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7 Tesla (T) human cardiovascular magnetic resonance imaging using FLASH and SSFP to assess cardiac function: validation against 1.5 T and 3 T

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Abstract

We report the first comparison of cardiovascular magnetic resonance imaging (CMR) at 1.5 T, 3 T and 7 T field strengths using steady state free precession (SSFP) and fast low angle shot (FLASH) cine sequences. Cardiac volumes and mass measurements were assessed for feasibility, reproducibility and validity at each given field strength using FLASH and SSFP sequences. Ten healthy volunteers underwent retrospectively electrocardiogram (ECG) gated CMR at 1.5 T, 3 T and 7 T using FLASH and SSFP sequences. B1 and B0 shimming and frequency scouts were used to optimise image quality. Cardiac volume and mass measurements were not significantly affected by field strength when using the same imaging sequence ($P > 0.05$ for all parameters at 1.5 T, 3 T and 7 T). SSFP imaging returned larger end diastolic and end systolic volumes and smaller left ventricular masses than FLASH imaging at 7 T, and at the lower field strengths ($P < 0.05$ for each parameter). However, univariate general linear model analysis with fixed effects for sequence and field strengths found an interaction between imaging sequence and field strength ($P = 0.03$), with a smaller difference in volumes and mass measurements between SSFP and FLASH imaging at 7 T than 1.5 T and 3 T. SSFP and FLASH cine imaging at 7 T is technically feasible and provides valid assessment of cardiac volumes and mass compared with CMR imaging at 1.5 T and 3 T field strengths.

Keywords

7 Tesla; high field strength; cardiovascular magnetic resonance imaging; cardiac function; clinical validation

INTRODUCTION

Cardiovascular magnetic resonance imaging (CMR) is the gold standard modality for the assessment of cardiac anatomy and function because of its high spatial resolution, true 3D capability and lack of radiation (1,2). However, CMR provides information on many other aspects of cardiac physiology, such as perfusion, coronary lumen and wall, tissue oxygenation (BOLD), and cardiac metabolism (spectroscopy) (1,2). These advanced CMR techniques are currently suboptimal at field strengths of 1.5 T, and even at 3 T, due to an insufficient signal to noise ratio (SNR) (2–4). Since SNR is approximately proportional to field strength (5), development of CMR at the ultrahigh[†] field strength of 7 T offers the potential for robust imaging of these more complex parameters of cardiac physiology. With the increasing number of 7 T systems currently being installed at clinical research centres worldwide, and some progress being made to address the complex problem of imaging the human torso at ultra high field strengths (6,7), it is anticipated that coming years will see a major development effort in ultrahigh field CMR imaging and spectroscopy. However, interpretation of more complex parameters such as oxygenation levels or metabolism will always require parallel assessment of cardiac anatomy and function. Therefore, the first step in the development of CMR at 7 T is to establish these methods already proven at 1.5 and 3 T. Our group has reported on the technical feasibility of CMR at 7 T, in particular using mapping techniques to address the previously limiting off resonance banding artefacts and signal loss from B0 and B1 field heterogeneity that is more prominent at higher field strengths (8,9). Given that this technology is now available, the important next step is to directly validate data for cardiac function obtained with (cine) imaging sequences at 7 T against the established measurements obtained at the “conventional” field strengths of 1.5 and 3 T (7,10).

Furthermore, assessment of cardiac volumes and function is affected by the type of sequence used. At 1.5 T and 3 T, it has been consistently observed that fast low angle shot (FLASH) imaging understates volumes and overstates cardiac mass compared to steady state free precession (SSFP) imaging (11,12). One reported explanation for this finding is that FLASH imaging is inferior to SSFP at delineating epicardial fat and fails to accurately delineate the endomyocardial border in trabeculated regions of the ventricle (12). This poor border definition may be attributable to the inferior myocardial to blood contrast-to-noise ratio (CNR) and SNR, properties that would improve at higher field strengths. Thus, a second goal of this study was to systematically compare quantitative measurements of cardiac volumes and function obtained by SSFP and FLASH sequences at 7 T vs. 1.5 T and 3 T field strengths.

