Phase contrast MRI in intracranial aneurysms
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PHASE CONTRAST MRI IN INTRACRANIAL ANEURYSMS

Pim van Ooij

Intracranial aneurysms
are outpouchings of intracranial arteries that cause brain hemorrhage after rupture. Unrepaired aneurysms can be treated but the risk of treatment may outweigh the risk of rupture. Local intraneurysmal hemodynamics can contribute substantially to the rupture risk estimation of the individual aneurysm. The only technique capable of measuring threedimensional flow patterns over time in vivo is time-resolved three-dimensional phase contrast MRI (PC-MRI).

In this thesis in vitro PC-MRI was compared with Particle Image Velocimetry and Computational Fluid Dynamics (CFD). In vivo PC-MRI was compared with patient-specific CFD in right aneurysms. Two acquisition strategies to improve PC-MRI were tested: 1) PC-MRI in combination with k-i BLaST® was compared with PC-MRI in combination with parallel imaging; 2) PC-MRI at T= was compared with PC-MRI at T=. Furthermore, a novel algorithm to calculate wall shear stress from PC-MRI data is presented, tested in software phantoms and applied to PC-MRI data of an in vitro and in vivo intraneurysmal aneurysm.

This thesis demonstrates that PC-MRI can be used to quantify and visualize intraneurysmal flow patterns and wall shear stress.
PHASE CONTRAST MRI IN INTRACRANIAL ANEURYSMS

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General Introduction
Intracranial aneurysms

Intracranial or cerebral aneurysms are outpouchings of intracranial arteries that occur mainly on bifurcations in the vicinity of the Circle of Willis, a ring-like vessel structure at the base of the brain. The majority of intracranial aneurysms occur on the posterior communicating artery, anterior communicating artery and the middle cerebral artery, see figure 1.1. Rupture of intracranial aneurysms causes subarachnoid hemorrhage, which has a high case fatality rate. Since the majority of unruptured aneurysms do not inflict any symptoms on patients, patients are mostly treated after rupture. As the use of MRI and other imaging techniques increases, unruptured aneurysms are discovered more frequently.

Treatment of ruptured and unruptured aneurysms consists of clipping and coiling. In the clipping procedure, craniotomy is performed to access the aneurysm and a clip is permanently placed across the neck of the aneurysm, excluding it from circulation, see figure 1.2a. During coiling, a microcatheter is inserted in the femoral artery and, with the use of angiographic monitoring, advanced into the aneurysm. Detachable coils are then deployed to decrease the amount of blood flowing into the aneurysm and to induce thrombus formation, see figure 1.2b. Morbidity and mortality rates for clipping range from 4.0 to 10.9 percent and 1.1 to 3.0 percent respectively.
Morbidity and mortality rates for coiling range from 3.7 to 5.3 percent and 1.1 to 1.5 percent respectively [1]. Coiling is therefore preferred to clipping.

For both aforementioned interventions, the risk of treatment of incidentally detected unruptured aneurysms may outweigh the risk of rupture of the aneurysm, and therefore careful consideration whether to treat the aneurysm...
must be made. At the moment the consensus is that aneurysms of the ante-
rior circulation of more than 7 mm in size and those located in the posterior 
circulation need treatment [2]. Unfortunately, aneurysms excluded from 
potential treatment with these guidelines may be subject to rupture as well. 
A better risk assessment would therefore allow a more optimal decision to 
treat, potentially leading to lower morbidity and mortality and more efficient 
health care.

There are several possibilities for improving rupture risk assessment. 
Amongst these, assessment based on local hemodynamics is of particular 
interest. This is based on the sensitivity of vascular cells for wall shear stress. 
Such sensitivity is well documented for atherosclerosis, where high non-re-
versing flow is atheroprotective and low flow in combination with spatial 
and temporal gradients is atheroprone [3-4]. For intracranial aneurysm 
progression, hemodynamics have been suggested to have similar relevance. 
In addition to wall shear stress distribution, information on several coupled 
hemodynamic factors could help risk assessment. These include flow com-
plexity and stability, inflow jet concentration and impingement of flow on 
the aneurysmal wall [5-6]. Other more recently developed flow character-
istics are kinetic energy, strain rate and viscous dissipation [7-8]. Yet, firm 
evidence for their predictive value awaits improved methodology for their 
measurement at sufficient temporal and spatial resolution in intracranial 
aneurysms.

1.2 Blood Flow measurements in intracranial arteries and aneurysms

Several techniques exist for measurement of intracranial vascular hemody-
namics. Transcranial Doppler (TCD) [9], a technique based on ultrasound, 
is, depending on the experience of the clinician, an easy to use, quick and 
inexpensive modality to measure the blood velocity in the intracranial 
arteries located in the Circle of Willis. However, TCD merely measures the 
maximal velocity of blood flow, and without knowledge of the diameter of the 
vessels, the actual blood flow can not be determined. Furthermore, spatial 
velocity profiles are not resolved in TCD. TCD is therefore well-suited for the 
diagnosis of stenosis, but for hemodynamic measurements in intracranial 
aneurysms TCD would not be helpful.
Another relatively recent developed technique based on ultrasound combining flow measurements and imaging of intracranial vessels is transcranial colour-coded duplex sonography (TCCS) [10]. TCCS allows 2-dimensional imaging of brain parenchyma and color-coded imaging of the vessels [11]. TCCS is well-suited for detecting intracerebral hemorrhages and vessel occlusions. However, the technique is not able to resolve three-dimensional flow patterns.

Ultrasound can also be used based on intravascular techniques. A few studies have applied this in intracranial vessels and aneurysms, using either flow wires [12] or combowires with combined Doppler and pressure sensors [13] [14]. A drawback of using a Doppler wire is that it, again, merely measures the maximal velocity of the blood flow in vessel field of interest and that spatial velocity profiles are not resolved. They could however serve to provide information on flow in the entrance and exit vessels.

With magnetic resonance imaging (MRI) it is possible to measure spatial velocity profiles and quantify blood flow in the intracranial arteries and aneurysms. This thesis will focus on time-resolved three-dimensional phase contrast MRI (PC-MRI).

1.3 Phase Contrast MRI

Phase contrast MRI is based on the phenomenon that the velocity of hydrogen nuclei (protons, hereafter called spins) in blood moving along a magnetic field gradient translates in the phase of the image. To this end, a velocity-encoding gradient, which comprises two lobes of equal area and opposite polarity, a so-called bipolar gradient [15], is added to a gradient echo sequence. Because the net area of the bipolar gradient is zero, it produces no net phase accumulation for stationary spins [16]. The bipolar gradient is shown in figure 1.3. Since the phase of gradient echo images is sensitive to $B_0$ inhomogeneities, a second acquisition is performed with an inverted bipolar gradient (toggling). By subtraction of the two images phase errors are minimized.
The phase difference obtained after subtraction of the two images is proportional to the velocity with which the blood is flowing:

$$\Delta \varphi = 2 \gamma G v \tau^2$$  \hspace{1cm} (1.1)

Where $\gamma$ is the gyromagnetic ratio, $G$ is the gradient strength, $\tau$ is the gradient duration and $v$ is the velocity. The combination of $G$ and $\tau$ determines the amount of velocity encoding; $2G\tau$ is often rewritten as $\Delta m$, the change in the gradient first moment between consecutive bipolar gradients. By increasing $\Delta m$ of the velocity encoding gradients i.e. lowering the velocity encoding settings (VENC), the sensitivity for low velocities can be increased. However, since phase can only be measured between $-\pi$ (corresponding to $-\text{VENC}$) and $\pi$ (corresponding to $+\text{VENC}$) velocities higher than VENC will fold into the image (phase wrapping or aliasing). It is therefore necessary to choose VENC carefully.

By adding bipolar gradients to the slice-selective, phase and read-out directions, a three-dimensional velocity vector can be measured in one slice (2D PC-MRI). By adding a second phase encoding to the slice-selective direction, velocity measurements can be performed in a three-dimensional volume. This sequence is called three-dimensional phase contrast, which will be referred to as PC-MRI throughout the thesis, except in Chapter 4 where it will be referred to as 3D PC-MRI to prevent confusion with 2D PC-MRI.

Since each of the velocity encoding gradients is toggled to compensate for $B_0$ inhomogeneities, PC-MRI comprises six acquisitions, called six-point encoding. However, six-point encoding can be simplified to four-point encoding if one common reference image is used for all directions. Still, scanning time of phase contrast MRI remains inherently long. The majority of
data in this thesis is acquired using a two-sided four point encoding scheme, which is schematically displayed in table 1.1. Some pilot data in the early stage of the project was acquired using an enhanced four point or Hadamard encoding scheme, as displayed in table 1.2.

### Table 1.1 Gradient first moments for two-sided four point encoding.

<table>
<thead>
<tr>
<th>scan nr.</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Δm/2</td>
<td>Δm/2</td>
<td>Δm/2</td>
</tr>
<tr>
<td>2</td>
<td>-Δm/2</td>
<td>Δm/2</td>
<td>Δm/2</td>
</tr>
<tr>
<td>3</td>
<td>Δm/2</td>
<td>-Δm/2</td>
<td>Δm/2</td>
</tr>
<tr>
<td>4</td>
<td>Δm/2</td>
<td>Δm/2</td>
<td>-Δm/2</td>
</tr>
</tbody>
</table>

### Table 1.2 Gradient first moments for enhanced four point encoding.

<table>
<thead>
<tr>
<th>scan nr.</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Δm/2</td>
<td>Δm/2</td>
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<tr>
<td>2</td>
<td>-Δm/2</td>
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<td>3</td>
<td>-Δm/2</td>
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<td>-Δm/2</td>
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<tr>
<td>4</td>
<td>Δm/2</td>
<td>-Δm/2</td>
<td>-Δm/2</td>
</tr>
</tbody>
</table>

The Hadamard velocities are resolved using:

\[
\begin{align*}
2\varphi_x &= (\rho_2 + \rho_3) - (\rho_1 + \rho_4) \\
2\varphi_y &= (\rho_2 + \rho_4) - (\rho_1 + \rho_3) \\
2\varphi_z &= (\rho_3 + \rho_4) - (\rho_1 + \rho_2)
\end{align*}
\]

where \(\rho_i\) denotes the accumulated phase in the \(i\)th acquisition. The advantage of Hadamard velocity encoding is slightly increased signal to noise ratio (SNR). However, phase wrapping occurs for velocities lower than VENC and affects other flow directions [17], making it difficult to resolve the phase wraps.

To be able to acquire temporal information, synchronization with the cardiac cycle is carried out by either prospectively or retrospectively gating the phase contrast measurement with an electrocardiogram (ECG) or a peripheral pulse unit (PPU).

A typical PC-MRI acquisition results in a series of magnitude and phase images, as shown in figure 1.4 for one slice and one cardiac phase.
In this thesis several aspects and applications of PC-MRI are studied. This thesis is divided in three parts: validation of PC-MRI, improvements of PC-MRI and estimation of wall shear stress based on PC-MRI.

1.3.1 Part I: Validation

To test if PC-MRI in intracranial aneurysms meets its requirements and performs well in a clinical setting, in vitro and vivo verification and validation is needed. In this thesis, PC-MRI is performed in vitro and compared with Particle Image Velocimetry (PIV) and Computational Fluid Dynamics (CFD). In vivo PC-MRI is compared with CFD.

Particle Image Velocimetry

PIV is an optical method used to measure instantaneous velocity fields of in vitro flow seeded with particles. These particles should be small enough to follow the fluid acceleration but large enough to scatter light sufficient to form bright images. In order to illuminate the flowing particles of micrometer size, a pulsed laser source is used. An optical camera rapidly records images of the illuminated particles which provide the measurements of the particle displacement [18]. Since PIV requires a transparent reproduction of an intracranial aneurysm it can not be applied directly to in vivo aneurysms.

Computational Fluid Dynamics

The current method of choice for estimation of flow patterns in individual aneurysms is CFD [19]. CFD is a technique that numerically solves the Navier-Stokes equation, which for incompressible fluid and constant viscosity is:

\[
\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v} \cdot \nabla) \mathbf{v} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \mathbf{v} + \mathbf{g}
\]  

(1.3)
where $v$ is the velocity, $t$ is the time, $\rho$ is the density, $p$ is the pressure, $\nu$ is the kinematic viscosity and $g$ represents the gravitational acceleration constant. To perform such an approach in aneurysms, a few requirements need to be fulfilled. First, a patient-specific geometry of the aneurysm must be created. The geometry can be obtained from high resolution imaging data, e.g. three-dimensional rotational angiography (3D-RA), CT Angiography or contrast-enhanced magnetic resonance angiography (CE-MRA). Second, inflow boundary conditions are needed. In the majority of studies, these are not personalized but rather based on PC-MRI measurements in slices of intracranial vessels obtained in a few volunteers without aneurysms. Two ways of using these data have been described. First, based on these reference data and using the Womersley solution, fully developed velocity profiles are created and subsequently scaled by the area of the inflow vessel to obtain a mean wall shear stress of 15 dyne/cm$^2$ [5, 7, 20]. Alternatively, uniform velocities on extended inflow vessels are applied [21-22]. These different inflow prescriptions in CFD would result in slightly different outcomes. However, in either case the non-personalized boundary flows may cause deviations from the true velocity profiles that may well be substantial. Disadvantages of CFD are that CFD requires mesh generation, which is often strenuous manual labor, and CFD suffers from long computation times. Another drawback is the need for assumptions such as rigid walls and non-Newtonian fluid properties. An important advantage of CFD is the ability to simulate blood flow patterns at high spatial and temporal resolution. Therefore, CFD could allow estimation of the hemodynamic factors mentioned above and help unraveling their role in rupture risk.

1.3.2 Part II: Improvements

In PC-MRI different velocity values of flowing blood in one voxel are averaged. Therefore, the spatial resolution of PC-MRI in intracranial aneurysms needs to be as high as possible. Generally in MRI, increasing spatial resolution lowers SNR and increases scan time. Furthermore, since PC-MRI captures flow information over the heart cycle, the temporal resolution needs to be as high as possible to measure flow close to peak systole.

Our in vivo PC-MRI measurements in intracranial aneurysms are performed with a resolution of 0.8 x 0.8 x 0.8 mm, measuring 10 cardiac

General Introduction
phases. Normally such an acquisition would take around 30 minutes, which would be too long since other imaging sequences are played out as well and the total scan time is limited to 45 minutes per patient. Therefore, a parallel imaging (SENSE [23]) acceleration factor of 3 is applied, with the disadvantage of SNR degradation. In this thesis other possibilities to shorten scan time or acquire images with more SNR are described.

1.3.3 Part III: Wall shear stress

The current consensus in literature is that wall shear stress, the tangential force that blood exerts on the vessel wall, is an important marker for aneurysm formation, growth [24] and rupture [25].

As stated above, wall shear stress can be calculated using CFD. However, due to aforementioned drawbacks of CFD, alternative wall shear stress estimation methods can considerably contribute to aneurysm rupture risk assessment. In this thesis a novel method to calculate wall shear stress is presented and applied to PC-MRI data measured in an in vitro and in vivo aneurysm.

1.4 Outline of the thesis

Since PC-MRI is a relatively new technique for velocity mapping in intracranial aneurysms, extensive validation is needed. The general aim of this thesis is to validate and optimize PC-MRI. Validation of PC-MRI is described in Part I, optimization in Part II. Furthermore, the validation of wall shear stress calculated from PC-MRI data is described in Part III. In Chapter 2 PC-MRI is applied in a rigid intracranial aneurysm phantom with a size similar to in vivo aneurysms. These data are then compared with PIV in the same phantom and with CFD in a geometry of the phantom. In Chapter 3 a new technique to describe flow patterns, based on multi-scale algorithms, is presented and applied to PC-MRI data. In Chapter 4 a second validation study is described that compared in vivo PC-MRI in eight intracranial aneurysms with CFD. As previously noted, PC-MRI suffers from fairly long scan times. Therefore, in Chapter 5, two acceleration techniques to speed up the PC-MRI sequence are compared. In Chapter 6 the influence of higher field strengths on PC-MRI in intracranial aneurysms is described. A novel method to calculate wall shear stress PC-MRI data is described and validated in Chapter 7. This method is applied to the aneu-
rysm phantom and an in vivo aneurysm; the results are presented in Chapter 8. Finally, the findings of the studies and possible future work are discussed in Chapter 9.

1.5 References


VALIDATION
Complex flow patterns in a real-size intracranial aneurysm phantom: phase contrast magnetic resonance imaging compared with particle image velocimetry and computational fluid dynamics

Pim van Ooij, Annetje Guédon, Christian Poelma, Joppe Schneiders, Marcel Rutten, Henk Marquering, Charles Majoie, Ed van Bavel, Aart Nederveen

Abstract

To validate flow patterns as measured by high resolution time-resolved 3D phase contrast MRI (PC-MRI) in a real-size intracranial aneurysm phantom, retrospectively gated PC-MRI was performed in an intracranial aneurysm phantom at a resolution of 0.2 x 0.2 x 0.3 mm³ in a solenoid rat coil. Both steady and pulsatile flows were applied. The PC-MRI measurements were compared with Particle Image Velocimetry (PIV) measurements and Computational Fluid Dynamics (CFD) simulations. A quantitative comparison was performed by calculating differences between the magnitude of velocity vectors and angles between velocity vectors in corresponding voxels. Qualitative analysis of the results was executed by visual inspection and comparison of the flow patterns.

The root mean square error (RMSE) of the velocity magnitude in the comparison between PC-MRI and CFD was 5% and 4% of the maximum PC-MRI velocity and the median of the angle distribution between corresponding velocity vectors was 16° and 14° for the steady and pulsatile measurements respectively. In the PC-MRI and PIV comparison the RMSE was
12% and 10% of the maximum PC-MRI velocity and the median of the angle distribution between corresponding velocity vectors was 19° and 15° for the steady and pulsatile measurements respectively. Good agreement was found in the qualitative comparison of flow patterns between the PC-MRI measurements and both PIV measurements and CFD simulations. High resolution time-resolved PC-MRI can accurately measure complex flow patterns in an intracranial aneurysm phantom.
Blood flow velocity measurement using phase contrast MRI (PC-MRI) is performed since the advent of MRI in the early eighties [1]. At present the technique has become more mature by incorporating benefits from several technological advancements in MRI, e.g. parallel imaging, increased signal to noise ratio (SNR) of multichannel coils and increased gradient and field strength. Time-resolved measurement of blood flow velocity in three directions using cardiac gated PC-MRI [2] for the assessment of hemodynamic properties in cardiovascular diseases, such as atherosclerosis and intracranial aneurysms, is gaining interest for clinical use. PC-MRI has been extensively validated in the aortic arch [3-5] and the carotid arteries [6-8]; however, in small structures such as the cerebral arteries [9-10] or intracranial aneurysms [11-13], accurate velocity measurements are more challenging due to higher resolution demands and accompanying SNR loss.

Intracranial aneurysms are found in between 1 and 5 percent of the population [11]. The morbidity and mortality rates after rupture of intracranial aneurysms are high [12] and patients are therefore monitored with extreme caution. The decision to treat an incidentally found unruptured aneurysm is based on the rupture risk and the risks related to treatment with 3-6% morbidity and 1.5% mortality rates for coiling [13]. It is believed that additional value of hemodynamics such as inflow jet size, impingement zone size and wall shear stress can substantially improve rupture risk assessment [14].

At present, computational fluid dynamics (CFD) provides estimations of hemodynamic flow behaviour in intracranial aneurysms. The above mentioned hemodynamic risk factors for aneurysm rupture can be derived from these simulations [15-20]. However, straightforward clinical implementation of this method is hampered by the extensive computational time which is in the order of hours or days, or even weeks.

Hemodynamic information from rapid PC-MRI scans would therefore be preferable to CFD simulations for rupture risk assessment, especially in cases where quick treatment decisions need to be made. Unfortunately, the accuracy of PC-MRI in cerebral arteries and aneurysms remains uncertain. Previous studies showed promising results, but were carried out at relatively low resolutions [21-23], in thick slices through the aneurysm [24-26] or in up-scaled phantoms [27-28]. The goal of this study is the validation of a time-resolved three-dimensional PC-MRI sequence at high resolution in a real-size patient-specific phantom of an intracranial aneurysm by compari-
son with particle image velocimetry (PIV) and computational fluid dynamics (CFD).

2.2 Materials and Methods

2.2.1 Phantom

A glass reproduction was manually created based on a high-resolution 3D Rotational Angiography (3D-RA) dataset of an unruptured aneurysm located in the anterior communicating artery of a patient who supplied informed consent. The phantom is displayed in figure 2.1a. The inflow vessel is slightly curved, as is displayed in figure 2.1b, where a top view of the phantom is displayed. The inner diameter of the in- and outflow vessels was 2.1 mm, and the maximum dimensions of the lumen of the aneurysm were approximately 6 x 4 x 9 mm in x, y and z directions respectively. Wall thickness was 0.2-0.6 mm in the inflow vessel, 0.4-0.6 mm in the outflow vessels and 0.8 mm in the phantom itself.

2.2.2 Flow loop setup and pump setting

The aneurysm phantom was connected to a flow loop consisting of a reservoir, a centrifugal pump, a computer-controlled piston pump (pulse generator) and PVC tubes, as displayed in figure 2.1c. The pumps were placed outside the MRI room. Measurements were performed under steady as well as pulsatile flow. Pulsatile flow was created by the combination of steady action of the centrifugal pump, creating the mean flow, and pulsatile action of the computer-controlled piston pump. As input for the pulse generator, a flow signal was used that was obtained from the same patient. This flow was based on the velocity profile, given in figure 2.1d, as measured in the internal carotid artery of the same patient to ensure sufficient in-plane pixels [29] using a time resolved PC-MRI sequence with a resolution of 0.8 x 0.8 x 0.8 mm³. In the PC-MRI measurements, the pump generated an artificial electrocardiogram signal, which was used by the MRI scanner to synchronize the acquisition with the flow pulses.
2.2.3 Particle image velocimetry

PIV was chosen as an independent experimental modality to measure velocity in high resolution. PIV is an optical flow measurement technique that uses the displacement of small tracer particles to obtain instantaneous velocity fields [30]. The characteristics of the tracer particles (size, density and their concentration) are chosen such that the flow field is not influenced by the tracers.

For the PIV measurements, the phantom was fixed in a transparent plastic box and submerged in fluid of the same refraction index (1.471) as the glass of the model, so that optical distortion due to refraction at the curved surfaces was minimized, which is a requirement for accurate PIV measurements. This surrounding fluid was the same as the actual medium (i.e. blood mimicking fluid) and consisted of a 40% glycerol in water solution to match the kinematic viscosity of blood, taken as $2.95 \text{ mm}^2/\text{s}$. To further equalize the refraction index of the fluid, a concentration of 1075 g/L Sodium Iodide (NaI) was added to the water/glycerol solution. As tracer material, 12 micrometer hollow glass spheres (“Sphericel”, Potters) were added in a small amount.

Using a pulsed Nd:YLF laser (New Wave Pegasus XR), a thin light sheet was created to illuminate the tracer particles (and thus forming the measurement volume). The images of the tracers were recorded by means of a high-speed camera (Photron APX RS, 1024x1024 pixels). Using a cross-correlation algorithm the local velocity was estimated (for full details of the implementation used, see e.g. Poelma et al. [31]). This provided an instantaneous snapshot of the two in-plane velocity components. Due to the use of a high-speed camera (used at 300 frames/second), the temporal evolution of the pulsatile flow could be fully captured. Furthermore, the camera was phase-locked with the pump. After obtaining at least 15 cardiac cycles, the light sheet was translated in the vertical (out-of-plane) direction over 0.21
mm, so that the next slice could be measured. This was repeated 20-25 times to obtain velocity data over the entire phantom.

The PIV measurements resulted in datasets describing the velocity fields for both the steady and the pulsatile flow. The spatial resolution for both cases was $0.33 \times 0.33 \times 0.21 \text{ mm}^3$. The in-plane resolution was mainly determined by the concentration of tracer material and the camera resolution and magnification. The out-of-plane resolution was determined by the step size of the translation of the slices, which was chosen to match the expected in-plane resolution. For the pulsatile case, the cardiac cycle was described by 20 phases. Note that standard PIV only provides two out of three velocity components.

While the PIV measurement was relatively fast (a few seconds for one plane), slow data transfer from the high-speed camera to the computer was the limiting factor. The full measurement of all planes therefore took approximately 8 hours. PIV is traditionally an “off-line” method – analysis of the data to obtain velocity fields is done afterwards and can take minutes to days, depending on the complexity of the analysis scheme. Further details of the experimental setup and the measurement time are given in table 2.1.

2.2.4 Phase contrast magnetic resonance imaging

A retrospectively gated [32] PC-MRI scan with four points encoding [33] was performed on a 3T MR system (Philips Medical Systems, Best, the Netherlands). A solenoid rat coil (Philips Hamburg, Germany) with a diameter of 7 cm was used to obtain high SNR. Imaging parameters were: TE/TR: 3.86 / 11.13 ms, flip angle: 15°, non-interpolated spatial resolution: $0.2 \times 0.2 \times 0.33 \text{ mm}^3$, 50 coronal slices, FOV: $25 \times 25 \text{ mm}$, velocity encoding: $50 \times 100 \times 50 \text{ cm/s}$ in the x, y and z direction respectively (see figure 2.1a). 20 cardiac phases were measured.

To avoid pulsatile flow artifacts [34], water was used with a kinematic viscosity (1 mm$^2$/s at room temperature of 20°C) which led to necessary adjustments in pump amplitude and frequency according to the Reynolds and Womersley number as measured in the PIV experiment. The cardiac cycle was set to 3 seconds, resulting in a temporal resolution of 150 ms. Further details of the experimental setup and the scan time are given in table 2.1.

The phantom was placed in a plastic box and was submerged in agar gel. It was placed in the isocenter of the MRI scanner. In every image background
correction was performed by subtracting the mean phase of the stationary surrounding agar gel [35] to minimize influences of concomitant gradient terms [36] and eddy currents. The steady PC-MRI measurement was performed twice in one session to study the reproducibility of the technique. These repeated measurements were performed within 30 minutes.

2.2.5 Computational fluid dynamics

To create a geometry needed for CFD simulations, a 3D-RA dataset was obtained from the phantom filled with a contrast agent. This dataset was segmented using level set algorithms in VMTK [37] and subsequently meshed. For both the steady and pulsatile simulations, the spatial x-, y-, and z-components of the velocity profile of the inflow as measured in the PC-MRI measurements were applied as velocity-inlet boundary conditions. In the pulsatile simulation this was performed for every measured cardiac phase in PC-MRI.

The implementation of the boundary conditions in CFD obtained from PC-MRI was performed as follows: a mask in the PC-MRI data was created by segmenting the phantom with the use of contours created in the FFE images based on level set evolution algorithms [38]. These contours were manually corrected where needed. This mask was registered onto a mask of the CFD mesh using rigid body registration (rotation and translation) in 3DSlicer (http://www.slicer.org). The x-, y-, and z-components of the inlet velocity of the PC-MRI measurement were interpolated onto the faces of the velocity-inlet boundary of the CFD mesh. The velocity-inlet of the CFD geometry was manually clipped in VMTK to match the velocity-inlet of the PC-MRI measurement.

Since the CFD simulations were carried out using Fluent® software (ANSYS, Canonsburg, USA) a user defined function (UDF) was written for the application of the velocity-inlet boundary conditions. As the diameters of the outflow vessels were equal, outflow boundary conditions were applied that prescribed equal outflow for both vessels. The mesh consisted of 742,316 tetrahedral cells with a minimum, average and maximum node spacing of 0.075, 0.14 and 0.24 mm respectively. Further details of the numerical setup and the simulation time are given in table 2.1.
2.2.6 Postprocessing

The contours created in the FFE images were copied to the PC-MRI data to extract the velocity information. To reduce noise, each velocity direction was filtered with a 3D median filter with a kernel of $3 \times 3 \times 3$ voxels.

The PIV image data were analyzed using a three-step iterative algorithm with a final resolution of $32 \times 32$ pixels using 50% overlap, resulting in velocity vector fields with a spatial resolution of $0.33 \times 0.33$ mm$^2$. These vector fields were validated using the universal outlier detection scheme [39], which removed erroneous vectors efficiently. Removed vectors (1-2% of the total data at most) were replaced by linear interpolation of the 3D data set.

