls, and d patients with aortic stenosis versus aortic dilation. Significant differences (Wilcoxon rank sum test, P < 0.05) are color-coded in blue and red.
7.4 Discussion

The use of cohort-averaged 3D WSS maps derived from healthy or patient cohorts has the potential to serve as a means of comparing individual patient measurements with reference norms, or to compare measurements at specific anatomic locations between groups of subjects. This methodology is an improvement over previous methods which have used 4D flow-derived WSS at regions limited to manually positioned 2D analysis planes (18-21, 24-27, 35, 36). In contrast to the single slice approach, the strategy presented here creates a comprehensive cohort-averaged 3D WSS map covering the thoracic aorta, which allows for the visualization of regional WSS variations between healthy and disease cohorts. The methods described here can be modified to function with maps of other biomarkers, such as regional diameter, oscillatory shear index, velocity vector magnitude/direction, helicity/vorticity (37), or blood residence times. Furthermore, the comparison of single-subject measurements with the accompanying cohort-averaged maps is possible. The possibility exists to use the method to form a type of ‘aortic atlas’, allowing for the determination of whether (and where) a single subject expresses an abnormal biomarker, as defined by confidence intervals created from a large population control group.

The finding of significantly lower WSS in the dilated AAo group compared with the healthy control group is in good agreement with previously published results (23, 25). In contrast, patients with aortic valve stenosis exhibited significantly elevated WSS in the AAo group compared with healthy controls. Previous studies have speculated that this may occur (38), and this has been shown in cases with bicuspid aortic valve (26), but to our knowledge, this is the first study to demonstrate the extent and regional involvement of elevated WSS in patients with tricuspid stenotic valves. By means of the P-value maps, the location of significantly altered WSS for the disease groups is easily visualized. It is known that WSS estimates can vary substantially between studies due to methodological choices, including variables such as viscosity, spatial resolution, and velocity fitting techniques (39). Therefore, WSS differences between cohorts are emphasized by the use of P-value maps, rather than absolute WSS values. Noticeably, WSS values for 40% of the ascending aorta surface in patients with aortic dilation were significantly different compared with subjects with aortic valve stenosis. This was despite similar sinus of Valsalva (4.1 ± 0.6 cm versus 4.0 ± 0.4 cm; \( P = 0.38 \) (Wilcoxon rank sum test)) and mid-ascending aorta (4.0 ± 0.4 cm versus 4.2 ± 0.3 cm; \( P = 0.17 \) (Wilcoxon rank sum test)) diameters for both cohorts. Furthermore, intercohort differences in WSS direction were readily apparent. The deviation in WSS direction was highest in the AAo for the stenosis cohort compared with healthy controls. These findings illustrate the complex nature of hemodynamic changes that are associated with aortopathy and that simple metrics such as aortic diameter do not directly correlate with the underlying physiologic changes in blood flow or WSS. In this context, the proposed concept of creating cohort-averaged maps has the potential to provide a better understanding of the role hemodynamic forces may play when considering endothelial cell dysfunction, and thus, potential risk for aortic remodeling (40).

The primary motivation for the development of the cohort-averaged maps is to better understand what constitutes normal and abnormal parameter ranges, and to identify whether a single individual exhibits values within or outside these cohort-averaged ranges. For example, past studies have used cohort-averaged values to detect differences in WSS (23, 25, 26, 33); however, these studies have primarily investigated WSS at 2D slice locations or on regionally averaged surfaces. Thus, it is possible to miss regional variations in WSS if the 2D slice was placed elsewhere, or if the regional surface average did not constitute the complete abnormal region.
A methodology to detect abnormal relative WSS on the thoracic aorta using 4D flow MRI

Based on the technique proposed here, abnormal WSS in a single subject (rather than cohort averaged values) may be detected at a singular surface location with coverage over the entire thoracic aorta lumen. Regional outliers (i.e. the abnormal WSS) are detectable by comparing WSS measurements in an individual patient to the mean and standard deviation WSS map for a healthy age/sex-matched WSS group. Abnormal WSS may be found by simply identifying regional deviations from the map by 2 SDs. Future studies with larger cohorts and appropriate control groups (matched for age, sex, aortic size, etc.) are warranted to use this technique to investigate the association of abnormal WSS with risk for aortopathy development (41). Ultimately, with a sufficient number of subjects (and thus sufficient statistical power) cohort-specific WSS atlases could be created. In addition, aortic tissue resected during aortic graft procedures may also be evaluated to investigate the correlation between abnormal WSS behavior (determined by the cohort-averaged WSS map) and molecular expression of biomarkers postulated to be associated with aortic remodeling (42).

It is important to emphasize that many studies investigating WSS, including those from our group, have been based on a limited number of manually placed 2D planes in the thoracic aorta (18–21, 24–27, 35, 36). The WSS algorithm used in this study replaces the need for manual slice placement with a 3D segmentation step based on the systolic portion of the cardiac cycle. We have shown previously that WSS differences exist during the systolic portion of the cardiac cycle, whereas WSS in the diastolic portion is less active (33). This new methodology provides the opportunity to obtain a systolic WSS calculation over the entire thoracic aortic lumen, which reduces manual interaction to a single segmentation step and allows for comparisons of the entire aorta surface between cohorts. As a result, a comprehensive yet compact visualization of complex WSS patterns in multiple cohort-specific subjects is obtained, and WSS differences between patient groups can be easily interpreted, visualized, and quantified. In the future, these features may be beneficial for studies investigating risk stratification in patients with aortopathy and/or aortic valve disease.

A possible limitation of the study is the registration error of 20% found for the registration of the individual aortas to the cohort-specific aorta geometries or to the aorta geometry of the control cohort. This error metric was chosen to illustrate the differences of each individual aorta shape with the cohort-averaged geometry, and is designed to include every single voxel of the aortas. Even for very similar aortas, this error metric can generate large values. An important contribution to the error is the start and end point of each individual aorta. Not all aortas show the same signal enhancement in the left ventricle or the distal descending aorta. Therefore, the start and end point of the aorta segmentations is moderately variable. Furthermore, the location and length of the supra-aortic arteries and celiac trunk are different for each subject, contributing to the error. The main contributors to the error, however, are small differences in the aortic cross-section that cause substantial differences. This can be illustrated by eroding a specific 3D aorta segmentation by 1 voxel, which leads to a registration error of 40% with the same aorta. Therefore, it is quite remarkable that registration of different aortas with different diameters, supra-aortic arteries, and the celiac trunk lead to a registration error of only 20%. Note also that the percentage of the difference is determined by the average number of voxels between the individual aorta and the cohort-specific geometry (Equation 7.4 and Equation 7.5). An alternate error metric, the percentage defined by the total number of voxels (individual aorta+cohort-specific geometry), would result in a reduced error of 11% ± 2%, 11% ± 3%, and 13% ± 5% for the control, dilation, and stenosis cohort, respectively.

Interpolation of the 3D WSS vectors from the individual aorta shape to the cohort-specific
aorta geometry can introduce errors. However, it was found that the error was much smaller than the errors reported for registration: up to 5% for interpolation compared with 25% for registration. Therefore, the interpolation step is robust.

The aorta geometry used to create P-value maps can introduce errors in the comparison between cohorts. In this study, minor differences were found by comparing 3D WSS of the control and dilation cohorts on the control geometry and the dilation geometry. Therefore, the statistical results are largely independent of the reference geometry.

Another limitation of the study is the lack of a comparison of 3D WSS with previously used WSS algorithms calculated in 2D slices, manually placed perpendicular to the aorta. Such a comparison was outside the scope of this study, as the goal of the study was to describe the methodology and show the use of creating cohort-averaged 3D WSS maps. Previous studies have shown that both planar and volumetric WSS analysis can be sensitive to differences in resolution and vessel lumen definition. A systematic evaluation of both planar and volumetric WSS analysis is thus warranted to better understand the performance of both techniques. Comparison of the 3D WSS algorithm with previously developed WSS algorithms (based on 2D slice placement) is part of ongoing work.

It is possible that WSS calculations are influenced by displacement artifacts in the 4D flow MRI data related to rapid accelerations of blood flow, mainly present in the stenosis cohort. This implicates that the absolute WSS values calculated may be subject to error. By reporting relative WSS differences between different cohorts, errors in absolute WSS were minimized. Furthermore, it was demonstrated that the algorithm used for 3D WSS calculation based on spline fitting is robust in the presence of complex flow.

WSS underestimation as a function of resolution has been carefully studied and quantified. In aorta phantoms with perfect parabolic flow and a spatial resolution as used in this study, an underestimation in WSS of 5% of the theoretical value was found. Segmentation errors, however, could result in errors up to 30% of the theoretical WSS values. Therefore, future work will elaborate on interobserver variability of WSS due to segmentation of aortic lumen. Nonetheless, computational fluid dynamics have demonstrated good agreement with 4D flow data, when discretization effects are considered. Given that there is no gold standard for 3D WSS measurement, we have chosen to emphasize the relative differences between cohorts as examined by the same imaging protocol.

We chose not to examine 3D WSS in different size aortas or differing grades of stenosis given the relatively low number of subjects in these pilot cohorts. However, when we assume a difference of 0.22 Pa and an SD of 0.16 Pa on the distal outer curvature (the region assumedly mostly prone to remodeling) between the controls and dilations cohorts, only seven more subjects are needed to obtain a power of 0.8.

The majority of the subjects were included via retrospective chart review rather than using prospective randomized enrollment; however, the primary goal was not to perform a longitudinal study, but rather to present a methodology to create cohort-averaged WSS surface maps over the entire thoracic aorta, and demonstrate the feasibility in a small pilot study to detect differences in normal physiologic and disease biomarkers. The addition of subjects and cohorts is part of ongoing work.
7.5 Conclusion

In conclusion, the methodology and application of aortic geometry and WSS maps in a range of subject cohorts was demonstrated. In this pilot study, the technique facilitated the identification of regionally altered WSS in the presence of aortopathy and aortic valve disease compared with healthy controls. This technique may prove useful for the creation of large cohort atlases representing hemodynamic biomarkers. The insights provided by this technique, combined with large scale randomized trials, may help clarify the role of WSS in vessel wall remodeling.

