Published in final edited form as:

J Magn Reson Imaging. 2016 August ; 44(2): 383–392. doi:10.1002/jmri.25180.

Assessment of the Precision and Reproducibility of Ventricular Volume, Function and Mass Measurements with Ferumoxytol-Enhanced 4D Flow MRI

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Abstract

Purpose—To compare the precision and inter-observer agreement of ventricular volume, function and mass quantification by three-dimensional time-resolved (4D) flow MRI relative to cine steady state free precession (SSFP).

Materials and Methods—With research board approval, informed consent, and HIPAA compliance, 22 consecutive patients with congenital heart disease (CHD) (10 males, 6.4±4.8 years) referred for 3T ferumoxytol-enhanced cardiac MRI were prospectively recruited. Complete ventricular coverage with standard 2D short-axis cine SSFP and whole chest coverage with axial 4D flow were obtained. Two blinded radiologists independently segmented images for left ventricular (LV) and right ventricular (RV) myocardium at end systole (ES) and end diastole (ED). Statistical analysis included linear regression, ANOVA, Bland-Altman (BA) analysis, and intra-class correlation (ICC).

Results—Significant positive correlations were found between 4D flow and SSFP for ventricular volumes ($r = 0.808–0.972$, $p < 0.001$), ejection fraction (EF) ($r = 0.900–0.928$, $p < 0.001$), and mass ($r = 0.884–0.934$, $p < 0.001$). BA relative limits of agreement for both ventricles were between -52% to 34% for volumes, -29% to 27% for EF, and -41% to 48% for mass, with wider limits of agreement for the RV compared to the LV. There was no significant difference between techniques with respect to mean square difference of ED-ES mass for either LV ($F = 2.05$, $p = 0.159$) or RV ($F = 0.625$, $p = 0.434$). Inter-observer agreement was moderate to good with both 4D flow (ICC $0.523–0.993$) and SSFP (ICC $0.619–0.982$), with overlapping confidence intervals.

Conclusion—Quantification of ventricular volume, function and mass can be accomplished with 4D flow MRI with precision and inter-observer agreement comparable to that of cine SSFP.

Keywords

magnetic resonance imaging; ventricular myocardium; ventricular function; 4D flow

INTRODUCTION

The quantification of ventricular volume, function and mass is an essential goal of many cardiac MRI examinations, typically achieved with multiple short-axis bright-blood cine steady-state free precession (SSFP) acquisitions. The accuracy of ventricular volume, ejection fraction (EF), and mass measurements by cardiac MRI has been validated (1–5), and cine SSFP is now widely used in practice as a clinical reference standard (6, 7). However, cardiac MRI exams often require advanced operator skills to identify appropriate scan planes and to optimize acquisition parameters, particularly in the setting of congenital heart disease (CHD). Thus, these exams are often lengthy and frequently require prolonged deep anesthesia or sedation in the pediatric population (8).

Three-dimensional time-resolved (4D) flow MRI is an evolving imaging technique that has the potential to simultaneously acquire both flow and function information in a single acquisition, even without detailed operator knowledge of cardiac anatomy (9, 10). The use of contrast agents in 4D flow MRI has been shown to improve signal-to-noise ratio in magnitude data and noise reduction in velocity data (11). However, until the recent implementation of under-sampling methods, including parallel imaging, the clinical utility of 4D flow MRI had been largely limited by prohibitively long image acquisition times (12). To date, although flow and function assessment have been described with 4D flow imaging (9, 13–15), assessment of ventricular mass quantification has not yet been reported to our knowledge. Left ventricular (LV) mass quantification is commonly performed in the setting of congenitally corrected transposition of the great arteries after pulmonary arterial banding to assess feasibility of an arterial switch operation (16). Similarly, right ventricular (RV) mass quantification may have prognostic value in the setting of repaired tetralogy of Fallot (TOF) and other CHD (17–19).

Our clinical CHD practice has been greatly simplified by the implementation of 4D flow imaging. We have anecdotally found that cardiovascular MRI exams can be rapidly performed with a single ferumoxytol-enhanced 4D flow sequence, thus reducing the frequency, depth, and/or duration of anesthesia. However, when indicated, we have had to perform additional sequences for the evaluation of ventricular mass. Here, we aim to compare the precision and inter-observer agreement of ventricular volume, function and mass quantification by 4D flow MRI relative to the gold standard cardiac-gated cine SSFP. We hypothesized that the precision and inter-observer agreement of LV and RV volume, function and mass measurements would not be different between 4D flow and cine SSFP acquisitions.

MATERIALS AND METHODS

Patient Population

With institutional review board approval, informed consent and HIPAA compliance, we prospectively recruited consecutive patients with suspected or known CHD who were referred for 3T ferumoxytol-enhanced cardiac MRI over a one-year period from April 2014 to March 2015. Twenty-two patients were included, 10 males (45%), age range 0.2–25 years (mean 6.4 ± 4.8 years). The following data were abstracted for each patient through electronic

patient records: demographics, height, weight, body surface area and medical history including details of the patient's CHD (Table 1).