The CFD velocity information in every node was extracted and rewritten in matrix form with a resolution of $0.1 \times 0.1 \times 0.1$ mm$^3$.

To allow for a voxelwise comparison of the data, rigid body registration was performed between PIV and PC-MRI. A mask was created from the velocity magnitude of the PIV measurement. Since the PIV measurement only provided the $x$ and $y$ velocity components of the flow, it was not possible to register the velocities of the PIV measurement onto the PC-MRI measurement. Therefore, the previously created PC-MRI mask was registered onto the PIV mask and the resulting rotation and translation were applied on the PC-MRI velocities. After registration the velocity components of the PC-MRI measurement were linearly interpolated to the PIV grid. The resulting $z$-ve-

<table>
<thead>
<tr>
<th>Measurement/Simulation time</th>
<th>steady</th>
<th>1-2 days</th>
<th>1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIV</td>
<td>15 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFD</td>
<td>3 hours</td>
<td>1-2 days</td>
<td>3-5 days</td>
</tr>
</tbody>
</table>
locity component of the registered PC-MRI velocities was discarded since this component was not measured in the PIV measurement.

For the CFD and PC-MRI comparison both modalities provided the full 3D information. Consequently the CFD mask was registered onto the PC-MRI mask and subsequently the velocities were linearly interpolated to the PC-MRI grid. A flow chart summarizing these postprocessing steps is shown in figure 2.2. This flowchart was applied to both steady and pulsatile measurements and simulation.

![Figure 2.2 Flowchart of both steady and pulsatile measurements and simulation and accompanying postprocessing steps.](image)

### 2.2.7 Quantification and Statistics

To compare the different experiments, they need to be dynamically similar. This is established when both Reynolds (Re) numbers and Womersley (α) numbers are similar. Reynolds numbers (Re) were calculated according to:

\[
Re = \frac{\bar{v}D}{\nu} \tag{2.1}
\]

and Womersley (α) numbers according to:

\[
\alpha = \frac{fD^2}{\nu} \tag{2.2}
\]

In these formulas, \(\bar{v}\) is the mean velocity in the inflow vessel, \(D\) the diameter of the inflow vessel, \(\nu\) the kinematic viscosity of the fluid and \(f\) the frequency of the flow pulse. The kinematic viscosity of the fluid used in the PIV measurement was different from the fluids used in the PC-MRI measurements and the CFD simulations (see table 2.1). If the same inflow for the measurements were applied, different Reynolds and Womersley numbers would have been found, according to equations (2.1) and (2.2). Therefore,
the pump settings were adjusted in the PC-MRI measurement by decreasing
the amplitude and frequency of the pulse to match as closely as possible the
Reynolds and Womersley numbers of the PIV experiment. For steady flow,
only the Reynolds number needed to be matched. The Reynolds numbers
were determined based on the velocities obtained by measuring the outflow
volume during one minute.

Due to practical restrictions, it was not possible to exactly match the
Reynolds numbers between PIV and PC-MRI. The flow field is however not
expected to change fundamentally if a small discrepancy in Reynolds number
is present. If Reynolds numbers are similar and viscosity of the fluid used in
the PIV measurements is higher, the resulting velocities will be higher in the
PIV measurement as well. To allow for a quantitative comparison between
the velocities found in the PIV and PC-MRI experiments, the former need
to be scaled. The velocities in x and y directions, as measured in the PIV
measurement, were scaled independently to match the velocities in x and y
directions as measured in the PC-MRI measurement. The ratio between the
mean PIV velocity magnitude and the mean PC-MRI velocity magnitude in a
cross-section through the inflow vessel was used as scaling factor.

Consistency of velocity patterns between the various modalities was
tested using Bland-Altman plots, i.e. scatter plots over all voxels of differenc-
es between velocity magnitudes against their mean value. Direct subtraction
of corresponding voxels in PC-MRI and PIV and CFD would overemphasize
registration and interpolation errors and differences as a result of averaging
due to different voxel sizes. Therefore the difference between a PC-MRI ve-
locity magnitude voxel and a PIV or CFD velocity magnitude in a single voxel
was calculated by using the minimum of the differences between the PC-MRI
voxel and the corresponding PIV or CFD voxel and its 6 nearest neighbours.
In the Bland-Altman analysis of the repeated steady PC-MRI measurements,
the difference between corresponding voxels was calculated, since the posi-
tion and orientation of the measurements was identical.

For each comparison, the mean difference, the standard deviation of
the paired differences (SDp), the limits of agreement (equal to the mean
difference ± 1.96 times SDp), the root mean square error (RMSE) and the
distribution of the angles between vectors was calculated. Since the noise in
the PC-MRI measurement is highest for low velocities, the distribution was
also plotted for voxels with velocity magnitude higher than 20% of the maxi-
imum velocity to illustrate this dependency. Furthermore, the volumetric in-,
and outflow rates of the PC-MRI measurement were calculated. In figure 2.3, the orientation of the slices as displayed in the results section is shown.

2.3 Results

2.3.1 Steady measurements

Reproducibility of PC-MRI

In figure 2.4a the Bland-Altman plot is displayed for the difference of the velocity magnitude between the two PC-MRI measurements. Mean velocity in the total phantom was 10.46 cm/s in the first scan and 10.65 cm/s in the second. RMSE was 1.81 cm/s, which is 5% of the maximum velocity. A small significant difference of 0.19 cm/s (p<0.001) existed between the repeated measurements. In figure 2.4b the distribution of the angles between the velocity vectors in corresponding voxels in the phantom is shown in black, the distribution after discarding the angles at voxels where the velocity magnitude was lower than 20% of the maximum velocity magnitude is shown in gray. The mean and median for difference in direction were 14° and 10° (black dotted line), 8° and 6° (gray dotted line) after discarding voxels with velocity magnitudes of less than 20% of the maximum velocity.
Reynolds numbers as measured in the inflow tube were 284 and 261 for PIV and PC-MRI respectively. The x and y velocities of the PIV measurement were scaled accordingly to be able to compare the PIV and PC-MRI measurements. From figure 2.5a it can be seen that the error was largest at intermediate velocities, where the PC-MRI velocities were higher than the scaled PIV velocities. A small significant difference of 0.32 cm/s (p<0.001) existed between the PC-MRI and PIV measurements. Mean velocities were 7.80 cm/s and 7.65 cm/s for PC-MRI and the scaled PIV respectively. Note that these mean velocities were lower than the mean velocities in the repeated steady PC-MRI measurement since the z-component was not measured in the PIV measurement and discarded in the PC-MRI postprocessing (see flowchart in figure 2.2). RMSE was 4.18 cm/s, which is 12% of the maximum PC-MRI velocity. The mean and median for difference in direction were 35° and 19° (black line in figure 2.5b), 11° and 9° (gray line) after discarding vectors with a velocity magnitude less than 20% of the maximum velocity magnitude.
In figure 2.6a and b the x and y velocity vectors are shown in a slice through the aneurysm. The location of this slice is displayed in figure 2.3. It can be seen that the inflow jet of the scaled PIV measurement was skewed slightly to the right (arrow 1) with respect to the inflow jet of the PC-MRI measurement. Furthermore, a vortex exists at arrow 2, which was not found in the PC-MRI measurement. In figure 2.6g and h similar flow patterns are found but in the PIV measurements the velocity magnitude was higher in the middle of the phantom (arrow 3) while in the PC-MRI measurements the velocity magnitude was higher at the edges. This can also be seen in figure 2.6i where velocity difference in the middle of the phantom was negative, indicating that PIV-velocities were higher here, in contrast to velocity differences at the edges which are positive, indicating that PC-MRI velocities are higher here. Note that these figures are displayed at the resolution of the PIV measurement.
PC-MRI versus CFD

The Bland-Altman plot in figure 2.7a shows that differences between steady CFD and PC-MRI are close to zero, though a small systematic difference was found (0.27 cm/s, p<0.001). The error was largest in voxels with a velocity magnitude around 10 cm/s. Mean velocities were 10.50 cm/s for MRI and 9.38 cm/s for CFD. RMSE was 2.01 cm/s, 5% of the maximum PC-MRI velocity. The inflow measured from the steady PC-MRI data was 0.38 mL/s, the sum of the two outflows was 0.38 mL/s as well. The mean and median for difference in direction were 22° and 16° (black line in figure 2.7b) respectively, 14° and 10° (gray line) after discarding velocities lower than 20% of the maximum velocity. Figures 2.6d and e show similar flow patterns for PC-MRI and CFD. In figure 2.6k and l the velocity at the top is higher for CFD than for PC-MRI (arrow 4). Directions of velocity vectors were similar in these images, except in the middle of the phantom with low velocity in PC-MRI (arrow 5). Note that these figures are displayed at the resolution of the PC-MRI measurement.

2.3.2 Pulsatile measurements

PC-MRI versus PIV

The Womersley number in the PIV measurement was 1.2 and set accordingly for MRI by reducing the frequency of the pulsatile pump from 1 to 0.33 Hz. The Reynolds numbers for PIV and PC-MRI in the inflow vessel are displayed in figure 2.8a. The scaling factor averaged over time was calculated and the PIV measurement was scaled accordingly. The mean velocity in the total phantom for both measurements is displayed in figure 2.8b. A small significant difference of 0.25 cm/s (p<0.001) between PIV and PC-MRI was found. The Bland-Altman plot in figure 2.9a displays that the
largest errors were found in the velocity range near 20 cm/s. At higher mean velocities the PIV velocities were predominantly higher than the PC-MRI velocities. In the separate Bland-Altman plots for systole (at cardiac phase 5) and diastole (at cardiac phase 20) in the insets of figure 2.10a it can be appreciated that the errors (both mean and SDp) in diastole were smaller than in systole. RMSE averaged over time is 3.31 cm/s, 10% of the time-averaged PC-MRI maximum velocity. The mean and median for difference in direction were 30° and 15° respectively, 7° and 6° after discarding velocities below 20% of the maximum velocity. In figure 2.10b, where flow patterns in systole are shown, the inflow of the scaled PIV is slightly skewed to the right compared to PC-MRI measurements as was observed in the steady measurement. This also holds for figures 2.10g and h. Furthermore, a discontinuity of flow was found at arrow 6 in figure 2.10h. In figures 2.11a and b, the velocity was higher at the edges of the PC-MRI measurement, whereas the velocity was higher in the middle of the phantom in the scaled PIV measurement. In diastole (figures 2.11g and h) this is not seen, locations of relatively high velocities of the PC-MRI and PIV measurement corresponded better, especially at the edges (see figure 2.11i).
Complex flow patterns in a real-size intracranial aneurysm phantom: phase contrast magnetic resonance imaging compared with particle image velocimetry and computational fluid dynamics
Figure 2.11 Top row: peak systolic MRI (a) and PIV (b) velocity vectors and velocity magnitude difference (c). Second row: peak systolic MRI (d) and CFD (e) in plane velocity vectors and velocity magnitude difference (f) images in a similar slice. Third row and fourth row: same slices at end diastole. Velocities are in cm/s. See for slice orientation figure 2.3.
PC-MRI versus CFD

The Reynolds numbers in the inflow vessel for PC-MRI and CFD are displayed in figure 2.12a. The mean velocity in the total phantom for both measurements is displayed in figure 2.12b. It appears that both Reynolds numbers and mean velocity were lower for CFD than PC-MRI in systole. The Bland-Altman plot in figure 2.13a displays that the largest errors were found in the intermediate velocity range, whereas the highest velocities were more accurate. Here again a small significant difference of 0.20 cm/s (p<0.001) was present, whereas similar to PIV the errors were larger in systole than in diastole (see insets). RMSE averaged over time was 1.19 cm/s, 4% of the time-averaged maximum PC-MRI velocity. The mean inflow in the pulsatile PC-MRI measurement was 0.25 mL/s, the total mean outflow was 0.23 mL/s, resulting in a difference of 6%. The outflow was predominantly lower in systole. The mean and median for difference in direction were 20° and 14° respectively, 9° and 6° after discarding the velocities below 20% of the maximum velocity, (see figure 2.13b). The inflow jet of the PC-MRI measurement and CFD simulation corresponded nicely for both systole (figures 2.10d and e) and diastole (figures 2.10j and k). In figures 2.11d and e higher velocities are found at the edges of the phantom for both PC-MRI and CFD except at the top of the image, where the CFD velocity was slightly higher. In the middle of the phantom the PC-MRI shows colliding flow (arrow 7). In diastole (figures 2.11j and k) flow patterns were similar.

In figures 2.14a, b, e and f a small vortex in the tip and a large vortex in the middle of the phantom can be distinguished for both modalities, as well as a small vortex at the bottom of the phantom in diastole (e and f). In figures 2.14c, d, g and h, the vortex and the inflow jet are similar as well. In figure 2.15 similar flow details can be discerned such as the small vortex at the base of the inflow jet (all images) and the complex flow pattern in the tip of the phantom (c, d, g and h) in slice on the right.
Figure 2.13 (a) Bland-Altman plot of the velocity magnitude difference between PC-MRI and CFD in the pulsatile measurement: mean ± SDp = 0.20 ± 1.41 cm/s, inset up: Bland-Altman plot at systole, cardiac phase 5, with mean difference and SDp, inset down: Bland-Altman plot at diastole, cardiac phase 20, with mean difference and SDp. (b) Distribution of the angles between the 3D velocity vectors.

Figure 2.14 Top row: peak systolic MRI (a,c) and CFD (b,d) in plane velocity vectors in two sagittal cross-sections. Second row: end diastolic MRI (e,g) and CFD (f,h) in two sagittal cross-sections. Velocities are in cm/s. See for slice orientation figure 2.3.

Figure 2.15 Top row: peak systolic MRI (a,c) and CFD (b,d) in plane velocity vectors in two sagittal cross-sections. Second row: end diastolic MRI (e,g) and CFD (f,h) in two sagittal cross-sections. Velocities are in cm/s. See for slice orientation figure 2.3.

Validation
Discussion

In this study we have shown that a good qualitative and quantitative agreement exists between PC-MRI measurements, CFD simulations and PIV measurements of flow patterns in a real-size intracranial aneurysm. We demonstrated this agreement for both steady and pulsatile measurements. The difference between CFD simulations and PC-MRI measurements (RMSE 4-5 %) was smaller than that between PIV measurements and PC-MRI measurements (10-12 %). Velocity directions (median deviation less than 10° for velocities higher than 20% of the maximum) were comparable between the modalities.

Previous studies have shown that PC-MRI can measure flow patterns in intracranial aneurysms [21-23, 40] in patients, though the accuracy of the velocity fields remains uncertain. PC-MRI data provides valuable information on the severity of the disease and may subsequently aid in therapeutic decision making. PC-MRI is however not yet fully incorporated in the clinical setting. One of the reasons may be that, to fully and convincingly capture complex flow patterns in intracranial aneurysms, high resolution scans are mandatory. Since high resolution scans increase scan time and can be hampered by low SNR, the technique is mostly applied at relatively low resolutions (around 1 mm³), leading to loss of flow information due to averaging of velocity in a voxel, increased intravoxel dephasing and inaccurate vessel wall definition as a result of partial volume effects. To avoid scan time limitations and resulting flow artifacts, the accuracy of PC-MRI has been tested in phantoms. Several phantom experiments were carried out in upscaled phantoms [27-28]. Real-size phantoms were used as well, but in these studies PC-MRI was performed in a single cross-sectional slice [24-26] instead of a 3D volume with isotropic resolution. Furthermore, velocity comparisons on a voxel-by-voxel basis are rarely found in literature and are generally limited to a qualitative comparison.

Our study provides assessment of the accuracy of high resolution PC-MRI using two independent modalities in a real size aneurysm phantom under both steady and pulsatile flow conditions and presents a quantitative comparison between the modalities.

The steady flow measurement showed good reproducibility, indicating the precision of the PC-MRI measurement itself. The minor systematic error could have been caused by small differences in the speed of the pump that generated the mean flow. Interestingly, variation between PC-MRI and CFD
was comparable to that between repeated PC-MRI measurements, illustrating the good agreement between both modalities. This is supported qualitatively by figures 2.6d, e, k and l.

For both CFD and PIV, the mean difference, standard deviation, RMSE, mean and median angle for the pulsatile experiment were smaller than for the steady experiments, suggesting better correspondence between the pulsatile measurements than between the steady measurements. However, considering the Bland-Altman plots of systole and diastole in figure 2.9a and 2.13a, the differences and standard deviations in systole were larger, whereas the differences and standard deviations in diastole were smaller than those of the steady measurements. This indicates that the error scales with the input velocity. Since the duration of systole is shorter than the duration of diastole, more cardiac phases will produce a relatively small error compared to the steady measurements. When the error is subsequently averaged over the heart cycle, the error will be smallest in the pulsatile measurement.

In all cases small significant velocity differences remained between PC-MRI and CFD and PIV. In systole the systematic deviations were largest indicating that the discrepancies between the modalities depend on the velocity magnitude. These discrepancies can be attributed to several limitations of the present study. The fact that the geometry of the phantom for CFD was measured with 3D-RA, whereas the geometry for the PC-MRI was obtained by segmentation of the FFE images, may have introduced a small bias. A second limitation is that small inaccuracies in the measured PC-MRI velocity in the inflow vessel used for the inflow boundary conditions propagates in the velocity values simulated by CFD in the phantom. This may explain the lower mean velocity of CFD during systole in the pulsatile simulation.

The quantitative agreement between PIV and PC-MRI was somewhat less than that between CFD and PC-MRI. The Bland-Altman plot in figure 2.5a shows that differences can be as large as 30 cm/s when PC-MRI is compared with the scaled PIV velocities. This was mainly caused by the skewed inflow jet, as shown in figure 2.6b. Spatial restraints and slightly modified angles of inlet and outlet ports may have caused this difference. The skewed inflow jet led to differences in velocity magnitude and caused flow properties to develop slightly different, as can be seen by the earlier development of the small vortex in figure 2.6b at arrow 2 and the higher velocity in the middle of the phantom in figure 2.6b at arrow 3, in contrast to the low PC-MRI velocity at arrow 3 in figure 2.6g. When vortices occurred at different locations in the
phantom for PIV and PC-MRI, relatively large velocity vector angle differences were found as well. This explains the wide distribution of the velocity vector angle difference in figure 2.5b.

Another limitation in the PIV setup was that blood mimicking fluid was used, whereas water was used in the PC-MRI measurement. The blood mimicking fluid was also tested in the PC-MRI measurement but led to ghosting artifacts, possibly due to the high velocities and the accompanying imperfect synchronization of the PC-MRI acquisition with the pulses of the pump. Therefore, scaling of the results measured with PIV was necessary which may have introduced bias. A third limitation of the PIV study was discussed by Ford et al. [41] who showed that flow is difficult to measure close to the wall of the phantom. The discontinuity in the flow field as seen in 2.10b at arrow 6 is the result of a non-perfect refractive index match. In that region, one of the outflow vessels was attached to the lumen during fabrication. Cooling of the glass induced stress and a non-uniform refractive index. A thin reflection remained visible in the PIV images at the joint, which invalidated flow measurements locally.

Our results cannot be straightforwardly extrapolated to the clinic since our MRI setup is not suited for patients. The steady measurement has however a scan time that is acceptable in the clinic and if adequate MRI hardware is available this measurement can be translated to the in vivo situation. Furthermore, PC-MRI measurements of lower spatial and temporal resolutions and lower SNR can still provide valuable information about flow patterns in intracranial aneurysms. We indeed noticed that the in vivo PC-MRI measurement performed in the same patient showed similar flow patterns as observed in the phantom, see Chapter 5. Patient-specific CFD is needed to further validate these measurements, see Chapter 4.

In conclusion, these results show that high resolution time-resolved 3D PC-MRI can accurately capture complex flow patterns in an intracranial aneurysm phantom. Remaining differences between PC-MRI and other modalities are mainly attributed to small differences in the inflow conditions that are difficult to avoid in experimental setups.

2.5 Acknowledgements

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2.6 References


Complex flow patterns in a real-size intracranial aneurysm phantom: phase contrast magnetic resonance imaging compared with particle image velocimetry and computational fluid dynamics.

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Multi-scale flow patterns within an intracranial aneurysm phantom

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Abstract

Straight-forward quantification of variations of flow patterns within aneurysms fails to accurately describe flow patterns of interest. We applied a multi-scale decomposition of the flow in well-defined patterns to detect and quantify flow patterns in an aneurysm phantom that was studied with three different modalities: PC-MRI, CFD, and PIV. The method intuitively visualizes main patterns such as locally uniform flow, in- and outflow, and vortices. It is shown that this method is a valuable tool to quantitatively compare scale-dependent complex flow patterns in aneurysms.

chapter 3
3.1 Introduction

Intracranial aneurysms are found in approximately 5 percent of the population. Because the mortality rate after rupture is high [1], patients are monitored with extreme caution. The decision to treat is based upon careful consideration of risk of rupture since treatment is associated with a small but significant chance of morbidity and mortality. Blood flow patterns within aneurysms are believed to be associated with the growth and risk of rupture.

Currently, there are two approaches to assess the flow within an intracranial aneurysm: phase-contrast MRI (PC-MRI) and Computational Fluid Dynamics (CFD) simulations [2-5].

Despite the increasing quality of flow measurements using PC-MRI, measuring flow patterns in intracranial aneurysms is still challenging [4-5]. On the other hand, errors in the used geometrical model of the aneurysm [2] or simplifications such as Newtonian fluid behavior may generate errors in the computed CFD flow [4].

The accuracy of CFD and PC-MRI flow measurement and calculations remains uncertain. At low resolutions some promising results have been presented [4-6]. However, hemodynamic flow patterns are present at a broad range of spatial and temporal scales.

The quantification of differences in flow patterns is not straight-forward: differences in magnitude and direction of the flow fields only represent variations in the locally uniform, or laminar, flow and do not intuitively describe variations of typical flow patterns such as vortices. Furthermore, differences in magnitude and direction give no information on the scale of the flow patterns.

We present a multi-scale description of locally uniform and singular flow patterns for visualization and quantitative comparison of flow patterns in an intracranial aneurysm phantom using PC-MRI, CFD, and particle image velocimetry (PIV) measurements. The description of local flow as presented here, allows quantification of flow patterns by location and scale.
3.2 Materials and Methods

3.2.1 Phantom

Based upon a 3D Rotational Angiogram, a volume image data of an intracranial aneurysm located in the anterior communicating artery, a glass reproduction was manually created (figure 3.1). The luminal diameter of the in- and outflow arteries was 2.1 mm. 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.

3.2.2 Imaging

PC-MRI data were obtained using a four point method on a 3T MR scanner (Philips Medical Systems, Best, the Netherlands). A solenoid rat coil (Philips Hamburg, Germany) with a diameter of 7 cm was used. Additional scanner specific settings were previously reported in [7] and Chapter 2. The measurement was performed within 15 minutes. A 3x3x3 median filter was applied to reduce noise. Spatial resolution was 0.2 x 0.33 x 0.2 mm³.

Additionally, PIV [8] was performed to measure the velocity. For these measurements, the phantom was fixed in a transparent plastic box and submerged in a fluid with the same refraction index as the glass of the model. Full details of the implementation are presented in [9]. The spatial resolution was 0.33 x 0.33 x 0.21 mm³. The PIV measurements only assessed the in-plane velocity components.

The CFD simulations (Fluent 6.3, ANSYS, Canonsburg, USA) were performed on a model based upon 0.16 x 0.16 x 0.16 mm³ 3D Rotational Angiogram. This image was segmented with a level set algorithm [10]. The mesh consisted of 742,316 tetrahedral cells with an average node spacing of 0.14 mm. The 3D velocity profile of the inflow as measured in the PC-MRI measurements was applied as boundary condition. After computation, the CFD data was interpolated to an isotropic 0.1 mm grid.

The three data sets were registered using a rigid transformation allowing a voxel-wise comparison. After registration of the PC-MRI images, all the data were interpolated on an isotropic 0.1 mm³ grid.

Because 2D flow characterization is much better described in the literature, we focus here on analyzing in-plane flow, which is defined as flow within a single slice. Also, the dynamic aspect of the flow patterns is in this study not taken into consideration and we analyse a steady flow.
3.2.3 Scale space

Scale-space techniques originate in the context of image processing in the field of computer vision. Its potential for flow visualization has been explored only on a limited scale. Here, we follow the method developed by [11] and [12] to describe flow fields locally with scale-dependent basis functions. The local 2D vector-flow field \( F(z_0 + \Delta z) \) in the neighborhood of \( z_0 = (x + iy) \) with \( i = \sqrt{-1} \) and at scale \( \sigma \) is represented as a linear combination of complex basis functions:

\[
F(z_0 + \Delta z) = \sum_{k,l} A_{kl}(z_0, \sigma) \phi_{kl}(\Delta z, \sigma)
\]  

(3.1)

where the notation \( \Delta z \) is used to denote that the flow is described in the neighborhood of \( z_0 \). The local support size is controlled by a zero-mean Gaussian function \( G(z, \sigma) \) with standard deviation \( \sigma \) forming scale-dependent orthogonal basis functions:

\[
\phi_{kl}(\Delta z, \sigma) = \frac{\Delta z^k G(\Delta z, \sigma)}{[\Delta z^k G(\Delta z, \sigma)]} 
\]  

(3.2a)

and

\[
\phi_{kl}(\Delta z, \sigma) = \frac{i\Delta z^k G(\Delta z, \sigma)}{[\Delta z^k G(\Delta z, \sigma)]} 
\]  

(3.2b)

Without loss of generality we omit the underscore in \( z_0 \) in the following. The projection coefficients \( A_{kl}(z, \sigma) \) are calculated with a cross-correlation of the global flow field \( F(z) \) and the basis functions \( \phi_{kl}(z, \sigma) \):

\[
A_{kl}(z, \sigma) = F(z) \otimes \phi_{kl}(z, \sigma)
\]  

(3.3)

with \( \otimes \) the cross-correlation operator.
3.2.4 Feature extraction

Locally uniform flow, which is associated with non-singular flow, sometimes called laminar flow [13], is represented with the two coefficients $A_{0,1}$ and $A_{0,2}$. Singular points in vector fields are locations where the flow field vanishes, i.e. $F(z)=0$, which implies that $A_{0,1}=A_{0,2}=0$. The local flow field at a singular point can be approximated with the basis functions with $k$ larger than 0, which is therefore referred to as the singular base. The singular energy is defined as the contribution of the flow as given by the singular base as the squared sum of the singular projection coefficients:

$$E_{\omega}(z, \sigma) = \sum_{k>0} \sum_{l>0} A_{k,l}(z, \sigma)$$  \hspace{1cm} (3.4)

Previously, this expression has been applied to search for local maxima in scale and location of the singular energy in flow patterns of meteorological data [11]. We propose three additions to this approach to enable the accurate description of flow patterns in a cerebral aneurysm.

First, because there is a large range of flow magnitudes, a straight-forward implementation of this approach may obscure important low magnitude, singular flow patterns such as vortices: large velocity gradients have a non-zero energy projection on the singular base and may dominate the singular coefficients. This effect has already previously been described [14] in which a line integral convolution method to qualitatively and visually enhance flow features with low magnitudes is presented. We normalize the flow by its scale-dependent locally uniform flow in the calculations:

$$\tilde{A}_{k,l}(z, \sigma) = \frac{F(z) \otimes \psi_{k,l}(z, \sigma)}{\sqrt{A_{k,l}(z, \sigma) + \tilde{A}_{k,l}(z, \sigma)}}$$  \hspace{1cm} (3.5)

with $k>0$.

Second, because the flow is only present in a restricted part of the image, the velocity magnitude is zero in the larger part of the image. Therefore, straight-forward implementation of this approach results in leaking of energy outside the phantom. Consequently, the magnitude of the coefficients $\tilde{A}_{k,l}(z, \sigma)$ within the phantom decreases with increasing scale, which hinders the selection of an optimal scale. We here propose an alternative optimal scale selection in which the convolution is only performed within the aneu-
rysm, in practice this is achieved by normalizing the base of its contribution within the aneurysm:

$$\left| \phi_i(z, \sigma) \right| = \int_{\Omega_{\text{mask}}} \phi_i(z, \sigma) \cdot \phi_i(z, \sigma) dz$$

(3.6)

where $\Omega_{\text{mask}}$ is the mask of the aneurysm and is defined by the non-zero flow pixels.