Bibliography


Chapter 8

Multi-scale 3D+t intracranial aneurysmal flow vortex detection

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8.1 Introduction

Estimations of cerebral aneurysm prevalence range between 0.4% and 6% (1). Cerebral aneurysms have a low acute rupture risk, however, rupture results in aneurysmal subarachnoid hemorrhage and is associated with high mortality and morbidity (2). Treatment is based on excluding the aneurysm from circulation, thereby relieving the aneurysm from hemodynamic stress. Currently, endovascular coil embolization is the first therapeutic option. Although widely practiced, significant peri- and postoperative complications can occur due to these treatments (3, 4). These complications have to be carefully balanced against the risk of rupture to determine the choice of treatment.

In current clinical practice, only size and location are considered in the decision to treat. Additional risk factors are needed for more accurate estimations of aneurysmal rupture risk. Intra-aneurysmal hemodynamic risk factors for aneurysmal growth and rupture have been addressed in many studies. Both low and high wall shear stress (WSS) have been associated with aneurysmal growth and rupture (4, 5). Furthermore, unstable flow patterns were associated with aneurysm progression and rupture because of the potential for elevated oscillatory shear index (OSI) or larger regions of elevated mean WSS. In various studies, computational fluid dynamics (CFD) simulations have been performed on vascular models to associate rupture status with flow complexity, flow stability, and inflow jet size (6). Alternatively, intra-aneurysmal velocity can be measured using time-resolved 3D phase contrast MRI (PC MRI) (7). In a recent study, it was shown that ruptured aneurysms had complicated flow patterns in the aneurysm domes, whereas all of the unruptured cases showed a simple vortex (8).

Vortex characteristics such as vortex complexity, vortex stability and flow pattern category are assessed by visual inspection (9). In clinical research studies, intra-aneurysmal flow is commonly categorized according to the definitions previously introduced (9) using animations of intravascular flow velocities: i constant direction of inflow jet with a single associated vortex, ii constant direction of inflow with multiple and constant number of associated vortices, iii changing direction of inflow jet with a single vortex, and iv changing direction of inflow jet with the creation and destruction of multiple vortices. Illustrations of these flow categories can be found in (9) and are proposed here in Figure 8.1.

Type i flow is associated with unruptured status, whereas type iii and type iv flow is more common in ruptured aneurysms. This classification is well accepted among the community and has been used in multiple clinical studies (9–14). Because of the qualitative and manual assessment, these measurements are prone to interobserver variation. In a recent study of this research group, interobserver agreement was poor with intraclass correlation coefficients ranging from 0.47 to 0.70. Quantitative analysis of vortex characteristics has the potential to reduce interobserver variability and to improve the value of these parameters in risk assessment because of its continuous characteristic as opposed to the classification in a limited number of categories.

8.2 Methods

Hemodynamics, which can be assessed by CFD and PC MRI, are generally presented as time-resolved 3D velocity fields ($\vec{v}(\vec{x}, t)$). Below, we describe approaches to obtain quantitative information from these velocity fields.
8.2.1 Kernel deconvolution

The most commonly applied approaches for vortex detection are the $Q$- and $\lambda_2$-criteria (15). These approaches are based on local pressure characteristics. However, in our experience these criteria do not reflect the impression of radiologists of intra-aneurysmal vorticity because the radiologists interpret more global features. Bauer et al. described various methods for flow field feature visualization (16) and to trace the flow field in time. They used combinations of feature detection techniques, such as vortex core lines detection, with methods acting on the Jacobian of the flow field. Schafhitzel et al. presented an overview on analysis of shear stress layers in flow fields and described a visualization method for simultaneous tracking of vortices and shear layers as well as their interaction (17). More recent studies focus on vortex core lines and vorticity magnitude detection and their variation in time (18, 19). However, in clinical studies, analyses of aneurysmal vortex structures are still based on qualitative visual interpretation and a quantitative measure is still missing.

Furthermore, we noted that the $Q$- and $\lambda_2$-criteria are sensitive to high velocity gradients without an actual circular movement in, for example, aneurysmal neck areas. As such, we searched for more global descriptive methods that are able to capture the clinician’s impression of intra-aneurysmal vorticity. Previously, we have presented a 2D singular velocity pattern detection technique to analyze 2D velocity fields (20) based on the works of Liu and Ribeiro (21). This approach included vortex identification as one of the singular flow patterns. Here, this technique is extended to time-resolved 3D velocity fields. For this new approach, the local velocity field $\vec{v}(\vec{x}, t)$ in a small neighborhood $\Delta \vec{x}$ is represented by a combination of base functions $\phi_k(\Delta \vec{x})$

$$\vec{v}(\vec{x}, t) = \sum_k A_k(\vec{x}, t) \phi_k(\Delta \vec{x}) \quad (8.1)$$

where the projection coefficients $A_k$ are given by the cross-correlation of the global velocity field
Figure 8.2: Local velocity field base functions describing local laminar velocity (top row) and vortical velocity (bottom row). The length and color of the arrows depict the velocity strength. The center of the base functions is at (0.5 mm, 0.5 mm, 0.5 mm).

and the base functions

\[ A_k(\vec{x}, t) = \int \vec{v}(\vec{x} + \vec{\xi}, t) \cdot \vec{\phi}_k(\vec{\xi}) d\vec{\xi} \]  

(8.2)

Because we focus on vortex quantification in this study, only 6 base functions are used; 3 for describing the laminar flow \( \phi_k(\Delta \vec{x}) = \hat{e}_k \) for \( k = 1, 2, 3 \) with \( \hat{e}_k \) the Cartesian basis vectors where their dimension is m/s. This part of the velocity field is called laminar flow since it describes the local ‘non-singular’ velocity. The vortex base functions are a single class of the ‘singular’ velocity patterns. This term is called singular because of its diminishing contribution at \( \xi = 0 \). We refer to Liu and Ribeiro (21) for illustrations of different singular flow patterns. The three vortex projection coefficients are determined using the following equation

\[ A_v^i(\vec{x}, t) = \int \vec{v}(\vec{x} + \vec{\xi}, t) \cdot (\hat{e}_i \times \vec{\xi}) d\vec{\xi} \]  

(8.3)

where we have used the superscript \( v \) to indicate that these contributions are the vortex projections. The used base functions are illustrated in Figure 8.2.

### 8.2.2 Multi-scale space representation

To introduce a finite support size of the base functions and to be able to distinguish various scales of the vorticity, the analyses are performed in a multi-scale space approach. Multi-scale techniques operate on a source signal by a convolution with a Gaussian function (16). With increasing scale, smaller-scale details in the signal are removed. To assess the scale dependent flow patterns, we employ the 3D Gaussian function:

\[ G(\vec{x}, \sigma) = \frac{1}{(\sigma \sqrt{2\pi})^3} \cdot e^{-\frac{|\vec{x}|^2}{2\sigma^2}} \]  

(8.4)

where \( \sigma \) is the scale. The scale-space dependent velocity field \( \tilde{f}(\vec{x}, \sigma, t) \) can be obtained by the convolution of the Gaussian function with the velocity field \( \tilde{f}(\vec{x}, \sigma, t) = \tilde{v}(\vec{x}, t) \ast G(\vec{x}, \sigma) \). Using the multi-scale approach, we can write the kernel equations as a decomposition of scale-dependent base functions \( \tilde{\phi}_k(\Delta \vec{x}, \sigma) \), which are defined as the convolution of the initial base functions with
the Gaussian function $\tilde{\phi}_k(\Delta \vec{x}) * G(\Delta \vec{x}, \sigma)$:

$$\tilde{f}(\vec{x}, \sigma, t) = \sum_k A_k(\vec{x}, t, \sigma) \tilde{\phi}_k(\Delta \vec{x}, \sigma)$$  (8.5)

Again, the scale-dependent projection coefficients are determined by the convolution of the velocity field with the scale dependent base functions:

$$A_k(\vec{x}, t, \sigma) = \int \tilde{v}(\vec{x} + \vec{\xi}, t) \cdot \tilde{\phi}_k(\vec{\xi}, \sigma) d\vec{\xi}$$  (8.6)

Following the method by Marquering et al., we scale the singular projection coefficients by the magnitude of the laminar contributions to correct for the large range of flow magnitudes that can be present within intracranial aneurysms, and to avoid obscuring singular flow patterns at location with low velocities (20). $A^v_k(\vec{x}, t, \sigma)$ represents the vortex magnitude in the $x$-, $y$-, and $z$-direction for $k$ 1, 2 or 3 respectively. As such, the axis of the vorticity is given by the vector $(A^v_1, A^v_2, A^v_3)$ and the vortex magnitude $|A|$ by $\sqrt{A^v_1^2 + A^v_2^2 + A^v_3^2}$.

Note that the scale $\sigma$ and the neighborhood $\Delta \vec{x}$ are related: The larger the scale, the larger the neighborhood with non-zero contributions of the velocity field. In computational practice, the neighborhood is defined as $3 \times \sigma$ in all directions.