Image Acquisition

All imaging was performed on a 3T MRI scanner (GE MR750 3T, GE Healthcare, Waukesha, Wisconsin, USA) using a 32-channel cardiac coil (Invivo, Gainesville, Florida, USA), obtaining complete ventricular coverage with a standard two-dimensional (2D) short-axis multi-slice cine SSFP sequence and whole chest coverage with an axial 4D flow sequence.

The 4D flow sequence used minimum echo time (TE) flow-encoding gradients and a simple four-point encoding strategy (20, 21) in a cardiac synchronized 3D Cartesian RF-spoiled gradient echo sequence with variable density Poisson disk k-space under-sampling. Scan parameters included a flip angle of 15° , resolution of $0.8 \times 0.8 \times 1.4 \text{ mm}^3$, minimum TE of 1.8–1.9 ms, minimum repetition time (TR) of 3.9–4.3 ms with an additional 5.1 ms for fat-saturation, sampling reduction factor of 2.4×4.4 before k-space corner cutting, views-per-segment of 2–6 depending on heart rate, temporal resolution of 72.9–225.6 ms, bandwidth of $\pm 83.33 \text{ kHz}$, and velocity encoding range (VENC) of 150–300 cm/s. The VENC was selected empirically for each study based on the clinical indication. A combined parallel imaging and compressed sensing algorithm, 11-ESPIRiT, was used to reconstruct each cardiac phase separately (22). The total time for the 11-ESPIRiT reconstruction was less than one hour on a server with two 10-core CPUs. Scans were performed after injection of 0.1 mL/kg ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, Massachusetts, USA) for blood pool enhancement (23–25). General anesthesia was used in the majority of cases ($n=17$, 77.3%). Scan duration ranged from 4.6–13.0 min ($8.5 \pm 2.0 \text{ min}$).

Standard 2D multi-slice short-axis cine images were prescribed off a vertical long axis image, and acquired using balanced SSFP (GE Healthcare: FIESTA) ensuring coverage from the cardiac base to apex. The protocol followed published guidelines for cardiac MRI in patients with CHD (26). Scan planes were prescribed by board-certified radiologists with dedicated training in pediatric cardiovascular MRI. In patients capable of breath-holding ($n=4$, 18.2%), a single signal average breath-hold acquisition was performed. Otherwise, a free-breathing acquisition with two to three signal averages was used to reduce respiratory artefacts ($n=18$, 81.8%). Scan parameters included a slice thickness of 6–8 mm depending on patient size, matrix 160×224 , TR of 3.0–4.2 ms, TE of 1.5 ms, flip angle of 60° , views-per-segment of 10–18, and 3 signal averages with retrospective gating. Mean scan duration was $5.3 \pm 1.4 \text{ min}$.

Image Analysis

Two cardiovascular radiologists (AK and KH, with 8 and 3 years of experience, respectively) independently segmented both SSFP and magnitude 4D flow images in a blinded fashion. LV and RV endocardial and epicardial borders were manually contoured by each radiologist to assess for end-diastolic (ED) and end-systolic (ES) volumes (EDV and ESV, respectively), stroke volume (SV), EF and ventricular mass (at both ED and ES), thus yielding two blinded measurements of ventricular volumes and EF, and four blinded

measurements of ventricular mass for each ventricle, by each radiologist, in each subject. The phase of ED and ES were defined visually by the observer, as the phase with the largest and smallest ventricular volumes, respectively. Trabeculations and papillary muscles were included as part of the ventricular blood pool (27).

4D flow analysis was performed using dedicated software for reformatting and viewing of volumetric datasets (Arterys, Arterys Inc, San Francisco, CA). After user specification of anatomic landmarks on magnitude 4D flow images (mitral valve, aortic valve, left ventricle apex, tricuspid valve, pulmonic valve and right ventricle apex), images were reformatted to 6–12 short-axis slices of each ventricle, dynamically tracking the excursion of the apex and its orientation relative to the inlet valve. The valve plane and apex were cross-referenced on long-axis views to prevent errors in edge slice segmentation. Short-axis views were then manually segmented and summed to estimate volumes and mass at ED and ES. To facilitate consistent identification of ED and ES phases, as well as to visualize flow, velocity vector magnitudes were color-coded and blended over the magnitude data (Fig. 1).

SSFP image analyses were also performed using dedicated commercially available software (QMassMR; Medis, Inc, Leiden, NL) with each study manually processed without knowledge of the results from 4D flow. The valve plane and apex were cross-referenced on vertical long-axis images to prevent errors in segmentation.

Statistical Methods

Statistical analysis was performed using SPSS software version 22 (IBM SPSS, Chicago, IL). Continuous variables were described using mean and standard deviation and categorical variables using frequency and percentage. To compare 4D flow against SSFP, several null hypotheses were tested statistically. First, volume, EF and mass measurements are significantly different between 4D flow and SSFP. Second, there are significant differences in consistency between 4D flow and SSFP estimates of ventricular mass comparing ED and ES measurements. Given the conservation of mass, ED and ES estimations of ventricular mass should be equal, thus serving as an internal control for assessment of measurement precision of the two techniques. Third, there are significant differences in inter-observer agreement between 4D flow and SSFP estimates of ventricular volume, EF and mass.