EXPERIMENTAL

Study population

Ten healthy volunteers (8 males and 2 females; mean age 39 ± 11 yrs, range 24 to 60 yrs, mean height 1.78 ± 0.06 m, mean weight 78 ± 13 kg, mean heart rate 1.5 T: 65 ± 11 bpm; 3 T: 65 ± 10 bpm, 7 T: 64 ± 11 bpm) were carefully screened for contraindications to CMR. Entry and exit interviews were performed for each scan. Subjects were asked whether they noticed anything unusual; and specifically questioned as to whether they felt unusual tastes, nausea, dizziness, pins and needles or change in temperature. Specific absorption rate (SAR) limits at all field strengths were within Food and Drug Administration (FDA; USA) guideline limits. The study was undertaken according to the Declaration of Helsinki with the

[†]The frequency range 300 MHz to 3 GHz is defined as Ultrahigh frequency (UHF) (see http://en.wikipedia.org/wiki/Ultra_high_frequency). The hydrogen resonance frequency at 7 T is 300 MHz i.e. in UHF band. Therefore, 7 T to 70 T is defined as Ultrahigh Field (UHF).

approval of the institutional ethics committee and the University of Minnesota Institutional Review Board. Each subject gave written informed consent.

CMR protocol

Each subject was scanned using the same SSFP and FLASH sequences and parameters optimised within SAR limitations. CMR examinations were performed on horizontal 7 T MAGNETOM, 3 T Tim Trio and 1.5 T Avanto MR systems (all Siemens Healthcare, Erlangen Germany) equipped with VB15A software and equivalent gradient systems. At 7 T, a 16-channel transceive stripline array (13) driven by independent phase and gain controlled RF amplifiers (14) (16×1kW) (Communication Power Corporation (CPC), Hauppauge, New York), was tuned and matched to each subject (7). At 1.5 T and 3 T, standard clinical 12-channel receiver coils were used (Siemens Healthcare, Erlangen Germany). At 7 T, complex transmit B1 field distributions were optimized over the heart with B1 shimming for a trade-off between transmit efficiency and homogeneity based on a rapid single breath-hold calibration scan (9). Furthermore, at 7 T only, breath hold B0 shimming was performed with the three dimensional shim volume localized to the whole heart using prototype Siemens software obtained under a research agreement. To further optimize image quality, a frequency scout scan was performed to enable use of a B0 offset to optimise the transmit frequency. On each scanner, long axis and a stack of short axis images covering the entire left ventricle were acquired using both FLASH and SSFP sequences in the standard way (15).

The SSFP frequency scout was acquired using the following parameters: field of view (FOV) = 350 × 292 mm; 7 mm slice thickness; single-shot acquisition per heart beat; trigger delay 350 ms, TR = 2.9 ms, TE = 1.2 ms; generalised autocalibrating partially parallel acquisitions (GRAPPA) with 2 times acceleration (1.5 T, 3 T and three of ten subjects at 7 T), nominal flip angle 56 degrees, 930 Hz/pixel bandwidth with frequency offsets from -300 to 300 Hz in 50 Hz steps, and single breath hold acquisition. SSFP short axis cine images were acquired with the following parameters: FOV = 360 × 304 mm; slice thickness = 7 mm; slice interval = 3 mm; 1.9 × 1.9 mm resolution; matrix size 192×162; GRAPPA with 2 × acceleration (1.5 T, 3 T and three of ten subjects at 7 T); 44 reference lines (yielding a net acceleration of 1.30); sampled temporal resolution 41.7 ms (1.5 T), 44.2 ms (3 T), 39 ms (7 T); TR = 2.9 ms, TE = 1.2 ms, 930 Hz/pixel bandwidth; single breath hold acquisition (average duration 11 s with GRAPPA, 15 seconds without GRAPPA); and nominal flip angle 56 degrees (1.5 and 3 T) and 48 degrees (7 T) optimised within SAR limitations. FLASH short axis cine images were acquired with the same parameters as the SSFP sequence except for TR = 6.7 ms, TE = 3.1 ms, sampled temporal resolution 46.8 ms, 250 Hz/pixel bandwidth, and nominal flip angle of 15 degrees.

ECG gating

Retrospective ECG gating was obtained using the standard 3-lead wireless vector cardiogram (VCG) system (Siemens Healthcare, Erlangen, Germany) (16). Subjects' skin was shaved and carefully prepared with NuPrep gel (Weaver and Company, Aurora, CO, USA) to minimise impedance. At all field strengths, an experienced cardiologist placed three ECG dots in the same "standard position" over the sternal angle, base of the sternum and apex (Figure 1). An experienced cardiologist qualitatively assessed the resting ECG trace for at least fifteen seconds. If artefacts prevented adequate triggering, leads were moved to a more lateral "alternative position" in the left pre-pectoral, apex and at the mid-axillary line at the level of the apex. ECG leads were placed on the patient while the bed was completely outside the magnet. The VCG learning phase was performed with the bed fully retracted from the magnet, and the end of this phase was manually controlled. In the 7 T case where the normal mechanism for initiating and terminating the learning phase is absent,

this was controlled manually. At 1.5 T and 3 T this process is controlled by table position. ECGs were qualitatively assessed at each of the field strengths by two experienced operators for triggering and artefacts.

