Comparison of Standard Breath-Held, Free-Breathing, and Compressed Sensing 2D Gradient-Recalled Echo MR Elastography Techniques for Evaluating Liver Stiffness

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OBJECTIVE. The objective of our study was to compare standard breath-held, free-breathing, and compressed sensing (CS) accelerated 2D gradient-recalled echo (GRE) MR elastography (MRE) techniques for measuring liver stiffness.

SUBJECTS AND METHODS. Twenty-five adult volunteers (20 without liver disease and five with liver disease) underwent MRE with five different 2D GRE techniques: breath-held; free-breathing; and CS with acceleration factors of 1.5, 2, and 3. Four axial images were obtained through the mid liver with each technique, and liver stiffness measurements (in kilopascals) were made by three blinded readers using elastograms with 95% confidence maps. Liver stiffness measurements were compared between techniques using repeated-measures ANOVA. Absolute agreement between techniques was evaluated for each reader using single-measure intraclass correlation coefficients (ICCs). Bland-Altman analyses were performed to assess bias between techniques using breath-held MRE as the reference.

RESULTS. Individual subject mean liver stiffness values ranged from 1.35 to 5.25 kPa for the population. There was no significant difference in mean liver stiffness values between MRE techniques for readers 1 and 3 ($p > 0.05$). A significant difference ($p = 0.02$) due to higher stiffness measurements using free-breathing MRE was observed for reader 2. There was excellent absolute agreement between MRE techniques for each reader (all ICCs > 0.940). Bias between techniques ranged from –0.102 to 0.089 kPa for reader 1, –0.119 to 0.121 kPa for reader 2, and –0.074 to 0.085 kPa for reader 3.

CONCLUSION. Free-breathing and CS accelerated 2D GRE MRE techniques yield similar results to the conventional breath-held technique with only slight bias and may be useful in pediatric and adult patients with limited ability to breath-hold.

Keywords: comparative research, compressed sensing, gradient-recalled echo, liver, MR elastography

doi.org/10.2214/AJR.18.19761

Received February 25, 2018; accepted after revision May 1, 2018.

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Supplemental Data
Available online at www.ajronline.org.

AJR 2018; 211:1–9

0361–803X/18/2116–1

There has been remarkable progress over the past 2 decades with regard to the development and clinical implementation of hepatic MR elastography (MRE) [1]. MRE, which allows the noninvasive measurement of hepatic stiffness (a surrogate marker for liver fibrosis), has been shown to be clinically useful in chronic liver disease from multiple causes and has been shown to accurately detect different severities of liver fibrosis when using histopathologic grading as the reference standard [2–4]. The American College of Radiology's Appropriateness Criteria for "Variant 1: chronic liver disease, diagnosing liver fibrosis" [5] recommends MRE as "usually appropriate."

MRE is most commonly performed using a 2D gradient-recalled echo (GRE) technique, especially at a field strength of 1.5 T. The standard clinical MRE assessment described in the literature generally requires four consecutive breath-holds to acquire elastograms at four levels in the liver [2, 3]. Breath-hold times to acquire each of these four elastograms can range from 11 seconds to greater than 20 seconds, which can be too long for some children and adults who have limited breath-holding capacity (e.g., due to age, inability to cooperate, or medical comorbidities) [6]. Respiratory-gated MRE (e.g., using a navigator trigger pulse) has been described as a method to use to eliminate breath-holds, but this technique increases image acquisition time [7].

In recent years, utilization of the compressed sensing (CS) technique has been described as a means to shorten acquisition times for MRI through the undersampling of k-space [8]. CS, or sparse, MRI can be used to shorten pulse sequences that use cartesian filling of k-space, including breath-held se-

quences such as 2D GRE MRE, thereby improving the tolerability of the examination for the patient and potentially increasing diagnostic quality [9–12]. However, to date, there is a paucity of data in the published literature describing the application of CS to MRE. Furthermore, there are limited studies in the published literature assessing the agreement between liver stiffness measurements obtained using standard breath-held MRE and free-breathing MRE.

The purpose of our study was to explore methods to reduce or eliminate breath-holding for MRE examinations by comparing liver stiffness measurements obtained using conventional breath-held 2D GRE MRE, free-breathing 2D GRE MRE, and breath-held 2D GRE MRE with three levels of CS. We hypothesized that there would be excellent agreement and correlation between breath-held and CS MRE techniques and that free-breathing MRE measurements would show poorer agreement and correlation with breath-held measurements. As a secondary endpoint, we sought to compare ROI size across the various 2D GRE MRE techniques.

