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Chapter 4

Mitral valve blood flow quantification by 7D phase contrast SSFP - a feasibility study

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Abstract
Purpose: to assess the feasibility of a new 7D PC-SSFP sequence for single acquisition mitral regurgitation volume quantification.
Materials and Methods: The 7D PC-SSFP sequence implementation is based on a regular 3D balanced SSFP gradient scheme with velocity encoding. Accuracy of velocity quantification was confirmed using a flow-phantom. Mitral volume flow was measured in ten healthy subjects and additionally in two patients with mitral valve insufficiency: indirectly using aorta flow and left ventricular volume difference and also directly at the mitral valve using 7D PC-GE and the new 7D PC-SSFP sequence.
Results: Overall, image quality was good, although in some cases considerable respiratory motion artifacts were noted. No significant differences in cardiac output measurements were found between the methods, and regurgitation volumes in the healthy subjects were not significantly different from zero. In both patients a clear regurgitation was observed and no artifacts from regurgitation jets were observed.
Conclusion: The new 7D PC-SSFP sequence is a promising tool for the quantitative assessment of mitral regurgitation.

4.1 Introduction

Clinical management of patients with non-ischemic mitral regurgitation heavily depends on echocardiography. 2D echo provides a detailed assessment of valvular anatomy and left ventricular function, Doppler echocardiography with color display accurately visualizes the regurgitant jet in the left atrium and provides a qualitative assessment of its severity which is usually categorized as mild, moderate or severe [1]. Indirect measures of severity can be found through the evaluation of left atrial size, left ventricular size and the pulmonary venous flow pattern. An approximation of the regurgitant volume can be obtained by the proximal isovelocity surface area (PISA)-method, although the reliability of this calculation strongly depends on operator experience and type of jet [2, 3]. Three dimensional ultrasound techniques are a current topic in research [4, 5]. A more quantitative approach would allow fine-tuning of patient management and would facilitate serial assessment to monitor lesion severity or evaluate the effect of new nonsurgical treatment.

Accurate flow quantification can be obtained by MRI phase contrast measurements [6, 7]. It is possible to quantify the mitral regurgitant volume indirectly by measuring the ejection volume through the aorta using phase-contrast techniques and the morphological left ventricular volume change between systole and diastole derived from anatomical cine images [8, 9]. The difference yields the backward flow through the mitral valve. This method however, is sensitive to errors as a small volume is calculated by subtraction of two large volumes. This sensitivity increases even further when the aortic valve is also insufficient.

Direct measurement of the mitral regurgitating volume is still under research. The main challenges herein are continuous movement of the valve throughout the cardiac cycle and high velocity of the jets causing signal voids [10]. Moving the 2D image slice with the valvular plane throughout the cardiac cycle solves the first problem [11], but not the second. A measurement of the whole 3D velocity field in a 3D spatial volume around the valve with 7D PC gradient echo (GE) allows for slice movement correction while the use of a control volume to

work around the locations of signal loss [12]. However, this introduces a new problem, as conventional spoiled GE relies on signal enhancement from inflow of unsaturated spins, which is severely reduced in a volume acquisition [13, 14]. An recent approach from Westenberg et al. [15], Roes et al. [16] solved this problem by using separate SSFP-based acquisitions for sufficient blood-myocardium contrast.

This study investigated the feasibility of using an SSFP-based phase contrast sequence for a single acquisition mitral regurgitation assessment. SSFP is known to have better signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) than spoiled GE [13, 17, 18]. Phase contrast measurements using an SSFP sequence have been reported for cardiac 2D acquisitions [19–21]. The technique described by Overall et al. [20] can relatively straightforward be extended to a 3D sequence with 3D velocity encoding. Extension to a spatial 3D sequence with one-directional velocity encoding has previously been demonstrated [22]. In the present study, the technique was implemented as a full 7D PC-SSFP sequence with cine imaging in three spatial dimensions with three-directional velocity encoding. Others have also implemented 7D PC-SSFP; for applications with low velocities as cerebral blood flow and cerebrospinal fluid flow [23], or for areas with sufficient stationary tissue next to the region of interest [24] acquiring only one phase measurement (reference-less mode). Both implementations were not suitable for cardiac imaging. The new 7D PC-SSFP sequence was evaluated for mitral valve blood flow quantification and compared to the indirect measurement and the 7D PC-GE technique.