Finally, we choose to detect local maxima of each $A_i(z, \sigma)$ rather than the summed singular energy to focus on the specific flow patterns. The singular pattern scales are selected as extremes of the coefficients both in scale and spatial position using the SIFT descriptor [15], which includes downsampling of the data for larger scales.

### 3.3 Results

In figure 3.2 the coefficient representation of first four basis functions at $\sigma=0.2$ mm is shown. The $A_{i,0}$ coefficients represent the flow in the x-direction and show that at this scale the flow on the left half in the aneurysm is mainly directed to the left, and in the right half is to the right with a small area with the opposite direction. The $A_{i,1}$ coefficients represent the flow in the y-direction and shows that flow is mainly directed in the positive y-direction. The $A_{i,2}$ coefficients represent sources and sinks in which the flow is directed into or out of the plane. Figure 3.2c shows that the main inflow is at the base of the phantom. Finally, the $A_{i,3}$ coefficients represent vortices where the sign describes the angular direction. There is a large vortex in the clockwise direction just before the right artery and a smaller more proximal vortex with a counterclockwise direction. We suggest comparing this figure with the original basis functions [12] to enhance interpretation.

Figure 3.3 illustrates the scale dependency of the singular energy. This figure shows that on a small scale the inflow at the base of the phantom and the larger vortex dominate the singular flow (figure 3.3a), whereas at a larger scale the rotation of the flow corresponding with the flow into the right distal artery dominates the singular energy (figure 3.3c).
We detected a number of typical flow pattern features in the PC-MRI and CFD data, which are depicted in figure 3.4 for the CFD data. Table 3.1 shows a number of characteristics of these features for both modalities. The strongest vortex is found in both data sets close to each other. The scale of this vortex is in the CFD data slightly smaller and its magnitude weaker. The second vortex, with a smaller scale and magnitude, is detected more proximal to the aneurysm base, which scale is determined as 0.36 and 0.30 mm for CFD and PC-MRI respectively. The distance between the centers of this vortex is larger than the previous one. However, the scale and strength...
are rather similar. The inflow at the base is also described by a singular flow pattern. Here, the PC-MRI data suggest a slightly smaller scale than in the CFD computation. The position and magnitude are rather similar for both modalities.

<table>
<thead>
<tr>
<th></th>
<th>Vortex 1</th>
<th>Vortex 2</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFD</td>
<td>Position (mm)</td>
<td>9.2, 14.2</td>
<td>10.6, 12.3</td>
</tr>
<tr>
<td></td>
<td>Scale (mm)</td>
<td>0.62</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Magnitude</td>
<td>1.4</td>
<td>0.52</td>
</tr>
<tr>
<td>MRI</td>
<td>Position (mm)</td>
<td>9.2, 14.0</td>
<td>10.5, 13.1</td>
</tr>
<tr>
<td></td>
<td>Scale</td>
<td>0.76</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Magnitude</td>
<td>1.8</td>
<td>0.47</td>
</tr>
</tbody>
</table>

It was previously reported that the PIV measurements deviated somewhat from the PC-MRI measurements due to different viscosity of the fluid and a skewed inflow jet as a result of spatial restraints and slightly modified angles of inlet and outlet ports in PIV [7] and Chapter 2. Despite the differences, similar patterns were observed [7] and Chapter 2. Figure 3.5 shows the analysis of a registered slice of the PIV and PC-MRI measurements. Figure 3.5a and b show a different pattern of the vortex flow pattern, where
the PIV measurement (figure 3.5a) shows an isolated maximum of the vortex coefficient, which is not found in PC-MRI (figure 3.5b). However, in a next slice of the PC-MRI data, a similar vortex pattern is observed (figure 3.5c) with a similar scale and strength.

3.4 Discussion

We have presented a multi-scale flow feature extraction method to visualize and quantify flow patterns in an intracranial aneurysm phantom. In this approach, the aneurysm flow is locally represented as a linear combination of locally uniform background flow and singular flow contributions. Differences in locally uniform flow are accurately described by its difference in magnitude and direction. We have shown that the singular contribution of the flow can efficiently be described with scale-dependent flow patterns. The extracted features are highly distinctive, allowing feature matching for flow field comparison.

The scaling of the coefficients as we suggested here results in a visually improved representation of the singular flow contributions. To be able to select a scale for the singular flow patterns in this bounded flow area, we needed to exclude the region outside the phantom in the calculations.

In contrast to previous studies, the dominant scales of the vortices cannot be considered large as compared to the geometric structure [15-16].

The results show that there is a good correspondence between the PC-MRI and CFD measurements. Some subtle differences, such as scale and magnitude of the two vortices were found. Differences and similarities between flow patterns measured with PC-MRI and PIV, as described in [7] and Chapter 2 could also be detected with the presented method.

Flow in an aneurysm is 3D, however, the analysis is restricted to 2D in the x-y plane and neglects the vertical flow component, perpendicular to the plane of consideration. The vertical flow is expected to have an important
contribution to the flow patterns. However, even the simplified 2D approach is a valuable tool to efficiently study flow patterns on multiple scales. The results presented here advocate that this approach should be extended to a 3D description. A simple extension could be to analyze the flow patterns in e.g. coronal or sagittal planes. However, we believe that a full 3D extension of the theory as presented here should be investigated. The results presented here are applied to steady flow. This approach is well suited to be applied to pulsatile flow measurements, which is planned for the near future.

3.5 Conclusion

We applied a multi-scale evaluation of complex flow within a phantom of an intracranial aneurysm. The proposed method facilitates a scale-dependent comparison of singular flow patterns. We have shown that singular patterns are scale-consistent for multiple imaging modalities and occur at small scales compared to the structure.

3.6 References


Three-dimensional phase contrast MRI at 3T in intracranial aneurysms compared with patient-specific computational fluid dynamics

Pim van Ooij, Joppe Schneiders, Henk Marquering, Charles Majoie, Ed van Bavel, Aart Nederveen

Submitted for AJNR American Journal of Neuroradiology
chapter 4

Abstract

Background and Purpose

CFD has been proven valuable for assessing blood flow in intracranial aneurysms, which may add to better rupture risk assessment. However, this technique suffers from several drawbacks such as long computation times, which may hinder its clinical implementation. 3D PC-MRI is an alternative technique that enables fast measurements of blood flow. The purpose of this study was to compare flow patterns based on 3D PC-MRI with CFD estimates.

Methods

Eight intracranial aneurysms were studied. 3D PC-MRI data was acquired at 3T with 0.8 mm isotropic resolution for 10 cardiac phases. Patient-specific inflow boundaries for CFD were measured with a separate 2D PC-MRI sequence at high temporal and spatial resolution. 3D PC-MRI and CFD were quantitatively compared by calculation of differences between velocity vector magnitudes and angles. Differences in flow patterns expressed
as the presence and strengths of vortices were determined by calculation of singular flow energy.

**Results**

In peak systole, flow features such as vortex patterns were similar. In end diastole, 3D PC-MRI measurements appeared inconsistent due to low velocity-to-noise ratios. The average relative difference in velocity magnitude was 73.6±56.7% in systole and 35.6±26.2% in diastole. For singular energy this was reduced to 21.9±16.3% and 21.2±19.7%, indicating better agreement between 3D PC-MRI and CFD when flow patterns are considered instead of velocity magnitude.

**Conclusion**

In systole, a good agreement between 3D PC-MRI and CFD on flow pattern visualization and singular energy calculation was found. However, in diastole flow patterns of 3D PC-MRI differed from those obtained from CFD due to low velocity-noise ratios.
4.1 Introduction

Despite a decrease of case fatality of subarachnoid haemorrhage as a result of intracranial aneurysm rupture in recent years [1], this devastating event is lethal in one-third [2] to fifty percent [3] of the patients. Moreover, one-third of the surviving patients are disabled and need recovery treatment [2]. Treatment of incidentally found unruptured aneurysms consist of endovascular coiling or surgical clipping, with procedure-related morbidity and mortality rates slightly in favor of the former [4]. Since the risks of treatment potentially outweigh the risk of rupture [5], treatment decision should be based on as much available information on the individual aneurysm as possible. It is widely believed that intra-aneurysmal hemodynamics contribute substantially to rupture risk assessment and treatment planning assistance [6]. Many studies showed promising results when conducting assessment of risk factors such as intra-aneurysmal flow patterns and wall shear stress using patient-specific CFD [6-17]. A drawback of performing CFD is the difficulty in converting large numbers of patient-specific data into workable models [18]. Without patient-specific data for infl ow and outfl ow boundary conditions, assumptions have to be made regarding heart rate and blood flow, the shape of the inlet velocity profile and fl ow division ratios in the outfl ow branches [19]. Further drawbacks are the need for large computational power and extensive calculation time. Despite these drawbacks, CFD has recently been used to associate intra-aneurysmsal hemodynamics with rupture [7, 15, 18, 20].

The enormous advancements in MRI technology in the past decade now allow direct measurement of intra-aneurysmal flow, using time-resolved 3D PC-MRI (3D PC-MRI) [21-23]. This technique has been proven useful in large vessels such as the aorta [24-28] and the carotid arteries [29-30]. 3D PC-MRI was also used in intracranial aneurysms [31-36] with promising results. Moreover, the technique was validated against CFD in an up-scaled model at 1.5T [37] and at 3T in a real-size phantom [38]. However, clinical application of 3D PC-MRI in intracranial aneurysms is complicated by the requirements for high resolution, high SNR and realistic scanning times. In this study, a 3D PC-MRI sequence with a scan duration of approximately 10 minutes, and therefore clinically feasible, was applied to eight intracranial aneurysms. The results were compared with patient-specific CFD in which spatial and temporal boundary conditions obtained from a separate time-re- solved 2D PC-MRI (2D PC-MRI) acquisition were applied. The purpose of
this study was to assess if the results of 3D PC-MRI and patient-specific CFD are comparable and if 3D PC-MRI is able to measure important quantitative and qualitative features of intra-aneurysmal flow.

### 4.2 Materials & Methods

#### 4.2.1 Population

The study was approved by the local medical ethics committee. All patients supplied written informed consent. Age of the patients ranged between 44-65 years. Five patients were female, 3 patients were male. Locations and size of the aneurysms were determined on a 3D TOF MRA sequence and are listed in Table 4.1.

#### 4.2.2 MR imaging

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

First, a high resolution 3D TOF MRA sequence was performed with a scan resolution of 0.39 mm x 0.6 mm x 1 mm, interpolated to 0.39 mm x 0.39 mm x 0.5 mm. Imaging parameters were: TE / TR / FA: 4.2 ms / 21.4 ms / 20°; Field of view: 200 mm x 200 mm x 92 mm; parallel imaging factor: 2.5; scan time: 6.16 min.

Second, to acquire 2D PC-MRI data that served as inflow boundary conditions for CFD, a slice was placed perpendicular to the parent artery proximal to the aneurysm. The acquisition was retrospectively gated using

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>Location</th>
<th>Size (mm, length x width x height)</th>
<th>Isotropic voxel size 3DRA (mm³)</th>
<th>Mesh volume (mm³)</th>
<th>Number of mesh Elements</th>
<th>Element density (elements / mm³)</th>
<th>Input flow (mL/s)</th>
<th>2D PC-MRI</th>
<th>3D PC-MRI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Left MCA</td>
<td>13.1 x 7.6 x 8.1</td>
<td>0.22</td>
<td>554</td>
<td>1,765,310</td>
<td>3186</td>
<td>1.6</td>
<td>3.0</td>
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<tr>
<td>2</td>
<td>BA</td>
<td>8.7 x 6.3 x 7.4</td>
<td>0.22</td>
<td>272</td>
<td>1,422,476</td>
<td>5230</td>
<td>2.2</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Right MCA</td>
<td>14.7 x 8.1 x 9.6</td>
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<td>732</td>
<td>2,608,270</td>
<td>3583</td>
<td>2.1</td>
<td>4.3</td>
<td></td>
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<tr>
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<td>Right MCA</td>
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<td>261</td>
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<td>5623</td>
<td>2.0</td>
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<tr>
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<td>Right MCA</td>
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<td>0.17</td>
<td>260</td>
<td>1,168,002</td>
<td>4492</td>
<td>1.9</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
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<td>4282</td>
<td>2.0</td>
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<td></td>
</tr>
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<td>674</td>
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<td>2.3</td>
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<tr>
<td>8</td>
<td>BA</td>
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<td>0.22</td>
<td>687</td>
<td>2,599,296</td>
<td>3725</td>
<td>2.6</td>
<td>3.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1 Locations and size of the aneurysms; voxel size of the 3D-RA datasets; volumes, number of elements, element density of the meshes and input flows measured by 2D and 3D PC-MRI.
either ECG or PPU. Scan resolution was 0.64 mm x 0.65 mm x 3 mm. Further imaging parameters: TE / TR / FA: 5.7 ms / 8.5 ms / 10°; Field of view: 200 mm x 200 mm x 3 mm in one slice; parallel imaging factor: 2; for aneurysm 5 the VENC was 70 cm/s in all directions, for the others 100 cm/s in all directions. To keep the scan time close to 3 minutes and 30 seconds, the number of measured cardiac phases, i.e. temporal resolution, depended on heart rate and ranged between 23-36 cardiac phases. The view sharing factor for the retrospective sorting of acquired k-lines was set to 1.8 [39].

Third, the 3D PC-MRI acquisition was retrospectively gated using either ECG or PPU at an acquired resolution of 0.8 mm x 0.8 mm x 0.8 mm. Further imaging parameters: TE / TR / FA: 3.0 ms / 5.8 ms / 15°; Field of view: 200 mm x 200 mm x 20 mm in 25 transversal slices; parallel imaging factor of 3; the velocity encoding was 70 cm/s in all directions for aneurysm 5 and 100 cm/s in all directions for the others; scan time: 10.22 min at 60 beats/min. The number of acquired cardiac phases was 10.

For aneurysm 1, the 2D PC-MRI measurement was performed 9 months later than the 3D PC-MRI measurement, due to a failed initial attempt to acquire the 2D PC-MRI sequence.

4.2.3 MRI Postprocessing

Phase images were corrected for background phase offset errors by subtracting the average phase in a static region of interest near the aneurysm. Phase correction was performed for every velocity encoding direction and cardiac phase individually [40]. The segmentation of the vessel and aneurysms was performed with the use of a level set evolution algorithm [41] applied in the magnitude images of one of the complex phase contrast datasets, further referred to as the phase contrast magnitude images. This was done for every cardiac phase separately. Velocity values in pixels that were located outside the segmentation or suffered from partial voluming were set to zero. Pixels in the regions of interest that suffered from velocity aliasing were manually corrected in all three directions. The cardiac cycles were reordered such that the systolic phase occurred at the end of the cardiac cycle. These post-processing steps were performed with custom-built software in Matlab (Mathworks, Natick, MA, USA) and took about 4 hours to conduct. To calculate the flow ratios of the outflow branches, the data was imported into GTFlow (Gyrotools, Zürich, Switzerland).
4.2.4 CFD setup

The geometric vascular models used for CFD simulations were created from 3D-RA. Images were acquired with a single-plane angiographic unit (Integris Allura Neuro, Philips Healthcare, Best, The Netherlands). Contrast agent consisting of 320 mg I/mL of iodixanol (Visipaque, GE Healthcare, Cork, Ireland) was injected through a 6F catheter positioned in the ICA or VA. One hundred images were acquired during a 240° rotational run in 8 seconds with 15-21 mL of contrast agent at 3 mL/s. A 256 x 256 x 256 matrix image of the region of interest was reconstructed on a dedicated workstation. The resolution of the images of the individual aneurysms is given in table 4.1.

These images were imported into VMTK [42]. With the use of a level set algorithm, isosurfaces were created which were subsequently meshed using an average edge length of 0.1 mm, with a minimum of 0.1 μm and maximum 0.4 mm.

Meshes were created consisting of 1.168.002 to 2.608.270 tetrahedral elements with a mesh density of at least 3000 elements per cubic millimeter, in accordance with other studies [6, 43]. The sizes of the meshes are listed in table 4.1. All 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$^3$s. The pipeline for imposing velocity inlet boundary conditions in the CFD simulations is visualized in figure 4.1. First, the aneurysm in the TOF MRA measurement and the proximal vessel in the 2D PC-MRI slice were manually selected (figure 4.1a). Subsequently, the 2D PC-MRI data was positioned on the TOF MRA data using rotation and translation matrices extracted from DICOM headers (figure 4.1b). The CFD mesh was constructed (figure 4.1c) and a rigid registration of the TOF MRA measurement on the CFD mesh was conducted in FLIRT [44] (figure 4.1d). The velocities measured with 2D PC-MRI were rotated and translated likewise and interpolated onto the nodes of the CFD inflow boundary (figure 4.1e). The interpolated velocity vectors are shown in figure 4.1f. The velocity at the nodes at the edge of the vessel was set to zero. Steps E and F were performed for every measured cardiac phase in 2D PC-MRI. 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 measurement. Three heart cycles were sim-
ulated to eliminate transient effects. The third of these cycles was used in the comparison with the 3D PC-MRI results.

Flow through the outflow vessels of the CFD model was prescribed according to outflow measurements at every cardiac phase of the 3D PC-MRI data averaged over time. If an outflow vessel was too small to quantify flow, a combination of measured flow and Murray’s law [45] was applied. The average simulation time was 36 hours per aneurysm.

4.2.5 Data quantification and visualization

Calculations of the SNR of the phase contrast magnitude images at peak systole and end diastole of the 3D PC-MRI measurements were performed as described by Plein et al. [46], see Chapter 5 or Chapter 6. As region of interest for the SNR calculation, the total aneurysm with inflow and outflow vessels was taken. VNR equals the product of SNR and velocity divided by VENC. VNR is not calculated separately.

During postprocessing, the number of cardiac phases of CFD was reduced to equal the number of cardiac phases of the 3D PC-MRI measurement.

To quantify differences between 3D PC-MRI and CFD, the CFD data were registered and linearly interpolated to the 3D PC-MRI data. To take aneurysm pulsatility in the 3D PC-MRI data into account, registration was conducted for every cardiac phase separately. Peak systole and end diastole were defined as the cardiac phase where the spatially averaged velocity magnitude was maximal and minimal, respectively.

Further comparison consisted of visualization of the location and quantification of magnitude of vortices, by calculation of singular energy of the intra-aneurysmal flow [47], see Chapter 7. The technique used in the current study extends the original 2D approach to 3D by including the singular energy for the transverse, sagittal and coronal 2D slices. The singular energy was calculated according to:

$E_\sigma (x, \sigma) = \hat{\Lambda}_\tau (x, \sigma) + \hat{\Lambda}_\nu (x, \sigma)$

(4.1)
where $x$ is the location in the flow field, $\sigma$ is the scale, $\hat{A}_v$ and $\hat{A}_s$ are the normalized dimensionless projection coefficients describing vortices and sinks and sources respectively:

$$\hat{A}_v(x, \sigma) = \frac{F(x) \otimes \phi_v(x, \sigma)}{A(x, \sigma)} \quad (4.2)$$

and

$$\hat{A}_s(x, \sigma) = \frac{F(x) \otimes \phi_s(x, \sigma)}{A(x, \sigma)} \quad (4.3)$$

where $F$ is the flow-field, $\phi_v$ and $\phi_s$ are basis flow functions representing regional and scale dependent vortex flow and sinks and sources respectively [48]. $A$ represents the magnitude of the laminar flow and is determined by:

$$A(x, \sigma) = F(x) \otimes \phi_l(x, \sigma) \quad (4.4)$$

A scale $\sigma$ of 4 voxels (3.2 mm) was used. All quantification and visualization was performed with custom-built software in Matlab (Mathworks, Natick, MA, USA). Pathline images were created and flow quantification in the inflow vessel of the 2D and 3D PC-MRI was performed in GTFlow (Gyrotools, Zurich, Switzerland). The input flow values for the aneurysms are given in table 4.1.

### 4.2.6 Statistics

The difference in velocity magnitude and singular energy between CFD and 3D PC-MRI was determined for every voxel and subsequently averaged over space to yield a mean paired difference (MDif) at every cardiac phase:

$$MDif = \frac{\sum_{i=1}^{N} MRI_{i} - CFD_{i}}{N} \quad (4.5)$$

where $N$ is the number of voxels. The standard deviation of the paired difference (SDif) was calculated as well. Its significance was tested with a paired t-test; $p<0.05$ was considered statistically significantly different. A relative difference in velocity magnitude between both methods was based on the mean CFD velocity magnitude per subject:
Differences in flow direction were calculated from the angle difference between corresponding velocity vectors. Since these differences are positive by definition, median rather than mean values were calculated. Bland-Altman plots for the velocity magnitude and singular energy at systole and diastole were created.

4.3 Results

The averaged SNR of the 3D PC-MRI velocity measurements of all aneurysms was 13.5±2.2 in peak systole and 10.6±1.9 in end diastole.

Figure 4.2 shows intra-aneurysmal flow patterns in the aneurysms. In systole, the circular motion in the vortices and the direction of inflow jets was qualitatively similar for both methods. This can further be appreciated from the pathlines in figure 4.3. In figure 4.2, in systole the maximum inflow jet velocity magnitude of aneurysm 1 and 4 was almost two times lower in CFD than in 3D PC-MRI. In diastole, the vortices of the 3D PC-MRI measurement appeared disrupted and irregular in most aneurysms.

For most aneurysms, the 3D PC-MRI measurements resulted in higher velocity magnitude values than CFD (MDif in table 4.2). This is a result of the higher velocities in the inflow vessel in 3D PC-MRI than in 2D PC-MRI (table 4.1). These differences were most prominent in systole, as can be seen in the spatially averaged velocity magnitude curve displayed in 4.4. In most cases, the SDif and the RDif were higher in systole than in diastole and differences in estimated local flow direction were found primarily in diastole, see table 4.2.

\[
RDif = \frac{MDif}{\sum_{CFD, N}}
\]

Validation
Figure 4.2 Velocity vector images in a characteristic slice depicting the main vortex in all aneurysms and inflow jet in most of the aneurysms. The images depict the aneurysms at peak systole and diastole in isosurfaces (gray) for 3D PC-MRI and CFD.

Figure 4.3 Pathlines over the entire cardiac cycle depicting similar complex flow in aneurysm volumes (gray background) of aneurysms 1, 4, 5 and 7 for 3D PC-MRI (top row) and CFD (bottom row).

Three-dimensional phase contrast MRI at 3T in intracranial aneurysms compared with patient-specific computational fluid dynamics.
In figure 4.5, the locations with singular energy magnitude higher than half the maximum are displayed for four aneurysms. For aneurysm 2 and 3 the locations and magnitudes of the maximum singular energy were similar. For aneurysms 8, the vortex center location was different for 3D PC-MRI and CFD, in agreement with the different intra-aneurysmal flow patterns that were shown in figure 4.2. For aneurysm 6 and 8, the magnitude of the singular energy was twice as low for CFD.

RDif averaged over all aneurysms in systole was a factor three smaller for singular energy than for velocity magnitude. Better correspondence in singular energy than in velocity magnitude in systole can also be observed in the Bland-Altman plots in figure 4.6.

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>MDif (cm/s)</th>
<th>SDif (cm/s)</th>
<th>RDif (%)</th>
<th>Median angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diastole</td>
<td>Systole</td>
<td>Diastole</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21.1*</td>
<td>2.0*</td>
<td>12.7</td>
<td>6.3</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>-0.0</td>
<td>17.1</td>
<td>8.5</td>
</tr>
<tr>
<td>3</td>
<td>9.2*</td>
<td>5.2*</td>
<td>18.0</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>19.5*</td>
<td>4.9*</td>
<td>17.9</td>
<td>10.2</td>
</tr>
<tr>
<td>5</td>
<td>10.4*</td>
<td>2.8*</td>
<td>20.0</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>4.8*</td>
<td>4.8*</td>
<td>14.2</td>
<td>12.2</td>
</tr>
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<td>14.7*</td>
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<tr>
<td>8</td>
<td>10.9*</td>
<td>5.0*</td>
<td>19.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Average</td>
<td>11.4±7.0</td>
<td>4.0±2.3</td>
<td>16.6±12.9</td>
<td>10.4±2.2</td>
</tr>
</tbody>
</table>

Table 4.2 Differences between velocity fields as determined with 3D PC-MRI and CFD. Indicated are MDif and SDif, RDif and the median angle, as determined on a voxel basis and averaged over the whole aneurysm and connecting vessels, between 3D PC-MRI and CFD. * indicates significant difference.

Figure 4.4 Spatially averaged velocity magnitude for all aneurysms during the cardiac cycle for 3D PC-MRI and CFD.
Figure 4.5 Singular energy magnitude and location at peak systole in aneurysm volumes (gray) of aneurysms 2, 3, 6 and 8 for 3D PC-MRI (top row) and CFD (bottom row). For visualization purposes only the areas with singular energy above half the maximum value are indicated.

Figure 4.6 Bland-Altman plots for (left) velocity magnitude difference and (right) singular energy at peak systole and diastole for all aneurysms.

Table 4.3 Differences between singular energy fields as determined with 3D PC-MRI and CFD. Indicated are MDif, SDif and RDif as determined on a voxel basis and averaged over the whole aneurysm and connecting vessels, between 3D PC-MRI and CFD. * indicates significant difference.

<table>
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<th>Aneurysm</th>
<th>MDif Systole</th>
<th>MDif Diastole</th>
<th>SDif Systole</th>
<th>SDif Diastole</th>
<th>RDif (%) Systole</th>
<th>RDif (%) Diastole</th>
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</thead>
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<td>1</td>
<td>0.02</td>
<td>-0.05*</td>
<td>0.66</td>
<td>0.55</td>
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</tr>
<tr>
<td>3</td>
<td>-0.08*</td>
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<td>0.83</td>
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</tr>
<tr>
<td>4</td>
<td>0.16*</td>
<td>0.30*</td>
<td>0.60</td>
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<td>43.8</td>
</tr>
<tr>
<td>5</td>
<td>-0.39*</td>
<td>-0.13*</td>
<td>1.43</td>
<td>0.86</td>
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<td>12.6</td>
</tr>
<tr>
<td>6</td>
<td>-0.31*</td>
<td>0.08*</td>
<td>0.97</td>
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<tr>
<td>7</td>
<td>0.33*</td>
<td>0.41*</td>
<td>0.85</td>
<td>1.09</td>
<td>41.9</td>
<td>47.9</td>
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<tr>
<td>8</td>
<td>0.33*</td>
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<td>1.13</td>
<td>0.75</td>
<td>39.0</td>
<td>41.7</td>
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</tbody>
</table>

avg 0.01±0.27 0.10±0.20 0.89±0.28 0.95±0.22 21.9±16.3 21.2±19.7

Three-dimensional phase contrast MRI at 3T in intracranial aneurysms compared with patient-specific computational fluid dynamics.
In this study, both 3D PC-MRI and CFD were applied in eight intracranial aneurysms. In systole, the results showed good qualitative agreement for complex flow properties such as inflow jet behavior and vortical flow patterns. In diastole, the estimated intra-aneurysmal flow patterns were irregular due to decreased velocity to noise ratio in the 3D PC-MRI measurements. Quantitative differences in velocity magnitude were observed in both systole and diastole. Vortex quantification based on singular energy calculation demonstrated similar vortical flow behavior in flow patterns measured with 3D PC-MRI and simulated with CFD. In systole, the vortex-related singular energy showed better quantitative agreement than the velocity magnitude and directions.

Studies comparing 3D PC-MRI with CFD on a voxel-by-voxel basis in aneurysms at 3T are not available in the literature. One study compared 3D PC-MRI with CFD in the aorta [49], and one study in five intracranial aneurysms on 1.5T at relatively low spatial resolution [35]. Both studies found a good qualitative agreement between both techniques and a moderate quantitative agreement.