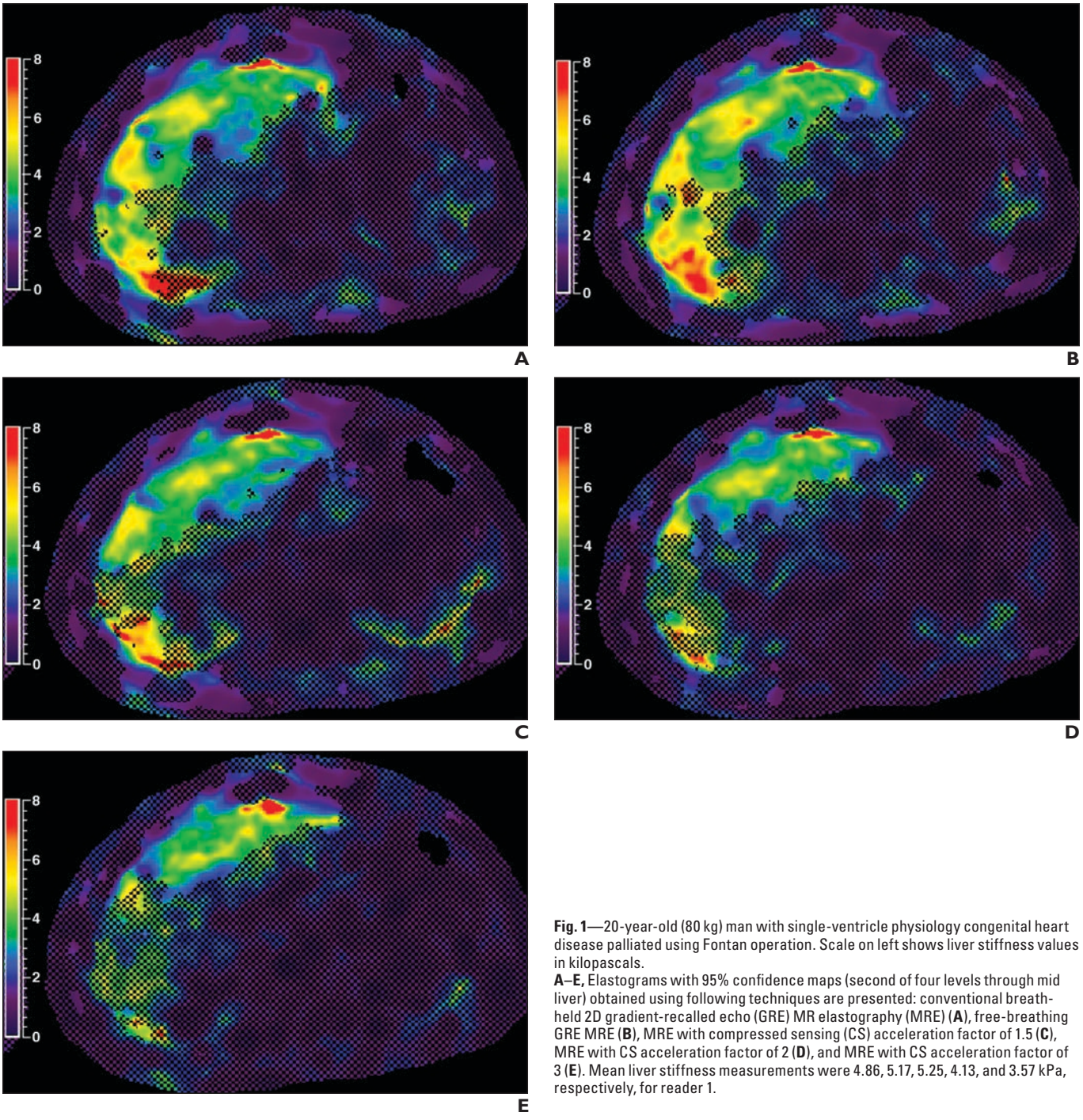

Fig. 1—20-year-old (80 kg) man with single-ventricle physiology congenital heart disease palliated using Fontan operation. Scale on left shows liver stiffness values in kilopascals.
A–E, Elastograms with 95% confidence maps (second of four levels through mid liver) obtained using following techniques are presented: conventional breath-held 2D gradient-recalled echo (GRE) MR elastography (MRE) (**A**), free-breathing GRE MRE (**B**), MRE with compressed sensing (CS) acceleration factor of 1.5 (**C**), MRE with CS acceleration factor of 2 (**D**), and MRE with CS acceleration factor of 3 (**E**). Mean liver stiffness measurements were 4.86, 5.17, 5.25, 4.13, and 3.57 kPa, respectively, for reader 1.

Subjects and Methods

Institutional review board approval was obtained for this HIPAA-compliant cross-sectional agreement study. Written informed consent was obtained from all participants.

Study Cohort

An a priori sample size calculation based on Pearson correlation (*r*) and pairwise comparison of liver stiffness measurements between MRE techniques was performed. Assuming a type I error (α) of 0.05 and a type II error of 0.2 (power = 80%), 23 participants would be required to show that an anticipated correlation coefficient of 0.55 or greater was significantly different from zero. Based on this calculation, 25 adult (> 18 years old) volunteers were recruited for this study. Specifically, we prospectively recruited 20 adults without a known history of liver disease and five adults with a history of Fontan palliation of congenital heart disease and known liver stiffening based on MRE performed in the previous 12 months. The purpose of including the patients with a history of Fontan palliation was to include a range of liver stiffness values in the study. Exclusion criteria were the following: known liver disease based on patient report (excluding the five participants with a history of Fontan palliation who were recruited specifically because of their known liver disease) and contraindication to MRI (e.g., non–MRI-compatible implantable device, claustrophobia, pregnancy).

MR Elastography Examination

All imaging examinations were performed at Cincinnati Children's Hospital Medical Center using a 1.5-T MRI scanner (Ingenia, Philips Healthcare), a 16-channel anterior torso coil, and a 12-channel posterior coil integrated into the scanner table. For each participant, five 2D GRE MRE acquisitions were performed during a single imaging session and were randomized in order: breath-held MRE (breath-hold time, 13.3 seconds per slice [anatomic level]); free-breathing MRE (53.2 seconds total acquisition time) without navigator gating, respiratory triggering, or any other type of respiratory compensation; MRE with CS acceleration factor of 1.5 (breath-hold time, 8.9 seconds per slice); MRE with CS acceleration factor of 2 (breath-hold time, 6.9 seconds per slice); and MRE with CS acceleration factor of 3 (breath-hold time, 4.9 seconds per slice) (Figs. 1, S1, and S2). Figures S1 and S2 can be viewed by clicking "Supplement" at the top of this article.

