Title: Comparison of breath-hold, respiratory navigated and free-breathing MR elastography of the liver

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Abstract:

Purpose: Hepatic magnetic resonance elastography (MRE) is currently a breath-hold imaging technique. Patients with chronic liver disease can have comorbidities that limit their ability to breath-hold (BH) for the required acquisition time. Our aim was to evaluate whether stiffness measurements obtained from a navigator-triggered MRE acquisition are comparable to standard expiratory breath-hold, inspiratory breath-hold or free-breathing in healthy participants.

Materials and methods: Twelve healthy participants were imaged using the four methods on a clinical 1.5T MR system equipped with a product MRE system. Mean liver stiffness, and measurable area of stiffness (with a confidence threshold > 95%) were compared between sequences using the concordance correlation coefficient. Repeatability of each sequence between two acquisitions was also assessed.

Results: The standard BH expiratory technique had high concordance with the navigated technique (r=0.716), and low concordance with the BH inspiration (r=0.165) and free-breathing (r=0.105) techniques. The navigator-triggered technique showed no statistical difference in measurable area of liver or in repeatability compared with the standard expiratory acquisition (p=0.997 and p=0.407 respectively). The free-breathing technique produced less measurable liver area and was less repeatable than the alternative techniques. The increase in acquisition time for navigator techniques was 3 minutes 6 seconds compared to standard expiratory breath-hold.

Conclusion: Navigator-based hepatic MRE measurements are comparable to the reference standard expiratory breath-hold acquisition in healthy participants.

1. Introduction:

Liver biopsy remains the gold standard for assessment of liver parenchyma, but is an invasive technique and uncomfortable for patients [1]. The risk of a significant haemorrhage requiring transfusion or intervention due to the procedure is estimated in the literature at approximately 1 in 200 [1] [2] [3]. Mortality, though rare, is a recognized complication. An investigation that could obviate these risks would be clinically advantageous. There is increasing evidence for the use of magnetic resonance elastography (MRE) in the diagnosis of liver fibrosis [4] [5] [6] . Fibrotic livers have, amongst other factors, a higher collagen content which results in an increase in stiffness that can be quantified by MRE [7] [8].

Standard MRE techniques are phase-based and are therefore sensitive to motion artefact from respiration and blood flow [9]. Hepatic MRE is currently performed at end-expiration, and typically requires four breath holds in order to replicate the position of the liver and four slices in four breath holds to get a large sample of liver [10] [11,12]. Breathing has been shown to affect liver stiffness measurements. Horster et al reported that Valsalva manoeuvre resulted in falsely elevated measurements of liver stiffness [13]. Sequential breath holds may result in slightly differing diaphragmatic positions and different position of the liver and other viscera, which may result in misregistration effects[14]. In addition, some patients may not be able to manage the breath-holds. Respiratory triggering, using navigator echo diaphragm tracking, is an alternative method to breath-hold acquisitions [15] but is not currently supported in product MRE sequences.

The aims of this study are to 1) evaluate whether a navigated MRE sequence produces equivalent stiffness values compared to standard BH end-expiration (BHE), and evaluate the utility of the currently alternatives: BH inspiration (BHI) and free-breathing (FB); and 2) to assess and compare the relative repeatability of each technique.

2. Methods:

2. 1 Study Cohort

Ethical approval was provided for the study and all participants gave informed written consent. The studies were carried out on 12 healthy participants, with no known history of hepatobiliary or cardiovascular disease, who fasted for at least 6 hours prior to the scan. There were eight male and four female participants, with a mean age of 30 years, range [24-42 years].

2. 2 Image Acquisition

Examinations were performed on a 1.5T whole-body MRI scanner (MR450, GE Healthcare, Waukesha, WI) using an eight-channel receive array coil.