The need for reliable patient-specific CFD simulations has been described by many authors. However, the prescription of inflow boundary conditions that produce accurate CFD results is still a matter of debate. Several studies used flow rates that were measured with 2D PC-MRI in separate volunteers as inflow boundary conditions in CFD. Based on these reference data and using the Womersley solution, fully developed velocity profiles are then created and subsequently scaled by the area of the inflow vessel to obtain a mean wall shear stress of 15 dyne/cm² [15, 20, 50]. Other studies applied uniform velocities on extended inflow vessels [36, 51]. Spatial and temporal velocity vector values as measured with 3D PC-MRI at each node of the inflow boundary have been applied at low resolution in only two studies [35, 49]. These last two studies used inflow boundary conditions obtained from the same imaging sequence that they wish to validate. Furthermore, 3D PC-MRI needs to cover the entire head in anterior-posterior and right-left direction to avoid fold-over and thus has limited spatial and temporal resolution compared to a 2D acquisition. Therefore, in the current study, spatial and temporal velocity vectors from a separate 2D PC-MRI acquisition were applied as inflow boundary conditions for the CFD simulations.
The singular energy measure as presented in this study is introduced to facilitate the comparison between 3D PC-MRI and CFD. Singular energy provides a quantitative measure of flow patterns. It is unclear if it may lead to more insight in the nature of the aneurysm with respect to rupture, as has been discussed in the literature recently [52-53]. While this is an intriguing possibility, it was not the purpose of the current work to address the predictive value of this quantity.

While flow patterns between 3D PC-MRI and CFD agreed qualitatively, a mismatch in velocity magnitude between CFD and 3D PC-MRI was encountered. This mismatch can mainly be attributed to a discrepancy between the total inflows measured by 3D and 2D PC-MRI, where boundary conditions were based on the latter. On average the 3D PC-MRI measurements resulted in 50% higher flow estimates than the 2D PC-MRI ones. Discrepancies between flow measurements from 2D and 3D PC-MRI (±18%) [24] or 2D and endovascular sonography (±15%) [54] have been reported in the literature earlier. Wentland et al. concluded that flow measurements in healthy volunteers in the renal vasculature revealed that 3D measurements tended to be more internally consistent than 2D measurements [55]. This difference may increase when small intracranial arteries are considered. One cause of the difference may be variation of the actual flows between the scans. The 3D PC-MRI was always performed first, followed by the 2D PC-MRI, and some adaptation of flow might have occurred during the scanning session. Yet, cerebral flow is strongly autoregulated and it seems therefore rather unlikely that such flow variations would lead to 50% differences. Alternatively, the calculated inflows for either 2D or 3D PC-MRI might systematically deviate from the true one. Without a ground truth, it is difficult to deduct which of the two methods causes this systematic difference. Possibly, the relatively large thickness (3 mm) of the 2D PC-MRI slice compared to the 3D measurement (0.8 mm) induces averaging of measured velocities resulting in underestimation of flow.

The inflow boundary of the angiographic mesh used for CFD contains more points than the vessel area of the 2D PC-MRI contains pixels. The required upsampling of the measured velocity information to the inflow boundary could result in lower velocity inflow boundary conditions.

To study the influence of the inflow boundary conditions, a second series of simulations was performed with inflow boundary conditions obtained from 3D rather than 2D PC-MRI. Six simulations were performed, in two
cases the inflow of the CFD mesh was located outside the FOV of the 3D PC-MRI sequence. We have included these results in the supplement. This reduces the systematic differences in local velocity 5-fold for MDif and a factor 2.5 for RDif. Random differences (SDif) were similar for both inflow boundary conditions. The results for the singular energy and the median angle did not change significantly. We therefore conclude that different inflow boundary conditions have a large influence on magnitude of velocity values. However, velocity vector directions and locations and magnitude of vortices are fairly independent on inflow boundary conditions.

Another limitation is the semi-automatic segmentation of the 3D-RA dataset, resulting in possible under- or overestimation of neck width [56]. Also limitations with regard to the 3D PC-MRI setup may contribute to the found discrepancies between both techniques. In our study SNR values within aneurysms were relatively low due to small voxel sizes and the use of parallel imaging [57]. Therefore, at low velocities during diastole, the velocity may be overestimated due to noise. It is clear that more accurate estimation of intracranial aneurysm hemodynamics from 3D PC-MRI requires improved technology. With improvements in acquisition techniques such as varying velocity [58] or dual VENC encoding [59], sufficient velocity-to-noise ratio may be obtained in diastole. Furthermore, with acceleration techniques such as radial undersampling [31] and compressed sensing [60], scan times of 3D PC-MRI may be shortened in the near future. Higher field strengths can improve SNR [61]. One last recently developed promising technique to improve 3D PC-MRI measurement is divergence-reduction processing [62].

4.5 Conclusion

In this study, high resolution 3D PC-MRI was compared with patient-specific CFD on a voxel-by-voxel basis in eight aneurysms. In peak systole, qualitative similarities in flow features such as vortical flow patterns and inflow behavior were evident. In end diastole, the flow patterns of the 3D PC-MRI measurements were different compared to those generated with CFD due to low velocity-to-noise ratio of the 3D PC-MRI measurements. Singular energy calculation revealed quantitative agreement between 3D PC-MRI and CFD in systole.
4.6 Acknowledgements

This work was supported by a grant from the Nuts Ohra Foundation, the Netherlands. A research grant for research into the role of hemodynamics in the rupture risk assessment of intracranial aneurysms.

4.7 References

1 Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurology 2009; 8:635-642.


Three-dimensional phase contrast MRI at 3T in intracranial aneurysms compared with patient-specific computational fluid dynamics


In this supplement we present the results of the CFD simulations in six aneurysms with spatial inflow boundary conditions obtained from 3D PC-MRI. In table 4.S1 the differences between velocity fields are given. In table 4.S2 the differences between singular energy are given. In figure 4.S1 the velocity vector fields are displayed, in figure 4.S2 the singular energy in three aneurysms.

### Table 4.S1 Differences between velocity fields as determined with 3D PC-MRI and CFD. Indicated are MDif, SDif, RDif and median angle, as determined on a voxel basis and averaged over the whole aneurysm and connecting vessels, between 3D PC-MRI and CFD. * indicates significant difference.

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>MDif (cm/s)</th>
<th>SDif (cm/s)</th>
<th>RDif (%)</th>
<th>Median angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systole</td>
<td>Diastole</td>
<td>Systole</td>
<td>Diastole</td>
</tr>
<tr>
<td>1</td>
<td>1.9*</td>
<td>-4.2*</td>
<td>17.0</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>-7.8*</td>
<td>-4.3*</td>
<td>16.5</td>
<td>9.9</td>
</tr>
<tr>
<td>3</td>
<td>9.2*</td>
<td>1.6*</td>
<td>17.8</td>
<td>12.0</td>
</tr>
<tr>
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<td>-5.7*</td>
<td>-2.6*</td>
<td>26.3</td>
<td>12.8</td>
</tr>
<tr>
<td>5</td>
<td>3.5*</td>
<td>0.7*</td>
<td>19.3</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>9.1*</td>
<td>4.0*</td>
<td>16.9</td>
<td>13.4</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>average</td>
<td>2.0±6.8</td>
<td>-0.8±3.4</td>
<td>19.0±3.7</td>
<td>11.4±2.0</td>
</tr>
</tbody>
</table>

### Table 4.S2 Differences between singular energy fields as determined with 3D PC-MRI and CFD. Indicated are MDif, SDif and RDif as determined on a voxel basis and averaged over the whole aneurysm and connecting vessels, between 3D PC-MRI and CFD. * indicates significant difference.

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>MDif (cm/s)</th>
<th>SDif (cm/s)</th>
<th>RDif (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systole</td>
<td>Diastole</td>
<td>Systole</td>
</tr>
<tr>
<td>1</td>
<td>0.00</td>
<td>-0.09*</td>
<td>0.67</td>
</tr>
<tr>
<td>2</td>
<td>-0.34*</td>
<td>-0.06</td>
<td>1.17</td>
</tr>
<tr>
<td>3</td>
<td>-0.37*</td>
<td>-0.22*</td>
<td>0.93</td>
</tr>
<tr>
<td>4</td>
<td>0.18*</td>
<td>0.32*</td>
<td>0.52</td>
</tr>
<tr>
<td>5</td>
<td>-0.32*</td>
<td>-0.18*</td>
<td>0.94</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.24*</td>
<td>0.35*</td>
<td>0.86</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>average</td>
<td>-0.07±0.25</td>
<td>0.02±0.25</td>
<td>0.85±0.23</td>
</tr>
</tbody>
</table>

Table 4.12 Differences between velocity fields as determined with 3D PC-MRI and CFD. Indicated are MDif, SDif and RDif as determined on a voxel basis and averaged over the whole aneurysm and connecting vessels, between 3D PC-MRI and CFD. * indicates significant difference.
Figure 4.1. Velocity vector images in a characteristic slice depicting the main vortex in the six aneurysms and inflow jet in most aneurysms. The images depict the aneurysms at peak systole and diastole in isosurfaces (gray) for 3D PC-MRI and CFD with inflow boundary conditions obtained from 3D PC-MRI.

Figure 4.2. Singular energy magnitude and location at peak systole in aneurysm volumes (gray) of aneurysm 1, 2, and 3 for 3D PC-MRI (top row) and CFD with inflow boundary conditions obtained from 3D PC-MRI (bottom row). For visualization purposes only the areas with singular energy above half the maximum value are indicated.
IMPROVEMENTS
$k-t$ BLAST and SENSE accelerated time-resolved three-dimensional phase contrast MRI in an intracranial aneurysm

Pim van Ooij, Annetje Guédon, Henk Marquering, Joppe Schneider, Charles Majoie, Ed van Bavel, Aart Nederveen

Accepted for Magnetic Resonance Materials in Physics, Biology and Medicine
Abstract

Objective

The objective of this study was to investigate the performance of $k-t$ BLAST accelerated time-resolved 3D PC-MRI compared to SENSE acceleration in an in vitro and in vivo intracranial aneurysm.

Materials & Methods

SENSE and $k-t$ BLAST accelerated PC-MRI measurements were performed in vitro and in vivo. Additionally, non-accelerated measurements were performed in vitro. We analysed the consequences of various temporal resolutions in vitro.

Results

Both in vitro and in vivo measurements showed that the main effect of $k-t$ BLAST was underestimation of velocity during systole. In the phantom, temporal blurring decreased with increasing temporal resolution. Quantification of the differences between the non-accelerated and accelerated
measurements confirmed that in systole SENSE performed better than $k$-$t$ BLAST. In both in vitro and in vivo measurements, $k$-$t$ BLAST had superior SNR compared to SENSE. Qualitative comparison between measurements showed good similarity.

**Conclusion**

The application of $k$-$t$ BLAST in aneurysms is limited by the occurrence of temporal blurring, though some benefit may be obtained from the increased SNR in $k$-$t$ BLAST compared to SENSE.
5.1 Introduction

Ruptured intracranial aneurysms constitute a major cause of subarachnoid haemorrhage, leading to a mortality rate up to 83% [1] or high morbidity. To prevent rupture of incidentally found aneurysms, endovascular coiling or surgical clipping are considered. However, both interventions have substantial mortality and morbidity risks, and are expensive [2]. An accurate estimation of risk of rupture is therefore needed to come to an optimal treatment decision. It is believed that apart from size and morphology of the aneurysm, hemodynamic parameters such as inflow jet size, impingement zone and wall shear stress contribute significantly to rupture risk assessment [3].

Estimations of hemodynamics within aneurysms are mostly obtained using Computational Fluid Dynamics (CFD), an extensively validated simulation technique. However, this approach is hampered by long computational times and various assumptions such as the use of non-patient-specific boundary conditions [4].

Another, direct and non-invasive, technique for measurement of intracranial aneurysm hemodynamics is time-resolved three-dimensional phase contrast MRI (PC-MRI) [5]. It has been shown that PC-MRI can be used to assess hemodynamic properties in intracranial aneurysms (6-10). However, for a number of reasons long scanning times are needed. A spatial resolution is needed that is sufficient to estimate local velocity patterns. Temporal resolution needs to be high enough to record peak systolic velocities. The signal-to-noise ratio (SNR) needs to be as high as possible to maximize blood-flow direction certainty and the accuracy of blood flow quantification [6]. Finally, at least three flow-sensitized acquisitions are needed to resolve x, y and z components of the flow velocity, as well as one flow compensated acquisition to remove unwanted background phases due to main field inhomogeneities, eddy currents and other factors [7]. In order to reduce scanning times for PC-MRI to clinically feasible durations with these conditions, acceleration techniques are required.

PC-MRI imaging time can be reduced by accelerated parallel imaging and reconstruction techniques, e.g. SENSE [8]. In SENSE, the scan times decrease in proportion to the acceleration factor. However, SNR decreases in proportion to the square root of the SENSE acceleration factor times the coil geometry factor g. It has been shown by Thunberg et al. [9] that at high acceleration factors the SNR of the magnitude and phase images can be
drastically reduced, particularly in the center of the field of view. Intracranial aneurysms are mostly found at arterial branch points in the circle of Willis located in the subarachnoid space in the center of the brain [10]. PC-MRI image quality at this location may thus be compromised by a lower SNR due to parallel imaging acceleration.

An alternative acceleration technique is \( k-t \) BLAST [11]. This technique is developed for dynamic imaging, and acceleration is achieved by exploiting correlations in \( k \)-space and time. By means of simulations, the feasibility of \( k-t \) BLAST in combination with time-resolved three-dimensional PC-MRI has been shown by Marshall et al. [12]. Clinical studies using \( k-t \) BLAST in the carotid bifurcation [12], the aorta [13-14], the myocardium [15] and the heart [16] showed that the technique leads to temporal blurring due to subtraction of a temporally averaged \( k \)-space from the data. However, other data showed minimal influence of temporal blurring [17-18]. Furthermore, compared with SENSE, SNR may be higher in \( k-t \) BLAST accelerated PC-MRI as a consequence of limited temporal frequency content [19-20].

This study presents a comparison between \( k-t \) BLAST and SENSE acceleration applied to time-resolved three-dimensional PC-MRI in an aneurysm as well as in a glass phantom of this aneurysm. Furthermore, we used the phantom for a comparison to non-accelerated PC-MRI, a procedure that could not be applied to the patient due to long scanning time. Finally, we analyzed the effect of varying temporal resolution in the phantom. Our comparison includes the SNR and differences in velocity magnitude and direction between these acceleration techniques.

### 5.2 Materials & methods

#### 5.2.1 In vivo aneurysm and phantom

A glass reproduction of an unruptured aneurysm located in the anterior communicating artery was manually blown by a glass-blower based on a 3D Rotational Angiography (3D-RA) dataset (figure 5.1a). Informed consent was given by this patient. The study protocol was approved by the local ethics committee. The lumen of the patient aneurysm had a maximum length, maximum width and maximum height of approximately 8, 6 and 9 mm in \( x \), \( y \) and \( z \) directions respectively (see figure 5.1a). The diameter of the neck of the aneurysm was approximately 2 mm.
The lumen of the phantom had maximum dimensions of approximately 6, 4 and 9 mm in x, y and z directions respectively (see figure 5.1b). The inner diameter of the in- and outflow vessels was 2.1 mm, and wall thickness was 0.2-0.6 mm in the inflow vessel, 0.4-0.6 mm in the outflow vessels and 0.8 mm in the phantom itself.

5.2.2 Phantom PC-MRI measurements

The flow loop consisted of the aneurysm phantom in a plastic box filled with agar gel, a reservoir, a centrifugal pump, a computer-controlled piston pump (pulse generator) and tubes, as displayed in figure 5.2. The dimensions of the agar block were: 7 cm in length, 5.5 cm in width and 3 cm in height. Pure water was used as a fluid. The combination of the centrifugal pump, delivering the steady mean flow, and the computer-controlled piston pump created the pulsatile flow used in the measurements. The MRI scanner used an artificial electrocardiogram signal to synchronize the PC-MRI acquisition with the flow pulses of the pump. The frequency of the pulses was set to 1 Hz to create a heart cycle duration of 1 second. Further information on this set-up can be found in [21] and Chapter 2.

Non-accelerated and SENSE accelerated scans were performed using a retrospectively gated [22] three-dimensional PC-MRI scan, whereas the $k-t$ BLAST accelerated measurements were prospectively gated. A one-dimensional SENSE acceleration factor of 3 was applied in right-left direction. An acceleration factor for the $k-t$ BLAST acquisitions of 5 was set, to be able to acquire a temporal resolution of ten cardiac phases. This means that k-space was undersampled by taking every fifth k-line in phase encoding direction. For each subsequent cardiac phase the undersampling scheme was shifted up by one k-line. This acceleration factor did not take into account the ac-
quisition of the training lines. Eleven training lines were acquired in the $k$-$t$ BLAST measurements [23]. Therefore, the actual reduction in scan time was a factor of approximately 4 (see scan times in table 5.1). Note that a SENSE factor of 4 would result in equal scan time as the $k$-$t$ BLAST measurements, but would further decrease SNR [24].

<table>
<thead>
<tr>
<th></th>
<th>Non-accelerated</th>
<th>$k$-$t$ BLAST</th>
<th>SENSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE / TR (ms)</td>
<td>3.2 / 5.9</td>
<td>2.9 / 6.1</td>
<td>3.2 / 5.9</td>
</tr>
<tr>
<td>Scan time 10/20/40 cardiac phases (min)</td>
<td>17/33/66</td>
<td>4/8/17</td>
<td>6/12/24</td>
</tr>
</tbody>
</table>

Three temporal resolutions were used: 10 cardiac phases or 100 ms, 20 cardiac phases or 50 ms and 40 cardiac phases or 25 ms. Sequence parameters for non-accelerated, $k$-$t$ BLAST and SENSE accelerated measurements are summarized in table 5.1. Further sequence parameters were: flip angle: 15°; field of view: 100 x 100 x 20 mm³; 25 coronal slices; velocity encoding (VENC): 80 cm/s x 120 cm/s x 80 cm/s in the x, y and z-direction respectively (see figure 5.1b); NSA: 1. All PC-MRI scans were performed with two sided [25] four point encoding [7] on a 3T MR system (Philips Healthcare, Best, The Netherlands) in an 8-channel head coil at an acquired (non interpolated) resolution of 0.78 x 0.78 x 0.8 mm³.

5.2.3 In vivo aneurysm

PC-MRI with SENSE and $k$-$t$ BLAST acceleration was performed in the same patient of whom the 3D-RA data was used to create the phantom. For both the SENSE and $k$-$t$ BLAST acquisition, imaging parameters were: TE/TR: 2.8/5.6 ms, flip angle: 15°, acquired resolution: 0.78

$k$-$t$ BLAST and SENSE accelerated time-resolved three-dimensional phase contrast MRI in an intracranial aneurysm
x 0.78 x 0.8 mm³, 25 transversal slices, field of view: 200 x 200 x 20 mm³, velocity encoding: 100 cm/s x 100 cm/s x 100 cm/s in all three directions and NSA: 1. Ten cardiac phases were measured. The same 8-channel head coil as in the phantom scans was used. Scan time with a SENSE factor of 3 was 12 minutes. For the k-t BLAST acquisition with an acceleration factor of 5 and 11 training lines the scan time was 8 minutes, again an actual acceleration factor of 4. Non-accelerated measurements were not acquired.

5.2.4 Data analysis

Measured velocity encoded phase images were corrected for background phase by subtraction of the average phase in a region of interest in the agar gel close to the aneurysm phantom and the amygdala in the in vivo case. Phase correction was performed for every velocity encoding direction and cardiac phase individually [26]. The phantom lumen was segmented with the use of a level set evolution algorithm applied to the non-accelerated magnitude images at peak systole [27]. The in vivo aneurysm was segmented for every slice and cardiac phase individually. Pixels that suffered from velocity aliasing were manually corrected by adding two times VENC to aliased pixels with a velocity below zero and by subtracting two times VENC to aliased pixels with a velocity above zero. Signal to noise ratios were calculated in all PC-MRI acquisitions according to Price et al. [28], Dietrich et al. [29] and Plein et al. [30]. In short, let $S_1$ and $S_2$ represent magnitude signals in a ROI during different cardiac phases of similar mean velocity. These cardiac phases were chosen such that a subtraction of the images resulted in minimal signal. This was done for each dataset individually. SNR is then estimated from [31]:

$$SNR = \frac{\text{mean}(S_1 + S_2)}{\sqrt{\text{std}(S_1 - S_2)}}$$  \hspace{1cm} (5.1)

As ROI we chose the total aneurysm phantom and the aneurysm with connected arteries for the in vivo measurement. Since the SNRs of the magnitude and phase images are proportional [9, 32-33] we did not separately estimate SNR in the phase images. Velocity to noise ratio (VNR) equals SNR times velocity divided by VENC. VNR was not calculated separately.

The mean velocity at peak systole and diastole were defined as the maximum and minimum of the mean velocity magnitude curve, respectively. The means of the paired differences between the full non-accelerated acquisition
and the accelerated measurements were determined at peak systole and diastole by subtracting the velocity magnitude in corresponding voxels and subsequently averaging over the number of voxels. Standard deviations of the paired differences (SDp) at these cardiac phases were determined. Differences in flow direction were calculated from the angle difference between corresponding velocity vectors. Since these differences are positive by definition, median rather than mean values were calculated. Statistical comparison was done for paired groups (Wilcoxon-signed rank test) as data was not normally distributed. Differences were considered significant at p < 0.05. All post-processing steps and visualizations were performed with custom-built software in Matlab (Mathworks, Natick, MA, USA).

5.3 Results

5.3.1 Phantom measurements

Figure 5.3 shows three phase contrast magnitude images for the non-accelerated, $k$-$t$ BLAST and SENSE measurement at 10 cardiac phases. The SNR of the non-accelerated, $k$-$t$ BLAST accelerated and SENSE measurement was 72, 100 and 31 respectively. The SNR degradation due to SENSE is clearly visible in figure 5.3c. Phase offsets close to the phantom (1 mm) before correction were low (< 1.4 cm/s).

Figure 5.4 shows the mean velocity curves in the phantom for the non-accelerated, $k$-$t$ BLAST and SENSE measurement. Mean peak systolic, diastolic velocity and the pulsatility are given in table 5.2. Results of the statistical analysis are presented in table 5.3. Application of the acceleration techniques resulted in altered estimates of mean velocity magnitude as compared to the non-accelerated measurements (figure 5.4). Both acceleration techniques underestimated systolic velocity. This was particularly the case
for $k$-t BLAST (table 5.2). The differences between both acceleration techniques were also significant (table 5.3). As a result of these deviations from non-accelerated measurements, systolic-diastolic pulsatility (last column in table 5.2) is underestimated by notably the $k$-t BLAST technique, which can be attributed to temporal blurring. Temporal blurring was higher at 10 cardiac phases than 20 and 40. At 40 cardiac phases (figure 5.4c) the mean velocity curve derived from the SENSE measurement became less smooth than the non-accelerated and $k$-t BLAST mean velocity curve. This behavior was reported previously in the aorta at similar SENSE acceleration factors [9].

The above analysis quantifies systematic deviations in velocity resulting from the acceleration techniques. Table 5.3 indicates that the standard deviations of the paired differences and the median angle were similar for $k$-t BLAST and SENSE accelerated measurements. Note that the median angle increased in diastole compared to systole for all measurements. Since in diastole the velocities were generally lower than in systole the VNR decreased, introducing more uncertainty in direction of local flow.

<table>
<thead>
<tr>
<th>Nr of cardiac phases</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>10</th>
<th>20</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-accelerated</td>
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<td>46</td>
<td>45</td>
<td>29</td>
<td>29</td>
<td>28</td>
<td>16</td>
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<td>$k$-t BLAST</td>
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<td>42</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>9</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>SENSE measurement</td>
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<td>44</td>
<td>44</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>15</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 5.2 Mean velocity at systole and the difference

![Figure 5.4 Mean velocity curve in the phantom of the full non-accelerated, $k$-t BLAST and SENSE measurement at (a) 10 cardiac phases, (b) 20 cardiac phases and (c) 40 cardiac phases.](image_url)
Figure 5.5a, b and c show velocity field vectors in a sagittal plane through the phantom at peak systole for the non-accelerated measurement, k-t BLAST measurement and SENSE measurement, respectively, acquired at a temporal resolution of 100 ms. Figure 5.5d, e and f show the velocity vectors at diastole. Qualitative similarities in velocity patterns such as the large vortex in the centre of the phantom and the small vortex at the upper left side of the phantom can be appreciated in figure 5.5. In figure 5.6 systolic transversal and coronal characteristic slices are displayed. The vortex on the right side (arrow 1) of the phantom in the transversal slices and the vortex in the tip of the aneurysm in the coronal slices (arrow 2) were well resolved for all three measurements. Quantitative differences can be appreciated for the k-t BLAST measurements, notably in the inflow region in systole (5.5b, 5.6b and 5.6e). The lower velocity for k-t BLAST can be attributed to temporal blurring. In contrast, the velocity field vectors acquired with SENSE acceleration at systole (5.5c, 5.6c and 5.6f) showed good similarity with the ones derived from the non-accelerated acquisition (5.5a, 5.6a and 5.6d). In diastole the flow patterns were qualitatively and quantitatively similar for all methods.

Table 5.3 Performance of k-t BLAST and SENSE in the phantom: mean of the paired difference where * indicates a significant difference, standard deviation of the paired difference (SDp) and the median of the angle distribution between the non-accelerated measurement, the k-t BLAST measurement and the SENSE measurement at systole and diastole.

<table>
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<tr>
<th>Nr of cardiac phases</th>
<th>Mean paired difference systole (cm/s)</th>
<th>Mean paired difference diastole (cm/s)</th>
<th>SDp systole (cm/s)</th>
<th>SDp diastole (cm/s)</th>
<th>Median angle systole (°)</th>
<th>Median angle diastole (°)</th>
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<tbody>
<tr>
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<td>10 20 40</td>
</tr>
<tr>
<td>k-t BLAST measurement</td>
<td>6.4* 3.8* 2.4* 0.1 0.0 -0.3*</td>
<td>10.4 10.2 14.8 6.3 9.4 8.9</td>
<td>10.3 9.7 11.0 12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENSE measurement</td>
<td>2.7* 1.8* 0.5* 1.6* 1.3* 1.6*</td>
<td>10.1 11.5 18.3 5.9 6.0 9.8</td>
<td></td>
<td>12.2 10.8 10.9 13.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k-t BLAST - SENSE</td>
<td>-3.7* -2.1* -1.9* 1.6* 1.3* 1.9*</td>
<td>11.9 13.2 12.8 6.9 7.8 7.6</td>
<td>10.1 12.3 11.5 12.1</td>
<td>15.4 12.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.5 Velocity magnitude and direction at systole (top row) and diastole (bottom row) in a sagittal slice through the phantom of (a) the non-accelerated acquisition (b) the k-t BLAST measurement and (c) the SENSE measurement. All images are obtained at a temporal resolution of 100 ms.
5.3.2 In vivo aneurysm measurement

The SNR of the SENSE and k-t BLAST accelerated measurement was 12 and 21 respectively. Temporal blurring i.e. underestimation of the mean velocity in systole, similar to the phantom measurement at 10 cardiac phases, occurred in the k-t BLAST measurement (figure 5.7). Table 5.4 shows similar systematic and random differences between SENSE and k-t BLAST as was found for the phantom.

The directions of the velocity vectors in the SENSE and k-t BLAST accelerated measurement, displayed in figures 5.8a and b respectively, showed many similarities. The large vortex in the centre of the aneurysm was found in both measurements. The magnitude of the velocity vectors in the k-t BLAST measurement was lower than in the SENSE measurement.
This was seen earlier in the phantom measurements, and again resulted from temporal blurring. The SENSE measurement in diastole (figure 5.8c) suffers from low VNR, leading to irregularities in measured flow direction. Due to higher SNR, this effect was less pronounced in the $k-t$ BLAST measurement (figure 5.8d).