For each MRE technique, four 10-mm axial slices were obtained through the mid liver. Elastograms with 95% confidence maps based on MRI displacement data (four phase and four magnitude images per slice) were generated on the scanner using a direct inversion algorithm, which is based on the Helmholtz equation [2]. As other investigators have previously described [2], the elastogram confidence map and area of measurable voxels are based on MRI magnitude signal-to-noise ratio, MRI phase signal-to-noise ratio, and motion artifacts that can obscure wave data.

The parameters of the MRE pulse sequences are presented in Appendix 1. All major parameters—including section thickness, in-plane resolution, flip angle, TE, and TR—were kept identical for all sequences. The pneumatic passive driver used to generate mechanical waves in the liver was driven by an active driver located outside the scanning room at 60 Hz for all participants and sequences. The 2D GRE MRE sequence used in this study was implemented through a modification of a standard phase-contrast pulse sequence to include a motion-encoding gradient (16.7 ms and 18.4 mT/m) along the slice-select direction. The breath-held and free-breathing MRE sequence parameters were identical.

Our implementation of MRE with CS was similar to the 2D GRE MRE technique described earlier; however, a hybrid k-space undersampling pattern was used. Specifically, the center of the k-space was measured using a regular (cartesian) sampling pattern with an acceleration factor (SENSE) of 2, while the outer portion of the k-space was undersampled using a nonuniform pseudorandom pattern. The density of sampling in the outer portion of k-space also decreased (decayed), moving away from the center of k-space. Three different levels of k-space undersampling were used, which resulted in increasing amounts of image acquisition acceleration.

CS is a mathematic framework that reconstructs data from highly undersampled measurements and was first developed by Donoho [13] and Candes et al. [14]. Lustig et al. [8] applied this technique to MRI. Our MRE with CS method is built on both CS theory and parallel imaging (SENSE) technology by leveraging a balanced variable density incoherent undersampling acquisition scheme and iterative reconstruction method to solve an inverse problem with a sparsity constraint. Mathematically, the reconstruction is to solve the following minimization:

$$minimize \left\| F_u m - y \right\|_2^2 + \lambda \left\| \Psi m \right\|_1$$

where Ψ is a sparsity transform to convert the image *m* into the wavelet domain, *y* is the undersampled k-space data acquired, F_u is the Fourier transform, and λ is the regularization factor to balance the sparsity constraining and data consistency in the iterative solution. An iterative reconstruction scheme was used with a regularization factor corresponding to a denoising level of 10%. The regularization factor impacts the balance between reliance on the measured data and on prior knowledge based on the use of wavelets—therefore, the higher the regularization factor, the greater the strength of wavelet regularization [15].

Image Analysis

Pertinent images, including MR elastograms with 95% confidence maps, were independently reviewed by three readers, two physicists and one radiologist, to subjectively assess diagnostic quality; nondiagnostic image acquisitions were documented. Liver stiffness measurements were then made by the same three readers for each participant and MRE technique, and the readers were blinded to the other readers' measurements. Each reader drew ROIs on the generated elastograms within the boundaries of the 95% confidence maps. ROIs included as much liver parenchyma as possible while avoiding major blood vessels, the peripheral 1 cm of the liver, and the lateral section of the left hepatic lobe. MRE phase and magnitude images were available to readers to guide ROI placement. Mean liver shear stiffness (in kilopascals) and ROI size (in square millimeters) were recorded for each of the four slices for each MRE acquisition. These data were used to calculate overall mean liver stiffness (a weighted mean adjusted for ROI size) for each technique in each participant.

Statistical Analysis

Continuous data are summarized as means, SDs, and ranges, and categoric data are summarized as counts and percentages. Mean liver stiffness measurements and ROI sizes were compared between MRE sequences for each reader using repeated-measures ANOVA. Repeated-measures ANOVA also was used to compare mean liver stiffness measurements and ROI sizes between readers for each MRE technique.

Absolute agreement between MRE sequences for each reader was evaluated using two-way single-measure intraclass correlation coefficients (ICCs). ICC strength of agreement was classified on the basis of the following definitions: ICC value of 0–0.39, poor agreement; 0.40–0.59, fair; 0.60–0.74, good; and 0.75–1.00, excellent [16].

For each reader, Pearson correlation coefficients were used to assess the correlation between liver stiffness values obtained with the various MRE techniques under investigation, with breath-held MRE serving as the reference technique. Pearson correlation coefficients were classified using the following definitions: *r* value of 0–0.19, very weak correlation; 0.20–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, strong; and 0.80–1.00, very strong [17]. Bland-Altman analyses were

TABLE 1: Comparison of Liver Stiffness Measurements Between MR Elastography (MRE) Techniques and Readers

Reader	MRE Technique					p^b
	Breath-Held 2D GRE	Free-Breathing 2D GRE	CS With Acceleration Factor of 1.5	CS With Acceleration Factor of 2	CS With Acceleration Factor of 3	
Reader 1						0.09
Liver stiffness (kPa), mean[a] ± SD (range)	2.47 ± 1.08 (1.55–5.19)	2.59 ± 1.09 (1.69–5.17)	2.45 ± 1.06(1.61–5.25)	2.27 ± 0.88 (1.54–4.60)	2.26 ± 0.69 (1.51–4.01)	
No. of participants included in calculation	25	24	24	22	21	
Reader 2						0.02
Liver stiffness (kPa), mean[a] ± SD (range)	2.38 ± 0.96 (1.57–4.78)	2.56 ± 1.07 (1.67–4.96)	2.36 ± 0.92 (1.55–4.62)	2.32 ± 0.94 (1.44–4.40)	2.36 ± 0.76 (1.40–3.86)	
No. of participants included in calculation	25	21	24	22	21	
Reader 3						0.06
Liver stiffness (kPa), mean[a] ± SD (range)	2.27 ± 0.89 (1.46–4.28)	2.36 ± 0.97 (1.35–4.71)	2.24 ± 0.85 (1.49–4.21)	2.20 ± 0.78 (1.42–3.98)	2.27 ± 0.68 (1.44–3.69)	
No. of participants included in calculation	25	25	25	25	23	
p^b	0.002	0.0009	0.002	0.01	0.009	

Note—GRE = gradient-recalled echo, CS = compressed sensing.
[a]Weighted mean adjusted for ROI size.
[b]Repeated-measures ANOVA.

used to assess bias and 95% limits of agreement between techniques, again using breath-held MRE as the reference technique.

