Summary and General Discussion

The research described in this thesis was aimed at improving velocity measurements of blood flow in the ventricles using cardiac Magnetic Resonance Imaging. The incentive for this work was the clinical need to quantify the severity of mitral valve regurgitation in an absolute sense. MRI is an important non-invasive diagnostic tool in cardiology. Besides imaging the anatomy, the MR phase contrast technique has the capability of quantitative velocity measurements of blood flow in the heart and great vessels. Phase contrast measurements can therefore be used to quantify mitral valve regurgitation. As any other technique, also the phase contrast technique has its limitations. To improve the quantification of blood flow measurements, two issues of interest for cardiac MRI have been addressed in this thesis.
In Part I alternative sequences based on steady state free precession (SSFP) for the current standard phase contrast spoiled gradient echo (PC-GE) sequence were investigated. The PC-GE technique is less suitable for mitral valve regurgitation assessment because of its long acquisition time and insufficient signal intensity. The SSFP technique has a better contrast and may therefore be helpful in solving these problems. In Part II velocity offset behaviour originating from uncompensated eddy currents was studied in a multi-vendor set-up. These velocity offsets translate into significant errors in cardiac blood flow quantification and thus may hamper accurate assessment of mitral valve regurgitation.

Part I - Flow quantification of the mitral valve: combining phase contrast with SSFP sequences

Quantification of flow through the mitral valve is important in the clinical management of patients with mitral valvular regurgitation. A leaking valve may lead to the development of heart failure, therefore accurate measurements of the regurgitant volume will support clinical decision making on treatment. The first method of choice is echocardiography. A rough approximation of the regurgitant volume can be obtained, however these measurements are only an approximation since they use geometric assumptions. Using echocardiography the degree of mitral regurgitation can only be quantified by using categories: mild, moderate or severe. Furthermore, not all patients have a good acoustic window.

Magnetic resonance imaging, in contrast, is capable of accurate quantitative velocity measurements in combination with an unobstructed view on the heart. However, direct measurements at the mitral valve are still a challenge due to continuous valvular motion through-out the cardiac cycle. One possible approach for direct mitral valve regurgitation assessment requires a velocity measurement in a 3D spatial volume, with velocity encoding in all three orthogonal directions and time information (7-dimensional). For this, the existing
implementation of the phase contrast technique in a 7D spoiled gradient echo sequence (PC-GE) falls short in terms of acquisition time and signal intensity. Steady state free precession (SSFP) based sequences are often applied in cardiac MR because of their relatively short acquisition times and high intrinsic blood-myocardial contrast. Consequently, there have been attempts to combine the phase contrast technique for velocity measurements with SSFP sequences. Three different approaches were published by Overall et al. [1], Markl et al. [2] and Pai [3]. However preservation of the steady state in an area with high blood flow velocities is a challenge, even without velocity phase encoding [4, 5]. Therefore the sequences should be tested specifically in the clinical setting to evaluate the severity of artifacts. Part I of this thesis evaluated two of these PC-SSFP implementations, to see whether SSFP is a better approach for mitral valve blood flow quantification.

Pai [3] introduced a very time efficient implementation of PC-SSFP using a multi-echo approach. In Chapter 2 this approach was implemented for cardiac flow quantification. Firstly, the sequence was validated in vitro for stationary flow. Subsequently, the sequence was evaluated on cardiac output measurements in the aorta in ten healthy volunteers in comparison to the existing PC-GE technique. The use of two different echo times in the multi-echo approach introduced some specific problems. The difference in echo times made the velocity maps sensitive for waterfat shifts and B0-drifts, which in turn made velocity offset correction problematic. Furthermore the prolonged TR resulted in considerable flow artifacts from high and pulsatile through-plane flow. Although the results from multi-echo PC-SSFP still gave on average the same results as PC-GE, the limits of repeatability of PC-SSFP were four times larger than those of PC-GE. Given the significantly poorer repeatability of PC-SSFP, this approach is unsuitable for cardiac applications.

The approaches of Overall et al. [1] and Markl et al. [2] are basically similar. The approach of Overall et al. [1] however, was more suitable for extension to 7D acquisitions. Therefore, in Chapter 3, the approach of Overall et al. [1] was implemented and tested on velocity quantification in the heart at the level of the mitral valve.
This first implementation was not a full 7D acquisition yet, since it comprised three spatial dimensions, and only one directional velocity encoding and used prospective cardiac gating. However, the results from a comparison with a similar PC-GE sequence in healthy volunteers were good. Artifact levels did not increase and blood-myocardial contrast improved significantly, resulting in more reproducible velocity measurements.