### 8.2.3 Vortex-shear discrimination

The kernel deconvolution method described above is suitable for vortex (center) detection. However, it is unable to discriminate vortex fields from shear fields. For this reason, it is necessary to differentiate vortex dominated flow fields from shear dominated flow fields. The widely used $Q$-criterion based on the decomposition of the Jacobian $\tilde{J}(\vec{x}, t)$ is commonly used for this task (15), where the Jacobian is defined as:

$$\tilde{J}(\vec{x}, t) \equiv \nabla \tilde{v}(\vec{x}, t) = \tilde{S}(\vec{x}, t) + \tilde{\Omega}(\vec{x}, t)$$  (8.7)

with

$$S_{ij} = \frac{1}{2} \left( \frac{\delta v_i}{\delta x_j} + \frac{\delta v_j}{\delta x_i} \right)$$  (8.8)

and

$$\Omega_{ij} = \frac{1}{2} \left( \frac{\delta v_i}{\delta x_j} - \frac{\delta v_j}{\delta x_i} \right)$$  (8.9)

where $S$ denotes the rate of strain and $\Omega$ represents the rotational part of the velocity field. In Equation 8.8 and Equation 8.9, we omitted the dependencies $\vec{x}$ and $t$ for brevity. To take scale into consideration, Equation 8.7 is modified as follows:

$$\tilde{J}(\vec{x}, \sigma, t) = \nabla (\tilde{v}(\vec{x}, t) * G(\vec{x}, \sigma)) = \tilde{v}(\vec{x}, t) * \nabla G(\vec{x}, t)$$  (8.10)

This way, we take advantage of scale space properties and perform the convolution with the derivative of the Gaussian function instead of deriving the velocity field. Vortex dominated areas are detected as regions where $||\Omega(\vec{x}, \sigma, t)|| > ||S(\vec{x}, \sigma, t)||$, which is known as the $Q$-criterion (15). Because the result of the $Q$-criterion is binary rather than a continuous measure, Schafhitzel et al. suggested to use the second invariant of $S$ as a continuous measure for high shear stress region
identification (17):

\[ S_m(x, \sigma, t) = \frac{1}{2} \sum_{i=1}^{3} \sum_{j=1}^{3} (S_{ii}S_{jj} - S_{ij}S_{ij}) \]  

(8.11)

where we have omitted the spatial, scale, and time dependencies on the right side of Equation 8.11 for brevity. A region is classified as shear dominated if \( S_m < 0 \) and the shear stress magnitude is inversely related with \( S_m \). As such we can use the \( S_m \)-criterion as a complementary measure for identifying high-stress areas next to identifying the vortices.

### 8.2.4 Kernel deconvolution with \( Q \)-criterion masking

To come to a vortex identification and quantification method that excludes shear fields, we here combine the \( Q \)-criterion and the kernel deconvolution analysis. We propose to use the \( Q \)-criterion to create a mask applied to kernel deconvolution results such that we remove shear dominated areas. To depict centers of vortices, local spatial maxima of the vortex magnitude for a given time and scale are detected using a 26-connected neighborhood. The time resolved multi-scale kernel deconvolution with \( Q \)-criterion masking is called ‘kernel deconvolution with \( Q \)-masking’ in the remainder of this paper. The purpose of this method is to visualize, quantify, and discriminate 3D velocity features both in time and in scale to support clinicians in their treatment decisions. The method is evaluated in the comparison of CFD and time-resolved 3D PC MRI data of an aneurysm phantom and patient-specific aneurysmal CFD flow data of 3 patients described below.

![Figure 8.3: Surface rendering of the 3 patient aneurysms used in this study.](image)

### 8.2.5 Phantom data

The aneurysm phantom was based on an intracranial aneurysm located in the anterior communicating artery. The maximal dimensions of the dome were approximately 6, 4 and 9 mm in the \( x \), \( y \), and \( z \) direction respectively. The phantom was connected to a flow loop setup. Details on this phantom can be found in (22).

Time-resolved 3D PC MRI data of the phantom was obtained using three-directional velocity encoding on an 3 T MR scanner (Intera, Philips Medical Systems, Best, the Netherlands). Additional scanner specific settings were previously reported in (22). The measurement was performed within 3 hours. Spatial resolution was 0.2 x 0.33 x 0.2 mm³.

CFD simulations (Fluent 6.3, ANSYS, Canonsburg, USA) were performed on a vascular model based on a 3D Rotational Angiogram of the phantom with an isotropic resolution of 0.16 mm. This image was segmented with a level set algorithm (23). A mesh was created consisting of 742,316 tetrahedral cells with an average node spacing of 0.24 mm. The 3D velocity profile of the inflow as
measured in the PC MRI measurements was applied as boundary condition in the CFD. The MRI and CFD data sets were registered using a rigid transformation and interpolated on a 3D isotropic 0.2 mm grid.

8.2.6 Patient data

The patient-specific vessel models for CFD-based flow data in the three patients were generated using 3D rotational angiography imaging (see Figure 8.3). The vascular tree was segmented using a level set algorithm (VMTK). The segmentations were converted into a tetrahedral elements mesh with an average node spacing of 0.07 mm. CFD boundary velocities were based on time-resolved three-directional single-slice PC MRI acquisitions in the afferent artery. CFD simulations were performed using the PC MRI velocity measurements as boundary condition (7). Three cardiac cycles were calculated of which the last cycle was used for analysis. Because of the limited temporal resolution of the MR measurements, only 36 time frames per cardiac cycle were determined resulting in 36 timeframes for the CFD with an average time step of 0.028 s. CFD iterations were continued until the continuity residual was below 0.001.

Figure 8.4: Employed analysis pipeline for flow feature analysis. The 3D-t velocity data consisted of either phantom CFD or MR data or patient CFD velocity data. Vortex centers were detected for two scales and rendered in 3D. At these locations 2D orthogonal slices with velocity profiles were generated inspect the vortex behavior. By monitoring this behavior for all time steps, the stability of the vorticity was assessed. A similar approach was followed to assess the shear stress analysis using the $S_{m}$-criterion.

8.2.7 Experiments overview

The phantom and patient velocity data sets were processed to detect dynamic and scale-dependent vortices and shear stresses using the kernel deconvolution with $Q$-masking and the $S_{m}$-criterion respectively. The analysis was conducted for two scales: a small scale with $\sigma = 0.28$ mm, which is similar to the resolution of our datasets, and a large scale with $\sigma = 1.00$ mm, which reflects the dimension of the intracranial arteries. A schematic overview of the analysis pipeline is presented in Figure 8.4. Using the kernel deconvolution with $Q$-masking, vortex centers were detected for a given scale and time step. Simultaneously, shear stress regions were detected. These regions were rendered in 3D. At local maxima of the masked kernel deconvolution, three orthogonal 2D slices
were generated to visualize the flow in detail at these positions. Vortex and shear stress evolution during the heart cycle was subsequently tracked to study the vortex stability.

8.3 Results

8.3.1 Kernel Deconvolution with $Q$-masking: Phantom Data

Figure 8.6 shows the results of the PC MRI and CFD velocity field analysis in the aneurysm phantom measured for a single time step and scale of $\sigma = 0.28 \text{ mm}$. The direction of the arrows in the 3D rendering figures denotes the vortex axis of rotation, the length and color represent the vortex magnitude. This 3D view allows a quick overview of flow characteristics. In one of the vortex cores, 2D slices are generated to inspect detection results and explore the region of interest in more detail. The blue small arrows in the 2D planes depict the flow velocity within that plane. Figure 8.6 shows that the flow indeed rotates around the detected vortex center. As can be seen in this figure, two main vortex areas are located in the central part of the aneurysm for both imaging modalities. Comparison of the analysis of the CFD and MRI generated velocity fields indicates that there is only a small difference in direction and magnitude, suggesting that MRI- and CFD-based velocity assessment are quite similar.

8.3.2 Kernel Deconvolution with $Q$-masking: Patient data

For the patient data, we here also present the multi-scale analysis. Figure 8.5 indicates that the flow behavior is rather different at different scales. Figure 8.5 shows that the vortex rotation axis flips from the $z$- to $x-y$- direction at increasing scale. In the cutting planes of the $\sigma = 0.28 \text{ mm}$ image, two local vortex areas are visible. A blank area separates the two vortex areas, which is the result of the masking with the $Q$-criterion. For a larger scale of $\sigma = 1 \text{ mm}$, only one large vortex region remains.

This means that the global velocity pattern inside the aneurysm is dominated by one large vortical motion having its rotation axis in the $x-y$ direction while locally small vortices with different rotation axes are present. In this case, both at small and large scale, vortices are found in the same position whereas Figure 8.7 illustrates that locally detected vortices for patient 2 and 3 also vary...
Figure 8.6: Aneurysm phantom flow pattern analysis of PC MRI data (top) and CFD data (bottom) in the aneurysm phantom. In the left figures the phantom surface is rendered. The arrows represent the vortex axes. The strength of the vortex is depicted by the length and color of the arrow. In the right figures the 2D visualizations of the velocity (arrows) and vorticity quantification (colored surfaces) are shown. The dark red colors of the surface visualization depict the center and magnitude of the vortex.

in position and rotation axis at the two different scales; it shows that a general (large or small local scale) description of vortex patterns is not enough to fully grasp flow behavior inside an aneurysm because details at different scales may be missed.

The dynamic behavior of the vorticity during the heart cycle is illustrated in Figure 8.8. During the heart cycle, flow changes considerably, which is also illustrated by the change of vortex center position, direction, magnitude and number of vortex centers. The identification of the vortices at different times allows the tracking of these variations and inspection of their evolution. For example, in patient 3 at the beginning of the cardiac cycle ($t = 2$ in Figure 8.7) small vortices are present rotating around $x - y$ axis whereas at time $t = 12$ and $t = 24$ we find completely different patterns with axis of rotation perpendicular to the initial axis of rotation. Please note the difference in magnitude of the vorticity between patients. This may be explained by differences in flow patterns, or flow magnitudes in the afferent arteries.

8.3.3 Time-resolved $S_m$-criterion

The evolution of shear stress using the $S_m$-criterion is illustrated in Figure 8.9. The arrow color plotted according to $|S_m|$ represents shear stress strength; the arrow direction and length reflect the local velocity vector field. This kind of visualization is employed to inspect unstable shear stress regions, which are often associated with aneurysm growth in literature (24). In patient 2, the local maximum shows a constant behavior over the heart cycle. In the two other cases, shear stress profiles are dynamically unstable. For example, in patient 1, strong shear components are found at $t = 2$ in the direction of the vessel inflow, which migrate towards more distal locations. In patient
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Figure 8.7: Kernel deconvolution with Q-masking results for patient 2 and 3 for $\sigma = 0.28$ mm (left) and $\sigma = 1.00$ mm (right).