A p value < 0.05 was considered significant for all inference testing; 95% CIs were calculated to indicate the reliability of estimates, as appropriate. All statistical analyses were performed using MedCalc (version 17.9.7, MedCalc Software).

Results

The mean age of the 20 participants without known liver disease was 34.0 ± 9.6 (SD) years (range, 22–61 years); 13 (65%) were women and seven were men (35%), and their mean weight was 78.8 ± 15.3 kg (range, 60–105 kg). The mean age of the five participants with known liver disease (congestive hepatopathy due to Fontan-associated liver disease) was 32.0 ± 14.7 years (range, 20–56 years); three (60%) were women and two (40%) were men, and their mean weight was 79.4 ± 16.0 kg (range, 55–100 kg).

None of the conventional breath-held 2D GRE MRE acquisitions were considered nondiagnostic by any of the three readers. For free-breathing 2D GRE MRE, one, four, and 0 acquisitions were considered nondiagnostic by readers 1, 2, and 3, respectively. The number of acquisitions considered nondiagnostic increased with increasing CS acceleration factor. Specifically, the number of nondiagnostic MRE acquisitions was one, one, and 0 for CS with an acceleration factor of 1.5 and three, three, and one for CS with an acceleration factor of 3 for readers 1, 2, and 3, respectively. The MRE sequence

TABLE 2: Comparison of ROI Sizes Between MR Elastography (MRE) Techniques and Readers

Reader	MRE Technique					p^a
	Breath-Held 2D GRE	Free-Breathing 2D GRE	CS With Acceleration Factor of 1.5	CS With Acceleration Factor of 2	CS With Acceleration Factor of 3	
Reader 1						< 0.0001
ROI size (mm^2), mean ± SD (range)	2618 ± 766 (1060–4086)	2156 ± 757 (470–3281)	2096 ± 782(453–3542)	1719 ± 594 (535–2667)	1170 ± 389 (359–1644)	
No. of participants included in calculation	25	24	24	22	21	
Reader 2						< 0.0001
ROI size (mm^2), mean ± SD (range)	2123 ± 581 (1000–3086)	1795 ± 474 (698–2490)	1737 ± 485 (629–2960)	1422 ± 399 (562–2213)	1102 ± 387 (492–1805)	
No. of participants included in calculation	25	21	24	22	21	
Reader 3						< 0.0001
ROI size (mm^2), mean ± SD (range)	3941 ± 1099 (1610–6205)	2465 ± 1040 (413–5007)	2705 ± 863 (653–4404)	2064 ± 861 (507–4830)	1253 ± 500 (286–2476)	
No. of participants included in calculation	25	25	25	25	23	
p^a	< 0.0001	< 0.0001	< 0.0001	0.0005	0.14	

Note—GRE = gradient-recalled echo, CS = compressed sensing.
[a]Repeated-measures ANOVA.

TABLE 3: Absolute Agreement Between MR Elastography (MRE) Sequences for Each Reader

Reader	ICC[a] for Five MRE Sequences	ICC[a] for Four MRE Sequences[b]
Reader 1	0.943 (0.896–0.973)	0.941 (0.890–0.973)
Reader 2	0.949 (0.902–0.977)	0.956 (0.917–0.980)
Reader 3	0.948 (0.908–0.975)	0.963 (0.932–0.982)

Note—ICC = intraclass correlation coefficient.
[a]Two-way single-measure ICC with 95% CI in parentheses.
[b]Excluding free-breathing 2D gradient-recalled echo MRE sequence.

with a CS acceleration factor of 3 was inadvertently not performed in one participant.

Comparison of Liver Stiffness Measurements Between MR Elastography Sequences Within Readers

There was no significant difference in mean liver stiffness values measured by the five MRE techniques for two of the three readers (repeated-measures ANOVA: all, $p > 0.05$) (Table 1). For reader 2, there was a significant difference in mean liver stiffness values between the various MRE techniques ($p = 0.02$) because of the slightly higher values obtained for free-breathing 2D GRE MRE compared with the other MRE techniques.

Comparison of Liver Stiffness Measurements Between Readers

There were significant differences using the repeated-measures ANOVA in mean liver stiffness values between the three readers for all five MRE techniques (Table 1). The greatest mean liver stiffness difference observed between readers was 0.23 kPa when using the free-breathing 2D GRE MRE sequence.

Comparison of ROI Sizes Between MR Elastography Sequences Within and Between Readers

There was a significant difference in mean ROI size between the five MRE techniques for each of the three readers (repeated-measures ANOVA: all, $p < 0.0001$) (Table 2). For all readers, the breath-held MRE sequence had the largest ROIs, and the free-breathing MRE ROIs were slightly smaller. ROI size decreased with increasing CS, with a CS acceleration factor of 3 having the smallest ROIs for all three readers. Additionally, ANOVA showed a significant difference in ROI size between readers for four of the five MRE sequences studied; only the MRE sequence performed with a CS acceleration factor of 3 showed no difference in mean ROI between the three readers ($p = 0.14$) (Table 2).

Absolute Agreement Between MR Elastography Sequences for a Given Reader

There was excellent absolute agreement in liver stiffness values between MRE sequences ($n = 5$) for each of the three readers; all ICCs were greater than 0.940 (Table 3). There was no significant change in ICC values after excluding the free-breathing 2D GRE MRE technique from the ICC calculations.