Image analysis

Image analysis was performed by experienced investigators (cardiologists) using Argus post-processing software (Version 25A, Siemens Healthcare, Erlangen, Germany). Experienced investigators blinded to subject identity traced endocardial and epicardial borders at end-diastole and endocardial borders only at end-systole in each short axis slice. Due to the inevitable clues in the images, it was not possible to blind investigators to sequence type or field strength. The basal slice was defined as the short axis slice in which at least 50% of the blood volume was surrounded by myocardium. The apical slice was defined as the final slice showing blood pool in the ventricular cavity. Papillary muscles were included in the mass and excluded from the volume calculations. The interventricular septum was included as part of the left ventricle. End-diastolic and end-systolic volumes, ejection fraction, stroke volume and mass were calculated ($\text{tissue volume} \times 1.05 \text{ g/cm}^3$).

Reproducibility

To determine interstudy reproducibility, all scans at 7 T were performed twice on each subject, with the patient being removed completely from the scanner between each scan. One observer analysed all images twice with a one week gap to assess intraobserver variability. Images were analysed twice by two blinded investigators to assess interobserver variability.

Statistical analysis

The sample size ($n = 10$) for normal volunteers was calculated from the standard deviation (SD) of our database of normal values to achieve at least 80% power of detecting a clinically significant difference of 10% in the left ventricular ejection fraction (LVEF) (15). Data are presented as mean $\pm$ SD unless stated otherwise. A univariate general linear model with fixed effects for sequence (SSFP and FLASH) and field strength (1.5 T, 3 T and 7 T) was used to test whether differences between sequences were related to field strength. Throughout the analyses a p -value of <0.05 was considered statistically significant in two-sided comparisons. Interstudy, interobserver and intraobserver variability were assessed using Bland Altman plots (17). Coefficient of variability (COV) was calculated as the SD of the differences between the two sets of measurements divided by the mean. All computations were performed using SPSS 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Subject experience

Exit interviews were performed on all subjects at each of the field strengths. Subjects were asked to describe any symptoms that they felt at the time of scanning. At 7 T, one subject experienced mild dizziness and 4 subjects reported a metallic taste in their mouths. One subject reported warmth and noticed redness of his skin at the left pre-pectoral area after scanning at 7 T. Two subjects reported mild peripheral nerve stimulation in their thigh at all field strengths, but this was more prominent at lower rather than higher field strengths.

Scan times were significantly longer at 7 T, while the 1.5 T and 3 T scan times were comparable (average scan time 7 T: 1 hr 33 min; at 3 T: 29 min; at 1.5 T: 28 min). Specific additional technical steps 7 T that increased scan times were coil tuning and matching (48 min) and shimming (9 min).

ECG triggering

Effective ECG triggering was obtained in all subjects with careful skin preparation and lead positioning. R wave distortion was present in 2 subjects at 1.5 T, 3 subjects at 3 T, and 6 subjects at 7 T (Table 1). At the 7 T field strength, mistriggering (R-wave that does not trigger, or trigger from something other than an R-wave) occurred in 3 subjects in the standard position; however, adequate triggering was obtained in these subjects after repositioning leads in the alternative position. As expected, the magnetohydrodynamic effect in the ST segment was more pronounced at 7 T than lower field strengths (Figure 2).

Cardiac volumes and mass

The blinded investigators judged that all datasets were of sufficient quality for analysis. At 7 T, B1 and B0 shimming improved image quality in all subjects. B1 significantly improved image homogeneity and B0 shimming significantly reduced off resonance banding artefacts. A typical example is shown in Figure 3. Typical horizontal long axis images at 1.5 T, 3 T and 7 T for FLASH and SSFP sequences are shown in Figure 4. There were no significant differences between the left ventricular end diastolic volume (LVEDV), end systolic volume (LVESV), ejection fraction, and mass at 1.5 T, 3 T and 7 T using SSFP and FLASH, respectively ($p > 0.05$ for all parameters, Table 2). However, there were significant differences between FLASH and SSFP at each given field strength. LVEDV acquired using SSFP was significantly larger than FLASH (by 24 mL at 1.5 T; 14 mL at 3 T; 11 mL at 7 T; $p < 0.001$). LVESV acquired using SSFP were also significantly larger than FLASH (by 11 mL at 1.5 T 10 mL at 3 T; and 5 mL at 7 T; $p = 0.03$). LV mass was significantly smaller using SSFP than FLASH (by 41 g at 1.5 T; 34 g at 3 T; and 8 g at 7 T; $p < 0.001$). Although there was no significant difference between field strengths for each given sequence, there was a significant interaction between sequence and field strength (LVEDV interaction $p = 0.03$; LVESV interaction $p = 0.03$; LV mass $p = 0.006$), suggesting that FLASH and SSFP image quality converges at higher field strengths.