4.2 Materials and Methods

Sequence description

The 7D PC-SSFP sequence is based on a regular 3D balanced SSFP gradient scheme with velocity encoding. The sequence was introduced for 2D imaging by Overall et al. [20] and further validated for cardiac flow quantification with a single velocity encoding direction by Rolf et al. [22]. In this study, the SSFP sequence was implemented with 3D spatial imaging and velocity encoding in three orthogonal directions.

Cine imaging of the cardiac cycle was implemented with prospective gating.

In more detail: after the read-out a bipolar velocity-encoding gradient was placed on the slice-selection, phase-encoding or read-out axis for through-plane or in-plane velocity encoding, respectively (Figure 4.1). To keep the two steady-states for phase contrast imaging as equal as possible, the polarity of the bipolar pulses was alternated at each cardiac trigger. All three velocity encoding directions were acquired, before updating the 3D slice encoding table. After switching between different slice encodings and velocity encodings, one heart beat without data recording was allowed for building up the new steady state. The 7D PC-SSFP sequence was implemented on a 1.5 Tesla scanner (Magnetom Avanto, Siemens, Erlangen, Germany) with a gradient performance of 40 mT/m and 200 T/m·s.

Validation on flow phantom

The velocity quantification of the 7D PC-SSFP sequence was tested in a custom-made flow phantom. The phantom consisted of a Perspex cube with 15 cm long edges, filled with stationary fluid. Inside the cube, fluid flowed through a tube with a diameter of 4.15 mm. The flow circuit was driven by a rotary vane pump (Procon, Murfreesboro TN, USA), creating a steady flow. A float displacement volume flow meter (Brooksmeter model 1307, Brooks Instrument B.V., the Netherlands) was mounted in the flow circuit and was calibrated for the actual viscosity of the phantom fluid. This setup could generate volume flow rates ranging up to 1.0 l/min, with peak velocities up to 200 cm/s. The phantom fluid consisted of water with 0.9 mass percent NaCl for coil loading and 0.05 mmol/l MnCl2 to lower relaxation times. To get a fluid viscosity comparable to blood ($\approx$3.5 mPa·s in normal population [25]), methylcellulose (4000 cP 0.2 vol%) was added, resulting in a viscosity of 4 mPa·s. Measurements were performed at 8 different volume flow rates. PC-SSFP sequence parameters were: spatial resolution $0.8 \times 0.8 \times 5$ mm^3, matrix $192 \times 132 \times 8$, FOV $160 \times 110 \times 40$ mm^3, v_{max} 200 cm/s (v_{max} is the maximum velocity that can be measured in the linear range, for detailed explanation see [20]), TR 7.0 ms, TE 3.3 ms, excitation angle 70°,