3 at time step 12, a strong shear component arises pointing towards the lobulation inside the dome and is present until the end of the heart cycle.

8.4 Discussion

We have presented a method for visualization and analysis of time-resolved 3D flow features in intracranial aneurysms. Kernel deconvolution with Q-masking applied at small scales provides an initial impression of the most interesting flow features, whilst vortex center detection at large scales, gives an impression of the global intra-aneurysmal behavior. With this method it is possible to identify regions with high vorticity and shear stress areas on different scales and to follow their evolution during the heart cycle. The method, successfully tested on artificial phantoms and on patient data, proved to be reliable and effective to visualize specific flow characteristics. CFD simulated velocity and PC MRI measured velocity data in the aneurysm phantom agreed well in location and orientation of the vertices. We have shown that these flow patterns evolve over time and are different for different scales, which emphasizes the importance of analysis of intra-aneurysmal scale for the whole heart cycle. Stability of vortex patterns in time, which is another important parameter in risk of rupture assessment, can be scored with the proposed pipeline. Moreover, changes in magnitude and location of shear stress are also detected and may have important relations with aneurysm growth. This algorithm has the potential to quantify vorticity behavior and help understanding aneurysm flow behavior. In current literature (6) (9), pipelines for qualitative aneurysm risk assessment are presented. However, the inner structure of flow at
Figure 8.8: Kernel deconvolution with Q-masking analysis results at different time steps applied to patient 1 (top), 2 (middle) and 3 (bottom) at a scale of 0.28 mm.

different scale is rarely taken into consideration. Furthermore, quantitative methods able to score local vortex stability and shear stress magnitude can be implemented in the algorithm and used in large-scale studies to improve intracranial aneurysmal risk assessment.

In clinical studies, vortex behavior has been associated with rupture status. In near-future studies, the quantified measures as presented here, need to be associated with these qualitative measures such as they are now included in studies that associate intracranial hemodynamics with aneurysm rupture risk. A quantitative approach as presented here may reduce the interobserver variability and potentially increase the predictive value of vortex instability. Since the generation and interpretation of the quantified results still requires quite some effort, future perspectives are to automatize the detection allowing quantification of parameters in large populations. We believe that this is helpful in future clinical treatment decision. However, the agreement of the presented quantitative measurements with qualitative assessments needs to be studied in more detail in future longitudinal studies with larger patient populations.

Vortex detection may appear relatively easy using animations of streamlines or similar visualization. However, the low interobserver agreement associated with vortex classification suggests otherwise. Moreover, especially for smaller scales, the presented algorithm suggested vortex cores that were not observed by the initial visual analysis of the streamlines. Only careful inspection of
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Figure 8.9: $S_m$ Criterion applied for different time steps (from left to right) and for different patients (top to bottom) at $\sigma = 0.28$ mm

The flow vectors in the 2D planes in the detected vortex centers showed that indeed small-scale vortices were present in the image data. Therefore, we believe that the suggested approach in which local maxima of vortex magnitude are detected and subsequent 2D planar visualization of the velocity vectors results in a more detailed and correct description of intra-aneurysmal flow.

The vortex quantification allows for a quantitative comparison of flow fields originating from different modalities. In van Ooij et al. the singular energy of flow characteristics obtained with MR and CFD were compared indicating good agreement in systole, and differences in diastole flow patterns due to low signal to noise ratios (7).

Aneurysm initiation and rupture is the result of vascular wall failure rather than resulting from hemodynamic behavior solely. When the cerebral artery wall has become too weak to resist hemodynamic pressure it distends. Subsequent wall degeneration may lead to impaired endothelial function. Intra-aneurysmal flow conditions may subsequently decellularize and degenerate the arterial wall making it prone to rupture (25).

We should notice that this study suffers from a number of limitations. First, the CFD computations depend on a number of assumptions that may not hold: Newtonian fluid, rigid vessel walls. Furthermore no mesh refinement studies have been performed prior to analyzing the CFD results.
We have presented a multi-scale analysis, but detailed information on the relevance of different vortex scales for aneurysm growth and risk of rupture remains unanswered. Based on current literature, we believe that both small-scale vortices (9, 26–28) and larger-scale vortices (14, 29) have a degenerative biological effect. Here, only two vortex scales were presented. Still, this confirms that there is indeed a scale-dependence of vorticity in the flow patterns. In a subsequent study, the scale selection for maximum agreement with clinical interpretation and rupture status will be addressed. However, this was beyond the scope of the current study. The multi-scale approach may result in a data increase rather than a simplification of the interpretation of the flow data. In future practice, large-scale vortices may be presented initially, after which smaller-scale structures may be studied consequently by decreasing scale with a graphical user interface. However, this approach has not been tested in this study. Our method has been applied for the quantification of intracranial aneurysmal flow. However, it is not limited to this application area. It may potentially quantify flow features in other applications such as intra-ventricular flow (30), flow in jugular veins (31), and aortic root flow patterns (32). However, this was beyond the scope of the current study.

8.5 Conclusion

We have presented a full-fledged scale dependent and dynamic vortex identification and quantification method. This method has been applied to a phantom model and patient-specific flow fields illustrating temporal and scale-dependency of the vortical flow patterns. The quantification of vortices has the potential to be implemented in large-scale clinical studies to associate rupture status with vortex stability, creation, and termination. The scale-dependence of this approach may allow the detection of smaller scale vortices that may be obscured in conventional visualization schemes.

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Chapter 9

Aortic wall shear stress calculations using variable venc 4D flow MRI

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9.1 Introduction

Wall shear stress (WSS) is the tangential force exerted by the flowing blood on the vessel wall. WSS has been correlated with endothelial function and wall thickness (1). Quantification of WSS from 4D flow MRI is possible in the aorta (2-4), but is challenging in the diastolic phase of the heart cycle due to the presence of a relatively low velocity to noise ratio in diastole. In a recent paper, it was shown in software simulations that the presence of noise deteriorates the precision of WSS estimation, especially at lower shear rates (5). The availability of WSS data both in systole and diastole is important for the determination of the oscillatory shear index (6), and the transverse WSS (7).

The velocity noise in 4D flow MRI scales linearly with the phase of the signal and is thus inversely proportional to the encoding velocity (venc). One could thus in theory decrease the velocity noise by lowering the venc. However, this will induce multiple phase wraps in systole. Multi-venc techniques account for this by measuring multiple datasets with a different venc. Although the techniques appear to be more accurate, they do increase scan time (8-11). Recently, Nilsson et al. presented a method to vary the venc throughout the heart cycle in 4D flow MRI scans (vPC) (12) and showed that a dynamic variation of venc over the heart cycle significantly reduces noise levels in local velocity during diastole without phase wraps in systole.

Here we hypothesize that the use of variable venc 4D flow MRI will also benefit the quality of WSS data in diastole. If the velocities used for WSS determination become less noisy, the gradient close to the wall can be determined more reliably. Therefore, our aim was to investigate whether the use of a variable venc will translate in reduced noise levels in diastolic wall shear stress (WSS) quantification.

9.2 Materials and methods

9.2.1 Subjects and MRI

The aortas of 7 volunteers (age 27.5 ± 2.2 year, 5 males) were scanned using both a 4D flow MRI sequence with both a static encoding velocity (4D PC) and a variable encoding velocity (4D vPC). Approval for this research was granted by the institutional Ethics Committee. All participants provided written informed consent. Data were acquired on a 3 T MRI scanner (Ingenia, Philips Healthcare, Best, the Netherlands, software version 4.1.3) using two 16-channel phased-array coils, positioned at the anterior and posterior side of the volunteer. Scan parameters were similar to those used in (12): TE/TR/FA: 3.5 ms/8 ms/8°, non-interpolated spatial resolution 1.5 – 1.7 x 1.5 – 1.7 x 2.0 mm, temporal resolution 64 ms. The static venc for the 4D PC acquisition was determined for each volunteer, and ranged between 150 – 200 cm/s (median 160 cm/s). The dynamic venc for the 4D vPC acquisition varied between 50 cm/s in diastole and 184 cm/s in systole. The scheme for venc variation in the 4D vPC was determined for each volunteer, as described in (12). In short, three 2D PC MRI (3 times 57 seconds) of the aorta were made with using a venc of 200 cm/s in three orthogonal directions, to determine the cardiac-resolved peak velocities. These peak velocities were then automatically converted to the required venc values in the 4D vPC sequence. Prospective cardiac triggering was performed based on the ECG. No correction for the respiratory motion was made. In order to maintain equal TE, TR and resolution...
between the two acquisitions, the bandwidth for 4D vPC (345 Hz/pixel) was higher than the 4D PC bandwidth (248 Hz/pixel), theoretically decreasing the SNR in the 4D vPC acquisitions by 15%. Phase difference images were automatically corrected for static phase offset errors on the MR scanner console and manually corrected for phase wraps if needed. For the analysis, systole was defined as the three consecutive time points with maximum flow and diastole was defined as the three consecutive end-diastolic time points.

Figure 9.1: a velocity in the feet-head direction in the diastolic phase contrast images of the 4D PC scan (left) and the 4D vPC scan (right). b Location of the back muscle region used for noise quantification (red area. c Noise quantification results. The dots on the left represent the individual volunteer measurements; the bars represent the average noise level ± standard deviation (SD).

9.2.2 Flow quantification

We quantified time-resolved flow rates using GTFlow 2.1.4 (Gyrotools, Zurich, Switzerland) in the ascending and descending aorta and performed a Bland-Altman analysis to compare the absolute flow rates, for a full cardiac cycle, between 4D PC and 4D vPC datasets.