For the MRE acquisition a passive 18.5-cm-diameter pneumatic driver was placed anteriorly over the right lower ribs superficial to the right lobe of the liver. The passive driver was connected to an active drive unit producing shear waves at 60 Hz. The product gradient-echo based MRE sequence was modified to incorporate a 2D cylindrical-excitation navigator tracking acquisition. Sequence parameters were TE/TR =22/50ms, matrix 256×64, field of view = 40×36cm, section thickness = 8 mm, gap = 5mm, bandwidth = ±31.25kHz, and flip angle =

30°. A parallel imaging (ASSET) acceleration factor of 1.5 was used. Four slices were acquired with four phase offsets (0°, 90°, 180°, 270°). In the breath-hold acquisitions each offset was acquired in a separate 17-second breath-hold. MRE shear modulus-based stiffness and wave confidence interval (CI) maps were subsequently computed.

Each participant was imaged using the free-breathing, breath-hold and navigator-triggered methods, with each acquisition performed twice without subject repositioning. The order in which the sequences were acquired was randomized. BHE images were acquired following two automated instructed deep breaths, followed by an additional deep inspiration for BHI. Each breath hold was followed by free breathing for approximately 9 seconds, then BH instructions were repeated.

2. 3 Image Analysis

Image analysis was performed on OsiriX (version 4.1.2, Pixmeo, SARL, Switzerland). Regions of interest (ROIs) were defined using the boundary of the liver on each of the four slices on the magnitude images and then mapped onto the same spatial locations of the corresponding stiffness maps using copy-and-paste functionality. Approximately 1 cm of liver parenchyma closest to the liver capsule was excluded as this has been shown on previous studies to contain a higher collagen content [16] [17]. The area within this where the CI was higher than 95% was then mapped. The mean stiffness and the percentage of analyzable liver area were calculated at a per subject level across all 4 slices (Figure 1).

Comparisons between the respective methods were assessed using the mean stiffness measurements obtained during repeat scan 1. The relative repeatability of each technique was determined by computing the absolute difference in mean liver stiffness between repeat scans 1 and 2.

The regions of interest were defined by a radiologist with 7 years' experience (IM).

2. 4 Statistical Analysis

Normality assumptions were formally assessed using the Shapiro-Wilk's test. Agreement between BHE and each alternative method was assessed using the concordance correlation coefficient. A one-way ANOVA was performed to assess if there was an overall difference between each acquisition strategy; to compare the percentage areas of analyzable liver and to evaluate the absolute differences in the repeated measurements. Pairwise comparisons were performed using the paired Student's T-test. A p-value <0.05 was defined as statistically significant. The statistical analysis was performed using the R programming language (version 3.2.1, The R foundation for Statistical Computing, Vienna, Austria).

3. Results:

The percentage mean area of liver where the stiffness was quantifiable (CI >95%) and mean stiffness values are summarized in Table 1.

Table 1. Comparison of different acquisition techniques.

	Area of liver with CI >95% (%)	Liver stiffness (kPa)	Concordance Correlation Coefficient (r)
BHE	56.3±11.0	2.18±0.16	-
Navigator	52.9±8.10	2.18±0.15	0.716§
BHI	53.8±17.9	2.36±0.34	0.165§
FB	33.0±12.6	2.40±0.35	0.105§

mean±stdev §Concordance Correlation was assessed relative to the standard MRE acquisition strategy BHE

3. 1 Mean Liver Stiffness

The highest agreement was noted between the standard BHE method and the navigated sequence (r=0.716). The concordance between BHE and the currently available alternative acquisition strategies were markedly lower (BHI: r=0.165, and FB: r=0.105). However, the overall difference in liver stiffness between the acquisition strategies was not statistically significant p=0.109 (Figure 2). We note that liver stiffness during inspiration is slightly elevated relative to expiration. The stiffness using the navigator method was not significantly different to the standard BHE method (p=0.997). The free-breathing approach showed a trend towards an elevated mean stiffness, but this was not statistically significant (p=0.06).

3. 2 Areas of Analysable Liver Stiffness

The overall differences in liver area where CI > 95% were statistically significant (p<0.001) (Figure 3). The navigated and standard BHE areas were equivalent (p=0.407). The navigated, BHE and BHI acquisitions all produced significantly larger areas of measurable liver stiffness compared to the FB acquisition (p<0.001, p<0.001 and p=0.003 respectively).