The interstudy variability at 7 T for LV ejection fraction and mass measurements ranged from 2.4 to 5% (Table 3). Interobserver variability was also excellent at 7 T for LV ejection fraction and mass (2.5 to 4.7%, Table 3 and Figure 5). Finally, intraobserver variability (1.6 to 3.4%) was similar to previously published validation studies at lower field strengths (11).

DISCUSSION

This study is the first validation of 7 T CMR assessment of cardiac volumes, function and mass using SSFP and FLASH sequences. Technical developments include the finding that the higher rate of ECG mistriggering at ultrahigh field strength (18) does not prevent adequate triggering despite the prominent magnetohydrodynamic effect. Performing the learning phase well clear of fringe field effects achieved ECGs of sufficient quality in all our subjects. This appears to prevent the ECG relearning based on distortions from the magnetohydrodynamic effect. Meticulous skin preparation and alternate lead positions achieved reliable ECG gating in both males ($n = 8$) and females ($n = 2$) across a wide age range (24 to 60 years). However, given the presence of ECG artefacts required repositioning in some patients at 7 T; alternative strategies that are insensitive to this magnetohydrodynamic effect may prove beneficial. Possible schemes include real-time imaging which avoids the issue of cardiac gating, ultrasound based gating (19), acoustic triggering (20,21), and pulse oxymetry based approaches. All these methods come with advantages and disadvantages.

SSFP sequences required careful optimisation with B1 and B0 shimming; nevertheless, high quality, analysable images were achievable. Images acquired with the FLASH sequences, in

particular, were much improved at 7 T compared to lower field strengths. There were no significant clinical complications experienced by subjects at 7 T.

Compared with the clinical gold standard of 1.5 T SSFP imaging, there were no significant differences in cardiac volumes or mass using SSFP at 3 T or 7 T. There were also no significant differences between cardiac volumes and mass assessed using FLASH imaging at 1.5 T, 3 T and 7 T field strengths. These results have important implications in validating the use of established low field databases for reference ranges and the use of different field strengths for serial assessment of cardiac parameters (15,22). This work is in line with previous comparative studies using SSFP and FLASH at 1.5 T and 3 T (11,12). Furthermore, on univariate analysis, although cardiac volumes and mass differed significantly according to sequence type but not field strength alone, there was a significant interaction between field strength and sequence type when considered together ($P = 0.03$). Observer variability for assessment of LV volumes and mass for each sequence at 7 T was similar to the high reproducibility described in previous research (11).

A limitation of our study is that slightly lower nominal flip angles were required to optimise SSFP imaging at higher field strengths so as to remain within SAR limits (Flip angle 1.5 T: 55°, 3T: 50° degrees, 7 T: 48°). The difficulty in measuring precise flip angles has been demonstrated by previous research at 3 T that showed the flip angle varies by as much as 50% from the nominal flip angle across the heart (23).

In conclusion, SSFP and FLASH cardiac imaging at 7 T is feasible, highly reproducible and can be validly compared with our current clinical gold standard of 1.5 T and 3 T. Reference ranges established at lower field strengths may be used at these higher field strengths, and conversely, data acquired at higher field strengths can be used for serial monitoring of patients previously assessed using CMR at 1.5 T and 3 T field strengths.

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Abbreviations used

BOLD	blood oxygen level dependent
CNR	contrast to noise ratio
ECG	electrocardiogram
FLASH	fast low angle shot
FDA	Food and Drug Administration (USA)
FOV	field of view
GRAPPA	generalised autocalibrating partially parallel acquisitions
LVEDV	left ventricular end diastolic volume
LVESV	left ventricular end systolic volume
SAR	specific absorption rates
SNR	signal to noise ratio
SSFP	steady state free precession

VCG vector cardiogram

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Figure 1.
Standard (S1, S2, S3) and alternate (A1, A2, A3) ECG electrode positions.

Figure 2. Electrocardiography using the same lead placement in the same patient at different field strengths. The magnetohydrodynamic effect becomes more pronounced at higher field strengths.

Figure 3. Horizontal long axis (HLA) steady state free precession (SSFP) image at 7 T before B0 shimming (A), after B0 shimming (B) and after both B1 and B0 shimming (C).