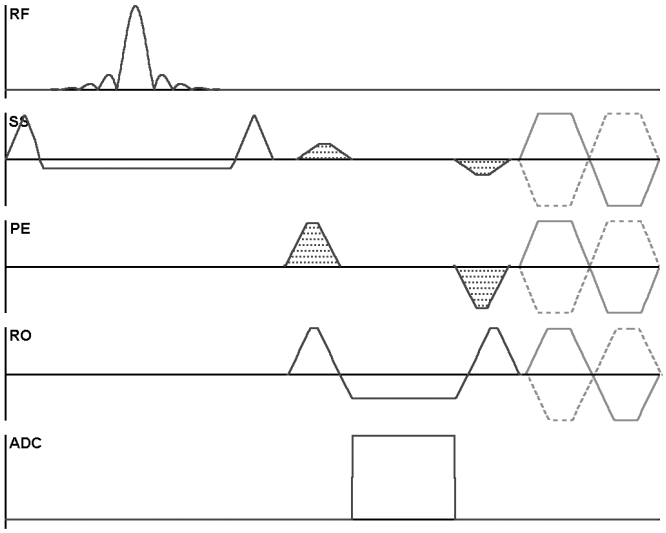

Figure 4.1: The 7D PC-SSFP pulse sequence diagram. The bipolar velocity encoding pulse are positioned on the slice-selection (SS), the phase-encoding (PE), and the readout (RO) axis for complete three-directional velocity encoding. Each heart beat the sequence alternates positive and negative velocity encoding. The different imaging encoding steps are shown by the dotted lines on both the SS-axis and PE-axis for three-dimensional imaging.

bandwidth (BW) 900 Hz/pix, and the body coil for RF receiving. Cross-sectionally averaged velocity in the tube was measured in the 7D PC-SSFP images using dedicated cardiac MR analysis software (Mass v2011-EXP, Leiden, the Netherlands). Regions of interest were drawn with an area matching the known tube diameter to limit partial volume errors. Velocity offset was corrected by a separate stationary phantom acquisition [10, 26]. The measured velocities were then used to calculate the volume flow and compared with the volume flow meter readings. The validity of the flow measurements was tested by comparing the slope and intercept outcomes of linear regression with the line of identity.

In vivo measurements
The mitral valves of ten healthy volunteers were scanned. The study was approved by the local ethics committee and all subjects gave written informed consent. In each subject the volume flow through the mitral valve was measured in three different ways: 1. indirectly using aorta flow and left ventricular volume difference, 2. directly at the mitral valve using a 7D PC-GE sequence, and 3. directly at the mitral valve using the new 7D PC-SSFP sequence. Additionally, two patients with mitral regurgitation were scanned with the same protocol as the healthy subjects. The patients were selected on their confirmed mild mitral regurgitation by ultrasound echocardiography and having a normal sinus rhythm.

All acquisitions used a 8-channel phased-array receiver coil, with retrogating to the electrocardiogram [27] and 30 reconstructed phases, v_{enc} 150 cm/s. For the indirect method the through-plane velocity measurements were performed in a transverse plane in the ascending aorta at the level of the bifurcation of the pulmonary artery trunk using a conventional phase-contrast spoiled gradient echo (PC-GE), see Figure 4.2a. Left ventricular cardiac output was measured using a continuous stack of short axis cine-SSFP images with a slice distance of 1 cm (slice thickness 5 mm, slice gap 5 mm) covering the whole left ventricle [28, 29], see Figure 4.2b. The measurements at the level of the mitral valve were planned using a four-chamber view. The volume consisted of ten slices of 5 mm thickness covering the valve during the whole cardiac cycle, see Figure 4.2c. The four-chamber view was acquired using a cine-SSFP sequence and took 40 seconds to capture multiple respiratory cycles in order to be representative for the long 7D acquisitions. This four-chamber view was also used for localization of the mitral valvular plane in the 7D PC-GE scan. The direct mitral flow measurement was performed using a 7D PC-GE sequence and using the new 7D PC-SSFP, both custom implemented. The 7D PC-GE parameters were: spatial resolution $1.3 \times 1.3 \times 5$ mm^3, matrix $256 \times 208 \times 10$, FOV $320 \times 260 \times 50$ mm^3, TR 9.9 ms, TE 6.3 ms, non segmented, excitation angle 10°, bandwidth 260 Hz/pix, temporal resolution 39.7 ms, and parallel imaging factor 4 (GRAPPA);

Figure 4.2: Planning of acquisitions. a: Aorta flow was measured in a transverse plane at the level of bifurcation of the pulmonary artery trunk. b: Left ventricular morphology was measured using a continuous stack of short axis cine-SSFP images covering the whole left ventricle. c: Mitral valvular flow was measured in a volume of ten slices of 5 mm thickness covering the valve during the full cardiac cycle.