9.2.3 Velocity noise quantification

Noise levels in the velocity images were determined using the method described in [12]. In short, we selected a region in static muscle tissue close to the aorta (see Figure 9.1 b) and calculated
9.2.4 Wall shear stress calculation

WSS was calculated as previously (13, 14). In short: at each location on the vessel wall, we fitted a smoothing spline to three velocity vectors, equally spaced along a 1 cm inward normal. The velocity at the vessel wall was forced to zero. We manually segmented the aortic lumen in both the PC and vPC scans using the average systolic image (using three peak-systolic time points) using ITK-SNAP (19). Side branches, proximal ascending aorta and the distal descending aorta were excluded from the segmentation. To compare WSS in 4D PC and 4D vPC data, we quantified mean aortic WSS in the ascending aortic arch, descending aortic arch and descending aorta separately. The average WSS results from 4D PC and 4D vPC for the entire aorta were compared using Bland-Altman analysis. P values of < 0.05 were considered statistically significant. To quantify the difference in WSS noise levels in the 4D PC and 4D vPC data for systole and diastole, the WSS variation was analyzed using 2D WSS maps of cut-open aorta segmentations. The Vascular Modeling Toolkit (VMTK version 1.2, www.vmtk.org) was used to cut open the vessels in a standardized fashion, after which 2D WSS magnitude maps were created in both systole and diastole (Figure 9.2). The distance along the centerline and the circumferential angle was used to project the original aorta WSS on a 2D WSS map.

![Figure 9.2: a circumferential angle, b distance along the centerline from aortic root, c 3D WSS magnitude map and corresponding and d calculated 2D WSS magnitude map (horizontal: angle; vertical: distance along centerline).](image)

The WSS map has no static region that would allow calculation of the noise levels based on standard deviation. We, therefore, decided to use the local spatial variation as an approximation for the noise levels in these 2D WSS maps. We know from fluid dynamics that for the main portion of the (healthy) aorta, true WSS maps would be smooth without sudden changes. The local spatial variation [Pa/cm] was obtained from the WSS map by means of convolution with a forward-difference kernel. The kernel consisted of a Sobel operator multiplied with a Gaussian filter (σ = 1.5 mm, similar to the spatial resolution). The histogram of this WSS variation map is considered here as a surrogate of the true noise in the WSS map. The distribution of WSS variation of 4D PC data was compared to 4D vPC using Levene’s test, both in systole and diastole.
In systole, both PC and vPC were measured with an almost equal venc and their mean WSS is therefore expected to be similar. Thus, the two measurements can be used to assess WSS reproducibility in systole as a quality indicator of the current datasets. For this purpose, we calculated the repeatability index (RI) for the systolic, mean WSS. The RI is defined as 1.96 times the standard deviation of the paired differences between WSS of successive 4D vPC and 4D PC scans, divided by the mean WSS, and expressed as a percentage:

\[
RI = \frac{1.96 \cdot SD_{diff}}{mean} \tag{9.1}
\]

9.3 Results

9.3.1 Flow quantification

The flow rates for the 4D PC images were on average 6% ± 10% lower than for the 4D vPC data. This difference was not significant (paired two-tailed student t-test). A Bland-Altman analysis of the flow quantification (Figure 9.3) also showed a bias in flow rates between 4D PC and 4D vPC of −5.6 mL/s with a wide 95% confidence interval from −26 mL/s to 15 mL/s.

Figure 9.3: Bland-Altman of absolute flow in ascending and descending aorta with a bias of −5.6 mL/s (limits of agreement: −26 to 15 mL/s).

9.3.2 Velocity noise quantification

Both visual inspection and velocity noise quantification (Figure 9.1) showed a lower velocity noise for the 4D vPC sequence both in systole (P = 0.03) and diastole (P < 0.01). The difference in velocity noise in systole was −0.26±0.24 cm/s and the difference for diastole was −0.46±0.23 cm/s.

9.3.3 Wall shear stress

The average WSS over the entire aorta for 4D PC was 1.33±0.35 Pa in systole and 0.20±0.09 Pa in diastole and for 4D vPC 1.29±0.30 Pa in systole and 0.20±0.10 Pa in diastole. No significant differences in WSS mean or standard deviation were observed between 4D PC and 4D vPC results, neither globally nor for separate aorta parts (Figure 9.4). There were also no significant differences for the WSS minimum, median and maximum (data not shown). Visually, however, a smoother
appearance of the WSS patterns on the vessel wall is observed for 4D vPC, which can be especially appreciated by looking at the directionality of WSS in diastole (Figure 9.5).

The histogram of the WSS variation maps (Figure 9.6) shows the distribution of WSS variation over the entire aorta. It shows that 4D vPC based WSS has lower WSS variation compared to 4D PC based WSS. The same phenomenon was observed in all individual volunteers (data not shown). Levene's test indicated a significant difference between the SDs of the WSS variation (P < 0.01) in each volunteer and for all the volunteers combined. Although the differences are subtle, the WSS variation maps do show a decrease in WSS variation in the 4D vPC WSS maps compared to the 4D PC WSS maps.

RI for the systolic WSS was 6.8% for the entire aorta, and 8.6%, 8.7% and 8.1% for the ascending, descending arch and the descending aorta respectively.

![Figure 9.4: a Systolic and b diastolic WSS results for all seven volunteers (mean and standard deviation). Data shown is the global WSS in the aorta (black) and the separate parts ascending arch (red), descending arch (green) and descending aorta (blue).](image)

### 9.4 Discussion

In this study, we confirmed that the use of a variable venc reduces noise and increases the spatial homogeneity of WSS in the aorta compared to standard static venc acquisitions. In addition, we found that systolic and diastolic WSS can be calculated using both 4D PC and 4D vPC, yielding
Figure 9.5: Typical example of a systolic and diastolic vectorial WSS map. 

- a Systolic WSS based on 4D PC data. 
- b Systolic WSS based on 4D vPC data. 
- c Diastolic WSS based on 4D vPC data. 
- d Diastolic WSS based on 4D vPC data.

WSS patterns that appear very similar to existing literature (5).

Figure 9.6: a Example WSS variation maps from 1 volunteer. From left to right: systole 4D PC, systole 4D vPC, diastole 4D PC, diastole 4D vPC. The colors depict low (blue) to high (red) local variations in WSS. b Combined histogram of 2D WSS variation map values for all volunteers. Low values on the x-axis indicate low noise. High values indicate high WSS variation. The red lines show the systolic data and the blue lines show the diastolic data.

We found that velocity noise quantification improved in vPC compared to PC for both systole and diastole. This can be explained by the automatically determined venc, which was lower in the vPC case, both for systole and diastole.

The average systolic and diastolic WSS magnitude was higher in this study than in existing literature (2, 3, 16), which can be explained by our higher spatial resolution combined with a slightly tighter segmentation of the aorta. We found no significant differences in the mean systolic and diastolic WSS between 4D PC and 4D vPC. The RI is in agreement with the recent paper on WSS reproducibility using the same WSS calculation method (17).

Despite a smoother visual appearance of the WSS from 4D vPC data, especially in the ascending aorta and aortic arch, the decrease in velocity noise did not result in a decrease of standard deviation in the derived WSS. This suggests that WSS distribution across the aorta is influenced by other factors as well. Such factors could, for example, be the presence of flow impingement zones, diameter differences along the aorta, velocity vortices, segmentation errors and the lack of breathing motion correction (5).

Although no differences were found between PC WSS and vPC WSS in magnitude and standard deviation, the histograms of the WSS local variation maps that were tailored to show small-scale WSS differences did show significant differences in all volunteers. The WSS maps based on 4D vPC
scans contain relatively less spatial WSS variations, indicating the presence of less noise in WSS maps when using 4D vPC data as compared to 4D PC data. One explanation for the relatively small differences observed here is that the WSS algorithm, which uses smoothing splines, already filters the velocity noise, such that the effect of velocity noise is dampened (5).

This work suffers from some limitations. Due to the difficulty of accurate segmentation from the diastolic data, we used systolic segmentations also for diastole. This may have induced WSS errors, especially near the aortic root in diastole. Furthermore, the increased bandwidth for the 4D vPC scan will have limited (±15%) the velocity to noise gain of the 4D vPC sequence, dampening the hypothesized effect. However, the choice of a fixed TE, TR and resolution was made to avoid those confounding factors in the comparison. TE and TR were fixed to obtain a similar signal, whereas the resolution was mainly fixed to avoid differences in WSS quantification (2, 5).

In conclusion, we have shown that WSS can be derived using both 4D vPC and 4D PC data. The decrease in noise in 4D vPC gives a smoother WSS map, but the improvement is small, suggesting that other factors than the quality of the velocity data also influences WSS variations. The present results highlight the small yet significant benefit of variable velocity encoding beyond decreasing the noise occurring in the velocity data itself.

Bibliography


Chapter 10

Summary and general discussion
10.1 Summary

Phase contrast MRI (PC MRI) measurements, also called 4D flow MRI or velocity-encoded MRI, and computational fluid dynamics (CFD) simulations continue to be the only techniques for non-invasive quantification of the direction and magnitude of blood velocities within a large field of view. The techniques can be applied to any vessel of substantial size, and over the last years more and more research groups are using these blood velocities to calculate wall shear stress (WSS). WSS based on 4D flow MRI or CFD have become a readout tool in cardiovascular research, especially in the greater vessels. The aims of this thesis, entitled ‘Wall Shear Stress Calculations Using Phase Contrast MRI’, 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.

In Chapter 2 of this thesis, the application of PC MRI for the calculation of WSS is reviewed. The basics of PC MRI and WSS calculation are explained, and different methods for PC MRI-based WSS calculation are presented. We observe a trend from 2D towards 3D WSS calculation methods in recent years. Additionally, a large variation was found between the results of the different WSS calculation methods in both the carotid and aorta. The future of MRI-based WSS calculations depends on its prognostic and diagnostic value, both of which need to be further explored in clinical studies. In this context, both further improvements of the quality of PC MRI data and scan time reduction are pivotal.