Correlations Between MR Elastography Techniques and Bland-Altman Analyses

There were very strong positive correlations between liver stiffness values obtained with the conventional breath-held 2D GRE MRE technique and the free-breathing MRE technique for all three readers (all, $r \geq 0.961$; all, $p < 0.0001$) (Table 4). Similarly, there were very strong positive correlations between stiffness values obtained with the conventional breath-held MRE technique and the MRE techniques with various amounts of CS (all, $r > 0.960$; all, $p < 0.0001$). Scatterplots for all three readers combined showing the relationships between the conventional breath-held MRE technique and the other MRE techniques evaluated are presented in Figure 2.

Bias in liver stiffness measurements for each of the MRE techniques under investigation compared with breath-held MRE are detailed in Table 4. All mean bias values were less than 0.130 kPa. For reader 1, MRE with a CS acceleration factor of 1.5 had the smallest mean bias (–0.053 kPa) and MRE with a CS acceleration factor of 3 had the greatest mean bias (–0.102 kPa) versus breath-held MRE. For reader 2, MRE with a CS acceleration factor of 1.5 had the smallest mean bias (–0.058 kPa) and free-breathing MRE had the greatest mean bias (0.121 kPa) versus breath-held MRE. For reader 3, MRE with a CS acceleration factor of 1.5 had the smallest mean bias (–0.037 kPa) and free-breathing MRE had the greatest mean bias (0.085 kPa) versus breath-held MRE.

Bland-Altman difference plots for each of the four sequence pairs presented in Table 4 are displayed in Figure 3 for all three readers combined. For all sequences, the difference

TABLE 4: Pearson Correlation Coefficient and Bland-Altman Bias by Reader for Four MR Elastography (MRE) Techniques Compared with Breath-Held MRE

MRE Technique Versus Breath-Held 2D GRE[a]	r^b (p)	Bland-Altman Bias (kPa)	
		Mean	95% Limits of Agreement
Reader 1			
Free-breathing 2D GRE ($n = 24$)	0.975 (< 0.0001)	0.089	–0.394, 0.571
CS with acceleration factor of 1.5 ($n = 24$)	0.989 (< 0.0001)	–0.053	–0.378, 0.271
CS with acceleration factor of 2 ($n = 22$)	0.985 (< 0.0001)	–0.093	–0.519, 0.332
CS with acceleration factor of 3 ($n = 21$)	0.962 (< 0.0001)	–0.102	–0.938, 0.735
Reader 2			
Free-breathing 2D GRE ($n = 21$)	0.969 (< 0.0001)	0.121	–0.398, 0.639
CS with acceleration factor of 1.5 ($n = 24$)	0.984 (< 0.0001)	–0.058	–0.403, 0.288
CS with acceleration factor of 2 ($n = 22$)	0.967 (< 0.0001)	–0.119	–0.628, 0.390
CS with acceleration factor of 3 ($n = 21$)	0.969 (< 0.0001)	–0.105	–0.771, 0.562
Reader 3			
Free-breathing 2D GRE ($n = 25$)	0.970 (< 0.0001)	0.085	–0.392, 0.563
CS with acceleration factor of 1.5 ($n = 25$)	0.987 (< 0.0001)	–0.037	–0.326, 0.252
CS with acceleration factor of 2 ($n = 25$)	0.976 (< 0.0001)	–0.074	–0.497, 0.348
CS with acceleration factor of 3 ($n = 23$)	0.961 (< 0.0001)	–0.038	–0.672, 0.596

Note—GRE = gradient-recalled echo, CS = compressed sensing.
[a]Number in parentheses is number of participants included in calculations.
[b]Correlation coefficient.