3. 3 Repeatability

The group-wise comparison of MRE repeatability (Figure 4) shows that the navigator method has comparable repeatability to the expiration and inspiration methods, whereas the free-breathing approach was more variable. The overall difference between the groups was not statistically significant (p=0.195)

3. 4 Acquisition Time

The mean acquisition time for the navigator-triggered acquisition was 4 minutes 55 seconds. The mean time was 1 minute 7 seconds for the FB technique and 1 minute 49 seconds for both the expiration and inspiration techniques due to the recovery between breath-holds. The overall mean time increase for the navigator-triggered compared with the standard BHE acquisition was 3 minutes 6 seconds.

4. Discussion:

This study is the first report of hepatic MRE in which we demonstrate that a navigator triggered free-breathing approach results in equivalent liver stiffness measurements to the standard BHE approach. The results also demonstrate that free-breathing without triggering, which occurs in practice when patients fail to comply with BH instructions, had a trend towards higher hepatic stiffness values and generated stiffness confidence maps with significantly less liver area with CI > 95%.

Methods for overcoming respiratory motion artefact in hepatic MRI exist [18,19]. MR Elastography presents certain specific difficulties in this regard. For synchronization with continuous vibration of the external driver, the TR is an integer multiple of the number of cycles of external vibrations (CEV) [20], which for four slices, requires a 22 s breathhold. We used a parallel imaging acceleration factor of 1.5 to give a 17 second breath hold, to make it more tolerable. Elderly and cirrhotic patients, who may have cerebral, cardiac and respiratory co-morbidities, may have difficulty managing even 17 seconds, or the 11 seconds that has been achieved using other acceleration techniques [20]. Breath-holding failure is likely to yield results closer to the non-triggered free-breathing technique. We speculate that, in patients with likely co-morbidities, a navigator-triggered acquisition will give more consistent results, for a time increase of approximately three minutes. Preliminary reports in a single participant from the Mayo Clinic suggest that times as low as 4 seconds may be achieved using techniques such as echo planar imaging and parallel imaging [21] which may allow for even faster navigator triggered acquisitions. Other factors are known to influence the measured hepatic stiffness, in particular the post-prandial state, due to the increased portal venous blood flow associated with digesting a meal, can increase the stiffness, hence we ensured that all participants were fasting for at least 6 hours prior to the procedure [22,23]. Similarly, a study examining the effect of breathing techniques using ultrasound elastography has shown that end-expiratory and end-inspiratory timing can produce different measurements of stiffness [24]. The point at which a subject feels they are at end-expiration or end-inspiration is subjective. The use of free breathing, with navigator triggering, allows a more reproducible measurement. Qualitatively the addition of the navigator did not alter or degrade the quality of the MRE images, and the stiffness measurements between navigated and non-navigated were very similar, see figure 5.

The study has certain limitations. The study population is small but sufficient to demonstrate that that navigated images are comparable to standard expiratory imaging. There were no participants with chronic liver disease, only healthy participants, so the dynamic range of liver stiffness was much smaller than in a clinical population. Future work would need to evaluate the navigated approach in a larger population of patients with chronic liver disease ideally with a range of severity of liver fibrosis. The use of newer acceleration techniques and echo-planar acquisitions are also likely to facilitate improved results and reductions in motion related artefacts. These methods may also benefit from the use of navigated based acquisitions avoiding the need for breath-holding.

5. Conclusion

Our study shows that a navigator-triggered hepatic MRE technique is comparable in terms of mean liver stiffness, measurable area and repeatability to a standard expiratory breath-hold sequence. This technique may prove useful clinically in patients with chronic liver disease unable to breath-hold.