To identify differences in measurements between 4D flow and SSFP techniques, two-tailed paired Student t tests were used. The sample size was calculated to detect a difference in indexed LV mass measurements between techniques of 8 g/m² with a standard deviation of 12 g/m² using a paired t-test (28). To detect this difference with a power of 80% and alpha error of 0.05, a total of 20 subjects were needed. The agreement between any two measurements was evaluated using both Pearson correlation coefficient (r) and Bland-Altman analysis (as a percentage of the mean). Bland-Altman limits of agreement were calculated as percentage differences from the mean of 1.96 SDs. To evaluate the variance in 4D flow and SSFP estimates of ventricular mass, the mean square difference of ED and ES measurements was calculated for each technique. The difference between ED and ES measurements was assumed to be approximately normal with a mean of zero. An F test was then performed on this statistic. Inter-observer agreement was assessed via the intra-class

correlation coefficient (ICC). The ICC model used was two-way mixed and the type was absolute agreement. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

There was no difference in heart rate between 4D flow and SSFP acquisitions (92.0 ± 23.4 vs. 92.2 ± 23.7 bpm, $p=0.637$).

Comparison of Ventricular Volumes

EDVs, ESVs and SVs were well correlated between techniques for both LV ($r = 0.964$ – 0.972 , $p < 0.001$) and RV ($r = 0.808$ – 0.934 , $p < 0.001$), as shown in Table 2. No statistically significant difference was observed between 4D flow and SSFP measurements of LV volumes. RV measurements of EDV and ESV were significantly lower at 4D flow compared to SSFP ($p < 0.05$), with differences of 8.8 mL/m^2 (8.5% of the mean) and 4.8 mL/m^2 (6.4% of the mean), respectively. The mean difference in volumes between techniques was within 10% of zero for all measurements, and Bland-Altman relative limits of agreement were between -22% to 20% for the LV and -52% to 34% for the RV (Fig 2 A–F). For all measurements, the limits of agreement were wider for the RV compared to the LV.

Comparison of Ejection Fractions

Ejection fractions were well correlated between techniques for both LV ($r = 0.928$, $p < 0.001$) and RV ($r = 0.900$, $p < 0.001$). No statistically significant difference was observed between 4D flow and SSFP measurements of LVEF or RVEF. The mean difference in EFs between techniques was near zero, and Bland-Altman relative limits of agreement were -11% to 7% for the LV and -29% to 27% for the RV (Fig 2 G–H).

Comparison of Ventricular Mass

Ventricular mass measurements at both ED and ES were well correlated between techniques for both LV ($r = 0.910$ – 0.934 , $p < 0.001$) and RV ($r = 0.884$ – 0.918 , $p < 0.001$). No statistically significant difference was observed between 4D flow and SSFP measurements of LV and RV mass at both ED and ES. The mean difference in mass between techniques was near zero for all measurements, and Bland-Altman relative limits of agreement were between -23% to 26% for the LV and -41% to 48% for the RV (Fig 2 I–L). For all measurements, the limits of agreement were wider for the RV compared to the LV.

Mean bias between ED and ES mass measurements as a percentage of the mean for 4D flow and SSFP were $-1.4 \pm 8.9\%$ and $4.2 \pm 4.7\%$, respectively for the LV, and $1.7 \pm 8.1\%$ and $1.1 \pm 10.0\%$, respectively for the RV (Fig 3). There was no significant difference between 4D flow and SSFP with respect to mean square difference of ED-ES mass for the LV ($F=2.05$, $p=0.159$) or RV ($F=0.625$, $p=0.434$).

Inter-observer Agreement

Inter-observer agreement was moderate to high with both 4D flow and SSFP for the LV (ICC 0.605 – 0.993 and 0.801 – 0.982 , respectively) and RV (ICC 0.523 – 0.934 and 0.619 –

0.952, respectively), with overlapping confidence intervals (Table 3). For all measures, agreement was greater for the LV compared to the RV.

DISCUSSION

The results of this study demonstrate, for the first time to our knowledge, that 4D flow can be performed with sufficient resolution to allow assessment of left and right ventricular mass with precision and reproducibility comparable to that of cine SSFP. We also recapitulate results from earlier works showing that equivalent ventricular volume and function measurements can be obtained from 4D flow, but now with ferumoxytol enhancement.

The essential goals of many cardiac MRI exams include quantitative assessment of ventricular volumes, function and mass, in addition to evaluation of systemic and pulmonic flow rates (29). Given that 4D flow yields not only a temporally resolved velocity field allowing quantification of flow, but also concomitant magnitude images which may be used to extract ventricular volumes, function, and mass, this technique has the potential to fulfill all the essential goals of a cardiac MRI exam in a single free-breathing comprehensive 10–15 minute acquisition (9, 30).