With the promising results from the previous study, this PC-SSFP sequence was extended to acquire full 7D data-sets with retrogated cardiac triggering. In Chapter 4 the feasibility of mitral regurgitation volume quantification by this sequence was tested on healthy volunteers and additionally on two patients with mitral insufficiency. Comparative measurements were made with the indirect method (using aorta flow and left ventricular volume difference) and also directly at the mitral valve using 7D PC-GE technique. Overall, image quality was good, although in some cases considerable respiratory motion artifacts were noted. The regurgitation volumes observed in the healthy subjects were not significantly different from zero. In both patients a clear regurgitation volume was measured and no artifacts from regurgitant jets were observed. However, the standard deviations between the different measurement methods were considerable. This was partly due to normal physiological variations, but respiratory motion and low resolution in the slice direction might have caused further inaccuracies. Before a more extensive patient study can be conducted these issues should be addressed. The sequence, measurement protocol and accompanying image analysis need further development to optimize for patient motion and resolution.

**Discussion part I**

Part I of this thesis showed that cardiac phase contrast measurements based on SSFP-sequences is feasible with current fast gradient systems. However, full 7D acquisitions require inherently longer acquisition times (up to 30 min), which are opposite to the demands in busy clinical practice. Unfortunately, the most time efficient solution of Pai [3] was not suitable for cardiac application. The next step in further research should be focussed on reducing the acquisition times.
Parallel imaging techniques like k-t BLAST and k-t SENSE [6] have been successfully used in SSFP sequences [7] and in phase contrast [8–10] to reduce those acquisition times. Applying these techniques to the new 7D PC-SSFP sequence might be equally successful. The challenge herein lies with the preservation of the steady state, which is more difficult when large steps in k-space are taken [7]. Furthermore, parallel imaging techniques that undersample data in the temporal direction have shown to underestimate peak velocities as they have a low-pass filtering effect [8–10]. Especially with the high velocities and turbulence that are associated with valve insufficiencies this should be carefully attended.

After implementation of parallel imaging, the acquisition times will be much shorter and leaving space to optimize other acquisition parameters. In Chapter 4 the results were limited by the low resolution in the through-plane direction and respiratory motion artifacts. When acquisition times are reduced the protocol parameters should be optimized for sufficient through-plane resolution. As a next step, the effect of respiratory gating should be investigated. Motion artifacts will be reduced by respiratory gating, however the acquisition times will increase again [11]. The best choice for this application should be carefully evaluated.

After successful acquisition of the data, the image analysis starts. With a full 7D acquisition the possibilities are numerous. In the analysis from this thesis (§4.2) a fairly straightforward approach was chosen using only the acquisition itself. For acquisitions based on PC-GE sequences several visualization strategies have been developed [12, 13]. These strategies had to use a separate planar SSFP acquisition to overcome the low blood-myocardial contrast in the PC-GE acquisition. Although, the low contrast issue is solved using PC-SSFP, the planar SSFP acquisitions also have a better spatial resolution. In further development of quantification of mitral regurgitation volume using the 7D PC-SSFP sequence, the potential benefit of additional 2D SSFP acquisitions should be investigated as part of the optimization of the image analysis strategy.
Part II - Velocity offsets: characterization in a multi-vendor study

Velocity measurements using phase contrast techniques were introduced over thirty years ago [14]. Upon introduction the technique has been validated well [15], and amongst others found application in cardiac and great vessel volume flow quantification. Unfortunately, with the advance of gradient systems in the scanners the technique became less trusted as the sensitivity to background velocity offset errors became more prominent [16–19]. These velocity offsets become apparent in stationary tissue having small non-zero velocities. Because calculations of volume flow are based on the summation of velocities over the whole cross sectional area of a vessel and over all phases of the cardiac cycle, the small background velocity offset accumulates to a significant error in the calculated volume flow [20]. Although the physical causes of these velocity offsets and accompanying correction methods are known, translation of this knowledge to clinical practice was not adequate. In 2007 Kilner et al. [21] made a plea to the manufacturers and users that phase contrast flow measurement is a unique strength of cardiovascular magnetic resonance that needs joint efforts towards optimisation.

As a consequence of this plea the EuroCMR Working Group of the European Society of Cardiology initiated a study to investigate the problem of background phase offsets. In a multi-center multi-vendor set-up the severity of uncorrected velocity offset errors across sites and CMR systems was studied. In Chapter 5 the results of this study are reported. In this study the velocity offsets were studied in static phantom using protocols that represented clinical practice as close as possible. Thereafter image analysis yielded the worst-case offset that might affect typical flow measurements in the aorta and pulmonary artery. The outcomes showed that none of the tested CMR systems stayed consistently below the maximum acceptable offset of 0.6 cm/s. This value of 0.6 cm/s was derived from an acceptable offset error of 5% in average cardiac output.