resulting in an acquisition time of 12 minutes at a heart rate of 60 beats per minute. Parameters of the 7D PC-SSFP sequence were: spatial resolution $1.8 \times 1.8 \times 5$ mm^3, matrix $192 \times 156 \times 10$, FOV $340 \times 276 \times 50$ mm^3, TR 5.7 ms, TE 2.3 ms, 6 segments, excitation angle 70°, bandwidth 900 Hz/pix, temporal resolution 34.4 ms, no parallel imaging, and a locally adjusted shim; resulting in an acquisition time of 26 minutes at a heart rate of 60 beats per minute. All velocity measurements were corrected for phase offsets by a separate acquisition on a stationary phantom in the same imaging session [26]).

All image analysis was performed using dedicated software (Mass v2011-EXP, Leiden, the Netherlands). Contours were drawn on the magnitude images of the 2D flow measurements through the aorta, after which the average volume flow through the area at every phase in the cardiac cycle was determined. Analysis of the left ventricular volume was performed by manually drawn endocardial contours on the short axis slices at endsystole and end-diastole [28–30], resulting in the stroke volume. At each cardiac phase, the position of the mitral valve was manually drawn on the four-chamber long-axis view on which the 7D PC-GE was planned. Subsequently, the three dimen-

sional volume of the 7D PC-GE acquisition was resliced through this mitral valve position for each cardiac phase. In the resliced magnitude images the contours of the mitral valve were manually drawn. From the 7D velocity data a through-plane velocity image was reformatted on this valvular plane for each phase, and using the mitral valve contours the volume flow was assessed. From the spatial position of the resliced images the contribution of the mitral valvular motion to the blood flow was quantified. The distance to the preceding and following slice was calculated from the center of each contour area. The blood flow due to valvular motion was calculated from the slice displacement multiplied by the valve area. The 7D PC-SSFP acquisitions were analyzed in the same way, except that the 4- chamber view was generated by multi-planar reformatting from the data itself.

From the flow curves cardiac output was calculated by integration of the volume flow over the whole cardiac cycle. The differences between the methods were tested using a paired Students t-test. Mitral regurgitant volume flow was calculated by subtraction of the cardiac outputs of the aorta flow and left ventricle for the indirect method. Direct quantification of the regurgitant volume flow by 7D PC-GE and 7D PC-SSFP was performed by integration of the mitral volume flow during systole. Average regurgitant volume flow over all ten healthy subjects was tested using a Students t-test from being significantly different from zero.

4.3 Results

Validation on flow phantom

In vitro volume flows measured in the 7D PC-SSFP velocity maps were compared to the volume flow meter measurements. MRI measurements showed excellent agreement with the flow meter readings, see Figure 4.3. Data were consistent with the line of identity (slope 0.98 P=0.17, offset 0.00 l/min P<0.01); and the residual error was small (RMS <0.01 l/min).

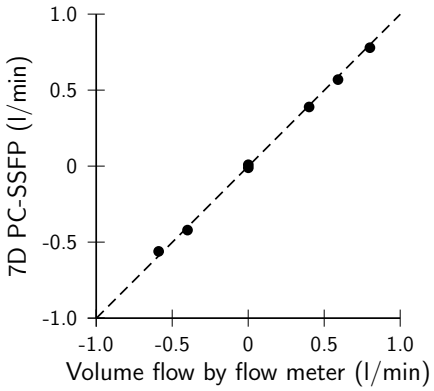

Figure 4.3: In vitro flow validation: volume flow (with corresponding peak velocities up to 200 cm/s) through the tube measured with 7D PC-SSFP against flow meter measurements as assessed in a phantom. Dashed line shows the line of identity. Data were consistent with the line of identity (slope 0.98 P=0.17, offset 0.00 l/min P<0.01); and the residual error was small (RMS <0.01 l/min).