5.4 Discussion

In this study $k-t$ BLAST and SENSE acceleration for PC-MRI in an intracranial aneurysm were compared, in vitro as well as in vivo. The main effect of $k-t$ BLAST was temporal blurring. Acceleration using SENSE rendered more accurate velocity measurements in peak systole than $k-t$ BLAST. Pulsatility of local flow and wall shear stress is considered to be an important causal factor in vascular pathology [34]. The diagnostic value of PC-MRI could therefore suffer from the underestimation of peak velocities due to temporal blurring. The effect of temporal blurring could be dimin-

<table>
<thead>
<tr>
<th></th>
<th>Mean paired difference systole (cm/s)</th>
<th>Mean paired difference diastole (cm/s)</th>
<th>SDp systole (cm/s)</th>
<th>SDp diastole (cm/s)</th>
<th>Median angle systole (°)</th>
<th>Median angle diastole (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k-t$ BLAST - SENSE</td>
<td>-5.7*</td>
<td>1.7*</td>
<td>8.9</td>
<td>7.2</td>
<td>19.5</td>
<td>28.6</td>
</tr>
</tbody>
</table>
ished by increasing the number of cardiac phases, as was shown in the phantom measurements. For both the in vitro and in vivo case, good qualitative agreement between all measurements was found. As a result of temporal blurring and the high SNR of training data used for \( k-t \) BLAST reconstruction, a higher SNR was present in the \( k-t \) BLAST accelerated measurements as compared to SENSE.

While the performance of \( k-t \) BLAST in intracranial aneurysms has not been studied in detail elsewhere, PC-MRI in combination with \( k-t \) BLAST in larger structures such as the carotid bifurcation [12], the aorta [13-14] and the heart [16] suffered from temporal blurring as well as cardiac cine imaging [35] and quantification of myocardial motion [15]. Temporal blurring can be attributed to the view-sharing nature of \( k-t \) BLAST. However, temporal blurring was minimized in \( k-t \) BLAST accelerated cardiac steady-state free precession [18] and in flow measurements accelerated with \( k-t \) BLAST in aortic valve stenosis [17]. Therefore, since the training data contains low resolution information of the imaging geometries, the temporal blurring effect may be more severe in the case of small structures such as aneurysms than in applications visualizing larger organs. The observed decrease in blurring at increased temporal resolution can be understood from details of the \( k-t \) BLAST algorithm. An increase in temporal resolution will result in larger x-f arrays for the training and undersampled data, and will therefore contain more information on the unaliasing process, resulting in a more reliable \( k-t \) BLAST reconstruction [11].

A limitation of the study was the fact that different acceleration factors were used for SENSE and \( k-t \) BLAST. The clinical protocol in our institution requires measurement of 10 cardiac phases. Therefore, a \( k-t \) BLAST acceleration factor of 5 was used since a factor 3 or 4 is not possible without altering the number of measured cardiac phases. This would imply that a SENSE factor of 4 should have been used to account for equal acceleration factors, which is not feasible when using an eight channel coil.

Further quantitative differences between \( k-t \) BLAST and SENSE in the in vivo setting can be attributed to the fact that the \( k-t \) BLAST measurement was prospectively gated, whereas the non-accelerated and SENSE measurements were retrospectively gated. The combination of retrospective gating and \( k-t \) BLAST acceleration was not available. By applying the shortest trigger delay timing in both the in vitro and in vivo measurements, differences between the two gating techniques in vitro, for the first and last (of

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Improvements
ten measured) cardiac phases were limited. In the in vivo case the timing
difference for the first and last cardiac phase was 16 ms and 37 ms respec-
tively. The time coverage of the total acquisition was therefore similar for
both retrospective and prospective gating.

In the phantom study, the SNR of the SENSE measurement was approxi-
mately a factor 2.3 lower than that of the non-accelerated measurement. This
number agrees well with the expected decrease in SNR with a factor of \( g\sqrt{R} = 2.25 \) [8], calculated using a g-factor of the 8-channel 3T coil array of 1.3 [36]
and an acceleration factor \( R=3 \).

The high SNR for \( k-t \) BLAST may reflect a better reproducibility of \( k-t \)
BLAST acceleration than SENSE acceleration. This can be beneficial in var-
ious situations where the precision of the measurement is more important
than its accuracy, e.g. in longitudinal studies.

Only two acceleration techniques were studied. Other acceleration tech-
niques exist, e.g. PC-VIPR [37], compressed sensing [38] and \( k-t \) PCA [39].
These techniques are presently unavailable at our institution.

5.5 Conclusion
It was found that in systole, SENSE acceleration produces
more accurate result than \( k-t \) BLAST acceleration as a result of temporal
blurring in an in vivo and in vitro aneurysm. Higher SNR levels in \( k-t \) BLAST
than in SENSE may be beneficial depending on the application of the PC-
MRI measurement.

5.6 Acknowledgments
The authors would like to thank Gertjan Bon from
the University of Amsterdam for the glass blowing of the phantom and Paul
Groot of the Department of Radiology of the Academic Medical Centre/Uni-
versity of Amsterdam for the inventive ECG signal acquisition. The authors
would also like to thank Gustav Strijkers of the Department of Biomedical
NMR of the University of Technology Eindhoven for advice on the manu-
script.
5.7 References


16 Carlsson M, Toger J, Kanski M, Bloch KM, Stahlberg F, Heiberg E, Arheden H. Quantification and visualization of cardiovascular 4D velocity mapping accelerated with parallel imaging or k-t BLAST: head to head comparison and validation at 1.5 T and 3 T. *Journal of Cardiovascular Magnetic Resonance* 2011; **13**:55.


Quantification and visualization of flow in the Circle of Willis: time-resolved three-dimensional phase contrast MRI at 7T compared with 3T

Pim van Ooij, Jaco Zwanenburg, Fredy Visser, Charles Majoie, Ed van Bavel, Jeroen Hendrikse, Aart Nederveen

Abstract

The assessment of both geometry and hemodynamics of the intracranial arteries has important diagnostic value in internal carotid occlusion, sickle cell disease and aneurysm development. Provided that SNR and resolution are high, these factors can be measured with time-resolved three-dimensional phase contrast MRI (PC-MRI). However, within a given scan time duration, an increase in resolution causes a decrease in SNR and vice-versa, hampering flow quantification and visualization. To study the benefits of higher SNR at 7T, PC-MRI in the Circle of Willis was performed at 3T and 7T in 5 volunteers. Results showed that the SNR at 7T was roughly 2.6 times higher than at 3T. Therefore, segmentation of small vessels such as the anterior and posterior communicating arteries (ACoA and PCoA) succeeded more frequently at 7T. Direction of flow and smoothness of streamlines in the ACoA and PCoA were more pronounced at 7T. Mean velocity magnitude values in the vessels of the Circle of Willis were higher at 3T due to noise compared to 7T. Likewise, areas of the vessels were lower at 3T. In conclusion, the gain in SNR at 7T compared to 3T allows for improved flow visualization and quantification in intracranial arteries.

chapter 6

Improvements
Introduction

The Circle of Willis acts as an essential collateral pathway to maintain blood flow to the cerebral cortex in case of vessel occlusion due to thrombosis, atherosclerosis or vasospasm [1]. Knowledge of local hemodynamics and geometry of the Circle of Willis is beneficial in diagnosis, treatment, or screening of a number of pathologies. First, it may be beneficial in treatment planning in patients with symptomatic internal carotid artery occlusion [2]. Secondly, overt cerebral infarcts are common in children that suffer from sickle cell disease. The elevated blood flow in the internal carotid and cerebral arteries can be used as a screening method for infarct risk assessment [3]. Furthermore, intracranial aneurysms, a common cause for subarachnoid haemorrhage or cerebral stroke, often develop at arterial branch points in the Circle of Willis [4-5]. One risk factor for aneurysm development is the asymmetry and incompleteness of the Circle of Willis [6-8].

Studies attempting to understand the mentioned pathologies and its relation to the anatomy of and hemodynamics in the Circle of Willis are based on transcranial Doppler ultrasonography (TCD) [9], morphometric [6, 10-11], or computational analysis [12-14]. A disadvantage of TCD is its incapability to access the vessels higher in the brain and the acquisition of merely the maximum velocity magnitude in a vessel [15]. Morphometric studies lack flow information whereas computational studies suffer from various assumptions such as Newtonian fluid behaviour, rigid vessel walls and non-patient-specific boundary conditions [16].

A promising technique to non-invasively measure blood flow is time-resolved three-dimensional phase contrast MRI (PC-MRI) [17-18]. PC-MRI can combine anatomical information with spatial and temporal blood flow velocity information and the derived hemodynamic properties in the Circle of Willis, provided that the resolution of the measurement is high (voxel size \(< 1 \times 1 \times 1 \text{ mm}) [19-21]. These flow measurements have successfully been applied to measure redistribution of blood flow after Internal Carotid Artery (ICA) occlusion [22-25] or to measure elevated blood flow in sickle cell disease [3]. The feasibility of characterizing blood flow patterns in intracranial aneurysms has been proven successful as well [26-30].

PC-MRI measurements may prove particularly valuable in the cases of the small communicating arteries in the Circle of Willis, since redistribution of flow in the Circle of Willis occurs through these arteries and since the instability and complexity of the flow may explain the incidence of aneurysms.
at these sites [31-32]. However, segmentation of these small vessels may be hampered by insufficient resolution of the PC-MRI measurement. Furthermore, image quality may be compromised in high resolution acquisitions since SNR decreases with increasing resolution. A decrease in SNR of PC-MRI data increases segmentation failure, blood-flow direction uncertainty and hampers flow quantification [21]. The application of parallel imaging [33] to decrease long scan times inherently related to PC-MRI, decreases SNR even further.

A straightforward option to increase SNR while maintaining sufficient spatial resolution would be to perform acquisitions at higher field strengths. To our knowledge, so far no blood flow velocity measurements with the use of time-resolved PC-MRI have been conducted at 7T. We hypothesize that at 7T the SNR is superior to 3T and that more detailed flow information can be gathered. In this study time-resolved PC-MRI is performed in the Circle of Willis of five volunteers at 3T and 7T at two different resolutions, to investigate the benefit of 7T in quantifying blood flow in the vessels of the Circle of Willis.

6.2 Materials & Methods

6.2.1 Volunteers

MR examinations were performed on 5 subjects (2 males, 3 females) without any known history of cardiovascular abnormalities or neurological symptoms. Age varied between 21 and 55 years old. Written informed consent was given by all volunteers in accordance to the Institutional Review Board of the University Medical Center Utrecht.

6.2.2 MR imaging procedure

Examinations were performed using PC-MRI based on a spoiled gradient echo with standard four point encoding [34] on a 3T MR system (Achieva, Philips Healthcare, Best, The Netherlands) in an 8-channel head coil (with a width of 220 mm diameter ) and a 7T MR system (Achieva, Philips Healthcare, Cleveland, USA) in a volume transmit and 16-channel receive head coil (with a width of 180 mm diameter, Nova Medical, Wilmington, MA, USA). The examinations were retrospectively gated [35]. A specific $k$-line was repeatedly acquired during a complete RR-interval; this was repeated for the next $k$-line until all $k$-lines were acquired.
The temporal interpolation factor for the retrospective sharing between successive heart phases of acquired $k$-lines was set to 2. Gating information was acquired with the use of a peripheral pulse unit (PPU). PC-MRI was performed at two (non-interpolated) resolutions: 0.47 mm x 0.47 mm x 0.5 mm, referred to in the remainder of this paper as 0.5 mm, and 0.75 mm x 0.75 mm x 0.8 mm, referred to in the remainder of this paper as 0.8 mm. Imaging parameters for both sequences were: flip angle: 20°; field of view: 180 mm x 180 mm x 20 mm (Anterior-Posterior x Right-Left x Feet-Head); velocity encoding: 150 cm/s x 150 cm/s x 150 cm/s; SENSE: 3 (in RL direction); TE/TR at 0.5 mm: 4.1/8.6 ms; TE/TR at 0.8 mm: 3.9/7.8 ms. Number of slices at 0.5 mm: 40; Number of slices at 0.8 mm: 25. In each volunteer the temporal resolution was kept constant by means of adjusting the measured number of cardiac phases in the heart cycle. For acquisitions at 0.5 mm the number of reconstructed cardiac phases ranged from 5 to 11 cardiac phases at a heart rate of 85 to 41 beats per minute respectively, resulting in a temporal resolution of 147±7.0 ms. For acquisitions at 0.8 mm the number of reconstructed cardiac phases ranged from 10 to 24 cardiac phases at a heart rate of 86 to 40 beats per minute respectively, resulting in a temporal resolution of 69±3.6 ms. For both resolutions, scan times ranged from 17 to 9 minutes depending on the heart rate. Time in between the 3T and 7T scans was no longer than 60 minutes.

6.2.3 Data quantification and visualization

Phase images were corrected for background phase offset errors by subtraction of the average phase in a nearby static region of interest (amygdala). Phase correction was performed for every velocity encoding direction and cardiac phase individually [36]. The lumen of the Circle of Willis and its surrounding vessels was segmented semi-automatically with the use of a level set evolution algorithm [37] applied to the sum of the magnitude images derived from the complex phase contrast data, referred to in the remainder of this paper to as the phase contrast magnitude images, and the complex difference reconstruction images [38]. The lumen was segmented at all cardiac phases and in every slice using the same algorithm. When the majority of cardiac phases showed a full segmentation of a certain vessel, the vessel was regarded as segmented. False segmentations due to cerebrospinal fluid or noise were manually removed. To remove outliers in the velocity vector fields, each velocity direction (RL,
AP and FH) of the phase contrast data was filtered with a custom-built filter, which used the maximum observed velocity difference between subsequent cardiac phases to define outliers. In pixels that showed differences higher than 30% of the maximum velocity difference, the filter prescribed the mean velocity of the non-zero surrounding pixels. This was repeated for pixels that now showed differences higher than 60% of the maximum velocity difference between subsequent cardiac phases.

To quantify differences between PC-MRI at 3T and 7T, the 7T phase contrast magnitude data was registered to the 3T phase contrast magnitude data using affine registration in FLIRT [39]. The means of the paired differences between the 3T and 7T PC-MRI acquisitions were determined by subtracting the velocity magnitude in corresponding voxels in every cardiac phase and subsequently averaging this difference over the number of voxels and over the number of cardiac phases. Standard deviations of the paired differences (SDp) and the median of the difference in angles of velocity vectors were calculated. Significance of the mean of the paired differences was tested with a t-test; p<0.05 was considered statistically significantly different.

Signal to noise ratios were calculated according to Price et al. [40]. Let $S_i$ and $S_j$ represent phase contrast magnitude signals in a region of interest selected in static tissue (amygdala) during different cardiac phases of similar mean velocity magnitude. By subtracting these images, an image containing minimum signal and maximum noise is obtained. SNR is estimated from [41]:

$$\text{SNR} = \frac{\text{mean}(S_i + S_j)}{\sqrt{2 \text{ std}(S_i - S_j)}}$$

(6.1)

Since the SNR of the phase images is proportional to the SNR of the phase contrast magnitude images [42], SNR estimations were not performed in the phase images separately. These post-processing and quantification steps were performed with custom-built software in Matlab (Mathworks, Natick, MA, USA). The postprocessed data were subsequently imported in GTFlow (Gyrotools, Zurich, Switzerland) to perform blood flow visualization and quantification in the arteries in the Circle of Willis. A perpendicular slice was manually positioned in the artery of interest and all segmented pixels were included in the mean velocity magnitude, area and flow calculation. Note that flow was calculated by multiplication of the area with the average through-plane velocity. The latter value is not given. For all vessels that were
found at both 3T and 7T, a t-test was performed to investigate whether the differences between mean velocity magnitude, area and flow at 3T and 7T were significant. Flow patterns were visualized by vector and streamline fields. Theoretically, streamlines are disrupted when divergence of the local velocities is high or smooth when divergence is low.

6.3 Results

In table 6.1 the segmentations of the Posterior Communicating Arteries (PCoA) and Anterior Communicating Arteries (ACoA) at the four different PC-MRI sequences are shown. Most communicating arteries were segmented at 0.5 mm resolution at 7T and none at 0.8 mm at 3T. Note that the left PCoA of volunteer 5 was segmented at 0.5 mm at 3T, but not at 7T. This was due to movement of the subject, who moved the PCoA outside the field of view at 7T after field of view positioning. The direction of the flow in the small vessels, deduced from the PC-MRI sequence at 0.5 mm at 7T, is added to table 6.1.

Table 6.2 provides SNR values and differences between the measured velocities at 3T and 7T. Signal to noise ratios were higher at 7T than at 3T and at 0.8 mm than at 0.5 mm. Averaged over all volunteers, the increase in SNR at 7T was approximately a factor of 2.6 compared to 3T. It is shown that the means of the paired differences were small for both resolutions and all volunteers, albeit significant in most cases. Positive mean differences indicate that the velocities at 3T were higher than at 7T. The standard deviation of the paired difference and the median angle were higher at 0.5 mm than at 0.8 mm.
In figure 6.1a, stacks of segmented phase contrast magnitude images are shown of the Circle of Willis of volunteer 1 at 7T (left) and 3T (right). The ACoA (red) and right PCoA (green) were visible at both field strengths. Note that the neurological convention was used here. Some posterior vessels were more apparent at 7T, whereas the right ophthalmic artery was more apparent at 3T. The former was a result of an increase of SNR at 7T, the latter of field of view placement. In figure 6.1b, velocity vector visualization with a magnified inset of the flow in the ACoA at begin diastole is displayed. At 7T it can be seen that the ACoA had a blood flow direction from the right ACA to the left ACA. This was less obvious at 3T where noise levels were higher than at 7T. Increased noise hampered streamline visualization at 3T compared to 7T, as shown in figure 6.1c. Similar advantages of the higher field strength could be seen in the right PCoA, displayed in figure 6.1d and e. Blood at 7T flowed from PCA to ICA, which was less clear at 3T, and streamlines were slightly more disrupted at 3T.

Another example is displayed in figure 6.2, where, apart from the ACoA (red) and the right PCoA (blue), the left PCoA (green) and both Anterior Choroidal Arteries (AChA, blue and green) of volunteer 2 were segmented. Again, the ACoA blood flow direction was from the right ACA to the left ACA, which was clearer at 7T compared to 3T, see figure 6.2b. At 3T the segmentation of the ACoA at displayed cardiac phase failed. Therefore, disrupted streamlines through the ACoA were seen at 3T in figure 6.2c. It is clear in figure 6.2d that in the left PCoA the blood flow direction was from the PCA to the ICA, which was more difficult to see at 3T. This was supported by the streamline visualization in figure 6.2e. Note in figure 6.2d and e that upward flow in the AChA could be visualized at 7T. In figure 6.2f it can be seen that, due to lower SNR, segmentation of the right PCoA and the right AChA failed.

<table>
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<tr>
<th></th>
<th>Volunteer 1</th>
<th>Volunteer 2</th>
<th>Volunteer 3</th>
<th>Volunteer 4</th>
<th>Volunteer 5</th>
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<td>0.8</td>
<td>0.5</td>
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<td>3T</td>
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<td>6</td>
<td>13</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>SNR</td>
<td>13</td>
<td>34</td>
<td>41</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Mean (cm/s)</td>
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<td>0.1*</td>
<td>1.4*</td>
<td>2.1*</td>
<td>0.7*</td>
</tr>
<tr>
<td>SDp (cm/s)</td>
<td>10.0</td>
<td>6.9</td>
<td>16.4</td>
<td>9.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Angle (º)</td>
<td>21.6</td>
<td>12.0</td>
<td>27.6</td>
<td>13.5</td>
<td>26.0</td>
</tr>
</tbody>
</table>

Table 6.2 SNR, mean of the paired difference (3T minus 7T) where * indicates a significant difference (p<0.001), standard deviation of the paired difference (SDp) and the median of the angle distribution between the 3T and 7T PC-MRI measurements.
at 3T, whereas at 7T flow from ICA to PCA in the right PCoA and upward flow in the AChA could be visualized.

In figure 6.3a and b the flow in the PCoAs measured at 7T for 0.5 mm and for 0.8 mm, respectively, is plotted. The flow in the PCoAs measured at 0.8 mm, displayed in figure 6.3b, corresponded well with the flows in the same PCoAs measured at 0.5 mm in figure 6.3a. In two of the three measured flows in figure 6.3b, pulsatility was more obvious than in figure 6.3a, due to the higher temporal resolution. Note that the curves do not change sign, indicating that no backflow was observed.
Figure 6.2 The Circle of Willis of volunteer 2 obtained from a measurement with a resolution of 0.5 mm at 7T (left column) and 3T (right column). In row a the top view of the three-dimensional Circle of Willis after segmentation of the phase contrast magnitude images is shown at peak systole. The ACoA is shown in the red square, the left PCoA in the green square and the right PCoA in the blue square. The neurological convention is used here. Row b shows velocity vectors in the ACoA at begin diastole. In row c accompanying streamlines are presented. In row d and e velocity vectors and streamlines are shown in the left PCoA at end systole. Note the visualization of blood flow in the left AChA in these images. Row f displays velocity vectors in the right PCoA and right AChA at end systole.

Improvements
In table 6.3, the mean velocity magnitude, area and flow averaged over all cardiac phases and all volunteers is given for the vessels in the Circle of Willis. At 0.5 mm, the mean velocity magnitude was higher (p<0.005) at 3T than at 7T for all vessels in all subjects; the area, however, was lower (p<0.005). Flow values were similar for both field strengths (p=0.4).

These effects were not seen for the mean velocity magnitude, area and flow at 0.8 mm, see table 6.4 (p=0.86, p=0.49, p=0.17 respectively).

For 3T the mean velocity magnitudes at 0.8 mm (table 6.4) were consistently lower than at 0.5 mm (table 6.3, mean difference: 6.9 cm/s, p<0.001), whereas areas were larger (mean difference: 3.4 mm², p<0.001). There was no significant difference in mean flow between 0.8 and 0.5 mm (p=0.22).

For 7T the mean velocity magnitudes at 0.8 mm (table 6.4) were lower than at 0.5 mm as well (table 6.3, mean difference: 3.0 cm/s, p<0.001), whereas the areas were larger (mean difference: 2.7 mm², p<0.001). There was no significant difference in mean flow between 0.8 and 0.5 mm (p=0.59).

![Figure 6.3 Flow in the Posterior Communicating Arteries (PCoAs) of the volunteers measured at 0.5 mm (left) and 0.8 mm (right) at 7T. Flow from the ICA to the PCA is defined as positive flow whereas flow from the PCA to the ICA is defined as negative flow. The flow is measured at the same locations as in table 6.3. Note that the curves do not change sign, indicating that no backflow was observed.](image)

### Table 6.3

<table>
<thead>
<tr>
<th>Field strength</th>
<th>Mean velocity magnitude (cm/s)</th>
<th>Mean area (mm²)</th>
<th>Mean flow (ml/s)</th>
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<tbody>
<tr>
<td></td>
<td>3T</td>
<td>7T</td>
<td>3T</td>
</tr>
<tr>
<td>ICA</td>
<td>34.6±5.9</td>
<td>29.7±6.3</td>
<td>11.8±2.0</td>
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<tr>
<td>MCA</td>
<td>30.9±7.2</td>
<td>28.6±5.8</td>
<td>9.7±2.5</td>
</tr>
<tr>
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<td>21.9±5.8</td>
<td>9.3±2.5</td>
</tr>
<tr>
<td>ACA1</td>
<td>30.7±8.0</td>
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<td>4.9±0.8</td>
</tr>
<tr>
<td>ACA2</td>
<td>29.8±7.4</td>
<td>24.0±6.7</td>
<td>4.9±1.2</td>
</tr>
<tr>
<td>ACoA</td>
<td>12.3±1.4</td>
<td>12.0±8.7</td>
<td>2.1±0.9</td>
</tr>
<tr>
<td>PCA</td>
<td>20.5±12.1</td>
<td>17.5±3.6</td>
<td>5.1±1.4</td>
</tr>
<tr>
<td>PCoA left</td>
<td>10.7±7.0</td>
<td>8.9±5.3</td>
<td>2.6±0.3</td>
</tr>
<tr>
<td>PCoA right</td>
<td>8.3±1</td>
<td>8.4±2.4</td>
<td>2.2±1</td>
</tr>
</tbody>
</table>

Quantification and visualization of flow in the Circle of Willis: time-resolved three-dimensional phase contrast MRI at 7T compared with 3T.
6.4 Discussion

To our knowledge, this is the first study to perform time-resolved PC-MRI at 7T. The results undoubtedly support the hypothesis that SNR is superior at 7T to 3T. Apart from the higher calculated SNR at 7T, the gain in SNR at 7T resulted in an increased amount of segmentations of the small vessels in the Circle of Willis. Furthermore at 3T, the magnitude of velocity vectors, indicated by the mean velocity magnitude, is significantly higher due to noise in the data, whereas the areas of vessels are lower. A last indication of higher SNR at 7T is that the streamlines appear smoother at 7T than at 3T, due to the lower noise levels at 7T. The median angle indicates the difference in velocity vector direction between 3T and 7T. Since the SNR is higher at 7T, the direction of the velocity vectors is more accurate than at 3T. The median angle value is therefore mainly caused by velocity vector alterations due to noise at 3T. The SNR values found by Bammer et al. [21] at 3T ranged from 43-56, slightly higher values than presented in this study at 3T (28-41 at 0.8 mm). This is consistent, however, with the larger voxel volume used by Bammer et al., namely 0.96 mm³ compared with 0.51 mm³ used here. Between 3T and 7T, the SNR averaged over all volunteers and both resolutions increased by a factor of 2.6, roughly the expected gain. A small additional gain in SNR may have resulted from the use of a 16-channel coil at 7T, with a somewhat tighter fitting, compared to an 8-channel coil at 3T. Also, the 16-channel coil may have improved the parallel imaging performance compared to the 8-channel coil, improving SNR further.

<table>
<thead>
<tr>
<th>Field strength</th>
<th>Mean velocity magnitude (cm/s)</th>
<th>Mean area (mm²)</th>
<th>Mean flow (ml/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3T</td>
<td>7T</td>
<td>3T</td>
</tr>
<tr>
<td>ICA</td>
<td>27.2±2.5</td>
<td>26.2±4.9</td>
<td>17.1±1.9</td>
</tr>
<tr>
<td>MCA</td>
<td>25.3±5.7</td>
<td>27.0±6.6</td>
<td>12.7±2.6</td>
</tr>
<tr>
<td>BA</td>
<td>19.7±0.8</td>
<td>19.6±4.3</td>
<td>12.9±2.6</td>
</tr>
<tr>
<td>ACA1</td>
<td>19.0±4.6</td>
<td>19.7±4.8</td>
<td>7.2±1.9</td>
</tr>
<tr>
<td>ACA2</td>
<td>16.6±5.3</td>
<td>20.0±6.0</td>
<td>5.4±2.0</td>
</tr>
<tr>
<td>ACaA</td>
<td>-</td>
<td>6.0±1.1</td>
<td>-</td>
</tr>
<tr>
<td>PCA</td>
<td>15.9±3.9</td>
<td>15.1±3.1</td>
<td>8.0±2.4</td>
</tr>
<tr>
<td>PCaA left</td>
<td>-</td>
<td>4.1</td>
<td>-</td>
</tr>
<tr>
<td>PCaA right</td>
<td>-</td>
<td>5.7±3.0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.4 The mean velocity magnitude, area, and flow in vessels in the Circle of Willis averaged over all cardiac phases and volunteers for 0.8 mm resolution. Standard deviations are calculated over the 5 volunteers.

- Measured in 2 volunteers: hypoplastic, not present or not segmented in others
- Measured in 3 volunteers: hypoplastic, not present or not segmented in others
- Measured in 1 volunteer: hypoplastic, not present or not segmented in others
- Measured in 4 volunteers: hypoplastic, not present or not segmented in the other

Improvements
A few other studies have attempted time-resolved PC-MRI in the intracranial arteries [3, 19-22]. Flow quantification in this study corresponded well with the values presented by these groups. The flow quantification in the PCoAs visible at both 0.5 and 0.8 mm showed similar results per individual vessel at 7T. Except for Bammer et al. [21], who found an incidental type 15 variation (De Almeida classification) of the ACAs and ACoA using PC-MRI at 3T in one volunteer, none of these studies were able to visualize or quantify flow in the ACoA or PCoA.

Other studies focusing on carotid occlusion used non-gated PC-MRI in a single slice capturing the ACoA and PCoAs [23-25]. With these data the direction of the flow could be established, but no quantification was conducted.