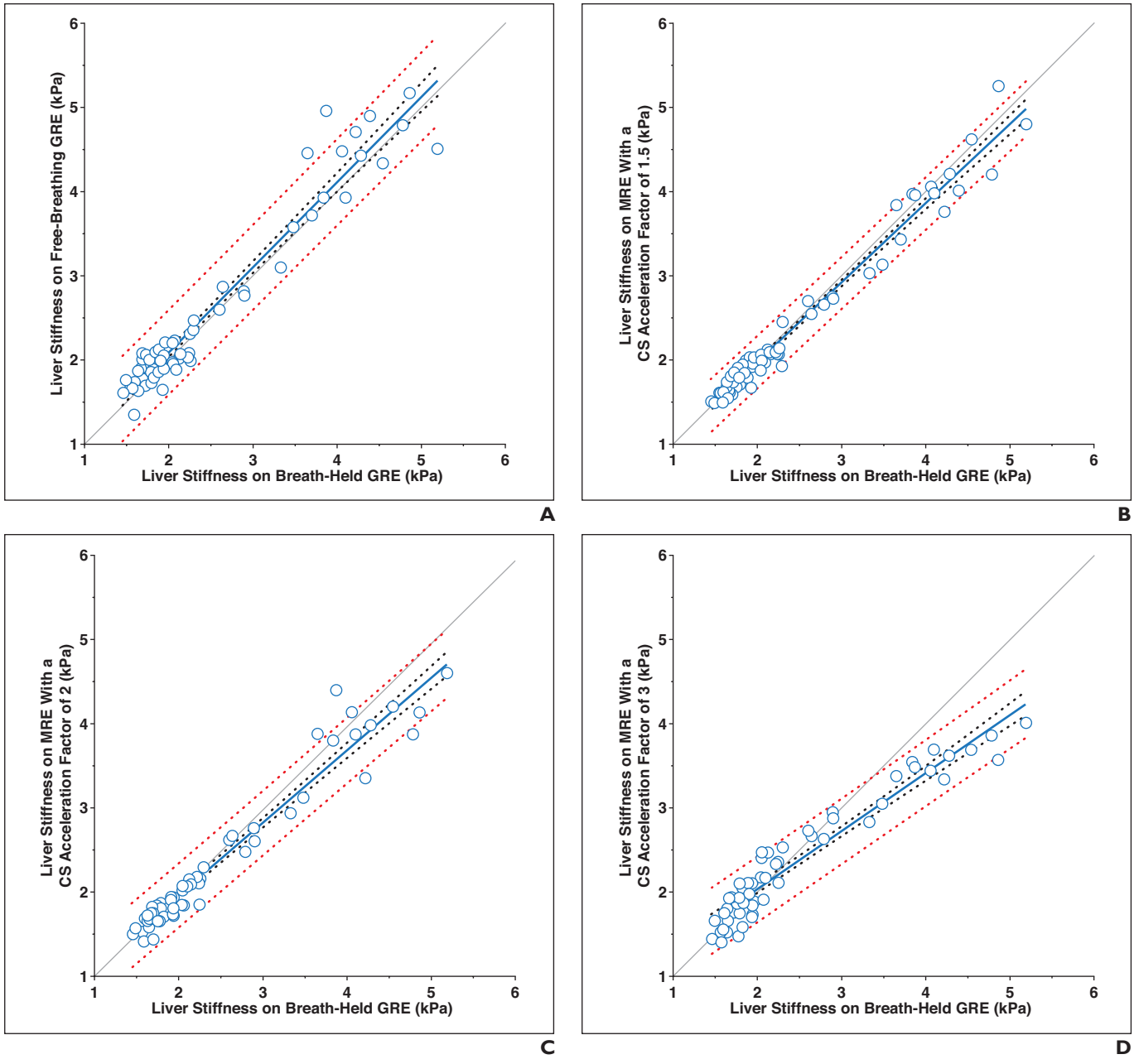

Fig. 2—Scatterplots for four MR elastography (MRE) technique pairs using combined data from all three readers. Solid line represents line of best fit, dotted black lines present 95% confidence band for line of best fit, and dotted red lines represent 95% prediction interval. Circles outside of 95% prediction interval are statistical outliers. Liver stiffness measurements of participants with history of Fontan palliation of congenital heart disease were greater than 3 kPa in four of five subjects; in fifth subject, reader 3 recorded liver stiffness measurements of 2.94 and 2.83 kPa for MRE with compressed sensing (CS) acceleration factor of 2 and 3, respectively. No healthy volunteer had mean liver stiffness value of greater than 3 kPa for any of five techniques under investigation.
A, Breath-held gradient-recalled echo (GRE) MRE versus free-breathing GRE MRE ($n = 70$).
B, Breath-held GRE MRE versus MRE with CS acceleration factor of 1.5 ($n = 73$).
C, Breath-held GRE MRE versus MRE with CS acceleration factor of 2 ($n = 69$).
D, Breath-held GRE MRE versus MRE with CS acceleration factor of 3 ($n = 65$).

between methods (breath-held 2D GRE MRE vs other MRE techniques) was small when liver stiffness was normal (i.e., < 2.5 to 3 kPa) and increased with increasing mean liver stiffness (Fig. 3D). These results suggest proportional error (bias), with the MRE technique with a CS acceleration factor of 3 showing lower liver stiffness measurements than breath-held MRE with increasing mean liver stiffness.

Discussion

The results of our study show that both CS MRE and free-breathing MRE are feasible in adult volunteers without and with liver disease and provide relatively comparable liver stiffness measurements with excellent agreement between techniques for all three readers. Non–breath-held and accelerated MRE techniques such as these have the potential to aid in the imaging of patients with limited breath-hold capacity.