Testing on healthy subjects

The ten healthy subjects were successfully scanned with 7D PC-SSFP. Example images from one of the healthy subjects is shown in Figure 4.4. Subjects with pronounced chest breathing presented motion blurred images. From the data, the volume flow curves were measured. Figure 4.5 shows the resulting curves from the same subject as in Figure 4.4. The mitral curves showed a general agreement, although some inaccuracies were observed during systole when the mitral valve is closed and zero volume flow is expected in healthy subjects. Small differences in timing of LV filling were observed between the techniques; probably due to differences in heart rate between the measurements.

From the left ventricular morphology and multiple flow curves, the cardiac output was calculated for all subjects. The results are presented in Figure 4.6. Within the ten healthy subjects no significant differences ($P \geq 0.6$) between the four separate measurements of

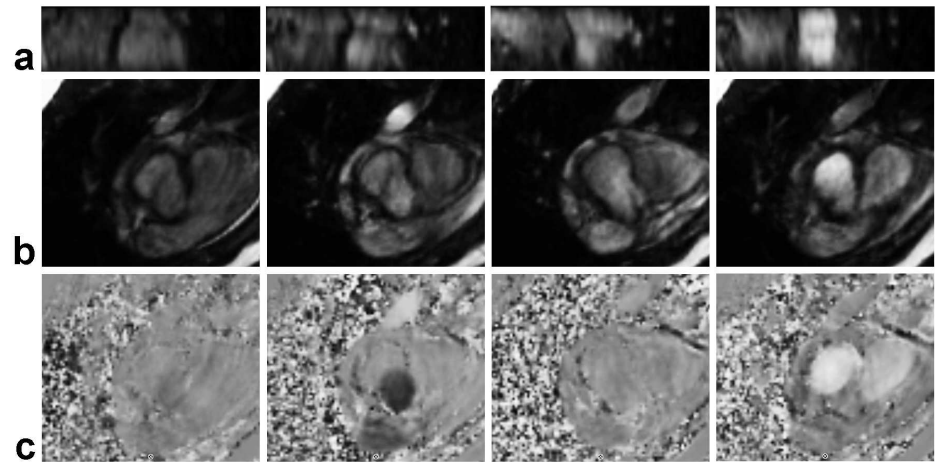

Figure 4.4: Example 7D PC-SSFP images from one of the healthy subjects. Images from four distinct time points in the cardiac cycle are shown, from left to right: end diastole (phase 1: t=0 ms), mid-systole (phase 4: t=109 ms), end systole (phase 10: t=326 ms), and mid E-wave (phase 14: t=471 ms). The first row (a) shows the four-chamber multiplanar reformat on which the position of the mitral valve was indicated. The next rows show the accompanying magnitude (b) and through plane velocity (c) images reformatted through the mitral valve plane.

cardiac output were observed, standard deviation between measurements was within normal physiological variation of 0.3 l/min. From the flow curves the regurgitant volume flow was also calculated and the results are shown in Figure 4.7. The average regurgitation volume flow over the healthy subjects was not significantly different from zero (P>0.4), however standard deviation was high; indirect measurement 0.05 ± 0.4 l/min, 7D PC-GE 0.07 ± 0.3 l/min, and 7D PC-SSFP 0.05 ± 0.3 l/min.

As an illustrative example, two patients with mitral insufficiency were scanned (subjects 11 and 12 in Figures 4.6 and 4.7). Image quality of both patients was equal to those of healthy subjects, no artifacts from regurgitation jets were observed. The differences between the