The visualization of the flow in the PCoAs may provide new insights in collateral flow pathways. From embryology it is known that the PCAs are fed with blood from the ICA via the PCoAs [43]. In our study, however, two of the six visualized PCoAs showed flow from PCA to ICA. The direction of flow in the ACoAs and PCoAs never altered over the cardiac cycle; only unilateral flow directions were found. These findings encourage further research concerning flow directions in the Circle of Willis in patients with collateral flow for instance related to internal carotid artery occlusions or severe stenosis. Furthermore, detailed flow analysis of the communicating segments of the Circle of Willis may also result in a better understanding of the preferential locations of intracranial aneurysm development e.g. close to the origin of the ACoA or PCoAs.

Several limitations of the study should be mentioned. Due to the need for an added flow-compensated acquisition alongside the flow-encoded one, PC-MRI inherently suffers from long scan times. In this study, the increased scan time due to the decrease in voxel size from 0.8 mm to 0.5 mm, was compensated by a decrease in temporal resolution. A decrease in temporal resolution results in underestimated flow measurements in the systolic phase.

Another method to save scan time was by using parallel imaging with a fairly high factor of 3. A well-known disadvantage of the use of high parallel imaging acceleration factors is the decrease in SNR [33]. Acceleration techniques that preserve SNR such as k-t BLAST [44] or compressed sensing [45] may be applied to time-resolved PC-MRI, although in these techniques impairments exist such as temporal filtering in the case of the former [46] or long reconstruction times in the case of the latter. Another limitation is the
use of two separate scanning sessions which may have introduced physiologic variations. However, variations were minimized by performing the scans as close to each other as possible. Unfortunately, one volunteer displaced the PCoAs outside the field of view in between a localizing scan and the PC-MRI sequence.

In conclusion, due to the gain in SNR, time-resolved PC-MRI at 7T yields better visualization and quantification of flow patterns in small vessel structures that require high resolution, potentially significantly contributing to diagnostic value in patients with carotid occlusion, sickle cell disease and intracranial aneurysms.

6.5 Acknowledgments
The author would like to thank Gérard Crelier of Gyrotools, Zürich for his GTFlow updates and advice.

6.6 Disclosures
Fredy Visser is an employee of Philips Healthcare, Best, the Netherlands.

6.7 References

5 Bor AS, Velthuis BK, Majoie CB, Rinkel GJ. Configuration of intracranial arteries and development of aneurysms: a follow-up study. *Neurology* 2008; **70**:700-705.


Quantification and visualization of flow in the Circle of Willis: time-resolved three-dimensional phase contrast MRI at 7T compared with 3T.


Improvements
WALL SHEAR STRESS
Validation of a generalized approach for calculation of wall shear stress from 3D phase contrast MRI

Wouter Potters, Pim van Ooij, Henk Marquering, Ed van Bavel, Aart Nederveen

Submitted for Journal of Magnetic Resonance Imaging
Purpose

Information on magnitude and direction of local wall shear stress (WSS) can provide insight in vascular disease progression. Here we present a generalized approach for quantification of spatiotemporal features of WSS using 3D phase contrast MRI (PC-MRI) data.

Materials and methods

Software phantoms simulating perfect parabolic flow were used. Both the accuracy and precision of the method were assessed at varying resolutions and vessel lumen segmentation accuracy. Additionally, in vivo PC-MRI data of one common carotid artery were acquired at different resolutions (0.4 to 0.8 mm) and WSS was estimated.

Results

For the software phantoms calculated WSS converged towards the theoretical WSS as resolution increased. To obtain 95% accuracy, 8 voxels over the diameter were sufficient. Segmentation errors caused a considerable decrease in both accuracy and precision of calculated WSS in the phantom data. In the in vivo data comparable effects were observed as in the phantom.
data for increasing resolution. For a constricted segmentation WSS values could change up to 50% for segmentation errors of 1 voxel.

Conclusion

Errors in the vessel lumen segmentation should be minimized to make WSS calculations reliable. The currently suggested approach can provide spatiotemporal information on magnitude and direction of WSS.
7.1 Introduction

The effect of flowing blood on the vascular endothelium has been suggested to be a critical determinant of vascular disease progression in atherosclerosis and aneurysms [1]. This effect is believed to be primarily related to the associated wall shear stress (WSS), i.e. the tangential force per surface area acting on the endothelial cells. Both low and oscillating WSS patterns have been reported to correlate with wall thickening [2-3], atherosclerosis [4] and plaque formation [5], whereas high WSS is a stimulus for physiological remodeling of blood vessels [4] and is atheroprotective. In addition, spatial gradients have been suggested to relate to intracranial aneurysm progression [6] and rupture risk [7], although compelling evidence is still lacking. For these reasons, information on magnitude, direction and spatial and temporal gradients of WSS may have diagnostic value, providing an early warning sign for cardiovascular disease progression and acute events such as stroke and aneurysm rupture. However, estimation of WSS in patients is far from trivial, and no truly validated technique is currently available.

The WSS can be estimated from spatial and temporal information on velocity direction and magnitude. Four-dimensional phase contrast magnetic resonance imaging (PC-MRI) is currently the only method to non-invasively determine such a time-resolved 3D velocity vector field in humans. Multiple methods have been presented to quantify WSS from PC-MRI velocity data [8-10]. However, most of the methods focus on specific geometries, i.e. the aorta and carotid artery, where WSS estimates are frequently limited to vascular cross-sections, rather than the full vascular wall. Bieging et al. [10] did use a method for WSS estimation over the full wall. Their approach is based on velocity gradients perpendicular to the vessel, which are approximated using a linear least squares method. While such methods have potential, there are many pitfalls, such as effects of resolution and segmentation as found in earlier research [8]. Such pitfalls remain to be carefully assessed.

The objective of the current study was to develop a WSS estimation strategy based on PC-MRI that can be applied in any vessel geometry in a standardized fashion. We evaluated this method with software phantoms and applied it to in vivo data. The accuracy and precision of WSS estimations depend on the algorithm parameters, resolution, segmentation strategies, in addition to vessel size and magnitude of flow velocity [8, 11-12]. We addressed the contributions of such factors in detail, providing guidelines for
choosing values that lead to valid WSS estimations in the phantom and to in vivo WSS estimations that, in the absence of a ground truth, are reliable.

7.2 Materials & Methods

We here present a post-processing algorithm for calculation of WSS. To assess the validity of our algorithm under varying conditions, the algorithm was first applied to multiple software phantoms with known theoretical WSS values. Secondly, we measured the common carotid artery of one healthy volunteer in which we also calculated WSS.

All simulations and calculations were performed using in-house software developed in Matlab (Version 2011b for Mac OS, The Mathworks, USA).

7.2.1 Wall shear stress algorithm

The input data for the algorithm consist of (I) a time-resolved three-dimensional surface of the vessel lumen and (II) the accompanying 3D velocity vector field. Both inputs are either simulated using software phantoms or measured with PC-MRI. The output of the algorithm is a collection of WSS vectors on the vessel lumen surface. A surface consists of vertices and faces. The vertices of the surface are called wall points. WSS vectors \( \bar{\tau} \) were calculated for each wall point:

\[
\bar{\tau} = 2\mu (\dot{\varepsilon} \cdot \hat{n})
\]

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

\[
\bar{\tau} = 2\mu \left[ \frac{1}{2} \left( \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} \right) \frac{\partial v_x}{\partial y} - \frac{1}{2} \left( \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} \right) \frac{\partial v_x}{\partial y} + \frac{1}{2} \left( \frac{\partial v_y}{\partial z} + \frac{\partial v_z}{\partial y} \right) \frac{\partial v_x}{\partial z} - \frac{1}{2} \left( \frac{\partial v_y}{\partial z} + \frac{\partial v_z}{\partial y} \right) \frac{\partial v_x}{\partial z} \right] \hat{n}
\]

To simplify this equation, two steps were performed:

- Selection of a local coordinate system for each point on the vessel wall such that the \( z' \)-axis aligns with the inward normal. This is accomplished by ro-
tating the original coordinate system with rotation $R$ determined using basic vector calculus:

$$[x' \ y' \ z'] = R[x \ y \ z] \quad (7.3)$$

$$\vec{n}(x', y', z') = [0 \ 0 \ 1] \quad (7.4)$$

- 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 becomes:

$$\vec{\tau} = \mu \left[ \frac{\partial v_x'}{\partial z} \frac{\partial v_y'}{\partial z} 0 \right] \quad (7.5)$$

For each wall point, at least two points along the inward normal were selected for which the velocity vectors were determined using natural neighbor interpolation [13]. To force the velocity to be zero on the wall ($\vec{v}_{wall} = 0$) in this calculation, zero velocity values can be enforced for the wall points (zero forcing).

A smoothing spline [14] was subsequently fitted through the velocities ($v_x'$ and $v_y'$) in the selected points along the inward normal. The spatial derivatives ($\frac{\partial v_x'}{\partial z}$ and $\frac{\partial v_y'}{\partial z}$) on the wall were analytically derived from the fitted splines. Multiplication of the spatial velocity derivatives with the viscosity resulted in the WSS vector. As a last step, the WSS vector was transformed back to the original coordinate system $[x \ y \ z]$ using the inverse rotation matrix ($R^{-1}$).

### 7.2.2 Analysis

WSS was calculated for the software phantoms and for the in vivo datasets; the results are reported as mean WSS ± standard deviation (SD). Using the software phantoms, the performance of the algorithm was described in terms of accuracy and precision. Accuracy was defined as:

$$\text{accuracy} = 100 \% \cdot \frac{\text{mean calculated WSS}}{\text{theoretical WSS}}$$

Precision was defined as the SD of calculated WSS values on the wall points. Note that for phantom data the SD defines the variation of WSS due to the algorithm only, while in the in vivo data the SD defines the variation due to the algorithm plus any natural variation of WSS over the wall.
7.2.3 Software phantom simulations

Multiple software phantoms were created to assess the effect of resolution, segmentation, vessel size and magnitude of flow velocity. All software phantoms were based on a high-resolution (0.05 mm isotropic) software phantom with a parabolic flow. In this high-resolution software phantom, partial volume effects in each voxel were simulated using the mean velocity in each voxel instead of the center velocity in each voxel. The theoretical WSS magnitude for cylindrical vessels with parabolic flow was calculated using the Hagen-Poiseuille formula. Details of the performed software phantom simulations are summarized in table 7.1.

7.2.4 Algorithm optimization – experiment 1 and 2

The algorithm has three customizable parameters: length of the normal vector used for the spline fitting, the distance between the sample points on this normal, and the use of either zero wall velocity forcing or no zero forcing. To investigate the parameters that yield the most accurate and precise results for the WSS calculations in the vessel software phantoms, multiple combinations of

<table>
<thead>
<tr>
<th>Experiment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel diameter (mm)</td>
<td>6</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Center velocity (cm/s)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>10, 20, ..., 440, 450</td>
</tr>
<tr>
<td>Viscosity (Pa·s)</td>
<td>0.0032</td>
<td>0.0032</td>
<td>0.0032</td>
<td>0.0032</td>
<td>0.0032</td>
<td>0.0032</td>
<td>0.0032</td>
</tr>
<tr>
<td>Theoretical WSS (Pa)</td>
<td>2.13</td>
<td>0.43</td>
<td>2.13</td>
<td>0.43</td>
<td>2.13</td>
<td>0.43</td>
<td>0.21 to 9.60</td>
</tr>
<tr>
<td>Net flow (ml/s)</td>
<td>14.14</td>
<td>353.43</td>
<td>14.14</td>
<td>353.43</td>
<td>14.14</td>
<td>353.43</td>
<td>1.41 to 0.562</td>
</tr>
<tr>
<td>Reynolds number</td>
<td>497</td>
<td>2484</td>
<td>497</td>
<td>2484</td>
<td>497</td>
<td>2484</td>
<td>59 to 2236</td>
</tr>
<tr>
<td>Original resolution (mm, isotropic)</td>
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<td>0.10</td>
<td>0.05</td>
<td>0.10</td>
<td>0.05</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>Resolution (mm, isotropic)</td>
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<td>0.2, 0.3, ..., 3.1, 3.2</td>
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<td>1.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmentation offset (mm)</td>
<td>0, 0, 0, 0, ..., -0.9, -1.0, -1.4, ..., 1.4, 1.5</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero forcing at wall</td>
<td>yes, no</td>
<td>yes, no</td>
<td>yes, no</td>
<td>yes, no</td>
<td>yes, no</td>
<td>yes, no</td>
<td>yes, no</td>
</tr>
<tr>
<td>Inward normal length (% diameter)</td>
<td>5, 10, ..., 45, 59</td>
<td>5, 10, ..., 45, 59</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Number of points on inward normal</td>
<td>3, 4, ..., 14, 15</td>
<td>3, 4, ..., 14, 15</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 7.1 Simulation parameters for phantom datasets. The table states the used parameters for variation of algorithm parameters (experiment 1,2), variation of resolution (experiment 3,4), variation of segmentation offset (experiment 5,6) and variation of WSS magnitude (experiment 7). In all simulations both a calculation with and without zero forcing at the wall points is performed.
the parameters were tested (table 7.1, experiment 1 and 2). The number of sample points on the normal was varied between 2 and 15. The length of the inward normal length was varied from 5% to 50% of the diameter.

7.2.5 Forcing zero velocity at the wall points - experiment 1 to 7

The velocity at the wall is generally assumed to be zero (no-slip condition), and one could argue that estimations of velocity profiles should obey to this. Yet, there are two reasons for also considering velocity profile fits where such zero wall velocity is not forced. First, slip may exist. Second and more importantly, uncertainty exist in the position of the wall, and forcing zero velocity at the wrong place might be expected to introduce errors. In the WSS calculation algorithm, we therefore investigated two conditions for all experiments: (I) velocity forced to zero on the wall. (II) Velocity not forced to zero on the vessel wall (table 7.1, experiments 1 to 7).

7.2.6 Resolution - experiment 3 and 4

In MRI, the physical resolution can be described using the point-spread function (PSF) [15]:

$$\text{psf} = \left(\Delta k \sin\left(\pi N \Delta k x\right) \sin\left(\pi N \Delta k y\right) e^{-\pi^2 \Delta k^2} \right) \left(\Delta k \sin\left(\pi N \Delta k y\right) \sin\left(\pi N \Delta k x\right) e^{-\pi^2 \Delta k^2} \right)$$

(7.6)

with $N$ the square matrix size, $\Delta k$ the width of one k-line in k-space and $(x,y)$ the voxel coordinates. The PSF accounted for both sampling and truncation effects in k-space. Note that this 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 this 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. After filtering with the PSF the data still has a large numeric resolution, therefore the phantom data was interpolated to a grid with voxel sizes matching the width of the PSF. Figure 7.1 visualizes the steps of the resolution reduction (table 7.1, experiment 3 and 4).
7.2.7 Segmentation – experiment 5 and 6
Effects of errors in the segmentation of the vessel wall lumen were induced to the software phantom by altering the original circular segmentation with an offset, while preserving the original velocity vectors (table 7.1, experiment 5 and 6).

7.2.8 Vessel size – experiment 1 to 6
To assess the effect of vessel size on our algorithm, most simulations were performed for two software phantoms, using diameters of 30 and 6 mm to respectively mimic the aorta and the common carotid artery diameters (table 7.1, experiment 1 vs. 2, 3 vs. 4, 5 vs. 6).

7.2.9 WSS magnitude
The WSS magnitude was varied by simulating different center velocities. The center velocity was varied between 10 to 450 cm/s resulting in theoretical WSS between 0.21 and 9.60 Pa (table 7.1, experiment 7).
7.2.10 In vivo experiments

In addition to software phantoms, we acquired in vivo PC-MRI datasets of the common carotid artery (CCA) at five resolutions in a healthy volunteer to verify the simulation results and to test the in vivo applicability of our algorithm. Informed consent was obtained in accordance with the guidelines of the local ethical committee. The data was acquired using a 3T MR system (Achieva, software version 3.2.1, Philips Healthcare, Best, The Netherlands) and a dedicated eight-channel carotid coil was used. The images were acquired for five different isotropic spatial resolutions of approximately 0.4, 0.5, 0.6, 0.7 and 0.8 mm, see table 7.2. Parameters other than resolution were not changed (table 7.2). Data were corrected for systematic phase offset errors by subtraction of the average phase in static muscle tissue close to the vessel of interest for each slice and time step. Aliasing artifacts were avoided by means of a high encoding velocity in the feet-head direction (100 cm/s).

A level set evolution algorithm [16] was used to segment the lumen in the 0.4 mm resolution dataset, resulting in a surface of the vessel lumen. The surface of the segmented vessel lumen was smoothed using a Laplacian filter [17]. The segmented vessel wall surface from the 0.4 mm dataset was used as for all five datasets to avoid differences in the WSS calculation due to differences in the segmentation.

All lower resolution datasets (0.5 - 0.8 mm) were coregistered to the 0.4 mm resolution dataset using mutual information to correct patient movement in between scans (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). To compensate for natural variation in heart rate and blood flow through the CCA, velocities for each acquisition were scaled to match the measured time-averaged flow in the 0.4 mm resolution dataset (5.59 ml/s). The flow was calculated by multiplication of the surface area of the segmentation and the time-averaged velocities perpendicular to that area. The flow was scaled to the 0.4 mm resolution using the time-averaged flows for each resolution.

All voxels overlapping with the vessel lumen surface were neglected during calculation of the WSS, thus avoiding contribution from voxels (partially) outside the lumen segmentation. WSS was calculated using a 1 mm inward normal with 5 points on this inward normal. The reason for using different settings for in vivo data is the complexity of velocity patterns (i.e. not parabolic). Using 5 points on a 1 mm inward normal we made sure
that velocity patterns that could be measured with the image resolution are not undersampled during the WSS calculation. The effect of resolution on calculated WSS was compared for each time step and additionally the effect of resolution on the time-averaged WSS was compared. We also assessed the effect of resolution separately in regions of low, medium and high WSS calculation (defined by the 0-33, 33-66 and 66-100% tertiles of WSS magnitude as calculated in the 0.4 mm resolution).

The effect of segmentation errors in in vivo data was assessed for the high-resolution 0.4 mm case. The original vessel wall was dilated and constricted along the inward normals by using offsets to the original surface from -1.5 mm to 1.5 mm. During this process the number of wall points remained the same. The effect of deviations in the vessel wall was assessed for time-averaged WSS. Additionally this effect was assessed separately for regions of low, medium and high WSS.

<table>
<thead>
<tr>
<th>Values</th>
<th>Spatial resolution* (mm)</th>
<th>Voxel volume (μl)</th>
<th>Matrix size</th>
<th>Field of view* (mm)</th>
<th>Flip angle (º)</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Velocity encoding values* (cm/s)</th>
<th>SENSE acceleration factor</th>
<th>Time frames</th>
<th>Average heart rate during scan (l/min)</th>
<th>Bandwidth (Hz/pixel)</th>
<th>Scan duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.38 x 0.38 x 0.40</td>
<td>0.058</td>
<td>160 x 160 x 100</td>
<td>60.8 x 60.8 x 8.0</td>
<td>25</td>
<td>10.98</td>
<td>3.98</td>
<td>30 x 30 x 100</td>
<td>1.7</td>
<td>5</td>
<td>46</td>
<td>433</td>
<td>9.23</td>
</tr>
<tr>
<td></td>
<td>0.47 x 0.47 x 0.50</td>
<td>0.111</td>
<td>128 x 128 x 85</td>
<td>60.2 x 60.2 x 8.5</td>
<td>25</td>
<td>7.68</td>
<td>3.83</td>
<td>30 x 30 x 100</td>
<td>1.7</td>
<td>5</td>
<td>48</td>
<td>434</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td>0.54 x 0.54 x 0.60</td>
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<td>25</td>
<td>7.68</td>
<td>3.73</td>
<td>30 x 30 x 100</td>
<td>1.7</td>
<td>5</td>
<td>53</td>
<td>434</td>
<td>1.46</td>
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<td>96 x 96 x 60</td>
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<td>25</td>
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<td>3.65</td>
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<td>434</td>
<td>2.07</td>
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<td>1.7</td>
<td>5</td>
<td>50</td>
<td>434</td>
<td>1.35</td>
</tr>
</tbody>
</table>

*Right-Left x Anterior-Posterior x Feet-Head

Table 7.2 In vivo acquisition parameters of common carotid artery. Isotropic spatial resolution was varied in steps of ± 0.1 mm. Time frames were obtained by retrospective triggering using a peripheral pulse unit (PPU).
7.3 Results

7.3.1 Algorithm optimization – experiment 1 and 2

Figure 7.2 shows the results from the variation of the algorithm parameters (table 7.1, experiment 1 and 2) in two different sized phantom vessels; a 6 mm vessel at 0.5 mm resolution and a 30 mm vessel at 1.0 mm resolution. In both vessel sizes, zero forcing at the wall lead to results closer to the theoretical value. Furthermore, we found that an inward normal length of 50% of the diameter with 3 points (2 points + wall point) resulted in the lowest WSS variation across different sized vessels (6 mm, 30 mm).

![Figure 7.2 Effect of algorithm parameters (inward normal length and number of points along normal) on the WSS calculation (table 7.1, experiment 1 and 2). Top row shows the results for a 6 mm vessel phantom (theoretical WSS 2.13 Pa), bottom row shows the results for a 30 mm vessel phantom (theoretical WSS 0.43 Pa). Left column represents the results with zero forcing; right column shows the results without zero forcing. Color of the surface represents the standard deviation of the calculated WSS. The gray dots represent the mean WSS calculations with the color proportional to their value. Note that without zero forcing, the WSS is underestimated.](image)

Wall shear stress
7.3.2 Resolution – experiment 3 and 4

Figure 7.3a and 7.3b show the effects of resolution on the calculated WSS (table 7.1, experiments 3 and 4). The mean WSS decreased with larger voxel size, while the SD increased. Both methods generally underestimate the WSS. However, WSS was more precisely and more accurately calculated with wall velocity forcing than without. In the 6 mm vessel (figure 7.3a) the WSS calculated without zero forcing was 52-60% of the theoretical WSS, the WSS calculated with zero forcing was 84-99% of the theoretical WSS. For the 30 mm vessel (figure 7.3b) these number were 52-65% and 95-99% for respectively calculation without and with zero wall velocity forcing.

7.3.3 Segmentation – experiment 5 and 6

Figure 7.3c and 7.3d show the effects of segmentation offsets on the calculated WSS in a phantom vessel of 6 mm diameter with 0.5 mm resolution (figure 7.3c), and in a phantom vessel of 30 mm diameter with 1.0 mm resolution (figure 7.3d, table 7.1, experiments 5 and 6). The results show that for a wider segmentation, the calculated WSS decreased in both the calculation with and without zero forcing at the wall points. For a narrower segmentation, the calculated WSS increased in case of zero forcing and slightly increased and then decreased slowly when the velocity is not forced to zero at the wall points.

7.3.4 Vessel size – experiment 1 to 6

The results of the experiments (table 7.1, experiments 3 vs. 4, 5 vs. 6) in figure 7.3a and 7.3b show that the effect of resolution is similar for different sized vessels. Figure 7.3c and 7.3d show that this also is the case for absolute segmentation offsets.

7.3.5 WSS magnitude

Figure 7.3e shows the theoretical WSS versus the calculated WSS with and without zero forcing for center velocity varied between 10 to 450 cm/s resulting in WSS values of 0.21-9.6 Pa (table 7.1, experiment 7). The calculations with zero forcing corresponded much better with the theoretical value than those without zero forcing. Calculated WSS depended strictly linear on the theoretical value, with slopes of 0.538 and 0.977 ($r^2=1.000$) without and with zero forcing respectively.
7.3.6 In vivo experiments - resolution

WSS calculation was performed in all datasets (table 7.2) for each of the five time steps. Figure 7.4 shows an example slice of the velocity and magnitude data plus the flow quantifications for each resolution. For lower resolutions, the WSS decreased (figure 7.5a, figure 7.6). This behavior is similar for all time steps. By dividing the WSS into 3 tertiles, we confirmed that this behavior also persists for different WSS magnitudes (figure 7.5b).

For points on the wall where the inward normal vector of 1.0 mm was located (partially) outside the available velocity data WSS could not be resolved. This occurred in 88 of the 1304 cases (6.7%), all of which were located at the top and bottom of the segmented vessel wall lumen. Figure 7.6 visualizes the WSS vectors on the vessel lumen surface.

Figure 7.3 Results from the WSS calculations in multiple software phantoms. The subfigures contain the theoretical WSS (green dashed line), the WSS calculated with zero forcing at the wall points (black line), the WSS calculated without zero forcing at the wall points (gray line). (a) Resolution variation versus calculated WSS for a 6 mm vessel (table 7.1, experiment 3). The theoretical WSS is 2.13 Pa. The standard deviations (SD) are visualized as lines without markers. (b) Resolution variation versus calculated WSS for a 30 mm vessel (table 7.1, experiment 6). The theoretical WSS is 0.43 Pa. The SD’s are visualized as lines without markers. (c) Segmentation offsets versus calculated mean WSS (table 7.1, experiment 5). The theoretical WSS is 2.13 Pa. The simulations were performed using a phantom dataset of 0.5 mm resolution. Negative offsets represent a constricted segmentation, positive offsets represent a dilated segmentation. (d) Segmentation offsets versus calculated mean WSS (table 7.1, experiment 6). The theoretical WSS is 0.43 Pa. The simulations were performed using a phantom dataset of 1.0 mm resolution. (e) Theoretical WSS versus calculated WSS in a 6 mm diameter, 0.5 mm resolution vessel phantom (table 7.1, experiment 7). The blue line represents the line at which the calculation matches the theoretical WSS. The black line, using a calculation with zero forcing, can be described using y=0.977x (r²=1.000). The gray line, using a calculation without zero forcing, can be described using y=0.5379x (r²=1.000).
7.3.7 In vivo experiments - segmentation

Figure 7.5c shows the results for variation in the segmentation (table 7.2, 0.4 mm measurement only). For a constricted segmentation, the WSS increased greatly, while for a dilated segmentation, the WSS decreased slightly. Also, the SD increased considerably for erroneous segmentations.
7.4 Discussion

In this study, a generalized approach for calculation of WSS was developed. This post-processing algorithm for PC-MRI data was validated using software phantoms of straight vessels and successfully applied to the PC-MRI data of an in vivo CCA.

The availability of spatiotemporal WSS information across the vessel is an improvement over existing 2D and slice-based WSS calculation methods [8, 18]. The current generalized approach can potentially be applied to any geometry, including more complex geometries such as vessel bifurcations and aneurysms. While the current phantom and in vivo analysis provides good arguments for the validity of this approach in more complex geometries, further research will be needed to substantiate this (Chapter 8). The WSS calculations in a straight vessel with parabolic flow as presented here are more accurate and precise compared to existing methods in literature [8, 10-12]. Multiple causes for these differences may exist. Stalder et al. [8] used manual segmentation of the phantom data, while in this research a perfect circular segmentation was used. Additionally these authors used Gaussian filtering of the velocity data before calculating WSS. A different point is that in the current methods forcing of zero velocity at the wall points is not reported [8, 11-12]. Also, differences may exist between the used PSF’s. For example, Stalder et al. [8] used a similar Cartesian PSF as in this study, whereas Cheng et al. [12] did not report on a PSF.

In addition to investigating previously described effects on WSS calculation, we investigated the effects of segmentation errors on the calculated WSS, which appeared to outweigh the errors in the WSS calculation due to a resolution decrease. For a high-resolution software phantom, an induced segmentation offset of +0.5 mm or -0.5 mm decreases the accuracy by 23% and 43%. It should be noted that the positive segmentation offsets in the phantom data simply cause the vessel wall to move outside the vessel where only zero velocity values are present, which does not represent in vivo measurements. In the in vivo experiment we noticed similar behavior as in the phantom, namely an increase in estimated WSS for constriction of the vessel. The dilatation of the vessel lumen surface only caused a slight decrease in magnitude, but a large increase in the SD of calculated WSS. This can be attributed to the noise in the velocity values outside the vessel lumen.