Acknowledgments

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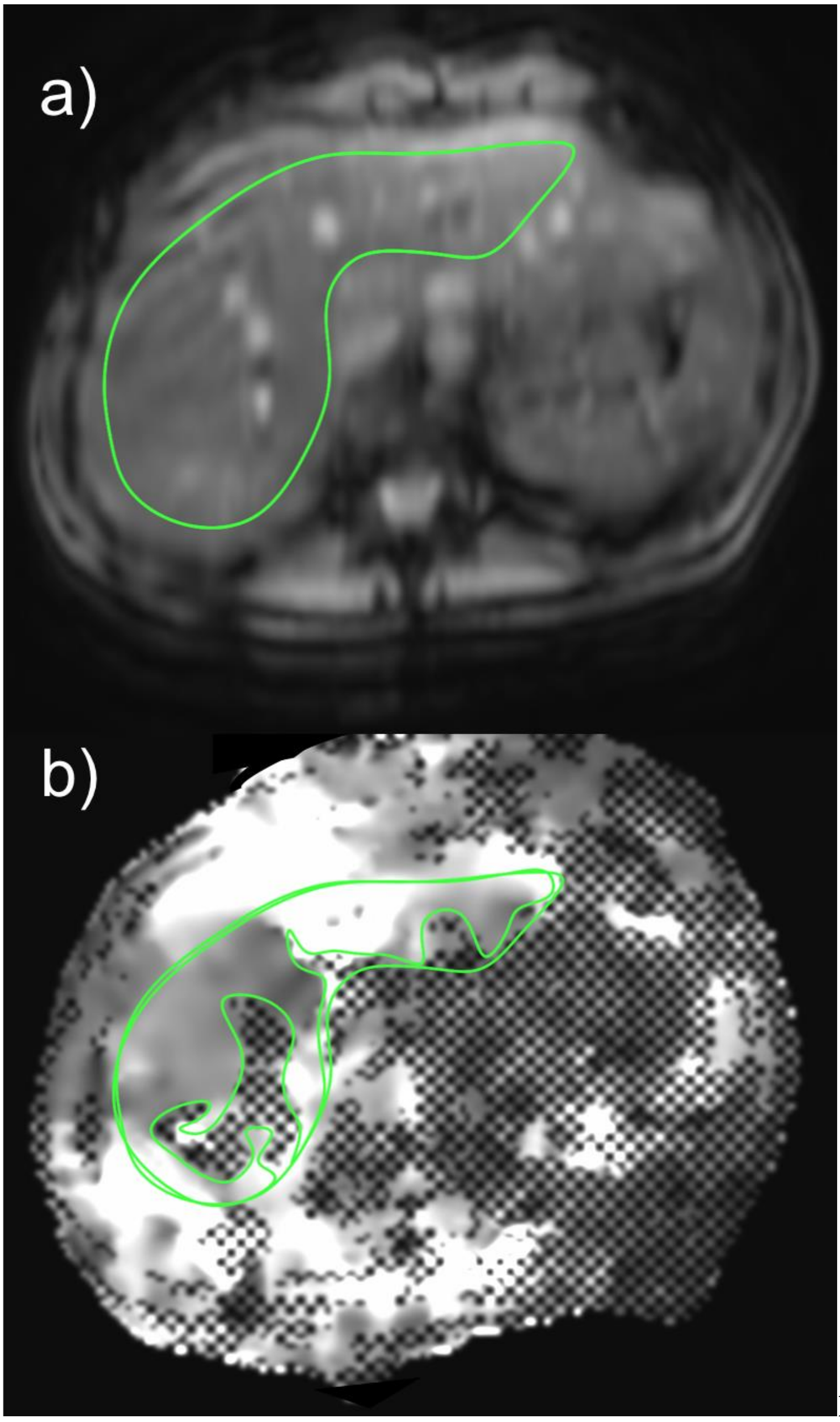

Figure 1.

Example MRE images obtained using the navigator-triggered method. Fig 1 (a) magnitude scan and (b) shear modulus-based stiffness maps, with areas with CI <95% cross-hatched. The ROIs show the outline of the liver (a) and the outline of the analyzable area in (b). The analysable percentage of liver (CI > 95%) was 48%. The mean liver stiffness was measured at 2.2 kPa +/- 0.45.