Although short-axis stack cine SSFP MRI is the current clinical standard for ventricular volume and function quantification, acquisitions are often lengthy and even an experienced MRI technologist may require considerable oversight from a trained cardiovascular imager to acquire appropriate imaging planes, particularly in the setting of CHD. The volumetric nature of 4D flow acquisitions allows for separation of the processes of image acquisition and interpretation, which may improve clinical workflow and reduce total scan times compared with traditional multi-sequence approaches. The clinical utility of 4D flow MRI was previously limited by prohibitively long image acquisition times (13). However, with the implementation of under-sampling methods including parallel imaging and compressed sensing, near-isotropic images can now be acquired in a scan time practical for clinical practice (9). Recent advances in motion-compensation and compressed sensing may further improve the temporal resolution of 4D flow imaging (31). Under-sampling methods and nonlinear reconstruction approaches have also been applied to real-time, free-breathing and single-breath hold cine acquisitions with promising results (32–34). However, in the setting of CHD, flow information is often required in addition to assessment of ventricular volumes and function. Thus the benefit of the 4D flow analysis approach proposed in this study is that both phase contrast and magnitude data are acquired concurrently, allowing for evaluation of both flow and function with a single comprehensive acquisition.

Cardiac MRI assessment of ventricular size, function and mass has been shown to inform clinical decisions in many types of CHD (35, 36). Accurate and reproducible assessment of ventricular volume, function and mass is especially important in conditions in which the ventricle is subject to chronic volume or pressure overload (19, 37). Furthermore, RV mass has been shown to correlate with functional health status and exercise capacity in the setting of repaired TOF (38, 39), highlighting the importance of this measure with respect to both patient perception and clinical decision-making.

We have confirmed the results of previous work demonstrating that ventricular volume and EF measurements are highly correlated between 4D flow and cine SSFP acquisitions (9). In our study, ventricular volume and EF measurements did not differ significantly between the two techniques with the exception of RV EDV and ESV. RV EDV and ESV were underestimated by 4D flow compared to SSFP, possibly attributable to differences in basal slice selection. We also demonstrated that there is no significant difference in LV or RV mass quantification with 4D flow compared to SSFP acquisitions. However, Bland Altman limits of agreement were relatively wide for all measurements, particularly for the RV, although similar to prior published values (9).

Second, we demonstrated equal internal consistency between 4D flow and SSFP estimates of ventricular mass comparing ED and ES measurements as an internal control. Due to conservation of mass, ED and ES mass measurements should be equal. Previously, both LV and RV mass measurements by cardiac MRI have been shown to accurately reflect actual ventricular weight on autopsy (40, 41). We did not have pathologic specimens or a reference standard in this study, and thus it was not clear which imaging method was truly more accurate.

Finally, we demonstrated moderate to high inter-observer agreement of 4D flow and SSFP estimates of ventricular volume, EF and mass, with no significant differences in agreement between techniques. Similar to prior studies using cine SSFP, we confirmed that for all measurements, the limits of agreement are wider for the RV compared to the LV (18, 42–44). Because of its complex geometry, accurate and reliable quantification of RV volume can be challenging, particularly in the setting of abnormal RV anatomy in patients with CHD (45). Values for inter-observer agreement of LV volumes and mass in our study (ICC 0.957–0.993) are similar to previously reported values (ICC 0.94–0.99) (18). However, the values we report for RV volumes and mass (ICC 0.742–0.934) are slightly lower than previous reports (18, 45), possibly due to the fact that patients included in our study had a range of underlying CHD, with varying and complex anatomy. Similar to prior reports, greater inter-observer variability was noted for EF measurements (ICC 0.525–0.605), which may be explained by the fact that error in two independent volume measurements may be increased by dividing them (18). Results from an earlier study suggested that assessment of ventricular mass in systole may improve reproducibility over diastole (17). However, we did not find a significant difference in precision or inter-observer agreement between ES and ED estimates of ventricular mass, consistent with findings from a more recent study (39).

Several earlier reports have suggested that axial measurements of RV volumes may be more reproducible than those obtained in short-axis orientation (46–48). Given the volumetric nature of 4D flow imaging, data may be segmented in virtually any orientation following acquisition, potentially facilitating assessment of different analysis orientations and methods retrospectively without the need to acquire separate data sets. The effect of different analysis methods on the quantification of RV parameters with 4D flow data sets remains to be tested.

This study is primarily limited by the relatively small number of subjects included. The subjects included in this study were heterogenous, including both pre- and post-operative patients, and differing forms of CHD. In addition, we did not assess intra-observer or inter-

study reproducibility. Cine SSFP imaging was performed using breath-holding in those patients who were able, and free-breathing in others, potentially confounding comparison of results. Unfortunately, respiratory navigation was not an available option on our scanner. Prior reports indicate good agreement between cardiac volumes acquired during free breathing and with breath hold commands (49).

All imaging was obtained following administration of ferumoxytol, likely resulting in improved blood-to-myocardium contrast and wall delineation (11). This is an off-label use of the agent, which is FDA approved for iron replacement therapy (24). In our institution, ferumoxytol has been used for over three years as part of our routine clinical practice, largely because it provides reliable high diagnostic image quality while reducing the depth, duration, and frequency of anesthesia. However, this agent must be used with caution, as it may produce significant hypotension, as well as serious hypersensitivity reactions (50). The FDA has recently issued a revised box warning emphasizing that serious, potentially fatal allergic reactions have occurred in patients treated with ferumoxytol (51). A prior study investigating potential differences in the assessment of LV parameters with cine SSFP found no significant difference between pre- and post-contrast acquisitions using gadolinium based contrast (52). However, it remains to be tested whether non-ferumoxytol enhanced 4D flow acquisitions would provide the same results as in the current study.