Figure 4.

A: Horizontal long axis (HLA) and short axis (SA) cardiac images acquired at 1.5, 3 and 7 T using fast low angle shot (FLASH) and steady state free precession (SSFP) sequences in the same subject. **B:** Full field of view (FOV) SSFP and FLASH images at 1.5 T, 3 T and 7 T field strengths during diastole and systole.

Figure 5. Interobserver reproducibility for LV mass and ejection fraction in 10 healthy subjects. Bland Altman plots are shown with mean differences (thin line) and 95% limits of agreement (thick line).

Table 1

Qualitative electrocardiograph (ECG) scoring. All ECGs were obtained in the standard position, except at 7 T in three subjects where the alternative lead placement was used

Subject	1.5 T	3 T	7 T
1	4	4	Standard 2, alternative 3
2	4	4	4
3	4	4	4
4	4	4	4
5	3	3	3
6	3	3	Standard 2, alternative 3
7	4	4	3
8	4	4	3
9	4	3	Standard 2, alternative 3
10	4	4	4

Score/ ECG Characteristics: 4 - Effective triggering, no R wave artefacts; 3 - Effective triggering, R wave artefacts present; 2 - Occasional miss triggering, R wave artefacts present; 1 - Persistent miss triggering, R wave artefacts present; 0 - No ECG obtainable.

Table 2

Left ventricular measurements using steady state free precession (SSFP) and fast low angle shot (FLASH) sequences at 1.5 T, 3 T and 7 T in healthy subjects*

Measurement	1.5 T			3 T			7 T			p-value	
	SSFP	FLASH	SSFP	FLASH	SSFP	FLASH	SSFP	FLASH	Sequence	Field Strength	Interaction
LVEDV (mL)	145 ± 35	121 ± 28	144 ± 40	130 ± 33	138 ± 32	127 ± 28	138 ± 32	127 ± 28	<0.001	0.40	0.03
LVESV (mL)	48 ± 18	37 ± 12	47 ± 17	37 ± 13	45 ± 16	40 ± 14	45 ± 16	40 ± 14	0.003	0.97	0.026
LVSF (%)	97 ± 19	84 ± 19	89 ± 20	92 ± 28	94 ± 19	87 ± 17	94 ± 19	87 ± 17	0.10	0.96	0.35
LVEF (%)	68 ± 5	70 ± 5	68 ± 7	71 ± 8	68 ± 5	69 ± 5	68 ± 5	69 ± 5	0.15	0.88	0.26
LV mass (g)	124 ± 32	165 ± 38	128 ± 31	162 ± 42	132 ± 40	140 ± 47	132 ± 40	140 ± 47	<0.001	0.26	0.006

* All data are mean ± standard deviation. Univariate general linear model with fixed effects for sequence and field strength was used. Non significant p-values for interaction confirm that differences between sequences were independent of field strength. Significant p-values are in bold. LVEDV = Left ventricular end diastolic volume, LVESV = Left ventricular end systolic volume, LVSF = Left ventricular stroke volume, LVEF = Left ventricular ejection fraction, LV Mass = Left ventricular mass.

Table 3

Variability of measurements at 7 T*

	Intraobserver		Interobserver		Interstudy	
	Bias* (95% limits of agreement)	CoV	Bias* (95% limits of agreement)	CoV	Bias* (95% limits of agreement)	CoV
LVEF %						
SSFP	0 ± 2.3 (-4.5 to 4.5)	1.6%	-1.2 ± 3.2 (-7.5 to 5.2)	3.3%	-2.8 ± 7.2 (-17.2 to 11.6)	1.7 %
FLASH	0.3 ± 1.7 (-3.7 to 3.2)	1.2%	0.9 ± 4.6 (-8.4 to 10.2)	2.5%	-0.7 ± 3.3 (-7.3 to 5.9)	2.4 %
Mass (g)						
SSFP	4.1 ± 8.5 (-12.9 to 21.0)	3.4%	2.6 ± 12.7 (-22.8 to 28.0)	4.7%	-1.6 ± 12.4 (-26.3 to 23.1)	5.2 %
FLASH	4.0 ± 8.1 (-12.2 to 20.1)	3.1%	-0.8 ± 13.6 (-28.0 to 26.5)	4.6%	1.4 ± 13 (-24.6 to 27.5)	4.0 %

Bias and limits of agreement were determined according to the Bland Altman method. CoV: coefficient of variability; LVEF: left ventricular ejection fraction; SSFP: steady state free precession; FLASH: fast low angle shot.