Wall shear stress calculations using phase contrast MRI
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Chapter 10

Summary and general discussion
10.1 Summary

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

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

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

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

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

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

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

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

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

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

10.2 Future of 4D flow MRI measurements

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

10.2.1 Shorter scan time

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

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

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

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

10.2.2 Improved cardiac triggering and breathing corrections

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

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

10.2.3 Improved velocity measurements

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

10.3 Future of 4D flow MRI post-processing

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

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

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

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

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

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

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

10.5 Concluding remarks

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

Bibliography


Summary and general discussion