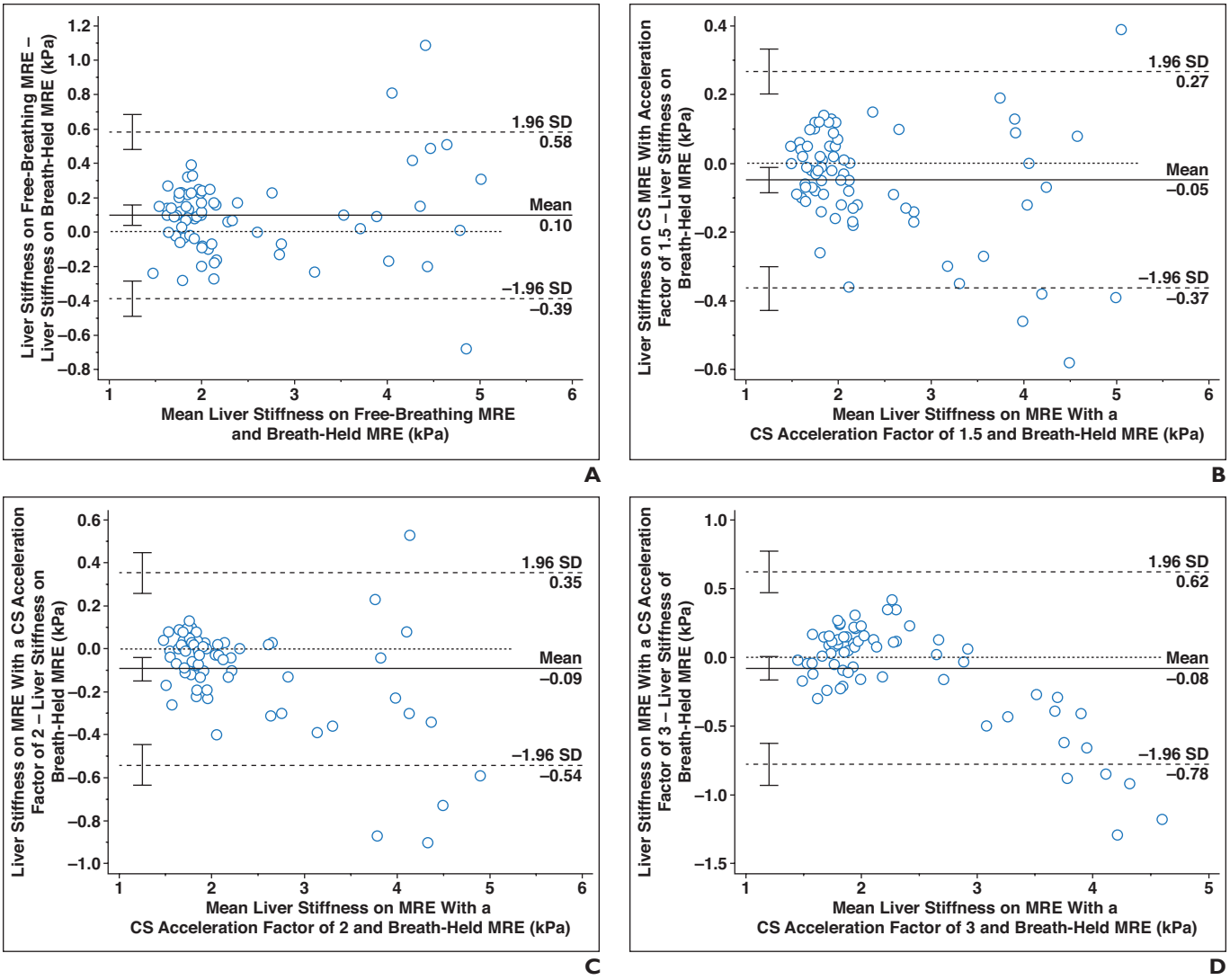

Fig. 3—Bland-Altman difference plots for four different MR elastography (MRE) technique pairs using combined data from all three readers. Note that *x*- and *y*-axes are scaled differently for each technique comparison to minimize overlap of data points. Whiskers show 95% CI for mean difference and 95% limits of agreement, respectively. **A–C,** Breath-held gradient-recalled echo (GRE) MRE versus free-breathing GRE MRE ($n = 70$) (**A**), breath-held GRE MRE versus MRE with compressed sensing (CS) acceleration factor of 1.5 ($n = 73$) (**B**), and breath-held GRE MRE versus MRE with CS acceleration factor of 2 ($n = 69$) (**C**). These plots suggest that there is increasing nonsystematic difference between two methods with increasing mean liver stiffness.
D, Breath-held GRE MRE versus MRE with CS acceleration factor of 3 ($n = 65$). This plot suggests proportional error (bias) with increasing systematic difference between two methods with increasing mean liver stiffness. This bias is observed only in patients with elevated mean liver stiffness (> 3 kPa).

In this study, we have implemented a hybrid CS approach to accelerating MRE, using parallel imaging (SENSE) as well as varying amounts of peripheral k-space undersampling to achieve image acquisition acceleration. Although there was no significant difference in measured mean liver stiffness when comparing breath-held MRE (13.3-second breath-hold) to MRE with any level of CS, MRE with a CS acceleration factor of 1.5 (8.9-second breath-hold per slice) showed the smallest amount of bias and narrowest 95% limits of agreement among the three CS MRE techniques. Mean bias ranged from –0.058 to –0.037 kPa for the three readers. In our experience, such small bias values are unlikely to be clinically relevant in most (if not all) patients with known or suspected liver disease. Bias between breath-held MRE and CS MRE techniques increased slightly with increasing imaging acceleration, although the largest mean bias was only –0.119 kPa for any given reader and acceleration factor (CS acceleration factor = 2).

For MRE with a CS acceleration factor of 3, a proportional or systematic bias was observed, with this technique consistently showing lower stiffness measurements than breath-held MRE in participants with abnormally stiff livers. Careful examinations of the breath-held MRE versus MRE with a CS acceleration factor of 3 scatterplots and Bland-Altman plots show that there is very strong correlation and minimal bias in participants with a normal liver stiffness and that the proportional error occurs with abnormally increased liver stiffness (> 3 kPa). Thus, although MRE with a CS acceleration factor of 3 may ultimately underestimate the severity of liver disease, our results suggest that this technique, which can be performed in a breath-hold of less than 5 seconds, is un-

likely to lead to a misdiagnosis of a normal liver as abnormally stiff.

The observed increases in liver stiffness bias and variability with increasing amounts of CS may be in part because of ROI size and smaller measureable areas on elastogram 95% confidence maps. An increasing amount of CS was significantly associated with decreasing ROI size for all three readers. It is likely that undersampling of k-space adversely impacts both the magnitude and phase signal-to-noise ratios, resulting in fewer voxels with statistically reliable data. As a result, smaller areas of the liver are measured on each image, which may result in increased measurement variability. Furthermore, it is possible that increasing CS acceleration and associated decreased magnitude and phase signal-to-noise ratios directly impact variability and bias independent of ROI size. All of these reasons likely explain why only two of 75 MRE examinations (< 3%) were considered nondiagnostic for MRE with a CS acceleration factor of 1.5 compared with six of 72 (8%) examinations for MRE with a CS acceleration factor of 3. Surprisingly, despite the use of phase and magnitude source images and 95% confidence maps to guide the creation of ROIs, there were also significant differences in mean ROI size between the three readers for four of the five pulse sequences under investigation.