In the phantom simulations, we showed that for a parabolic profile in a straight vessel, three points on an inward normal with a length of at least the...
radius provided the most accurate and precise results for both the 6 mm and the 30 mm vessel. These parameters may have a limited validity outside the software phantoms with perfect segmentation and parabolic flow. However, it should also be noted that in vivo velocity patterns near the wall are generally parabolic and thus the smoothing spline approach can still be valid close to the wall. More research is required to evaluate this.

We addressed zero forcing mainly because segmentation errors may cause velocity to be fixed to zero at the wrong place, potentially resulting in major deviations in WSS estimation, since the WSS depends on the velocity gradients near the wall. We show however that zero forcing of wall velocity improves accuracy of the WSS calculation. This was the case in not only perfectly segmented phantoms, as expected, but also in the presence of segmentation errors.

We can conclude for the effect of resolution that, given a perfect segmentation, the measurement resolution of WSS should be at least 8 voxels across the diameter to obtain 95% accuracy in a phantom dataset. This number is much higher than previously reported guidelines on resolution of flow quantification using PC-MRI, such as at least 3 voxels across the diameter [19].

The in vivo data showed that WSS converges towards higher values at higher resolutions, similar to what was found for the phantom data. However for the in vivo case, the SD did not decrease with better resolutions. This can be attributed to the natural variation of WSS across the vessel wall.

In contrast to existing WSS calculation methods [11], we noticed that the calculated WSS magnitude increased linearly with increasing WSS magnitude. Possible causes for this difference are the use of different simulation types for PC-MRI images (image based simulation versus Bloch equation based simulation) and secondly we only used laminar flow phantoms in our case.

A limitation of this work is that noise was not included in the phantom simulations. This does not resemble the in vivo situation and therefore some differences in the in vivo experiments with the segmentation offset were present compared to the phantom data. As noise in the phase difference images is normally distributed around zero [20], addition of noise will have little effect on accuracy of the WSS estimation, whereas the precision will decrease with increasing noise levels.

The results are limited by uncertainties in the velocity measurements using PC-MRI, such as phase offset errors induced by eddy currents and...
concomitant gradient errors, intravoxel dephasing, pulsatile flow artifacts and water-fat shift artifacts [21] and partial volume effects. The uncertainties in velocity quantification were minimized by optimization of scan parameters and post-processing i.e. phase offset correction, aliasing correction (if required) and omitting partial volume voxels at the wall.

The next step towards clinical usability will be to validate the described method by measuring complex geometries, which can be compared against CFD simulations, which are generally considered as the golden standard. A good approach would be to use a phantom measurement with a known fixed anatomy [22] with a flow configurable using computer-driven pumps. The calculated WSS in such a setup could then be compared to velocity and WSS resulting from CFD simulations. This work is partially carried out in Chapter 8.

In conclusion, the currently suggested generalized approach can provide spatiotemporal information on both magnitude and direction of WSS. The analysis of effects of, amongst others, finite resolution and segmentation errors provides suggestions for scan protocols and post-processing that provide reliable WSS estimations.

7.5 Acknowledgements

This study is supported by the Dutch Technology Foundation STW (CARISMA 11629).

7.6 References


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

Pim van Ooij, Wouter Potters, Annetje Guédon, Joppe Schneiders, Henk Marquering, Charles Majoie, Ed van Bavel, Aart Nederveen

Submitted for Journal of Magnetic Resonance Imaging
Abstract

Objective
The objective was to study the performance of an in-house developed wall shear stress (WSS) algorithm using PC-MRI in intracranial aneurysms.

Materials & Methods
First, the algorithm was applied to a high resolution in vitro PC-MRI measurement under steady and pulsatile flow conditions. A CFD simulation was performed with similar inflow boundary conditions. Second, WSS was estimated in steady PC-MRI data acquired at different resolutions. Third, the algorithm was applied to a pulsatile in vivo measurement and compared with CFD. The direction and magnitude of WSS vectors were computed and compared with Spearman’s correlation coefficient.

Results
Quantitative agreement was moderate for the phantom (Spearman $\rho=0.69$). The WSS magnitude of PC-MRI was lower than CFD for both the in vitro and in vivo case. However, there was qualitative agreement between PC-MRI and CFD, i.e. WSS vector direction was similar for both modalities.
Circular WSS patterns were found both in vitro and in vivo for PC-MRI and CFD. Increasing resolution uncovered complex WSS patterns with higher mean WSS magnitude.

**Conclusion**

The algorithm can robustly estimate wall shear stress patterns in aneurysm geometries with similar directions as CFD. PC-MRI based estimation of abnormal WSS patterns may aid in the identification of risk factors for aneurysm disease progression.
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. 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 [4]. 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) [5-6]. 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) [7-8], 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.

Oshinksi et al. [9] were the first to estimate wall shear stress in the aorta with through-plane PC-MRI data. Stokholm et al. [10] estimated 1D wall shear stress and oscillatory shear index by parabolic fitting to through-plane velocity profiles in the carotid artery. Papathanasopoulou et al. [11] 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. Stalder et al. [12] and Markl et al. [13] improved this method in the aorta by using b-splines for fitting purposes. 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.
Boussel et al. [15] were the first to estimate wall shear stress in intracranial aneurysms based on PC-MRI data acquired at a resolution of 1 mm\(^3\), followed by Isoda et al. [16] using a similar resolution. Petersson et al. [17] showed with the use of numerical simulations that wall shear stress calculation by parabolic fitting produced the most accurate results. Recently, a wall shear stress estimation algorithm was developed that can be applied in 3D in any vessel geometry (Chapter 7).

The purpose of the current study was to study the performance of this algorithm in intracranial aneurysms. The study consisted of three parts. First, wall shear stress in an intracranial aneurysm phantom under controlled steady and pulsatile flow [18] was estimated and compared to CFD estimates. Second, the effect of resolution of PC-MRI measurements on wall shear stress accuracy was studied. Third, wall shear stress estimates obtained from an in vivo PC-MRI measurement and CFD simulation were compared.

### 8.2 Materials & Methods

In the first experiment, wall shear stress estimated from high resolution PC-MRI was compared with wall shear stress calculated by CFD. In order to compare the two modalities, the wall shear stress was calculated with the use of velocity vectors obtained from PC-MRI and wall delineation obtained from 3D Rotational Angiography (3D-RA), which was the modality that was used for the creation of the CFD mesh. In the second experiment, wall shear stress estimated from PC-MRI acquired at multiple resolutions was compared. The wall segmentation was based on the PC-MRI magnitude data of the resolution under consideration. In the third experiment, wall shear stress was estimated from 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 8.1. Throughout the article, the vessel and aneurysmal wall are considered as the outermost part of the segmentation of the lumen.

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Experiment 2</th>
<th>Experiment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution PC-MRI</td>
<td>0.2 x 0.33 x 0.2</td>
<td>0.19-0.94 isotropic</td>
</tr>
<tr>
<td>Wall</td>
<td>3D-RA</td>
<td>PC-MRI</td>
</tr>
</tbody>
</table>

Table 8.1 Resolution and wall used for wall shear stress calculation in the three experiments.
8.2.1 Aneurysm phantom & flow loop set-up

A glass reproduction of an aneurysm located in the anterior communicating artery of a patient who supplied informed consent was manually created based on a 3D-RA dataset. The dimensions of the aneurysmal lumen were 6 mm x 4 mm x 9 mm in the x, y and z-directions (see figure 8.1a) 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 8.1b the flow loop setup is displayed, in figure 8.1c 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].

8.2.2 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 3T 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 mm x 0.33 mm x 0.2 mm and velocity encoding of 50 x 100 x 50 cm/s in x, y and z-direction respectively (see figure 8.1a). Other imaging parameters: field of view: 25 mm x 16.5 mm x 25 mm; flip angle: 15°; TE/TR: 3.9 / 11.1 ms. Scan time of the steady measurement was approximately 15 minutes. 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] or Chapter 2.
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 (3D-RA). The 3D-RA dataset was segmented and meshed in VMTK [19]. The wall of this 3D-RA 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] or Chapter 2.

8.2.3 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 8.2. Further imaging parameters were: field of view: 60 mm x 21 mm x 60 mm and velocity encoding of 30 x 60 x 30 cm/s in x, y and z-direction respectively.

<table>
<thead>
<tr>
<th>Voxel size (mm x mm x mm)</th>
<th>TE / TR (ms)</th>
<th>Scan time (min.s)</th>
</tr>
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<td>11.35</td>
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<td>0.19 x 0.19 x 0.2</td>
<td>5.4 / 11.7</td>
<td>36.33</td>
</tr>
</tbody>
</table>

8.2.4 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 3T 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 mm x 0.65 mm x 3 mm. Further imaging parameters: TE / TR / FA: 5.7 ms / 8.5 ms / 10°; Field of view: 200 mm x 200 mm x 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 [20].

Second, PC-MRI was acquired at a resolution of 0.8 mm x 0.8 mm x 0.8 mm. Further imaging parameters were: TE / TR / FA: 3.0 ms/ 5.8 ms/ 15°; Field of view: 200 mm x 200 mm x 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 in vivo CFD simulation was created from 3D-RA 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/uni2219s. 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 PC-MRI results. Flow through the outflow vessels of the CFD model was prescribed according to outflow measurements at every cardiac phase of the
PC-MRI data averaged over time. The simulation time was approximately 36 hours.

8.2.5 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).

The rigid registration between the PC-MRI data and 3D-RA wall delineation (experiment 1) was automatically performed in FLIRT (FMRIB’s Linear Image Registration Tool, FSL). After registration, PC-MRI voxels located outside the 3D-RA wall delineation were discarded.

8.2.6 Wall shear stress calculation

Wall shear stress vectors can be calculated by:

\[ \vec{\tau} = 2\mu (\varepsilon \cdot \vec{n}) \]  

(8.1)

where \( \vec{\tau} \) is the wall shear stress vector, \( \mu \) is the dynamic viscosity, \( \varepsilon \) is the rate of deformation tensor and \( \vec{n} \) is the normal vector.

By rotating the axes 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:

\[ 2\varepsilon \cdot \vec{n} = \left( \frac{\partial \nu_z}{\partial x} \frac{\partial \nu_y}{\partial x} 0 \right) \]  

(8.2)

The shear rates \( \frac{\partial \nu_z}{\partial x} \) and \( \frac{\partial \nu_y}{\partial x} \) are the spatial gradients at the wall of 1D smoothing splines [24] fitted through the rotated x- and y-velocity values.
in the direction of the normal. The rotated wall shear stress vector $\mathbf{\tau}'$ is then defined as:

$$\mathbf{\tau}' = \mu \frac{\partial v'_y}{\partial z}, \mathbf{\tau}' = \mu \frac{\partial v'_x}{\partial z}, \mathbf{\tau}'_z = 0$$

(8.3)

The length of the inward normal vector was 0.6 mm. Measured velocity values surrounding the inward normal were interpolated such that the spline was fitted through 3 velocity values. To obtain a smooth surface of the aneurysm wall, the segmentation obtained by postprocessing is smoothed using a Laplacian filter [25]. See Chapter 7 for further detail.

8.2.7 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).

8.3 Results

8.3.1 Experiment 1. In vitro wall shear stress from steady and pulsatile 3D PC-MRI compared with CFD

The SNR of the pulsatile in vivo PC-MRI measurements was 28. In figure 8.2, the wall shear stress patterns calculated from PC-MRI with 3D-RA wall delineation are shown for steady flow (8.2a) and for systole (8.2c) and diastole (8.2e) under pulsatile flow. Figures 8.2b,
d and f show the corresponding estimates from CFD using the same wall segmentation. For both PC-MRI and CFD, the wall shear stress patterns spread upward and left and right (“star-like”) in the region where the flow impacts the wall (arrow 1). Fluctuations of wall shear stress of PC-MRI are visible. 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 8.3 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 3D-RA wall delineation and CFD are quantified and summarized in table 8.3. 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 8.3 and the correlation and Bland-Altman plots for the total phantom in figure 8.4.

<table>
<thead>
<tr>
<th>Inlet/outlet</th>
<th>Steady</th>
<th>Systole</th>
<th>Diastole</th>
<th>Aneurysm</th>
<th>Steady</th>
<th>Systole</th>
<th>Diastole</th>
<th>Total</th>
<th>Steady</th>
<th>Systole</th>
<th>Diastole</th>
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<td>0.38±0.74</td>
<td>0.66±1.15</td>
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<td>0.29±0.50</td>
<td>0.43±0.88</td>
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<td>Median angle (°)</td>
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<td>11.1</td>
<td>9.1</td>
<td>24.0</td>
<td>25.8</td>
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<td>13.3</td>
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</table>
8.3.2 Experiment 2. In vitro wall shear stress from steady 3D PC-MRI at increasing resolutions

In figure 8.5 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 measurements, 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. Higher mean wall shear stress at higher resolution was found. This is graphically displayed in figure 8.6.
8.3.3 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 8.7 depicts wall shear stress for the in vivo aneurysm. Arrow 1 indicates circular wall shear stress at the side of the aneurysm which was resolved for PC-MRI as well as CFD. Elevated wall shear stress at the top of the aneurysm (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 simula-
tion, 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 8.8.

Figure 8.7 Wall shear stress vectors calculated in the in vivo PC-MRI data (left column) and CFD (right column) at systole (top row) and diastole (bottom row).

Figure 8.8 Mean and standard deviation of wall shear stress for the in vivo PC-MRI measurement and CFD simulation.
8.4 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 in vivo, wall shear stress patterns are qualitatively similar to their CFD predictions. It has been discussed in the literature [12, 26] that wall shear stress estimations improve with increasing resolution (Chapter 7). This is the first study that shows that wall shear stress estimations show higher values and more detail in an intracranial aneurysm 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. 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 for in vitro PC-MRI at 0.75 mm and 0.19 mm. Imperfect registration of the high resolution 3D-RA 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. [15], who remarkably found 6-12 fold higher maximum wall shear stress for PC-MRI than CFD in three in vivo aneurysms. 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 study 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 possibility of clinical use of wall shear stress estimation from PC-MRI.
data. Wall shear stress vectors calculated from PC-MRI have been visualized in the aorta [12] and the carotid bifurcation [11]. 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 structures can only be detected if wall shear stress vectors are derived and will go undetected if merely wall shear stress magnitudes are visualized. Circular wall shear stress behavior may be added to existing factors in the statistical analysis of ruptured versus unruptured aneurysms such as disturbed or stable flow patterns, small or large impingement regions and narrow or wide inflow jets [3].

This study underlines that the main concern of wall shear stress estimations based on PC-MRI is the limited spatial resolution of PC-MRI. A higher SNR may be beneficial for wall shear stress estimations as well. With recent technical advancements, 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 wall shear stress estimations from PC-MRI. One recently presented new approach to improve measured PC-MRI data is divergence reduction [30]. A requirement in wall shear stress 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 wall shear stress estimations significantly.

8.5 Conclusion

In conclusion, this study shows that the wall shear stress algorithm is capable of calculating wall shear stress vectors from PC-MRI data in an in vitro and in vivo intracranial aneurysm. The direction of the wall shear stress vectors was similar to the wall shear stress vectors simulated with CFD, both in vitro and in vivo. Qualitative agreement between PC-MRI and CFD was good, whereas quantitative agreement was moderate. Further-
more, in order to increase the accuracy of estimated wall shear stress values, the spatial resolution of PC-MRI measurements must be as high as possible. However, important wall shear stress vector patterns, such as circular wall shear stress and regions of high versus low wall shear stress can be resolved at lower resolutions.

8.6 Acknowledgments

This study is supported by the Dutch Technology Foundation STW (CARISMA 11629). The author would like to thank Gertjan Bon from the University of Amsterdam for the glass blowing of the phantom.

8.7 References


Wall shear stress


General Discussion
In this thesis the validation and improved strategies for clinical use of time-resolved three-dimensional 3D phase contrast MRI (PC-MRI) in intracranial aneurysms have been presented. Furthermore, the feasibility of wall shear stress estimations from PC-MRI data in intracranial aneurysms is demonstrated. The first part considers in vitro validation of PC-MRI by comparison with Particle Imaging Velocimetry (PIV) and Computational Fluid Dynamics (CFD) and in vivo validation with CFD. In the second part of this thesis possible improvements of PC-MRI are investigated, based on acceleration strategies and higher field strengths. The third part in this thesis describes a novel method for deriving wall shear stress from PC-MRI measurements and the application of this method to an in vitro and in vivo aneurysm.

Part I: Validation

PC-MRI is capable of measuring three-dimensional velocity vector fields in multiple phases in the cardiac cycle in vivo. In order to use PC-MRI in a clinical environment and eventually use the data for intracranial aneurysm rupture risk assessment, validation based on compar-
ison with existing methods is a prerequisite. However, no other techniques are currently available that can be used for non-invasive in vivo validation. Therefore PC-MRI was tested in a real-size aneurysm phantom and compared with 2D Particle Imaging Velocimetry (PIV), a well validated in vitro technique that enables optical measurement of 2D velocity fields of fluids seeded with tracer particles [1].

The geometry of the aneurysm phantom used in chapters 2, 3, 5 and 8 was based on patient data, obtained by the most accurate technique available in our institution: 3D Rotational Angiography. The model was hand-made by a glass-blowing artist. It was therefore not an exact replica of the patient aneurysm. As described in chapter 2, the comparison between PC-MRI and PIV measurements did not allow direct validation of PC-MRI, due to the 2D nature of PIV, while also the use of different fluids in PC-MRI and PIV and some experimental concerns complicated the comparison. A possible improvement may come from the use of 3D rather than 2D PIV imaging. However, this is an upcoming field and requires specific expertise which was not available to us [2]. Despite the above shortcomings, the comparison showed many similarities such as the locations of the main vortex and other small vortices.

Another possibility for validation of PC-MRI comes from computational fluid dynamics (CFD) [3]. CFD is increasingly used for visualization of hemodynamics in intracranial aneurysms. In CFD, the velocity patterns are not directly measured but simulated. This approach depends heavily on the accuracy of the geometry and the input, i.e. inflow boundary conditions. CFD is therefore not a gold standard for aneurysmal hemodynamics. Yet, a comparison of CFD and PC-MRI may help to understand the limits of either technique and may help improve their use. In this thesis CFD and PC-MRI were compared in a glass phantom of an aneurysm as well as in vivo aneurysms.

The inflow boundary conditions in the CFD simulation performed in the aneurysm phantom presented in chapter 2 were chosen as accurate as possible by prescribing spatial and temporal inflow boundary conditions obtained from the PC-MRI measurement. In this experiment the PC-MRI data matched the CFD predictions very well. Root mean square errors between the PC-MRI measurement and CFD were small: 4-5% of the maximum PC-MRI velocity.
However, in vitro validation of a technique is clearly not the same thing as in vivo validation. Following the successful in vitro validation, PC-MRI was compared with accompanying CFD simulations in eight in vivo aneurysms. The results agreed qualitatively, mainly in systole (Chapter 4). Due to use of a fairly high SENSE factor of 3 in the PC-MRI acquisition, the SNR of the PC-MRI measurements was low (around 12). Furthermore, in diastole, VNR was further reduced because diastolic velocities were well below VENC. These limitations resulted in velocity vector field degradation in diastole. In systole, velocity vector directions were similar as judged by visual inspection and by calculation of singular energy. This novel method to robustly quantify vortices by applying multi-scale algorithms to velocity vector fields was described in chapter 3, and performed well in diastole as well. In contrast to the similar velocity directions, large differences were found in velocity magnitude. This coincided with substantial differences between inflow as measured with PC-MRI and with the separate 2D PC-MRI measurement that was used for CFD boundary conditions. Indeed, simulations carried out with inflow boundary conditions obtained from PC-MRI showed better quantitative agreement. Since 2D PC-MRI has higher resolution and is well-validated, it should be more reliable as inflow boundary conditions. However, the discrepancy between flow calculated from 2D and 3D PC-MRI may be related to the thickness of the slice of the 2D measurements, which may have caused averaging of velocities. Perhaps some other systematic error was encountered. Further study regarding differences between 2D and 3D PC-MRI is needed. However, it was reassuring to see that the direction of velocity vectors and singular energy did not differ much between 2D and 3D PC-MRI input.

The comparison of PC-MRI with CFD made clear that a range of concerns complicates the use of PC-MRI for hemodynamic quantification in small intracranial aneurysms. Some of these concerns are discussed in more detail below.

In general, the limited spatial resolution inherently related to MRI remains a challenge in PC-MRI. Due to the limited resolution, both 2D and 3D PC-MRI measurements are subject to partial voluming effects. Partial voluming is a problem in PC-MRI that should be assessed with great care since signal from outside the vessel can cause large phase and velocity deviations in individual pixels. To minimize partial voluming, the delineation of vessels is chosen rather tight, thereby discarding pixels outside the delineation.
Usually these pixels contain low velocity values. Furthermore, limited spatial resolution causes velocity averaging, resulting in underestimated maximal velocities.

As indicated above, one other issue in in vivo PC-MRI imaging is limited SNR. Noise in velocity data will increase velocity magnitude and direction uncertainty, and will increase the divergence of the velocity field. Recently, a promising approach has been proposed to combine PC-MRI and CFD techniques by reducing the divergence of velocity fields [4]. This will be beneficial for the diagnostic value of PC-MRI, in particular when wall shear stress is considered, since wall shear stress vectors depend on the gradient of the velocity close to the wall. Other strategies to improve SNR in vivo will be discussed in the next section.

Recently, a paper was published in which Gatehouse et al. showed that small background phase offsets are a major problem when calculating cardiac output from through-plane 2D PC-MRI acquisitions [5]. A background phase offset of 0.4% of a VENC of 150 cm/s can cause about 5% miscalculation of cardiac output. In this thesis background phase offsets were corrected by selecting a region of interest close to the aneurysm or vessel of interest and subtracting the mean phase in this ROI from the image. This approach was proposed by Lotz et al. [6]. Another approach incorporates linear fitting of planes through the phase images [7]. However, background phase offsets can consist of second or even third order phase offsets and therefore more advanced correction methods are needed. Phantom experiments are now being performed to study the optimal manner for background phase offset correction [8].

A further drawback of PC-MRI is that it does not differentiate between slow flowing blood and thrombus. Signal intensity of slow flow and thrombus is similar, and segmentation of the thrombus is therefore cumbersome. Since slow blood flow and thrombus formation is more prominent in large aneurysms, the current application of PC-MRI in large aneurysms (>15 mm) need further improvement. Naturally, the imaging of very small aneurysms is hampered by the spatial resolution.

PC-MRI does not image the aneurysmal wall. In the wall shear stress algorithm we therefore assume that the segmentation represents the inside of the aneurysmal wall. Imaging the aneurysmal wall would be beneficial for segmentation purposes and could diminish the aforementioned differences between 2D and 3D PC-MRI. A second consequence is that the thickness
of the aneurysmal wall remains unknown. Imaging the aneurysmal wall could help improving rupture risk assessment. Some studies imaging the intracranial arterial wall [9] and aneurysmal wall [10] have been performed. The major pitfall of imaging thin vessel walls is that it heavily depends on spatial resolution since one can not measure a structure beyond the spatial resolution and intra-voxel averaging of signals will be present. Measuring the aneurysmal wall was beyond the scope of this thesis.

CFD is a powerful alternative for PC-MRI with the main benefit of high resolution imaging of flow patterns. However, several drawbacks of this technique can be mentioned such as inherent assumptions in CFD. As said, these include the boundary conditions, which remain depending on direct measurements when aiming at personalized data. In addition, wall segmentation and accompanying geometry accuracy is critical in CFD [11]. Due to limited resolution of 3D-RA or CTA, the aneurysmal neck can be overestimated leading to inaccurate simulations [12]. Moreover, vascular structures are distensible and pulsation may be present in aneurysms and feeding vessels that are not modeled in CFD. Other drawbacks of CFD are long simulation times and the consequential need for strong computational power.

In PC-MRI pulsation of the aneurysm and feeding artery can be visualized. However, the pulsation can be attributed to SNR differences and resulting segmentation differences between cardiac phases, and does not necessarily visualize true wall motion. Some studies investigating the assumption of rigid walls in CFD have been presented. It was shown that rigid walls tend to overestimate wall shear stress [13] but that the overall characteristics of the wall shear stress distribution do not seem to change considerably [14].

The major benefit for PC-MRI is that it is a direct measurement and with improvements, some discussed in the next section but more options are available, it may well serve as an option for rupture risk assessment.

10.2 Part II: Improvements

In the diastolic phase of the PC-MRI measurements as presented in chapter 4, the VNR was low, which resulted in velocity vector direction irregularities. One main contribution to the low VNR, which depends on SNR, is the high SENSE factor of 3 that we used. SENSE is an acceleration technique well-known for its SNR degradation. For clinical use
of PC-MRI, the VNR during diastole should be increased. In chapter 5 an alternative acceleration technique is evaluated. In chapter 6 the application of the PC-MRI sequence on 7T MRI is described.

10.2.1 Acceleration techniques

In chapter 5, the influence of $k$-$t$ BLAST on PC-MRI measurements is studied and compared with SENSE accelerated measurements. Although the SNR increased in $k$-$t$ BLAST accelerated PC-MRI, it was found that temporal blurring, including underestimation of systolic velocities, was severe. Since the systolic phase is probably important for rupture risk assessment in intracranial aneurysms, $k$-$t$ BLAST may not be the best candidate for PC-MRI acceleration in intracranial aneurysms. However, for longitudinal studies where precision of the measurement may be more important than its accuracy, $k$-$t$ BLAST acceleration may be beneficial. The field of acceleration of MRI sequences is rapidly expanding. Many new strategies were recently proposed in the literature. SENSE [15] and GRAPPA [16] are parallel imaging techniques exploiting spatial correlations by combining spatial information contained in the coils of the array. A second category is based on exploiting temporal correlations between images. A third category contains techniques that are based on spatiotemporal correlations between images. $k$-$t$ BLAST/$k$-$t$ SENSE [17] and $k$-$t$ GRAPPA [18] are acceleration techniques that belong to this third category. $k$-$t$ PCA [19] is an improved version of $k$-$t$ BLAST and new techniques based on sparsity, i.e. compressed sensing are continuously in development [20]. The first results of these techniques in combination with 2D PC-MRI are promising. However, the acceleration techniques in combination with PC-MRI remain to be validated in intracranial aneurysms.

10.2.2 Higher field strengths

Another possibility to increase SNR during the diastolic phase is by performing PC-MRI at higher field strengths. PC-MRI in the Circle of Willis was performed in five healthy volunteers at 7T and compared with 3T (Chapter 6). SNR was around 2.6 times higher at 7T compared with 3T. This resulted in more distinct velocity directions in small vessels such as the anterior and posterior communicating arteries at 7T than 3T. A remarkable finding was that, in healthy volunteers, blood can flow from the
posterior cerebral artery to the internal carotid artery, to our knowledge not yet reported in literature. A 3T versus 7T PC-MRI comparison study has not yet been performed in intracranial aneurysms. However, the first PC-MRI data at 7T are now available for analysis. In figure 9.1 it can be seen that the main vortex in the velocity vector field at 7T looks coherent in diastole as well as in systole.

10.2.3 Part III: Wall shear stress

Wall shear stress, the tangential force that blood exerts on the vessel wall, is thought to be an important marker for aneurysm formation, growth [21] and rupture [22]. The main drawback of using PC-MRI for wall shear stress calculation is the limited spatial resolution. Since the gradient of the velocity profile at the vessel wall is needed for wall shear stress, the velocity vectors need to be well-resolved close to the wall. The requirements for accurate wall shear stress estimations are therefore sufficient spatial resolution and SNR. In chapter 7 we show that an isotropic resolution of at least 0.8 mm is needed to reduce the error of wall shear stress magnitude to 5% in a vessel with a diameter of 6 mm with perfect parabolic flow. In chapter 8 we show that this is not the case for an in vitro and in vivo intracranial aneurysm. However, the direction of wall shear stress vectors during the cardiac cycle could be estimated reasonably accurate in vitro and in vivo at 0.8 mm isotropic resolution, compared with wall shear stress vectors calculated from CFD. Wall shear stress can now be estimated using PC-MRI data acquired at 0.5 mm isotropic at 7T. In figure 9.2 the wall

Figure 10.1 Main vortex in an aneurysm at (a) systole and (b) diastole. Data acquired at 7T with a resolution of 0.47 x 0.47 x 0.5 mm. Courtesy of Rachel Kleinloog of the University Medical Center Utrecht.
shear stress vectors at systole and diastole are displayed obtained from the same data shown in figure 9.1.