In conclusion, the results of this study demonstrate that ferumoxytol-enhanced 4D flow MRI determines cardiac ventricular volume, function and mass with comparable precision and inter-observer reproducibility relative to cine SSFP. 4D flow MRI enables rapid comprehensive imaging evaluation of patients with CHD in a single acquisition, potentially improving clinical workflow and reducing anesthesia-related costs due to shortened data acquisition times compared with traditional multi-sequence approaches. Further studies should assess inter-study reproducibility of measurements obtained with 4D flow imaging, which is particularly important in the setting of CHD, as patients may undergo repeated imaging and reliable comparison of measurements between studies is required.

Acknowledgments

None.

Grant support: None.

References

1. Sechtem U, Pflugfelder PW, Gould RG, Cassidy MM, Higgins CB. Measurement of right and left ventricular volumes in healthy individuals with cine MR imaging. *Radiology*. 1987; 163:697–702. [PubMed: 3575717]
2. Farber NJ, Reddy ST, Doyle M, Rayarao G, Thompson DV, Olson P, Glass J, Williams RB, Yamrozik JA, Murali S, Biederman RWW. Ex vivo cardiovascular magnetic resonance measurements of right and left ventricular mass compared with direct mass measurement in excised hearts after transplantation: a first human SSFP comparison. *J Cardiovasc Magn Reson*. 2014; 16:74. [PubMed: 25315015]
3. Moon JCC, Lorenz CH, Francis JM, Smith GC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. *Radiology*. 2002; 223:789–797. [PubMed: 12034951]

4. Koch JA, Poll LW, Godehardt E, Korbmacher B, Jung G, Modder U. In vitro determination of cardiac ventricular volumes using MRI at 1.0 T in a porcine heart model. *Int J Cardiovasc Imaging*. 2001; 17:237–242. [PubMed: 11587458]
5. Koch JA, Poll LW, Godehardt E, Korbmacher B, Modder U. Right and left ventricular volume measurements in an animal heart model in vitro: first experiences with cardiac MRI at 1.0 T. *Eur Radiol*. 2000; 10:455–458. [PubMed: 10756995]
6. Carr JC, Simonetti O, Bundy J, Li D, Pereles S, Finn JP. Cine MR angiography of the heart with segmented true fast imaging with steady-state precession. *Radiology*. 2001; 219:828–834. [PubMed: 11376278]
7. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *Eur Heart J*. 2006; 27:2879–2888. [PubMed: 17088316]
8. Serafini G, Zadra N. Anaesthesia for MRI in the paediatric patient. *Curr Opin Anaesthesiol*. 2008; 21:499–503. [PubMed: 18660661]
9. Hsiao A, Lustig M, Alley MT, Murphy M, Chan FP, Herfkens RJ, Vasanawala SS. Rapid pediatric cardiac assessment of flow and ventricular volume with compressed sensing parallel imaging volumetric cine phase-contrast MRI. *AJR Am J Roentgenol*. 2012; 198:W250–W259. [PubMed: 22358022]
10. Markl M, Chan FP, Alley MT, Wedding KL, Pelc NJ. Time-resolved three-dimensional phase-contrast MRI. *J Magn Reson Imaging*. 2003; 17:499–506. [PubMed: 12655592]
11. Bock J, Frydrychowicz A, Stalder AF, Bley TA, Burkhardt H, Henning J, Markl M. 4D phase contrast MRI at 3 T: Effect of standard and blood-pool contrast agents on SNR, PC-MRA, and blood flow visualization. *Magn Reson Med*. 2010; 63:330–338. [PubMed: 20024953]
12. Calkoen EE, Roest AAW, van der Geest RJ, de Roos A, Westenberg JJM. Cardiovascular function and flow by 4-dimensional magnetic resonance imaging techniques: new applications. *Journal of Thoracic Imaging*. 2014; 29:185–196. [PubMed: 24576838]
13. Hanneman K, Sivagnanam M, Nguyen ET, Greiser A, Crean AM, Ley S, Wintersperger BJ. Magnetic resonance assessment of pulmonary (QP) to systemic (QS) flows using 4D phase-contrast imaging: pilot study comparison with standard through-plane 2D phase-contrast imaging. *Acad Radiol*. 2014; 21:1002–1008. [PubMed: 25018072]
14. Hsiao A, Lustig M, Alley MT, Murphy MJ, Vasanawala SS. Evaluation of Valvular Insufficiency and Shunts with Parallel-imaging Compressed-sensing 4D Phase-contrast MR Imaging with Stereoscopic 3D Velocity-fusion Volume-rendered Visualization. *Radiology*. 2012; 265:87–95. [PubMed: 22923717]
15. Frydrychowicz A, Wieben O, Niespodzany E, Reeder SB, Johnson KM, François CJ. Quantification of thoracic blood flow using volumetric magnetic resonance imaging with radial velocity encoding: in vivo validation. *Invest Radiol*. 2013; 48:819–825. [PubMed: 23857136]
16. Duncan BW, Mee RBB, Mesia CI, Rosenthal GL, Seshadri SG, Lane GK, Latson LA. Results of the double switch operation for congenitally corrected transposition of the great arteries. *Eur J Cardiothorac Surg*. 2003; 24:11–20. [PubMed: 12853040]
17. Blalock SE, Banka P, Geva T, Powell AJ, Zhou J, Prakash A. Interstudy variability in cardiac magnetic resonance imaging measurements of ventricular volume, mass, and ejection fraction in repaired tetralogy of Fallot: a prospective observational study. *J Magn Reson Imaging*. 2013; 38:829–835. [PubMed: 23418153]
18. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. *J Magn Reson Imaging*. 2008; 28:67–73. [PubMed: 18581357]
19. Grotenhuis HB, Kroft LJM, van Elderen SGC, Westenberg JJ, Doornbos J, Hazekamp MG, Vliegen HW, Ottenkamp J, de Roos A. Right ventricular hypertrophy and diastolic dysfunction in arterial switch patients without pulmonary artery stenosis. *Heart*. 2007; 93:1604–1608. [PubMed: 17277348]
20. Bernstein MA, Shimakawa A, Pelc NJ. Minimizing TE in moment-nulled or flow-encoded two- and three-dimensional gradient-echo imaging. *J Magn Reson Imaging*. 1992; 2:583–588. [PubMed: 1392252]