Free-breathing MRE, or the acquisition of 2D GRE MRE images during normal quiet respiration without respiratory triggering or navigator gating, performed unexpectedly well compared with the standard-of-care breath-held MRE technique. One reader considered all 25 free-breathing sequences to be diagnostic, whereas the other two readers considered 21 (84%) and 24 (96%) free-breathing sequences to be diagnostic. In our study, correlation coefficients with breath-held MRE were very strong (all, $r >$ 0.960), and mean bias was relatively small for all three readers (range, 0.085–0.121 kPa). For two of the three readers, however, free-breathing MRE had the largest bias of any technique versus breath-held MRE. Interestingly, mean liver stiffness was slightly higher for the free-breathing technique compared with the breath-held technique for all three readers. ROI sizes were similar to those observed with MRE with a CS acceleration factor of 1.5 and were smaller than those obtained with breath-held MRE.

Murphy et al. [7] recently compared liver stiffness measurements obtained during free breathing, inspiration, and expiration and with navigator-gating in a small volunteer cohort consisting of 12 healthy participants. They found no significant difference in liver stiffness values between any of the four acquisition strategies. Interestingly, similar to our study, mean free-breathing measurements of liver stiffness were slightly higher than breath-held measurements (p = 0.06). Also, similar to our study, the free-breathing technique was associated with smaller measureable liver areas. The navigator-triggered MRE technique used in their study had a mean acquisition time of 4 minutes 55 seconds [7].

Another means to accelerate MRE was described by Chamarthi et al. [6]; they successfully accelerated breath-hold MRE in 16 volunteers and 14 patients with liver fibrosis by reducing the TR from 3 cycles of external vibrations to 1.5 cycles of external vibrations with a resultant decrease in scanning time per image from approximately 22 to 11 seconds [6]. There was no significant difference in liver stiffness measurements using their technique [6]. To carry out this technique, the authors also had to ensure that the polarity of the motion-encoding gradients was not alternated for every other TR, which is the standard with conventional 2D GRE MRE.

Spin-echo echo-planar imaging (SE-EPI) MRE, which is used at 3 T by some MRI manufacturers as a means of decreasing artifacts due to higher field strength, can also be used as an alternative to GRE MRE. With SE-EPI MRE, which effectively accelerates imaging, more than one image can be acquired per breath-hold (i.e., ≥ 16 images). Studies have shown that both GRE and SE-EPI yield comparable stiffness measurements and that SE-EPI generally yields larger ROIs [18, 19]. SE-EPI MRE currently is not available as a product on certain MRI systems, including the MRI system used in this investigation. A potential disadvantage of SE-EPI MRE compared with GRE MRE is increased image geometric distortion, which may adversely impact overall image quality.

A strength of our study was the use of three readers to perform liver stiffness measurements while blinded to the other readers' measurements. This allowed us to evaluate agreement across MRE techniques for multiple readers and to evaluate variation in measurements between readers for a given MRE technique. Interestingly, based on the results shown in Table 1, the differences in mean liver stiffness values between MRE techniques seems comparable to the differences in mean liver stiffness values between readers for a given sequence. For example, for reader 3, the maximum difference in mean liver stiffness across the five MRE techniques under investigation was 0.16 kPa, and the maximum difference in mean liver stiffness values between all three readers for the standard-of-care breath-held MRE technique was greater (0.20 kPa).

Our study has limitations. First, it is relatively small, including only 25 volunteers. However, unlike multiple prior MRE studies of volunteers [7], we included participants with known liver disease to assess correlation and agreement between techniques across a range of liver stiffnesses (not just healthy or diseased livers). Additionally, our study was appropriately powered to detect clinically relevant correlations between MRE techniques, which we did indeed identify. A second limitation is that it was not possible to reliably blind the three readers to the specific MRE technique being evaluated. Based on the presence or absence of motion artifacts on the magnitude images, the ROI size, and so on, it is possible to infer which MRE technique is being assessed. However, readers were blinded to one another's results, and it is reassuring that similar results were obtained across the three readers.

In conclusion, free-breathing MRE and MRE with CS are feasible and have the potential to yield results similar to conventional breath-held 2D GRE MRE in volunteers with liver disease and those without liver disease. There was excellent absolute agreement and very strong correlation between all five MRE techniques under investigation. MRE with a CS acceleration factor of 1.5 showed the strongest correlation with breath-held MRE as well as the least bias. Although MRE with greater acceleration (i.e., CS acceleration factor = 3) was considered diagnostic in most participants, it was associated with the smallest ROIs and showed systematically lower stiffness measurements in participants with liver disease. We believe MRE with some level of CS and even free-breathing MRE may be useful in pediatric and adult patients with limited breath-hold capacity and, therefore, deserve further exploration.

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APPENDIX 1: Key MR Elastography (MRE) Parameters

Parameter	MRE Technique				
	BH 2D GRE	FB 2D GRE	CS With Acceleration Factor of 1.5	CS With Acceleration Factor of 2	CS With Acceleration Factor of 3
TR (ms)	50	50	50	50	50
TE (ms)	20	20	20	20	20
Flip angle (°)	20	20	20	20	20
Acquisition matrix	256 × 64	256 × 64	256 × 64	256 × 64	256 × 64
Driver frequency (Hz)	60	60	60	60	60
Motion cycles per TR	3	3	3	3	3
Slice thickness (mm)	10	10	10	10	10
Slice gap (mm)	1	1	1	1	1
Parallel imaging acceleration factor	2	2	2	2	2
Extra CS acceleration (reduction) factor	—	—	1.5	2	3
Motion-encoding gradient (ms, mT/m)	16.7, 18.4	16.7, 18.4	16.7, 18.4	16.7, 18.4	16.7, 18.4
Breath-hold time per slice (s)	13.3	—	8.9	6.9	4.9

Note—Dash (—) indicates not applicable. BH = breath-held, GRE = gradient-recalled echo, FB = free-breathing, CS = compressed sensing.