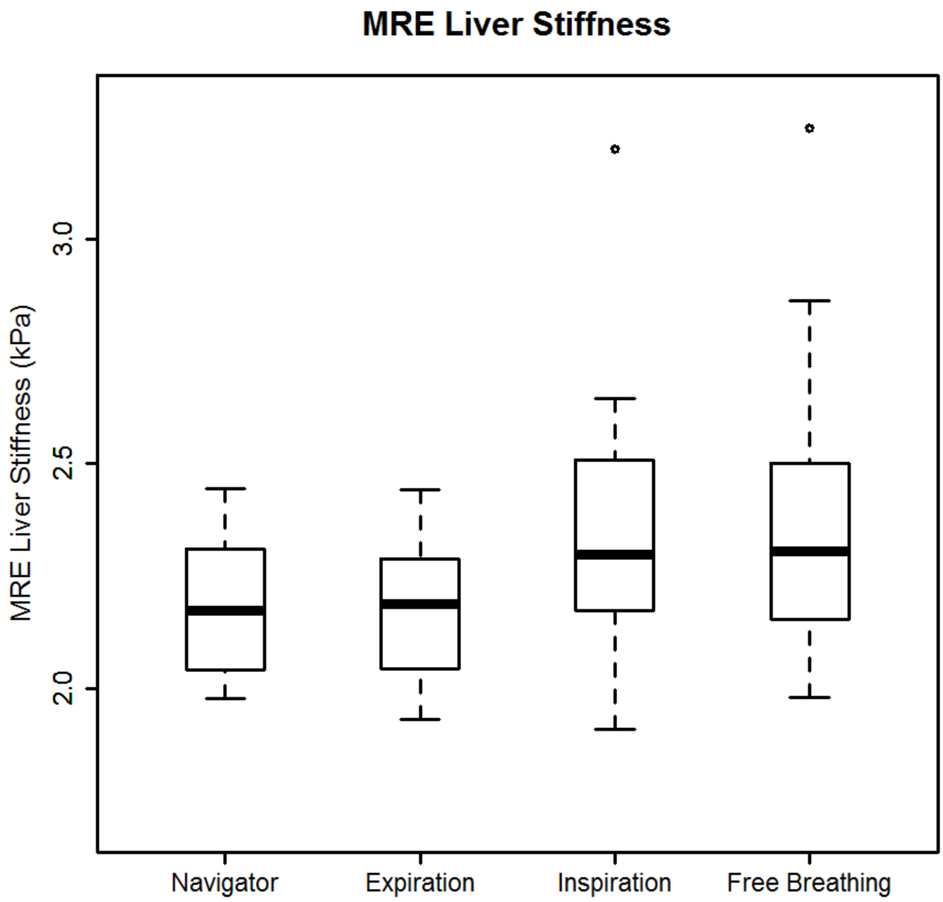

Figure 2. Liver stiffness measurements using different acquisition techniques. No statistically significant differences in liver stiffness were noted between acquisition strategies p=0.109