21. Pelc NJ, Bernstein MA, Shimakawa A, Glover GH. Encoding strategies for three-direction phase-contrast MR imaging of flow. *J Magn Reson Imaging*. 1991; 1:405–413. [PubMed: 1790362]
22. Uecker M, Lai P, Murphy MJ, Virtue P, Elad M, Pauly JM, Vasanawala SS, Lustig M. ESPIRiT-an eigenvalue approach to autocalibrating parallel MRI: Where SENSE meets GRAPPA. *Magn Reson Med*. 2014; 71:990–1001. [PubMed: 23649942]
23. Han F, Rapacchi S, Khan S, Ayad I, Sausky I, Gabriel S, Plotnik A, Finn JP, Hu P. Four-dimensional, multiphase, steady-state imaging with contrast enhancement (MUSIC) in the heart: A feasibility study in children. *Magn Reson Med*. 2015; 74:1042–1049. [PubMed: 25302932]
24. Ruangwattanapaisarn N, Hsiao A, Vasanawala SS. Ferumoxytol as an off-label contrast agent in body 3T MR angiography: a pilot study in children. *Pediatr Radiol*. 2015; 45:831–839. [PubMed: 25427433]
25. Li W, Tutton S, Vu AT, Pierchala L, Li BS, Lewis JM, Prasad PV, Edelman RR. First-pass contrast-enhanced magnetic resonance angiography in humans using ferumoxytol, a novel ultrasmall superparamagnetic iron oxide (USPIO)-based blood pool agent. *J Magn Reson Imaging*. 2005; 21:46–52. [PubMed: 15611942]
26. Fratz S, Chung T, Greil GE, Samyn MM, Taylor AM, Valsangiacomo Buechel ER, Yoo SJ, Powell AJ. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. *Journal of Cardiovascular Magnetic Resonance*. 2013; 15:51. [PubMed: 23763839]
27. Papavassiliu T, Kuhl HP, Schroder M, Suselbeck T, Bondarenko O, Bohm CK, Beek A, Hofman MM, van Rossum AC. Effect of endocardial trabeculae on left ventricular measurements and measurement reproducibility at cardiovascular MR imaging. *Radiology*. 2005; 236:57–64. [PubMed: 15955850]
28. Sarikouch S, Peters B, Gutberlet M, Leismann B, Kelter-Kloepping A, Koerperich H, Kuehne T, Beerbaum P. Sex-Specific Pediatric Percentiles for Ventricular Size and Mass as Reference Values for Cardiac MRI: Assessment by Steady-State Free-Precession and Phase-Contrast MRI Flow. *Circulation: Cardiovascular Imaging*. 2010; 3:65–76. [PubMed: 19820203]
29. Ntsinjana HN, Hughes ML, Taylor AM. The Role of Cardiovascular Magnetic Resonance in Pediatric Congenital Heart Disease. *J Cardiovasc Magn Reson*. 2011; 13:51. [PubMed: 21936913]
30. Cheng, JY.; Hanneman, Kate; Zhang, T.; Alley, MT.; Lai, P.; Tamir, JI.; Uecker, M.; Lustig, M.; Pauly, JM.; Vasanawala, SS. Impact of View Ordering Soft-Gating on Morphologic Assessment of Congenital Heart Disease with 4D Flow. *International Society of Magnetic Resonance in Medicine (ISMRM) 23rd Annual Meeting Abstract* (4548); 2015.
31. Cheng JY, Hanneman K, Zhang T, Alley MT, Lai P, Tamir JI, Uecker M, Pauly JM, Lustig M, Vasanawala SS. Comprehensive motion-compensated highly accelerated 4D flow MRI with ferumoxytol enhancement for pediatric congenital heart disease. *J Magn Reson Imaging*. 2015; in press. doi: 10.1002/jmri.25106
32. Vincenti G, Monney P, Chaptinel J, Rutz T, Coppo S, Zenge MO, Schmidt M, Nadar MS, Piccini D, Chevre P, Stuber M, Schwitzer J. Compressed sensing single-breath-hold CMR for fast quantification of LV function, volumes, and mass. *JACC Cardiovascular imaging*. 2014; 7(9):882–892. [PubMed: 25129517]
33. Liang D, DiBella EVR, Chen RR, Ying L. k-t ISD: Dynamic cardiac MR imaging using compressed sensing with iterative support detection. *Magnetic Resonance Med*. 2012; 68:41–53.
34. Xue H, Kellman P, LaRocca Gina, Arai AE, Hansen MS. High spatial and temporal resolution retrospective cine cardiovascular magnetic resonance from shortened free breathing real-time acquisitions. *Journal of Cardiovascular Magnetic Resonance*. 2013; 15:102. [PubMed: 24228930]
35. Warnes CA, Williams RG, Bashore TM, Bashore TM, Child JS, Connolly HM, Dearani JA, Del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2008; 118:2395–2451. [PubMed: 18997168]
36. Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE, del Nido PJ, Geva T. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. *Heart*. 2008; 94:211–216. [PubMed: 17135219]

37. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, Smith GC, Tat T, Pennell DJ, Gatzoulis MA. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. *J Am Coll Cardiol.* 2002; 40:2044–2052. [PubMed: 12475468]
38. O’Meagher S, Seneviratne M, Skilton MR, Munoz PA, Robinson PJ, Malitz N, Tanous DJ, Celermajer DS, Puranik R. Right Ventricular Mass is Associated with Exercise Capacity in Adults with Repaired Tetralogy of Fallot. *Pediatr Cardiol.* 2015; 36:1225–31. [PubMed: 25795311]
39. Lu JC, Christensen JT, Yu S, Donohue JE, Ghadimi Mahani M, Agarwal PP, Dorfman AL. Relation of right ventricular mass and volume to functional health status in repaired tetralogy of Fallot. *Am J Cardiol.* 2014; 114:1896–1901. [PubMed: 25438919]
40. Beygui F, Furber A, Delepine S, Helft G, Metzger JP, Geslin P, Le Jeune JJ. Routine breath-hold gradient echo MRI-derived right ventricular mass, volumes and function: accuracy, reproducibility and coherence study. *Int J Cardiovasc Imaging.* 2004; 20:509–516. [PubMed: 15856634]
41. Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, Peshock RM. Estimation of human myocardial mass with MR imaging. *Radiology.* 1988; 169:495–498. [PubMed: 2971985]
42. Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJM, Helbing WA. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging. *Int J Cardiovasc Imaging.* 2010; 26:57–64. [PubMed: 19757150]
43. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *American Heart Journal.* 2004; 147:218–223. [PubMed: 14760316]
44. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. *J Cardiovasc Magn Reson.* 2005; 7:775–782. [PubMed: 16353438]
45. Saskia EL, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJ, Helbing WA. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging. *Int J Cardiovasc Imaging.* 2010; 26:57–64. [PubMed: 19757150]
46. Clarke CJ, Gurka MJ, Norton PT, Kramer CM, Hoyer AW. Assessment of the accuracy and reproducibility of RV volume measurements by CMR in congenital heart disease. *JACC Cardiovasc Imaging.* 2012; 5:28–37. [PubMed: 22239890]
47. Fratz S, Schuhbaeck A, Buchner C, Busch R, Meierhofer C, Martinoff S, Hess J, Stern H. Comparison of accuracy of axial slices versus short-axis slices for measuring ventricular volumes by cardiac magnetic resonance in patients with corrected tetralogy of fallot. *Am J Cardiol.* 2009; 103:1764–1769. [PubMed: 19539090]
48. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. *J Magn Reson Imaging.* 2003; 18:25–32. [PubMed: 12815636]
49. Kharabish A, Mkrtchyan N, Meierhofer C, Martinoff S, Ewert P, Heiko S, Fratz S. Cardiac volumes can be quantified accurately during free-breathing in young patients with congenital heart disease by cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance.* 2014; 16:P124.
50. Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm.* 2012; 69:310–320. [PubMed: 22302256]
51. Rubin R. Black box warning for anemia drug. *JAMA.* 2015; 313:1704.
52. Rofe CJ, Fletcher AM, Murday DC, Harden SP, Peebles CR, Shambrook JS. Cardiac magnetic resonance left ventricular quantitative analysis post gadolinium: reliable and reproducible? *Journal of Cardiovascular Magnetic Resonance BioMed Central.* 2011; 13:P35–P35.

Fig. 1. 9-year-old male with aortic coarctation. Screen captures of multiple short-axis 4D flow images demonstrating LV and RV endocardial (upper row) and epicardial (lower row) end-diastolic contours, with color velocity overlay to facilitate identification of the myocardial blood boundary. Left: LV contours; Right: RV contours.

Fig. 2.