It is clear that improvement of wall shear stress estimation will benefit from further innovations in PC-MRI technology, including higher field strengths and advanced acceleration techniques. Additional image analysis methodologies such as divergence-free filters and improved wall segmentation will help this process. Yet, quantitative estimation of wall shear stress will remain a challenge, due to its nature as a gradient at infinitesimal distance from the wall. The question is whether a fully calibrated quantitative measurement is really needed. Wall shear stress is a vector, and the spatial and temporal gradients in direction may prove to be far more relevant for the biology of the aneurysm wall, progression and rupture, than its magnitude. For example, in figure 9.2, circular wall shear stress on the aneurysmal wall can be seen, which could provoke a different biological reaction than high or low or oscillating wall shear stress. We speculate that such circular wall shear stress patterns may be related to aneurysm rupture. In atherosclerotic processes, it has been well documented that wall shear stress gradients, notably a reversal of flow direction, is critical for plaque progression and plaque rupture [23].

10.3 Contri bution of this thesis to improved risk of rupture assessment in intracranial aneurysms

The first studies are now being presented that combine quantitative and qualitative flow characteristics simulated with CFD and relate these characteristics to aneurysm rupture [24-25]. These authors state that aneurysm rupture is statistically associated with concentrated inflow
streams, wall shear stress distributions with elevated levels of maximum wall shear stress and low aneurysmal viscous dissipation. In our institution, simulations of intra-aneurysmal flow are carried out in large patient cohorts (about 160 aneurysms). The advantage of our simulations is that patient-specific spatial and temporal inflow patterns measured with 2D PC-MRI are prescribed as inflow boundary conditions. The simulated flow patterns will be compared with flow patterns measured with PC-MRI, which provide improved methodology for rupture risk assessment.

10.4 Contribution of this thesis to cardiovascular research and health care

This thesis mainly focused on PC-MRI in intracranial aneurysms. However, PC-MRI may be beneficial for measuring flow in flow-related pathologies such as the atherosclerotic aorta [26], ascending aortic aneurysms [27-28] and internal carotid artery stenosis [29]. The presented wall shear stress algorithm is easily adaptable for application in different sets of data. It can therefore be beneficial to quantify wall shear stress in these pathologies and add substantially to the insight in the degradation process of vessels and atherosclerotic plaque and aneurysm development. Diagnosis and treatment of aforementioned conditions can be facilitated by combination of PC-MRI and wall shear stress calculation.

10.5 Future developments

As previously mentioned, the difficulties in PC-MRI measurements are its limited spatiotemporal resolution and SNR and its long scanning times. These limitations can be minimized in two manners: by using other hardware or by accelerating the PC-MRI sequence. As described in this thesis, scanners with higher field strengths can be used to increase SNR. Furthermore, coils with more phase arrays are becoming available, which will reduce the SNR degradation of SENSE acceleration. Increasing spatiotemporal resolution will increase scan time, which requires the use of acceleration techniques i.e. reduced k-space sampling patterns to speed up the acquisition. Each of these acceleration techniques has its own drawbacks in terms of temporal blurring and SNR degradation. New acceleration techniques are continuously being developed. However, these techniques are
not widely available and require validation. A promising candidate to speed up PC-MRI is compressed sensing [20]. Compressed sensing in combination with PC-MRI is expected to be used extensively in the near future.

PC-MRI data requires elaborate post-processing in terms of background phase correction, segmentation and phase unwrapping. In order for PC-MRI to gain interest in a clinical setting, these post-processing steps should be automated as far as possible so that manual labor is minimized. At the moment, the main vendors are developing and incorporating post-processing software in the scanners.

With these developments PC-MRI will be increasingly used for imaging and quantifying characteristics of cardiovascular flow-related diseases.

10.6 Conclusion

PC-MRI is currently the only in vivo technique able to measure 3D flow patterns in intracranial aneurysms. In this thesis we have shown that PC-MRI can be used to quantify and visualize intra-aneurysmal flow patterns and wall shear stress. In combination with CFD, PC-MRI may substantially improve rupture risk assessment of intracranial aneurysms. However, in order for PC-MRI to become widely used, the acquisition and post-processing should be further improved.

10.7 Implications of this thesis

- PC-MRI in an in vitro intracranial aneurysm phantom can accurately measure velocity vector field patterns compared with CFD. (Chapter 2)
- Multi-scale approaches can robustly calculate and visualize flow properties and can be used for comparison of flow patterns between different modalities. (Chapter 3, 4)
- In vivo PC-MRI can accurately measure velocity vector field patterns compared with CFD in systole. (Chapter 4)
- In diastole, velocity vector field patterns measured with in vivo PC-MRI are hampered by low VNR of the PC-MRI measurement. (Chapter 4)
• Hampered velocity vector visualization of flow due to low VNR in diastole can be overcome by using multi-scale visualization approaches. (Chapter 4)

• Accelerating PC-MRI in intracranial aneurysms by k-t BLAST results in underestimation of velocity vector magnitude in systole due to temporal blurring. (Chapter 5)

• Higher SNR by performing PC-MRI at higher field strengths can substantially improve blood flow direction uncertainty and flow quantification. (Chapter 6)

• In healthy volunteers blood flow through the posterior communicating artery can occur from posterior cerebral artery to internal carotid artery and vice-versa. (Chapter 6)

• At an isotropic resolution of 0.8 mm, the error in wall shear stress calculated from a perfect parabolic flow in a vessel with a diameter of 6 mm is smaller than 5%. (Chapter 7)

• The difference between wall shear stress measured with PC-MRI and simulated with CFD is larger than the difference between velocity vectors measured with PC-MRI and simulated with CFD. (Chapter 2, 8)

• Showing wall shear stress vector direction as well as magnitude improves wall shear stress visualization. (Chapter 8)

• Similar to vortical flow patterns in aneurysms, wall shear stress vectors show circular behavior as well. (Chapter 8)

• Wall shear stress vector magnitude is underestimated at low resolutions. By increasing spatial resolution the magnitude and complexity of wall shear stress vectors is better resolved in an intracranial aneurysm phantom. (Chapter 8)

• In an in vivo intracranial aneurysm the difference between wall shear stress calculated from PC-MRI data and simulated with CFD is substantial. However, wall shear stress direction is similar. (Chapter 8).
10.8 References

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Intracranial aneurysms are outpouchings of intracranial arteries that occur mainly on bifurcations in the vicinity of the Circle of Willis, a ring-like vessel structure at the base of the brain. Rupture of intracranial aneurysms causes subarachnoid hemorrhage, which lead to high morbidity and mortality in patients. Incidentally discovered unruptured aneurysms can be treated by either clipping or coiling. However, the risk of complications during treatment of unruptured aneurysms may outweigh the risk of rupture of the aneurysm and therefore careful consideration whether to treat the aneurysm must be made. It is now widely accepted that assessment of local intra-aneurysmal hemodynamics can contribute substantially to the rupture risk estimation of the individual aneurysm. Patient-specific hemodynamic parameters such as flow complexity and wall shear stress can be simulated with computational fluid dynamics (CFD).

CFD is a technique that can simulate flow patterns with extremely high spatial and temporal resolution. However, CFD is a simulation technique and its accuracy depends on the accuracy of the inflow boundary conditions and semi-automatic creation of geometries.

Summary

Intracranial aneurysms are outpouchings of intracranial arteries that occur mainly on bifurcations in the vicinity of the Circle of Willis, a ring-like vessel structure at the base of the brain. Rupture of intracranial aneurysms causes subarachnoid hemorrhage, which lead to high morbidity and mortality in patients. Incidentally discovered unruptured aneurysms can be treated by either clipping or coiling. However, the risk of complications during treatment of unruptured aneurysms may outweigh the risk of rupture of the aneurysm and therefore careful consideration whether to treat the aneurysm must be made. It is now widely accepted that assessment of local intra-aneurysmal hemodynamics can contribute substantially to the rupture risk estimation of the individual aneurysm. Patient-specific hemodynamic parameters such as flow complexity and wall shear stress can be simulated with computational fluid dynamics (CFD).

CFD is a technique that can simulate flow patterns with extremely high spatial and temporal resolution. However, CFD is a simulation technique and its accuracy depends on the accuracy of the inflow boundary conditions and semi-automatic creation of geometries.
The only technique capable of measuring three-dimensional flow patterns over time in vivo is time-resolved three-dimensional phase contrast MRI (PC-MRI). PC-MRI is based on the phenomenon that spins in moving blood in a magnetic field acquire a phase shift that is proportional to the velocity of the flowing blood. With this technique it is possible to measure flow patterns in, amongst others, the aorta, the carotid bifurcation, intracranial arteries and intracranial aneurysms.

The goal of this thesis is to validate and improve PC-MRI and to study the performance of PC-MRI in wall shear stress estimations in intracranial aneurysms.

In this thesis an in vitro validation study is presented in which PC-MRI is compared with Particle Image Velocimetry (PIV) and CFD in an aneurysm phantom of true size. This study showed that PC-MRI is able to very accurately capture flow patterns in an aneurysm phantom (chapter 2). Furthermore, PC-MRI was tested in eight in vivo intracranial aneurysms and compared with CFD. It was found that in systole, PC-MRI presents flow patterns that are comparable with CFD predictions. In diastole, however, the flow patterns appeared incoherent due to low signal-to-noise ratio (SNR). (chapter 4) Multi-scale analysis that enabled vortex quantification (chapter 3) showed quantitative agreement between PC-MRI and CFD in diastole (chapter 4).

To decrease the scan time, PC-MRI in the phantom and in an in vivo aneurysm was carried out in combination with two different acceleration techniques: k-t BLAST and SENSE. It was found that the SNR was higher for the former technique. However, severe smoothing of the velocity magnitude over time, i.e. underestimation of velocity in systole, was present in the k-t BLAST measurements (chapter 5).

Another method to acquire PC-MRI images with higher SNR is to perform the velocity measurements in scanners with higher field strengths. A comparison of PC-MRI data in 5 healthy volunteers acquired at 3T and 7T was performed. The results showed that, due to higher SNR at 7T, the segmentation of small vessels in the Circle of Willis and the velocity vector directions in these vessels were more accurate than at 3T. Furthermore, blood flow from posterior cerebral artery to internal carotid artery in healthy volunteers was determined (chapter 6).

An important marker for atherosclerosis and a possible indicator of aneurysm rupture is wall shear stress. Wall shear stress (WSS) is the tangential...
force of blood flow at the vessel wall and can be calculated using the gradient of velocity close to the wall. In this thesis a novel method to calculate wall shear stress vectors from PC-MRI data in any vessel geometry in a standardized fashion is presented. The technique was tested in analytical phantoms of the common carotid artery and the aorta under the assumption of perfect parabolic flow (chapter 7). Application of the technique in the aneurysm phantom and an in vivo aneurysm followed by comparison with CFD revealed lower WSS for PC-MRI than CFD, as a result of limited spatial resolution. However, the direction of WSS vectors was very similar. Circular WSS patterns were found for both the in vitro and in vivo aneurysm. Such circular WSS may be an important parameter for rupture risk estimation (chapter 8).

In conclusion, this thesis demonstrates that PC-MRI can be used to quantify and visualize intra-aneurysmal flow patterns and wall shear stress. However, PC-MRI imaging strategies can still be optimized to further improve the accuracy of the technique.
Intracraniële aneurysmata zijn uitstulpingen van bloedvaten in de hersenen die vooral voorkomen op bifurcaties van vaten in de buurt van de cirkel van Willis, een cirkelvormig stelsel van bloedvaten aan de onderkant van het brein. Ruptuur van een aneurysma leidt tot subarachnoidale bloeding, wat resulteert in hoge morbiditeit en mortaliteit in patiënten. Incidenteel ontdekte ongeruptureerde aneurysmata kunnen behandeld worden door het clippen of coilen van het aneurysma. Echter, het risico op complicaties tijdens de behandeling van een ongeruptureerd aneurysma kan hoger zijn dan het risico dat het aneurysma ruptureert. Daarom is zorgvuldige besluitvorming over het wel of niet behandelen van aneurysmata nodig. Het is momenteel algemeen geaccepteerd dat informatie over de hemodynamiek (de eigenschappen van de bloedstroom) in een aneurysma significant kan bijdragen aan de schatting van het risico van ruptuur van het individuele aneurysma. Patient-specifieke hemodynamische parameters zoals complexiteit van de bloedstroom en de schuifspanning van het bloed op de wand kunnen gesignaleerd worden met behulp van computational fluid dynamics (CFD).

**Samenvatting**

Intracraniële aneurysmata zijn uitstulpingen van bloedvaten in de hersenen die vooral voorkomen op bifurcaties van vaten in de buurt van de cirkel van Willis, een cirkelvormig stelsel van bloedvaten aan de onderkant van het brein. Ruptuur van een aneurysma leidt tot subarachnoidale bloeding, wat resulteert in hoge morbiditeit en mortaliteit in patiënten. Incidenteel ontdekte ongeruptureerde aneurysmata kunnen behandeld worden door het clippen of coilen van het aneurysma. Echter, het risico op complicaties tijdens de behandeling van een ongeruptureerd aneurysma kan hoger zijn dan het risico dat het aneurysma ruptureert. Daarom is zorgvuldige besluitvorming over het wel of niet behandelen van aneurysmata nodig. Het is momenteel algemeen geaccepteerd dat informatie over de hemodynamiek (de eigenschappen van de bloedstroom) in een aneurysma significant kan bijdragen aan de schatting van het risico van ruptuur van het individuele aneurysma. Patient-specifieke hemodynamische parameters zoals complexiteit van de bloedstroom en de schuifspanning van het bloed op de wand kunnen gesignaleerd worden met behulp van computational fluid dynamics (CFD).
CFD kan stromingspatronen op zeer hoge spatiële en temporele resolutie simuleren. Echter, CFD is een simulatietechniek en de juistheid van de resultaten hangt af van de nauwkeurigheid van de instroomrandvoorwaarden en de (semi-automatisch ontworpen) geometriën.

De enige techniek die drie-dimensionale stromingspatronen over de tijd in vivo kan meten is drie-dimensionale phase contrast MRI (PC-MRI). PC-MRI is gebaseerd op het fenomeen dat een spin in bewegend bloed in een magnetisch veld, dat linear verandert in de plaats, een fase verschuiving verkrijgt die proportioneel is met de snelheid van de bloedstroom. Deze techniek maakt het mogelijk om stromingspatronen te meten in, onder andere, de aorta, de bifurcatie van de carotiden, de intracraniële arteriëën en intracraniële aneurysmata.

Het doel van dit proefschrift is om PC-MRI in intracraniële aneurysmata te valideren en te verbeteren, en om deze techniek toe te passen voor het berekenen van de schuifspanning op de wand.

In een in vitro validatie studie werd PC-MRI vergeleken met Particle Image Velocimetry (PIV) en CFD in een aneurysma fantoom van ware grootte. Deze studie liet zien dat stromingsprofielen in een aneurysma fantoom zeer nauwkeurig kunnen worden gemeten met PC-MRI (hoofdstuk 2). PC-MRI werd ook getest in acht in vivo aneurysmata en vergeleken met CFD. We vonden dat, in systole, de stromingsprofielen van PC-MRI vergelijkbaar waren met die van CFD voorspellingen. In diastole echter leken de stromingsprofielen incoherent door een lage signaal-ruis verhouding (SNR) (hoofdstuk 4). Multi-scale analyse waarmee kwantificatie van vortices kan worden uitgevoerd (hoofdstuk 3) liet zien dat er ook in diastole kwantitatieve overeenkomst was tussen PC-MRI en CFD (hoofdstuk 4).

Om de scantijd van PC-MRI te verkorten werd de meting toegepast in combinatie met twee versnellingstechnieken, k-t BLAST en SENSE, in het fantoom en in een in vivo aneurysma. We vonden dat de SNR in k-t BLAST hoger was dan SENSE, maar ook dat de gemeten snelheidsveranderingen werden uitgesmeerd over de tijd, m.a.w. de snelheid in systole werd onderschat (hoofdstuk 5).

Een andere mogelijkheid om een hogere SNR te verkrijgen is om de metingen te doen op MRI-scanners met een hogere veldsterkte. PC-MRI metingen, verkregen op 3T en 7T, werden vergeleken in vijf gezonde vrijwilligers. De resultaten lieten zien dat, door de hogere SNR op 7T, de segmentatie van kleine vaten in de cirkel van Willis en de richting van de bloedstroom in
deze vaten nauwkeuriger konden worden bepaald dan op 3T. Verder werd vastgesteld dat bloedstroom van de arteria cerebri posterior naar de arteria carotis interna door de arteria communicans posterior mogelijk is bij gezonde vrijwilligers (hoofdstuk 6).

Een belangrijke marker voor de ontwikkeling van atherosclerose en een mogelijke indicatie voor ruptuur van aneurysmata is de schuifspanning op de vaatwand (WSS). De schuifspanning is de kracht parallel aan de wand die het bloed uitoefent op de vaatwand en kan berekend worden op basis van locale snelheidsgradiënten. In dit proefschrift wordt een nieuwe methode gepresenteerd die WSS op een gestandaardiseerde manier in diverse vaatgeometrieën kan berekenen. Deze techniek werd getest in analytische fantomen van de halsslagader en de aorta waarbij een perfect parabolisch stromingspatroon werd aangenomen (hoofdstuk 7). Het toepassen van deze techniek in het aneurysma fantoom en in een vivo aneurysma liet, na vergelijking met CFD, lagere WSS waardes zien voor PC-MRI dan voor CFD. Dit is een gevolg van de lagere spatiale resolutie van de PC-MRI meting. De richting van vectoren, echter, liet veel overeenkomsten zien. Voor zowel het in vitro als in vivo aneurysma werden circulaire WSS profielen berekend. Dergelijke circulaire WSS profielen kunnen een belangrijke parameter zijn voor de schatting van het risico op ruptuur (hoofdstuk 8).

Dit proefschrift demonstreert dat PC-MRI gebruikt kan worden om stromingsprofielen en schuifspanningen op de vaatwand in aneurysmata te berekenen en visualiseren. Echter, de acquisitie strategieën kunnen verder worden geoptimaliseerd om de nauwkeurigheid van de techniek verder te verbeteren.
## List of Abbreviations

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<thead>
<tr>
<th>A</th>
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<tbody>
<tr>
<td>ACA</td>
<td>Anterior Cerebral Artery</td>
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<tr>
<td>BA</td>
<td>Basilar Artery</td>
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<tr>
<td>$k$-t BLAST</td>
<td>$k$-t Broad-use Linear Acquisition Speed-up Technique</td>
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<td>CE-MRA</td>
<td>Contrast Enhanced Magnetic Resonance Angiography</td>
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<td>CFD</td>
<td>Computational Fluid Dynamics</td>
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List of Abbreviations

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<td>k-t PCA</td>
<td>$k$-$t$ Principal Component Analysis</td>
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<td></td>
<td>PC-MRI</td>
<td>Phase Contrast Magnetic Resonance Imaging</td>
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<td></td>
<td>PC-VIPR</td>
<td>Phase Contrast Vastly undersampled Isotropic voxel Radial Projection imaging</td>
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<td>PIV</td>
<td>Particle Image Velocimetry</td>
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<td>PPU</td>
<td>Peripheral Pulse Unit</td>
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<td>PSF</td>
<td>Point Spread Function</td>
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<td>RMSE</td>
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<td>ROI</td>
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<td>SNR</td>
<td>Signal to Noise Ratio</td>
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<td>TCD</td>
<td>Transcranial Doppler</td>
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<td>TCCS</td>
<td>Transcranial Colour-coded duplex Sonography</td>
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<td>Echo Time</td>
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<td>TOF</td>
<td>Time of Flight</td>
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<td>TR</td>
<td>Repetition Time</td>
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<th>VENC</th>
<th>Velocity Encoding</th>
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<td>VMTK</td>
<td>Vascular Modeling Toolkit</td>
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<tr>
<th>W</th>
<th>WSS</th>
<th>Wall Shear Stress</th>
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List of Publications
Journal articles


Journal articles in preparation

- **Pim van Ooij**, Annetje Guédon, Henk Marquering, Joppe Schneiders, Charles Majoie, Ed van Bavel, Aart Nederveen. *k-t BLAST and SENSE accelerated time-resolved three-dimensional phase contrast MRI in an intracranial aneurysm. Accepted pending minor revisions for MAGMA*

- Wouter Potters, **Pim van Ooij**, Henk Marquering, Ed van Bavel, Aart Nederveen Validation of a generalized approach to calculate wall shear stress from 4D phase contrast MRI. *Submitted for J Magn Reson Imaging*


Awards and Nominations

**Magna Cum Laude Merit Award**


**Traditional poster award nomination**

Dankwoord
Allereerst Aart bedankt voor de vier prachtig mooie jaren met jou als begeleider. We hebben lekker gediscussieerd en ruzie gemaakt, en veel gelachen. Ik heb in de afgelopen vier jaar meer geleerd dan tijdens heel mijn studie en dat is een grote verdienste die voor een groot deel op jouw conto mag worden bijgeschreven. Ik denk dat het voor jou ook wel een bijzondere ervaring was hoe twee zo verschillende personen zo goed kunnen samenwerken. Voor mij zeker. We blijven dat in de toekomst natuurlijk doen. Mooi om te zien hoe jij die anarchistische Zo draaiende weet te houden en altijd klaar staat voor je AIO’s. Succes met alles!


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Henk, jouw idee over vortex kwantificatie met behulp van multi-scale analyses is een mooi zijproject geworden van mijn promotiewerk. Aan onze samenwerking heb ik veel plezier aan beleefd. Ook jouw grondige revisies hebben mijn artikelen flink verbeterd. Bedankt!

Mijn twee superstudenten Annetje en Wouter: Annetje, na nachtelange scansessies, met de nodige spelletjes domino, hebben we drie artikelen uit onze data weten te slepen. Dat was zonder jouw hulp nooit gelukt, dus veel dank daarvoor. Je hebt het even geprobeerd in het bedrijfsleven, maar gelukkig doe jij nu ook gewoon weer promotie-onderzoek op de universiteit. Dat is toch een stuk leuker? Wouter, jij hebt in zeer korte tijd een wall shear stress berekeningsalgoritme in elkaar gedraaid dat de hele wereld wel zou willen gebruiken. Knap werk! Aart zag natuurlijk heel snel jouw kwaliteiten en heeft jou meteen een promotieplek aangeboden. Wij gaan nog veel samenwerken in de toekomst en ik zie je sowieso bij congressen. Beiden veel succes met jullie promotiewerk.


Beste (semi-)kamergenoten Dennis, Bram, Jos, Jasper, Marieke, Joena, Anne, Elsmarieke, Martin, Anne-Marieje, Sanne, Hyke en al die andere mensen die ik heb zien komen en gaan: bedankt voor de collegialiteit, gezellige lunches en borrels. Zeg nou zelf, werken op Zo is toch één groot feest? Allemaal succes met jullie verdere carrière.

Speciale dank voor Kevin en Matthan, wiens programmeerkwaliteiten en wetenschappelijk inzicht cruciaal zijn geweest voor de ontwikkeling van mijn tools. Zonder jullie was het niet gelukt. Paul, sorry als ik lichtelijk chagrinnig jouw kamer binnen kwam lopen, omdat ik weer eens niet kon printen, als de computer was gecrasht of andersoortig technisch malheur. Dank voor je geduld en hulp!

Beste Sandra & Raschel, bedankt voor alle scaninstructies, maar vooral voor jullie gezelligheid tijdens de congressen in Hawaii, Montréal en Stockholm. Wat hebben we gelachen!

Sanna, Sandra en alle andere collega’s van Radiologie en Biomedical Engineering & Physics bedankt voor de prettige samenwerking.

Thanks to the flowgroups of the University of California, the University of Wisconsin, George Mason University, Northwestern University, Philips, UMC Utrecht and the VU for giving me the opportunity to present my work at these institutions. A special thanks to Michael Markl and Alex Barker for offering me the post-doc job at Northwestern, I look forward to working with you in Chicago.

Paranimf Rob, al 13 jaar beste maten en al die jaren veel meegemaakt. Ook sinds we geen stadsgenoten meer zijn, is dat niet veranderd. En ik vertrouw erop dat we ook de afstand Nederland-Amerika weten te overbruggen. Voor mij was het vanzelfsprekend om jouw homo universalis kwaliteiten in te schakelen voor de ontwerpen van dit proefschrift en dat vond jij gelukkig ook. Het ziet er fantastisch uit. Bedankt jongen, we blijven nog vele jaren samen doen wat we het best kunnen: gesprekken voeren op het hoogste en laagste niveau onder het genot van een pint.

Paranimf Niels, jij bent een mooie aanwinst voor de familie Groneschild. slim en eigenwijs, net als de dochters van Theo. Als dat zo doorgaat, gaan wij samen nog veel tijd hebben om van de goeie dingen des levens te genieten.

Net niet paranimf Pim, helaas is mijn promotie precies tegelijk gepland met die van Deliane, met het gevolg dat je bij mij niet kon paranimfen. Gelukkig kon ik dat bij jou wel en daar hebben we zoals altijd weer een gigantisch feest van gemaakt. Dat blijven we natuurlijk doen, ook op de congressen als grote en kleine Pim.

Wat mij brengt tot de Heeren Lanistae, allen intelligente mannen met een gemiddelde lengte van 2 meter en een gemiddeld gewicht van 100 kilo. Zeven van die boys aan het ontbijt in het ouderlijk huis: mijn lieve moedertje was zwaar onder de indruk! Eindhoven hebben we inmiddels (bijna) allemaal verlaten, maar we weten elkaar nog regelmatig te vinden om onze mooie tradities voort te zetten.

Graag wil ik alle vrienden in Amsterdam bedanken voor de broodnodige ontspanning tussen het werken door de afgelopen vier jaar: Koen & Nieke, Mischa & Anouk, Jasper & Ine, bedankt voor de gezelligheid tijdens (‘kookclub’) etentjes en borrels. Sander, Jeroen, Maartje, Ai-Pin, Sanne, door jullie heb ik mijn nieuwe woonplaats beter leren kennen en allerlei fijne restaurants en kroegjes ontdekt. Dank daarvoor!
Theo & Mieke: het is altijd heerlijk tot rust komen in het Epense of Tilburgse. Dank voor jullie oprechte interesse in mijn onderzoek en alle gezellige dagen, er zullen er nog vele volgen. Tess, dat geldt ook voor jou, samen met jou en Niels is het altijd goed toeven.


Niet omdat het moet, maar omdat het kan: Pa & Ma heel erg bedankt voor jullie onvoorwaardelijke steun tijdens mijn studie en promotie. L’enfant terrible is toch nog een heel eind gekomen!

Jos, wij hebben al veel avonturen meegemaakt de afgelopen 11 jaar, eens kijken wat dit nieuwe avontuur ons brengt!

Pim van Ooij, Amsterdam, augustus 2012.
Curriculum Vitae

Pim van Ooij

was born on July 9, 1980 in Maastricht, The Netherlands. He attended the Lyceum at Jeanne d’Arc college in Maastricht from 1992-1998. After graduation, he went to Montpellier, France to study the French language at Paul Valéry University and a private school, acquiring the D. A. L. F. (Diplôme Approfondi de la Langue Française) diploma at the end of the year. In 1999 he started his Biomedical Engineering studies at the Eindhoven University of Technology.

During his studies, Pim went to Christchurch, New Zealand to do an internship on blood flow in the Circle of Willis in the group of prof. Tim David. In 2007 he graduated in the Materials Technology group of prof. dr. ir. Frans van de Vosse, supervised by dr. Peter Bovendeerd.

In 2008, Pim started working as a PhD student in the 3T MRI group of dr. Aart Nederveen and the aneurysm group of prof. dr. Ed van Bavel and prof. dr. Charles Majoie at the Academic Medical Center in Amsterdam. In 2010 he helped organizing the 3rd ISMRM Benelux in Hoeve. The subjects of this thesis were presented at several national and international conferences.

In the fall of 2012, Pim will join the group of Dr. Michael Markl as a postdoc at Northwestern University in Chicago under supervision of Dr. Alex Barker.