In Chapter 3, we created a volumetric WSS calculation algorithm, based on existing WSS calculation methods. This WSS calculation algorithm can quantify the WSS magnitude and direction on the entire surface of (segmented) vessels, both from 2D and 3D PC MRI. The accuracy and precision of this volumetric WSS calculation method were assessed with 2D software phantoms and 2D in vivo measurements. WSS algorithm parameters were optimized, and the influence of spatial resolution and segmentation was evaluated. We found that at least eight voxels across the vessel diameter were required to obtain a WSS accuracy of 5%. The in vivo measurements using 2D cine PC MRI exhibited an increase of estimated WSS at increasing spatial resolutions, similar to the results in our software phantoms. Finally, we applied the algorithm to 4D flow MRI data to calculate successfully volumetric WSS vectors in three healthy carotid bifurcations and aortas.

In Chapter 4, we validated the volumetric WSS approach in aneurysms using computational fluid dynamics (CFD), both in vitro and in vivo. We found a moderate quantitative agreement between CFD-based WSS and MRI-based WSS in an aneurysm phantom. The WSS magnitude based on PC MRI was lower than WSS magnitude based on CFD for both the in vitro and in vivo case, whereas the WSS distribution and direction was similar for both modalities. Increasing resolution resulted in more complex WSS patterns with higher mean WSS magnitude, closer to the CFD values. We concluded that the WSS calculation algorithm can use PC MRI data to estimate WSS patterns in aneurysm geometries and can discern similar WSS directions as CFD.

In Chapter 5, we continued our comparison between MRI- and CFD-based WSS calculations in the carotid arteries of six healthy volunteers. WSS magnitude resulting from the two methods were compared by quantifying the overlap between low, medium and high WSS tertiles. WSS directions were compared by calculating the angles between the CFD- and MRI-based WSS vectors. MRI-based WSS magnitude was lower than CFD-based WSS, but this difference diminished when CFD data was resampled at the MRI resolution. MRI-based WSS patterns matched well with CFD-based WSS; the overlap area was 68.7 ± 4.4% in low and 69.0 ± 8.9% in high WSS tertiles. The angles
between CFD WSS and MRI WSS vectors were small in the high WSS tertiles (20.3 ± 8.2°), but larger in the low WSS tertiles (65.6 ± 17.4°). Although MRI-based WSS magnitude was lower than CFD-based WSS, the spatial WSS patterns, which are more relevant to the vascular biology, were similar. PC MRI-based WSS can indicate regions of low and high WSS. The direction of WSS is comparable between CFD and MRI in regions of high WSS, but not in regions of low WSS.

In Chapter 6, we further looked into the effect of both spatial and temporal PC MRI resolution limitations on flow, peak flow, WSS and oscillatory shear index (OSI) using a carotid artery phantom. The carotid artery phantom was connected to a flow set-up supplying pulsatile carotid-like flow. MRI measurement planes were placed in the common carotid artery and internal carotid artery. Two-dimensional PC MRI measurements were performed with thirty different spatiotemporal resolution settings. We found that both mean flow and mean WSS are independent of temporal resolution, whereas peak flow and OSI are dependent on both spatial and temporal resolution. However, the magnitude of mean flow, peak flow, WSS, and OSI, as well as the spatial distribution of OSI and WSS did not exhibit a strong dependence on spatiotemporal resolution.

In Chapter 7, we introduced the concept of cohort-averaged WSS maps using three groups of retrospectively selected patients with aortic dilation, patients with valvular stenosis, and healthy controls. In the thoracic aorta of patients with aortic dilatation or valvular stenosis and the controls, we created a cohort-averaged segmentation, by coregistration of 3D segmentations of each aorta. The WSS vectors of each subject were projected onto the corresponding cohort-specific geometry to create cohort-averaged WSS maps. A Wilcoxon rank sum test was used to generate aortic P-value maps representing regional relative WSS differences between groups. Cohort-averaged systolic WSS maps and P-value maps were successfully created for all three cohorts and comparisons. The dilation cohort showed significantly lower WSS compared to controls on 7% of the ascending aorta surface, whereas the stenosis cohort showed significantly higher WSS compared to controls on 34% of the ascending aorta surface. The findings of this study demonstrated the feasibility of generating cohort-averaged WSS maps for the visualization and identification of regionally altered WSS in the presence of disease, compared with healthy controls.

In Chapter 8, we investigated the characteristics of aneurysmal vortices using the shear rate within the aneurysmal lumen. We presented a quantitative method for automatic time-resolved characterization of 3D flow patterns and vortex detection within aneurysms. This method combined kernel deconvolution and Jacobian analysis of the velocity field. The proposed algorithm was applied to CFD-based and MRI-based cardiac-resolved velocity fields of aneurysmal flow. Results showed that the proposed method efficiently detects, visualizes, and quantifies vortices in intracranial aneurysmal velocity patterns at multiple scales. Moreover, this method can follow the temporal evolution of these patterns. The quantitative analysis performed with this method has the potential to reduce interobserver variability in aneurysmal vortex classification.

In Chapter 9, we investigated whether reduced diastolic velocity noise levels, as mediated by dynamic velocity encoding in 4D flow MRI, results in an improved precision of diastolic WSS quantification. In seven young and healthy volunteers, the WSS distribution on the aortic wall was calculated in systole and diastole. The WSS values were compared between a 4D flow sequence with variable velocity encoding (4D vPC) and an equivalent sequence with constant velocity encoding (4D PC). WSS distributions from 4D vPC datasets appeared visually more smooth. Regarding noise differences between PC and vPC, a significant difference was detected between the standard deviations of the WSS spatial variation in each volunteer and for all the volunteers combined. The repeatability of mean aortic WSS between 4D PC and vPC datasets was good. WSS maps
deduced from 4D vPC data contained less noise than those from 4D PC acquisitions. These findings highlight the benefit of variable velocity encoding beyond a decrease of the noise present in the velocity data itself.

This thesis contributed to the 4D flow MRI field by introducing a new, open-source, algorithm to calculate WSS from 4D flow MRI data. The algorithm was validated with gold standard CFD simulations, the effect of scan parameters was assessed, and a method to compare WSS between patient groups was introduced. This information will help to improve future research on the role of WSS in vascular diseases, and to bring 4D flow MRI with its quantitative parameters a step closer to daily clinical practice.

10.2 Future of 4D flow MRI measurements

Despite the contributions to WSS calculation and validation described in this thesis, 4D flow MRI remains the Achilles heel of WSS quantification. Further clinical application of WSS calculations will depend on several challenges that can be addressed. Next, the following three main topics will be discussed: reduction of scan time, unreliable cardiac triggering and breathing motion, and the velocity measurement accuracy.

10.2.1 Shorter scan time

In the past decades, the performance of clinical MR scanners has improved. Larger coils, with more coil elements, can now cover larger anatomical areas. Cartesian acceleration techniques, such as GRAPPA and SENSE, are used to measure the velocity field in these larger volumes in less time. These enabled the field to move from multi-slice 2D protocols towards 3D MR imaging in daily practice. Large field of view 3D imaging with cardiac triggering was pivotal in the development of thoracic 4D flow MRI. Currently, the biggest hurdle for clinical 4D flow imaging is scan time. A regular 4D flow MR scan of the aorta, with Cartesian sampling as described in Chapter 9, can take up to 30 minutes.

Innovations in both acquisition and reconstruction from the past years led to novel MR acceleration techniques: compressed sensing, k-t GRAPPA, k-t PCA [1-6]. These techniques already made it feasible to decrease 4D flow MR acquisition time to 5 minutes, although with longer reconstruction times.

For Cartesian acceleration techniques (k-t PCA, k-t GRAPPA) reconstruction is feasible on a clinical system. However, for the non-Cartesian acceleration techniques, like the iterative reconstruction of compressed sensing data, the reconstruction becomes a computationally expensive task that limits their clinical applicability for 4D flow MRI on the short term.

Without the availability of fast offline reconstruction methods, we should thus better focus on the clinical application of accelerated Cartesian acquisition schemes on the short term.

10.2.2 Improved cardiac triggering and breathing corrections

Cardiac triggering is another challenge in PC MRI. Besides that it is time-consuming to prepare every patient with a peripheral pulse or ECG sensor before scanning, the ECG signal also suffers regularly from gradient-induced artifacts. Especially the maximal gradients used for velocity encoding in PC MRI contribute to this problem. New techniques proposed to circumvent this problem using the
intrinsic signal intensity of the acquired k-space lines instead of the ECG signal. The k-space lines, sorted based on signal intensity into cardiac bins, are then used for cardiac sorting (7, 8).

Another interesting application of such 'self-gating' technique is breathing motion correction (9). Currently, breathing motion correction is achieved using navigator-acquisitions for breathing-gating during the acquisition, which takes time and affects the steady state of MR imaging. With self-gating, steady state imaging is enabled, which improves image quality. Second, data in unfavorable breathing states could be motion-corrected and used, which decreases scan time. Schmidt et al. showed the feasibility of breathing correction in dynamic scans of the heart and coronaries (10). Similar principles could be applied to 4D flow MRI.

10.2.3 Improved velocity measurements

The accuracy of PC MRI flow quantification is reported to be between 1 – 10% (11, 12). Especially lower velocities are often difficult to quantify, as we observed in Chapter 5 in the low-velocity regions in the carotid sinus. Over the years, several solutions for measurement of low velocities have been presented. In Chapter 9, we used the multi-venc approach of Nilsson et al.; they proposed to vary the encoding velocity over the heart cycle (13). This method improved the diastolic (low) velocity measurements without increasing the scan time. Other groups proposed to vary the venc in multiple concurrent or subsequent scans, which provides an improved signal for low velocities in both systole and diastole (14–16). These methods come at the expense of scan time, but can be useful, e.g. for flow quantification of the abdominal arterial and venous circulation (17).

10.3 Future of 4D flow MRI post-processing

4D flow MRI post-processing is an intricate and well-validated step of the utmost importance for accurate velocity, flow, and WSS quantifications (18, 19). Fortunately, the most important corrections, namely first-order eddy-current corrections and Maxwell terms corrections are already implemented on the MR scanner consoles. Higher order corrections of eddy currents may contribute to even more accurate quantifications in the future (20).