Bland–Altman plots of the mean difference for left ventricular (LV) and right ventricular (RV) end-diastolic (ED) and end-systolic (ES) volumes, stroke volume, ejection fraction (EF), and mass between 4D flow and SSFP. For each parameter the average of measurements from both techniques is plotted on the x-axis and the percent difference between techniques is plotted on the y-axis. The solid gray horizontal line plots the mean percent difference and the dotted gray lines indicated the limits of agreement (differences from the mean of 1.96 SDs) for each parameter. **A**, LV EDV; **B** RV EDV; **C**, LV ESV; **D**, RV

ESV; **E**, LV SV; **F** RV SV; **G**, LVEF; **H**, RVEF; **I**, ED LV Mass; **J**, ED RV Mass; **K**, ES LV Mass; **L**, ES RV Mass.

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Fig. 3.

Bland–Altman plots of the mean difference between end-diastolic (ED) and end-systolic (ES) ventricular mass measurements for both 4D flow and cine SSFP. The average of ED and ES measurements is plotted on the x-axis and the percent difference between measurements is plotted on the y-axis. The solid gray horizontal line plots the mean percent difference for 4D flow measurements, and the solid black horizontal line plots the mean percent difference for cine SSFP measurements. The dotted gray lines indicated the limits of agreement (differences from the mean of 1.96 SDs) for 4D flow, and the dashed black lines indicated the limits of agreement for SSFP. **A**, LV mass; **B**, RV mass.

Table 1

Patient Demographics

	Patients (n=22)
Age (years)	6.4±4.8
Sex (male) *	45.5% (n=10)
Height (cm)	112.6±26.1
Weight (kg)	23.2±12.6
BSA (m ²)	0.83±0.31
Congenital heart disease *	
Tetralogy of Fallot, corrected	36.4% (n=8)
Congenitally corrected TGA	13.6% (n=3)
Coarctation of the aorta	13.6% (n=3)
Atrioventricular canal defect	9.1% (n=2)
Ventricular septal defect	9.1% (n=2)
Hypoplastic right ventricle	4.5% (n=1)
Bicuspid aortic valve	4.5% (n=1)
Other	9.1% (n=2)

Except where indicated, data are mean ± standard deviation.

* Data are percentage of patients, with number in parentheses.

BSA = body surface area; TGA = Transposition of the great arteries.

Table 2

Comparisons between ventricular volume, ejection fraction and mass measurements.

	Paired t-test		Correlation	
	4D flow	SSFP	p-value	r-value
Left ventricle				
LV EDV (mL/m ²)	71.4±23.1	72.5±23.9	0.365	0.972
LV ESV (mL/m ²)	31.8±9.5	31.6±10.3	0.738	0.971
LV SV (mL/m ²)	39.6±15.0	40.9±15.3	0.156	0.964
LV EF (%)	54.8±6.1	55.9±6.9	0.058	0.928
LV mass ED (g/m ²)	40.2±11.3	40.9±11.1	0.479	0.910
LV mass ES (g/m ²)	41.0±11.7	39.2±10.5	0.05	0.934
Right ventricle				
RV EDV (mL/m ²)	99.8±22.9	108.6±24.3	0.011	0.808
RV ESV (mL/m ²)	57.4±19.6	62.2±23.0	0.026	0.916
RV SV (mL/m ²)	42.4±13.1	46.4±13.0	0.087	0.683
RV EF (%)	43.3±12.2	44.1±13.6	0.501	0.900
RV mass ED (g/m ²)	21.5±8.9	21.3±10.5	0.872	0.884
RV mass ES (g/m ²)	21.2±9.3	21.4±11.7	0.819	0.918

Values are indexed to body surface area other than ejection fractions. Data are mean ± standard deviation.

LV = left ventricle; RV = right ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; ED = end-diastole; ES = end-systole.

Table 3

Inter-observer agreement

	4D flow	SSFP
Left ventricle		
LV EDV	0.993 (0.984, 0.997)	0.982 (0.957, 0.992)
LV ESV	0.957 (0.899, 0.982)	0.974 (0.938, 0.989)
LV SV	0.957 (0.899, 0.982)	0.970 (0.930, 0.988)
LV EF	0.605 (0.049, 0.836)	0.801 (0.580, 0.912)
LV mass ED	0.948 (0.880, 0.978)	0.960 (0.906, 0.983)
LV mass ES	0.936 (0.851, 0.973)	0.953 (0.890, 0.980)
Right ventricle		
RV EDV	0.934 (0.847, 0.972)	0.952 (0.885, 0.980)
RV ESV	0.800 (0.579, 0.912)	0.910 (0.796, 0.962)
RV SV	0.742 (0.474, 0.884)	0.848 (0.668, 0.934)
RV EF	0.523 (0.140, 0.770)	0.619 (0.276, 0.822)
RV mass ED	0.746 (0.481, 0.886)	0.629 (0.291, 0.827)
RV mass ES	0.883 (0.739, 0.950)	0.658 (0.337, 0.842)

Values are intra-class correlation coefficient (ICC) with 95% confidence intervals in parentheses.

LV = left ventricle; RV = right ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; ED = end-diastole; ES = end-systole.