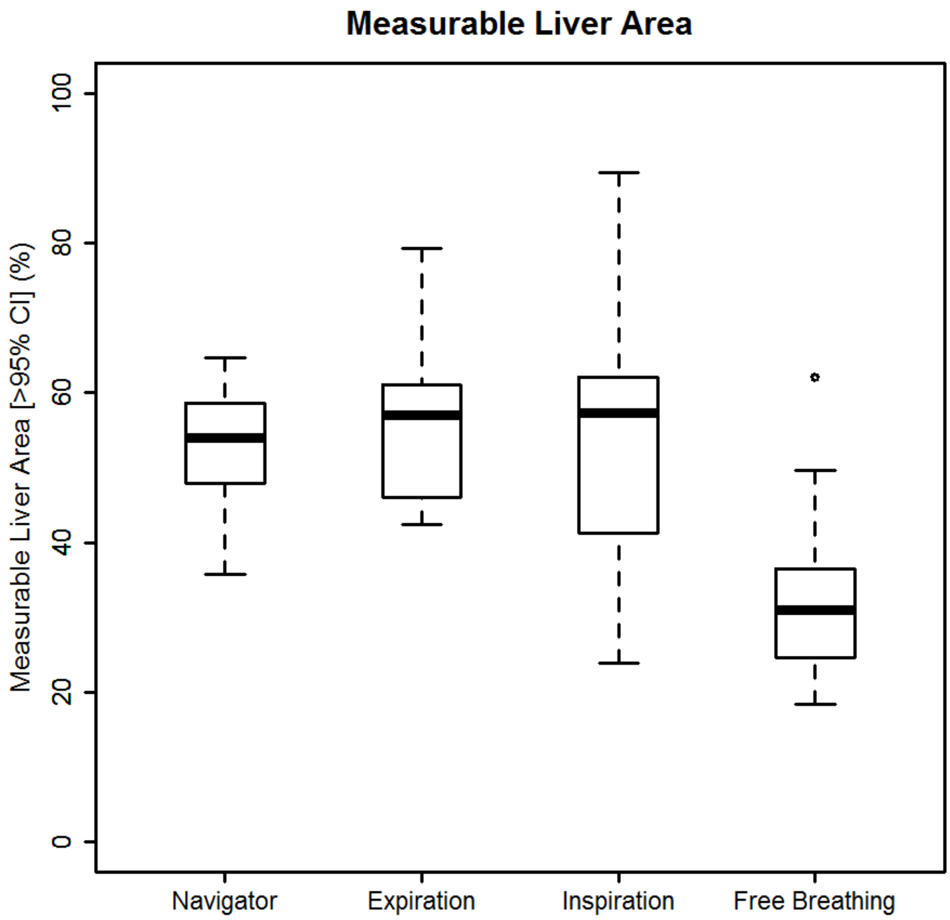

Figure 3. Measurable liver area (percentage with CI >95%) using different acquisition techniques. The navigated, BHE and BHI acquisitions all produced significantly larger areas of measurable liver stiffness compared to the FB acquisition ($p<0.001$, $p<0.001$ and $p=0.003$ respectively). The navigated and standard BHE areas were equivalent ($p=0.407$).