Recently, multiple approaches were introduced to minimize the vector field divergence in the PC MR datasets (21–24). In an automated pipeline, these techniques may further contribute to more accurate velocity quantification.

The most time-consuming and delicate task in post-processing is still the segmentation of the vessels at interest. Although we were able to apply automated segmentation in some of the chapters, accurate cardiac-resolved segmentation remains difficult. Conventional automated segmentation based on magnitude works well for 2D PC MRI (25, 26) (used in Chapter 3) or quick 3D streamline visualizations, but it is not suitable for accurate 4D flow MRI segmentations. Manual or semi-automated segmentation is therefore still common practice. In the future, we should adapt and fine-tune algorithms for automated segmentation of 4D flow MR images. This adaption might be achieved either by improving the image quality of 4D flow MRI or by the application of machine learning algorithms for PC MRI segmentation.

Automated segmentation could also automate the calculation of the average velocities, flow, WSS, flow vorticity (27, 28), energy loss by viscous dissipation (29), and turbulence (16, 30). This information could then be presented to the radiologist as visualization, or in the context of existing quantitative maps of healthy and diseased people.
10.4 Clinical future of volumetric wall shear stress

WSS is established as a biomarker that predicts endothelial dysfunction (31). However, calculation of WSS using several previous WSS calculation methods, mostly based on 2D PC MRI, yielded varying results among similar populations. Differences of up to one order of magnitude were observed between WSS studies, which we discussed in Chapter 2 (32). Now that 4D flow MRI, and volumetric WSS calculation are maturing, we showed in Chapter 7 that we can produce reproducible WSS maps for comparison of patient groups (33, 34). In this way, we can avoid spatiotemporal averaging that hampers comparisons between most studies and focus on what is really important: the location of high and low WSS (35) and the progression of WSS within the same patient.

It is important to keep in mind that a WSS map, although relevant, is not the only quantitative parameter that can summarize local disturbances of the endothelium. In Chapter 8 we showed already that other parameters may also be capable of summarizing the same or similar information. These parameters could be derived directly from the cardiac-resolved velocity measurements (relative residence time (36), vorticity of the velocity field (28), localized normalized helicity (37), pulse wave velocity (38–40)) or from the volumetric WSS vectors (oscillatory shear index and transverse WSS (41)).

Although WSS is currently relevant for patient groups and general trends, there is yet no direct clinical relevance of WSS calculations for individual patients. With the methods presented in this thesis, this fact might change. We are now able follow-up on the WSS values in individual patients and determine the WSS change over time, such measurements might prove useful to determine the predictive value of WSS for stroke or plaque progression (42, 43). A clinically relevant application is the infusion of personalized (nano)medicines in patients. Such medication is expensive, so if a local (low) shear rate or WSS could predict where the medication will be entering the vessel wall, this could aid in decisions which patients (not) to treat (44–47).

10.5 Concluding remarks

In conclusion, the results of this thesis demonstrated that, using our developed volumetric WSS calculation method, we can calculate WSS accurately based on 4D flow MRI in different complex vessel geometries. We showed how the different MRI measurement parameters affect the MRI-based WSS values. We showed to what extent MRI-based WSS can be compared with CFD-based WSS. Finally, we created a method to make WSS maps, which serve as a comparison method for WSS in different patient groups. These WSS maps enable future research to use volumetric WSS as a longitudinal readout tool.

Bibliography


Summary and general discussion


Samenvatting

Fase contrast MRI (PC MRI) metingen en numerieke stromingsleer (CFD) simulaties zijn nog steeds de enige technieken waarmede de snelheid en richting van stromend bloed in een groot in vivo volume bepaald kan worden. De laatste jaren gebruiken steeds meer onderzoeksgroepen de gemeten bloedsnelheden om de schuifspanning aan de wand (WSS) te bepalen. Deze WSS, gebaseerd op PC MRI of CFD, heeft zich dan ook ontwikkeld tot een cardiovasculair uitleesinstrument, met name voor de grote vaten. Het doel van dit proefschrift, getiteld ‘Wall Shear Stress Calculations Using Phase Contrast MRI’, is om een methode te ontwikkelen om volumetrische WSS te kunnen berekenen in iedere complexe vaatgeometrie, gebruikmakend van de met PC MRI gemeten snelheidsvectoren, en om deze methode te valideren met CFD-simulaties van de bloedstroom.

Dit proefschrift begint, in Hoofdstuk 2, met een overzicht van de beschikbare en gebruikte algoritmen en methoden om de schuifspanning aan de vaatwand te berekenen. Ook is de werking van PC MRI uitgelegd. We zagen dat de laatste jaren een trend is ontstaan om meer naar 3D WSS-patronen te kijken, in tegenstelling tot de 2D WSS in de jaren hiervoor. Daarnaast vonden we een grote variatie in de beschreven WSS-waarden van zowel de carotis als de aorta. De toekomst van MRI-gebaseerde WSS-berekeningen is afhankelijk van de prognostische en diagnostische waarde van WSS, welke beiden nog bewezen moeten worden in toekomstige klinische onderzoeken. Verdere verbetering van de kwaliteit van PC MRI data, alsmede de reductie van scantijd, is voor de haalbaarheid van deze klinische studies van WSS essentieel.

In Hoofdstuk 3 van dit proefschrift presenteren we een nieuw algoritme om WSS te berekenen. Met dit algoritme kunnen we op een gehele vaatwand zowel de richting als de grootte van de WSS bepalen. De accurate en precisie van deze techniek zijn geanalyseerd voor zowel de carotiden als de aorta met behulp van software fantomen. Ook zijn de algoritme parameters geoptimaliseerd. Uit dit onderzoek is gebleken dat tenminste 8 voxels in de diameter van een vat nodig zijn om een WSS-nauwkeurigheid te behalen van 5%. Ook vonden we dat een lagere spatiële PC MRI resolutie leidt tot een onderschatting van de WSS, zowel in de software fantomen als in vivo. Tot slot hebben we in de carotiden en de aorta van drie vrijwilligers volumetrische WSS succesvol kunnen meten.

In Hoofdstuk 4 van dit proefschrift passen we het algoritme uit Hoofdstuk 3 toe op in vitro en in vivo aneurysmata. Ook hebben we de WSS-waarden, gebaseerd op MRI, vergeleken met de theoretische WSS-waardes op basis van CFD. We vonden dat er een redelijke kwantitatieve overeenkomst was tussen de MRI- en CFD-resultaten. Daarnaast werd de WSS-magnitude wederom onderschat bij MRI gebaseerde WSS, zowel in vitro als in vivo. De richting van de WSS-vectoren liet echter geen verschillen zien tussen MRI en CFD gebaseerde WSS. Verhoging van de resolutie in de in vitro data liet meer complexe WSS-patronen zien, met hogere WSS-magnitude. We concluderen dat het nieuw ontwikkelde algoritme WSS-patronen in aneurysmata kan onderscheiden en dat de richting van WSS vergelijkbaar is tussen CFD- en MRI-resultaten.

In Hoofdstuk 5 van dit proefschrift is het algoritme uit Hoofdstuk 3 toegepast in de carotiden van zes gezonde vrijwilligers en zijn wederom de MRI met de CFD gebaseerde WSS-vectoren vergeleken. De WSS-magnitude is vergeleken door te kijken naar de locatie van lage, middel en hoge WSS tertiaLEN. De richting van WSS is vergeleken op basis van de hoek tussen de CFD en MRI gebaseerde WSS-vectoren. De MRI gebaseerde WSS was lager dan de CFD gebaseerde WSS, maar dit verschil verdween indien de spatiële resolutie van de CFD-data verlaagd werd tot...
de resolutie van de MRI-data. De MRI gebaseerde WSS-patronen hadden veel overlap met de CFD gebaseerde WSS-patronen; de overlap was $68.7 \pm 4.4\%$ voor de lage en $69.0 \pm 8.9\%$ voor de hoge WSS tertiel. De hoek tussen de CFD en MRI gebaseerde WSS-vectoren was klein in het hoge WSS tertiel ($20.3 \pm 8.2^\circ$), maar groter in het lage WSS tertiel ($65.6 \pm 17.4^\circ$). Hoewel de WSS-magnitude lager was op basis van MRI dan op basis van CFD, was de spatiële verdeling van WSS overeenkomstig. Concluderend, WSS op basis van MRI kan lage en hoge WSS-regio’s onderscheiden, vergelijkbaar met CFD. Daarentegen is de WSS-richting alleen vergelijkbaar tussen CFD en MRI in hoge, maar niet in lage WSS-regio’s.

In Hoofdstuk 6 van dit proefschrift is het effect van spatiële en temporele PC MRI resolutie op de kwantificatie van het debiet, het piek debiet, de WSS en de oscillerende schuifspanningsindex (OSI) verder bestudeerd. Hierbij is gebruik gemaakt van een siliconen carotis fantoom met een pulsatiele stroming, gebaseerd op de carotis van een gezond persoon. We hebben 2D PC MRI metingen uitgevoerd, net voor en net na de bifurcatie van deze carotide. In totaal is hiervoor met 30 verschillende spatiële en temporele resoluties PC MRI gemeten. De bevindingen waren dat zowel het gemiddelde debiet als de gemiddelde WSS onafhankelijk is van de temporele resolutie, terwijl het piek debiet en de OSI afhankelijk zijn van zowel de spatiële en temporele resolutie. Desalniettemin was de magnitude van het gemiddelde debiet, het piek debiet, de WSS, de OSI en de spatiële distributie van WSS niet sterk afhankelijk van de spatiotemporele resolutie.