In Chapter 5 the need for further optimisation of flow measurements was confirmed, giving way to two important questions regard-
ing the reliability of flow quantification in clinical practice. The first question comprises optimization of the acquisition protocol to minimize the background error in clinical routine. The second question concerns the reliability of post-acquisition velocity offset correction techniques. **Chapter 6** addressed the first question. Again in a multi-vendor set-up, the study tested the velocity offsets as a function of a selected set of protocol parameters in order to identify correlations between those protocol parameters and the resulting error in clinical CMR flow measurements. Unfortunately, none of the tested protocol settings consistently reduced the velocity offsets below the acceptable offset of 0.6 cm/s for all tested systems. Additionally, some exploratory measurements beyond the protocol yielded some new leads for further sequence development towards reduction of velocity offsets; however those protocols were not always compatible with the time-constraints of breath-hold imaging and flow-related artefacts. These findings implied that optimization of velocity acquisitions would have to be performed on a per scanner and per protocol basis. Furthermore, the necessity of post-acquisition corrections will continue to exist.

Some post-acquisition correction techniques depend on a separate phantom acquisition in which the velocity offsets are replicated [19, 20]. These techniques assume the background phase offsets to be constant over time. This assumption of temporal stability was tested in **Chapter 7**. A similar multi-vendor set-up was used as in the previous two studies. The stability of background offsets was assessed on an intra-scan session time-scale and on a long-term time-scale over weeks. The background offsets were steady on the tested systems on the short time scale of a patient scan, although high gradient power scanning should be handled with care. On the longer time scale of weeks, not all systems showed the desired stability.

**Discussion part II**

**Part II** of this thesis investigated velocity offsets from a clinical practice approach. The sources of velocity offsets have been studied before from a theoretical point of view; Maxwell terms and eddy currents are known sources of phase differences [17, 22]. Maxwell terms are
well corrected for on most commercial systems [17], but small residual eddy currents after first correction by pre-emphasis are still present [23, 24]. These residual eddy currents have not been solved by the theoretical approach. The studies performed for this thesis all set out from a clinical protocol and investigated residual eddy current behaviour from there. It showed that the resulting velocity offsets are a significant and widespread problem with highly unpredictable behaviour.

First of all these studies showed why no solution or correction method has been overall succesful in clinical practice. There are too many differences in offset behaviour between different types of scanners and even between different protocols within scanners. This means that proposed solutions should be verified extensively on several scanners and several protocols per scanner. Furthermore, stationary phantom scans were considered as the gold standard for velocity offset correction. However, the temporal behaviour observed in Chapter 7 showed the potential limitations of this standard by the heating effects of high gradient power scanning. Together with the time consumption of this approach, this is not a suitable correction method in clinical practice.

In this thesis it was found that the best velocity offset corrections will be those that are based on information from the acquisition itself. There are too many factors influencing the offsets, including influences of previous acquisitions. Currently, there are two approaches for velocity offset correction that are based on the acquisition itself. The first one is based on (linear) estimation from static tissue [16, 19]. This method needs further validation, as initial validation was performed on one scanner with a very limited range of protocols. Furthermore, it would need an inline implementation by the manufacturers on their scanners. The second approach is based on magnetic field monitoring [25, 26], where the magnetic field is measured with high temporal resolution during an acquisition. While this method is still in development phase, it is a very promising approach for this complex problem.
In Conclusion

Magnetic Resonance Imaging is an amazing diagnostic tool and the heart is a fascinating organ to study. However, doing accurate quantitative measurements on blood flow in the heart using MRI is a challenge. In this thesis two of those challenges were addressed. Part I, quantification of blood flow through the mitral valve. The valve is continuously moving and often high velocities are encountered at leaking valves. Current techniques suffered from low blood-myocardial contrast and long acquisition times. SSFP based sequences were considered as a better approach. Flow quantification using phase contrast SSFP sequence turned out to have improved results slightly, but acquisition times are yet too long for practical use in the clinical setting. Further research should focus on reducing the acquisition times. Part II, characterization of velocity offsets. In general cardiac blood flow measurements are sensitive to small velocity offsets. Although the problem was generally known, it was never studied thoroughly in practice and directions on minimization of the problem were ambiguous. A multi-vendor multi-center study was set up to finally characterize this phenomenon. The velocity offsets turned out to be a wide-spread problem with large variations between systems and even within systems. Further research should focus on robust correction methods rather than controlling the offsets.

Bibliography


SUMMARY AND GENERAL DISCUSSION