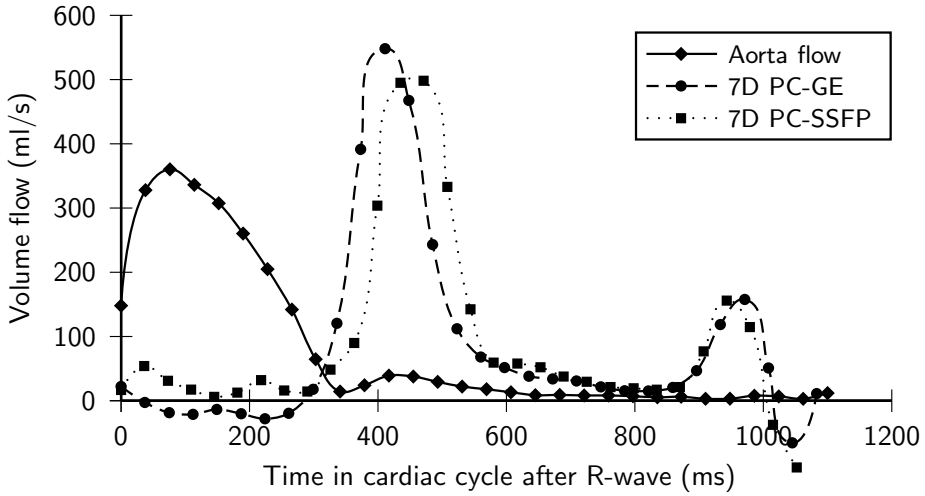

Figure 4.5: Example volume flow curves from one of the healthy subjects (same as in Figure 4.4). The flow curves at the mitral valve from 7D PC-GE and 7D PC-SSFP showed general agreement. Some inaccuracies were observed in the mitral flow curves during systole.

cardiac output measurements were larger than in the healthy subjects. One patient (subject 11) also had a small aortic insufficiency which explains the high left ventricular output. Mitral regurgitation could be observed clearly, however, the differences between the techniques were large.

4.4 Discussion

This study was designed to assess the feasibility of a new 7D PC-SSFP sequence for single acquisition mitral regurgitation volume quantification. Validation on a flow phantom showed accurate flow quantification. First results on healthy subjects showed tolerable image quality. However, the images of some subjects with pronounced chest breathing suffered from respiratory motion. Additionally to the healthy subjects, two patients with mitral regurgitation were scanned. The

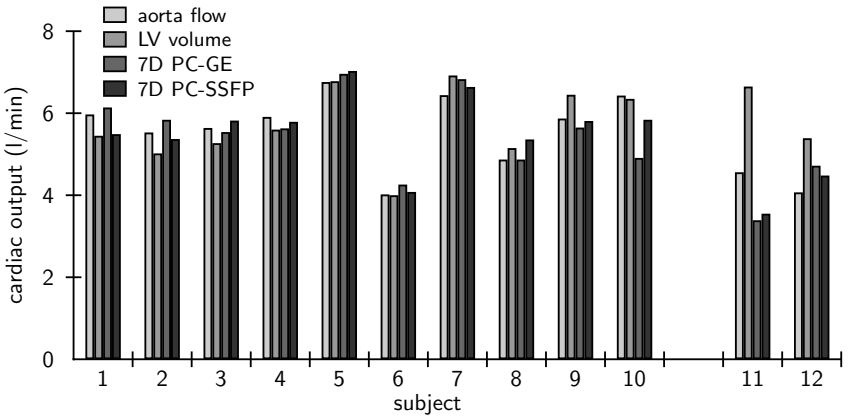

Figure 4.6: Cardiac output measured by the four different methods in all healthy subjects (subjects 1 to 10) and two patients with mitral insufficiency (subjects 11 and 12). No significant differences (paired t-tests $P \geq 0.6$) between the four different measurements of cardiac output in healthy subjects were observed, standard deviation between measurements was 0.3 l/min.

quality of the images from these two patients was similar to those of the healthy subjects; no artifacts from regurgitation jets were observed. When studying more patients a regular heart rate may become a point of concern. In this study, both patients showed a normal sinus-rhythm, but many patients suffering with mitral regurgitation may have atrial fibrillation with marked irregularity.