In Hoofdstuk 7 van dit proefschrift is er een nieuw concept geïntroduceerd om cohort-atlassen van de WSS-vectoren te maken voor verschillende patiënten cohorten. Uit een database zijn retrospectief drie groepen geselecteerd: patiënten met aorta verwijding, patiënten met aortaklepstenose en gezonde controles. Van de thoracale aortas zijn cohort-specifieke segmentaties gemaakt door 3D segmentaties van individuele patiënten en controles op elkaar te registreren. De WSS-vectoren van elk individu zijn vervolgens geprojecteerd op deze cohort-segmentatie om cohort-atlassen van de WSS-vectoren te maken. Met een ‘Wilcoxon rank sum test’ zijn de verschillende atlassen vergeleken om P-waarde atlassen te maken. Deze atlassen tonen het regionale relatieve verschil tussen de groepen. Het cohort met aorta verwijding liet op 7% van de aorta ascendens een significant lagere WSS zien ten opzichte van het gezonde cohort, terwijl het cohort met aortaklepstenose een significant hogere WSS liet zien op 34% van de aorta ascendens ten opzichte van het gezonde cohort. De resultaten van deze studie laten zien dat het haalbaar is om cohort-atlassen te maken om zo de regionale WSS-verschillen in groepen patiënten te visualiseren en identificeren, en te vergelijken met gezonde controles.

In Hoofdstuk 8 van dit proefschrift worden de karakteristieken van bloedstroom wervelingen onderzocht met behulp van de schuifspanningen in stromend bloed in intracraniële aneurysmata. Hiervoor presenteren we een kwantitatieve methode voor automatische tijdafhankelijke karakterisatie van 3D stromingspatronen en werveldetectie. Deze methode combineert ‘kernel deconvolutie’ en de eerste orde afgeleiden van het snelheidsvectorveld. De methode is op zowel CFD als MRI gebaseerde stromingsvelden in aneurysmata toegepast. De resultaten lieten zien dat de voorgestelde methode de wervelingen visualiseert en kwantificeert in intracraniële aneurysmata op meerdere schalen. Daarnaast is de methode in staat om de ontwikkeling van wervelingen in de tijd te volgen. Deze kwantitatieve methode heeft de potentie om bij classificatie van aneurysma wervelingen de variatie tussen de beoordelaars te beperken.

In Hoofdstuk 9 van dit proefschrift is onderzocht of verminderde ruis op de gemeten bloedstroomsnelheden, veroorzaakt door het gebruik van dynamische snelheidsencodering in de PC MRI sequentie, ook zorgt voor een verbetering van de WSS-precisie in diastole. Hiervoor zijn de aortas
van zeven jonge, gezonde vrijwilligers gemeten met zowel een dynamische (vPC) als een statistische (PC) snelheidscodering. Vervolgens hebben we de WSS-distributie op de vaatwand van de aorta bepaald in zowel systole als diastole. De WSS-waarden zijn vergeleken tussen de PC en de vPC methode. De WSS-waarden berekend uit de vPC metingen leken visueel beter te zijn, dat wil zeggen dat er minder scherpe overgangen waren in de WSS. Dit is vervolgens gekwantificeerd door lokaal de afgeleiden van de WSS-waarden te berekenen. Bij de analyse van de WSS-ruis zijn er significante, maar kleine, verbeteringen gevonden bij de vPC-methode in vergelijking met de PC-methode. Deze verschillen waren aanwezig voor zowel de individuele vrijwilligers als voor de combinatie van alle vrijwilligers. Daarnaast waren de gemiddelde WSS-waarden reproducibeler in beide methoden. Deze bevindingen laten zien dat dynamische snelheidscodering meer voordelen biedt, in aanvulling op het in het verleden aangetoonde voordeel voor snelheidskwantificatie.

Dit proefschrift heeft bijgedragen aan het PC MRI onderzoeksveld door een nieuwe, vrij te gebruiken, methode te ontwikkelen om WSS te berekenen met PC MRI data van complexe vaat geometriëen. Deze methode is gevalideerd met gouden standaard CFD-metingen en het effect van scan parameters is bepaald. Daarnaast is er een methode geïntroduceerd om de WSS tussen patiëntengroepen te vergelijken. Deze informatie zal toekomstig onderzoek naar de rol van WSS bij vasculaire ziektebeelden ten goede komen, en brengt PC MRI en gerelateerde kwantitatieve parameters een stap dichterbij de dagelijkse klinische praktijk.
List of publications

Papers in international journals

An up to date list can be found on ORCID: orcid.org/0000-0003-1249-1196 or on Google Scholar: scholar.google.nl/citations?user=1OeHAiQAAAAJ


3. Potters WV, Marquering HA, VanBavel E, Nederveen AJ. Measuring wall shear stress using velocity-encoded MRI. *Current Cardiovascular Imaging Reports* 2014; 7:9257. doi: [10.1007/s12410-014-9257-1](http://dx.doi.org/10.1007/s12410-014-9257-1)


15. **Potters WV***, Nillson A*, van den Berg S, Marquering HA, vanBavel E, Markenroth Bloch K, Ståhlberg F, Nederveen AJ. Aortic wall shear stress quantification using variable venc 4D flow MRI. *SUBMITTED*


* shared first authorship
About the author

Wouter Vincent Potters, eldest son of Laurens Antonius Potters and Noëlle Irene Eudokia Potters-Strijker, was born on September 15, 1986 in the city of Zoetermeer, The Netherlands. In 1987 he moved to Twello where he spent his childhood. He went to high school in Apeldoorn at the 'Stedelijk Gymnasium Apeldoorn’. In 2004, he left Twello to live in Enschede and study a bachelor and master Technical Medicine at the University of Twente. After finishing his master thesis on wall shear stress calculation in December 2011, he continued working on this subject as a PhD candidate at the department of Radiology in the Academic Medical Center in Amsterdam. In four years at the department of Radiology, he further improved and validated the wall shear stress calculation methods and worked on several other 4D flow MRI related topics, which resulted in his PhD defense on December 11, 2015. In 2016, he will continue his career as a ‘Technisch Geneeskundige’ (Clinical Physician) in the department of Clinical Neurophysiology in the Academic Medical Center in Amsterdam. Wouter lives together with Mechteld Lehr in Utrecht.
PhD training

This portfolio was created carefully. However, for brevity the smaller and local conferences, seminars and presentations are not all included.

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<th>General courses</th>
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## PhD training

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### Other

| Monthly or bi-weekly journal club                            | 2013-2014 | 1.4 |

## Education

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### Lecturing

- Lecturer in AMC Graduate school - MATLAB course 2012-2014 1.3
- Assistent teacher in various courses for medical and physics students 2011-2015 1

### Tutoring

- Tutor bachelor, master students Medicine
- Tutor bachelor students Physics
- Assistant tutor various other students (Technical Medicine, Medicine, Physics, Biomedical Engineering)
### Parameters of esteem

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### Reviewer for international journals

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<td>Journal of Magnetic Resonance Imaging</td>
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Acknowledgements

Gedurende de 4 jaar van mijn PhD (en daarvoor) ben ik elke dag met bijzonder veel plezier naar de afdeling Radiologie (Z0) in het AMC gegaan. Met een baan als PhD Candidate verveel je je nooit; niet in de laatste plaats door de vele samenwerkingen en discussies met collega-wetenschappers, technici en clinici, zowel binnen als buiten het AMC. Op deze pagina’s wil ik graag een aantal van jullie persoonlijk bedanken voor jullie bijdrage aan dit proefschrift.

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Co-promotor Dr. H.A. Marquering, beste Henk, hartelijk dank voor alle image processing en schrijf input van jouw kant. Ik heb nog steeds veel bewondering voor je bizar snelle reacties op de manuscripten. Ik denk dat je in bijna alle gevallen als eerste je commentaar terugstuurde, hoe snel Aart en Ed ook waren. Zonder al je studentprojecten had ik nooit zoveel geweten over aneurysma CFD en vortices.

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Ook al werkten jullie soms aan compleet verschillende onderwerpen; elke dag met plezier naar het AMC gaan kwam toch hoofdzakelijk door collega’s, in het bijzonder alle Z0-ers! Abdallah, André, Anne, Anne-Marije, Anouk, Bram, Claudia, Dennis, Dorien, Elsmarieke, Esther, Eva, Geor, Henk-Jan, Hyke, Joena, Jordi, Jos, JP, Jules, Jurgen, Kerry, Kevin, Lena, Marieke, Martijn, Martin, Matthan, Myrle, Oliver, Ot, Paul, Pim, Raschel, Remy, Sandra, Sanne, Sofieke, Tanja en de rest bedankt voor alle scansessies, overleggen, lunches, lunch runs, congressen, borrels, bbq’s, biertjes, bitterballen en feestjes!

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en voortvarende aanpak in het schrijven van papers, ook heb ik veel plezier gehad tijdens alle woensdag en vrijdagmiddagborrels die met jou nooit saai worden. En niet te vergeten, dankzij jou is de Potters & van Ooij methode (met kleine v!) de oceaan overgestoken. Al jouw inspanningen als super-postdoc in Chicago hebben voor geweldige exposure voor de WSS gezorgd. Veel succes de komende jaren op het AMC en veel geluk met Joske & Loek.

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Jordi & Paul, als experts van alles wat een ip-adres of stekker heeft op en buiten Z0, wil ik jullie bedanken voor de enorme snelheid waarmee jullie alles steeds regelden. Denk dat iedereen de komende jaren nog veel profijt gaat hebben van de vele pipelines op de XNAT en de radian servers. Raschel & Sandra, hartelijk dank voor alle researchondersteuning en het delen van jullie uitgebreide MRI scan ervaringen.

Eva & Lena, together with Pim you already are the 4D flow MR imaging experts in the AMC. It is nice to see that Aart found such good new colleagues. I really enjoyed working with you the last months at Z0. Eva, good luck with all the future pulse programming and reconstruction solutions. I am confident you will be the Z0 scanning and reconstruction expert for CS next year. Lena, thanks for all the how-do-you-say-this-in-Dutch-or-English questions and for sharing an continuously increasing amount of English expressions.

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