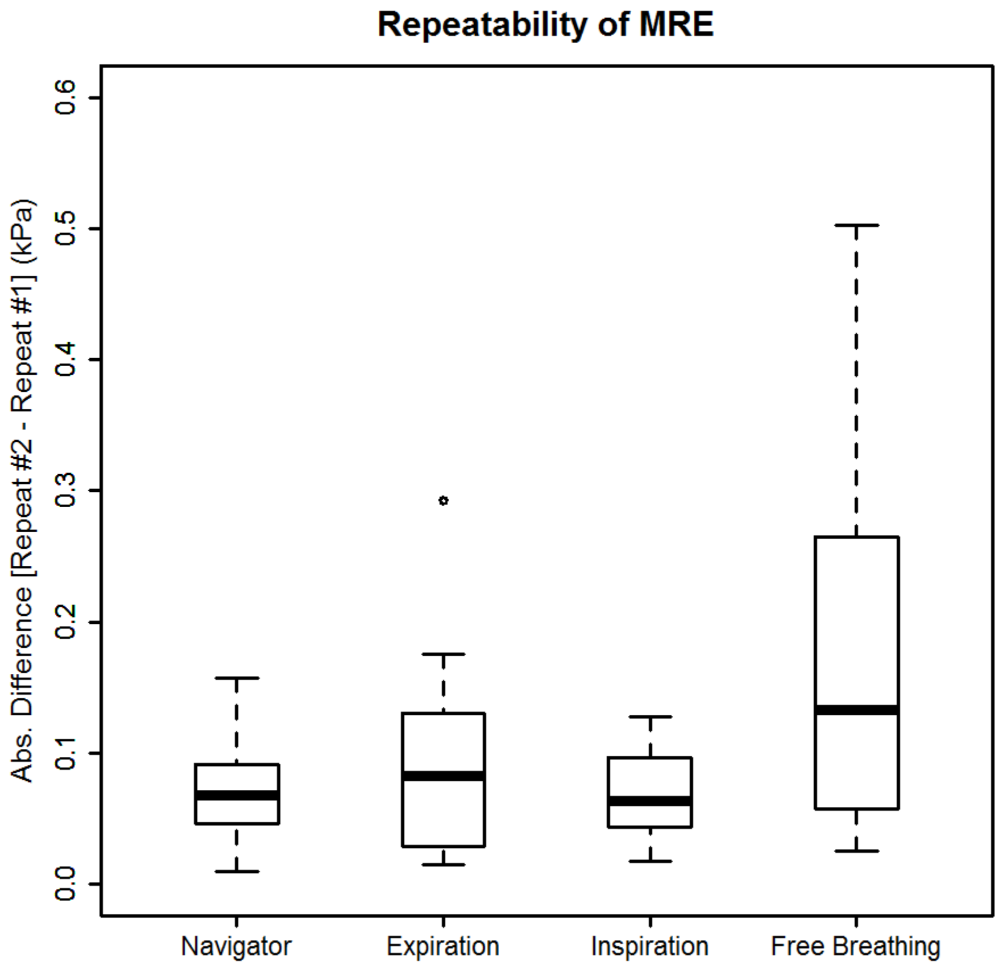

Figure 4. Repeatability of each acquisition techique. The navigator method has comparable repeatability to the BHE and BHI inspiration methods. The free-breathing approach was more variable.

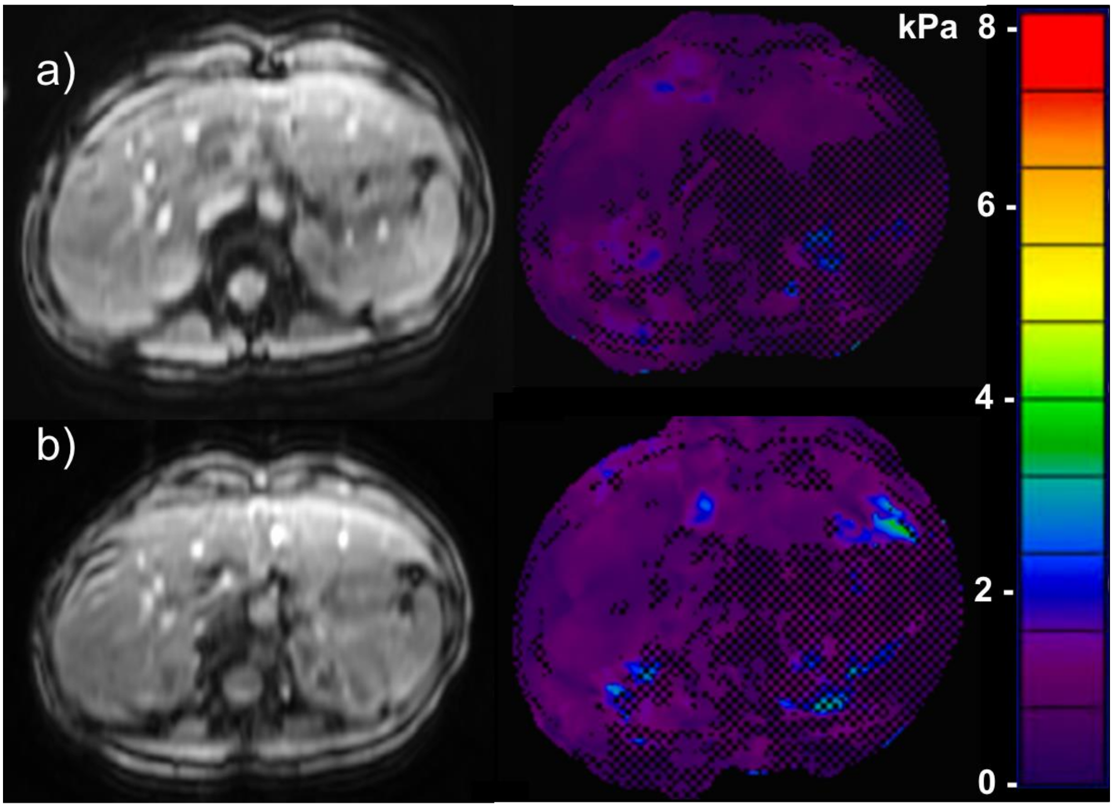

Figure 5. Comparison of image quality of magnitude images and colour stiffness maps for navigator triggered (a) and BHE (b), from the same slice position in the same patient. Qualitative assessment of image quality is very similar, and there is no visible artefact from the navigator. Colour kPa scale is shown on the right, liver parenchymal stiffness values are all within normal limits for healthy volunteers.

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