Quantification of cardiac output and regurgitation volume flow by 7D PC-SSFP was compared to the existing techniques of aorta flow and left ventricular volume (indirect quantification of regurgitation) and 7D PC-GE. The 7D PC-SSFP acquisition measured a clear regurgitation in both patients. No significant differences between the methods were found, and regurgitation volumes in the healthy subjects were not significantly different from zero. Standard deviations between techniques were considerable. This variability is comparable to the measurements shown earlier by Roes et al. [16] for 7D PC-GE. This can be partly ascribed to normal physiological variations and in

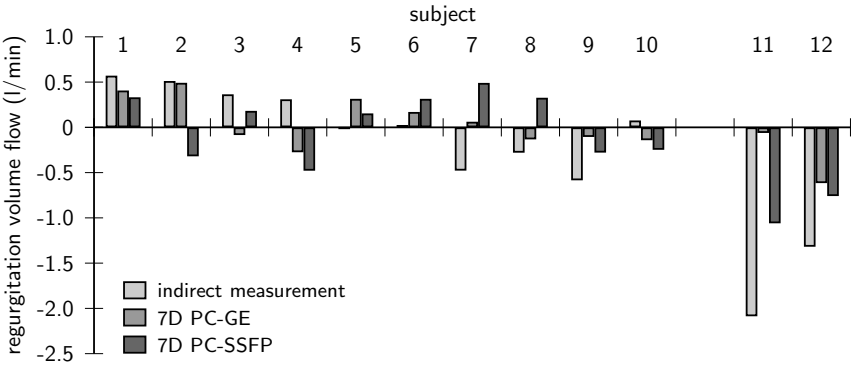

Figure 4.7: Regurgitant volume flows measured by the three different methods in all healthy subjects (subjects 1 to 10) and two patients with mitral insufficiency (subjects 11 and 12). Average regurgitation volume flow over the healthy subjects were: indirect measurement 0.05 ± 0.4 *l/min, 7D PC-GE* 0.07 ± 0.3 *l/min, and 7D PC-SSFP* 0.05 ± 0.3 *l/min. In the two patients a clear mitral regurgitation was observed, however with large differences between the different techniques.*

addition inaccuracies due to the differences between the techniques themselves. To name some of these differences: the stack of short axis slices was acquired in multiple breath holds whereas the other acquisitions were non breath holds. The aorta flow measurements did not comprise the volume flow to the coronary arteries (≈5%) [31], therefore yielding a slight underestimation of real cardiac output. The 7D PC-GE measurements used a separate four-chamber view for localization of the mitral valve, subject motion and differences in timing between those acquisitions might have caused inaccuracies. The 7D PC-SSFP measurements were from a single acquisition, here the low resolution in the z-direction and motion blurring from the long acquisition time were limiting in accurate mitral valve localization.

The 7D PC-SSFP acquisition showed a significant regurgitation in both patients, however, large differences were observed between the various techniques. Taking limitations from previous paragraph into

consideration further research on flow quantification by 7D PC-SSFP should focus on sequence development, optimization of acquisition parameters and image analysis. The sequence development should incorporate respiratory gating [31, 32] to reduce respiratory blurring, and parallel imaging to reduce acquisition times [33–35]. The optimization of acquisition parameters should concentrate on the balance between spatial and temporal resolution and overall scan time. Image analysis would benefit from more accurate localization of the mitral valve during the cardiac cycle. With these developments a more extensive patient study can assess the potentially additional value of the sequence for mitral regurgitation quantification.

With these improvements, 7D PC-SSFP imaging holds the promise of a complete quantitative evaluation of all four heart valves from a single acquisition [15, 16] as one 3D image volume could be set to include all valves. In addition, assessment of parameters that are commonly used in ultrasound [1, 36], such as peak velocities of early (E-wave) and atrial/late (A-wave) mitral valve flow, will become possible [37]. The regurgitant fraction could simply be calculated from the bidirectional volume flow through the mitral valve, instead of incorporating a separate measurement as left ventricular stroke volume.

In conclusion, the new 7D PC-SSFP sequence can be used for single acquisition mitral regurgitation volume quantification. Validation on a flow phantom showed accurate velocity measurements, and results on a series of healthy subjects were comparable with existing techniques. However, the method needs further optimization before evaluation in patients.

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