Magnetic Resonance Elastography of the Liver: Best Practices

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Introduction

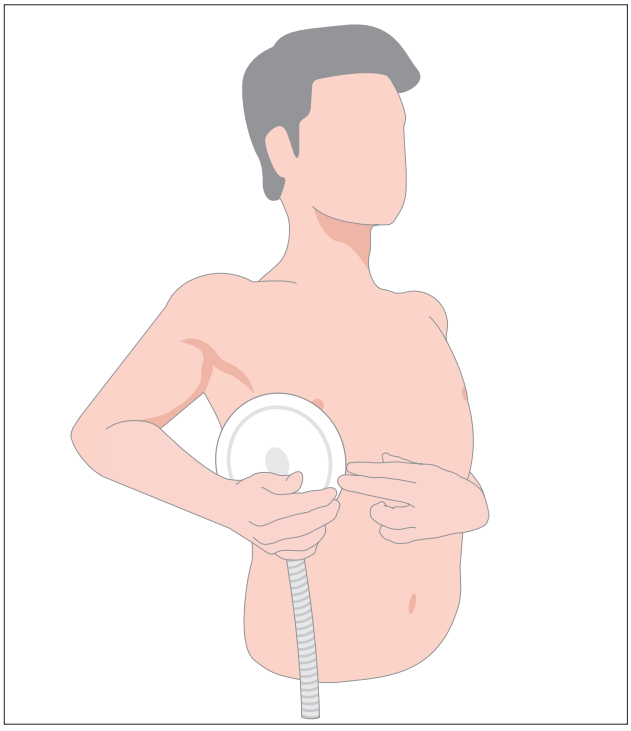
Liver is the largest solid internal organ of the human body. It performs a wide range of functions including aiding digestion, storing energy, removing metabolic waste and microorganisms from the circulatory system, and producing blood-clotting components. The liver can repair, regenerate and/or regrow itself to maintain its structure and functions, yet certain health conditions can overwhelm these capabilities leading to the progression of liver disease [1]. Alcohol abuse, obesity, and chronic illness can lead to excessive accumulation of extracellular matrix proteins including collagen. This results in diminished blood flow and the subsequent build-up of scar tissue in the liver known as liver fibrosis [2].

Liver fibrosis in its initial and moderate stages causes no clinical symptoms by itself and can often be missed by routine blood tests or by medical imaging examinations. Fibrosis can be treated and reversed on early detection; however, if this condition is left untreated for a long time, it may lead to a severe condition called cirrhosis. Once cirrhosis has developed, clinical symptoms and their associated problems may begin to appear, and eventually liver damage becomes permanent and irreversible [3]. Therefore, early detection of liver fibrosis plays an important role in treatment and disease management.

Traditionally, liver fibrosis is diagnosed and staged by percutaneous liver biopsy, an invasive technique. Lately, non-invasive methodologies such as blood serum tests and medical imaging techniques have emerged as an alternative to biopsy. However, serum tests such as APRI, FIB-4, and other commercial assays have proven less accurate than the imaging modalities [4] such as ultrasound (US) elastography and magnetic resonance elastography (MRE) for staging fibrosis. Several studies comparing MR- and US-based elastography techniques concluded that the MRE has been shown to exceed all other diagnostic methods in terms of accuracy, sensitivity, specificity, and organ coverage [5].

Magnetic Resonance Elastography

MRE is a non-invasive technique to estimate the stiffness of soft tissues. Given the non-invasive nature and accuracy of diagnostic results, in recent years MRE has become a standard clinical tool to stage liver fibrosis on both 1.5T and 3T scanners [6]. MRE can be acquired with or without contrast agent on board [8], meaning it can be performed at any point in a standard clinical examination, depending on site preference.



1 Illustration of the passive driver placement for liver MRE imaging. The entire flat surface of the drive should be in contact with the subject's upper abdomen at the fifth intercostal space and lateral to the mid-clavicular line.

The liver MRE technique can be separated into four elements as described below.

1. Inducing shear wave motion into the liver using an external mechanical driver
2. Acquiring wave images of the liver via motion encoding and phase-contrast imaging
3. Reconstructing stiffness maps from the wave images using an inversion algorithm
4. Reporting average stiffness values in ROIs identified in the liver stiffness maps as having good wave quality and no artifacts

Liver MRE has been described in a QIBA profile [10], which also gives practical guidance for performing MRE and interpreting the results. Conformance to this profile supports the claim that a change in measured hepatic stiffness of at least 19% is considered to be real with 95% confidence.

This article reviews the essentials of MRE and provides best practice for its routine clinical usage. To clinicians, the MRE technique offers the special benefit that all major MR manufacturers adopted the same standard solution, hardware and inversion algorithm, and high reproducibility has been demonstrated [6]. This uniformity makes the interpretation of diagnostic results much easier, especially in centers where multiple platforms are used. However, some image acquisition sequences and workflow options may differ, so in the following, the focus will be on the Siemens Healthineers platform.

The most commonly used and commercially available solution (Resoundant Inc, Rochester, MN, USA) induces continuous single frequency mechanical shear wave motion in the liver using a special hardware complement to the MR system that consists of an active driver (frequency generator) and a passive driver (plastic drum), and a standardized inversion algorithm implementation [17].

Insert 1: Best practice workflow

Pay attention to the following workflow elements to improve chances of performing a high quality MRE exam.

1. Inspect the hardware regularly for any damage to the passive driver diaphragm, or air leakage in the tubing system.

2. Turn the active driver (off and) on prior to each examination to wake it up from standby mode.

3. Place the elastic belt on the MR patient table at liver level and position the patient in a supine position with head-first. Position and secure the passive driver as explained in the section *Driver setup for liver MRE*. Lateral placement is preferred over anterior placement but good contact between the driver face and the subject's abdomen is critical.

4. Direct the end of the passive driver tubing towards where it will connect to the tubing from the active driver. In some cases this may be at the back of the bore.

5. Fasten the belt tightly. Ask the subject if they can breathe normally with the belt; if not, adjust the belt. Inform them about expected examination duration, order of sequences, that the Elastography is performed at end-expiration, and that they will feel vibrations coming from the driver during the activation. Repeat the latter to the patient just before the MRE sequence to avoid them being startled.

6. Verify passive driver positioning in scout images in relation to the liver at end-expiration and other landmarks. Adjust the driver as necessary.

7. Run the MR Elastography sequence and acquire the images at end-expiration.

8. Load the results into the Viewing Task Card and review image quality as described in the section *Postprocessing and evaluation* (magnitude for breathing artifacts, wave images for good propagation along with depth penetration, and confidence mask for successful inversion). In case of insufficient quality, check driver positioning and repeat, using a modified protocol where appropriate, e.g., in case of iron overload.

9. Measure stiffness via ROI evaluation as described in the section *Postprocessing and evaluation*.

Driver setup for liver MRE

Positioning of the passive driver on the subject (Figure 1) is one of the most critical steps in an MRE examination. Optimal driver positioning ensures that the externally generated mechanical waves are transferred to the subject efficiently and thereby penetrate deep into the liver. This helps achieve the desired anatomical coverage and obtain stiffness measurements with high quality.

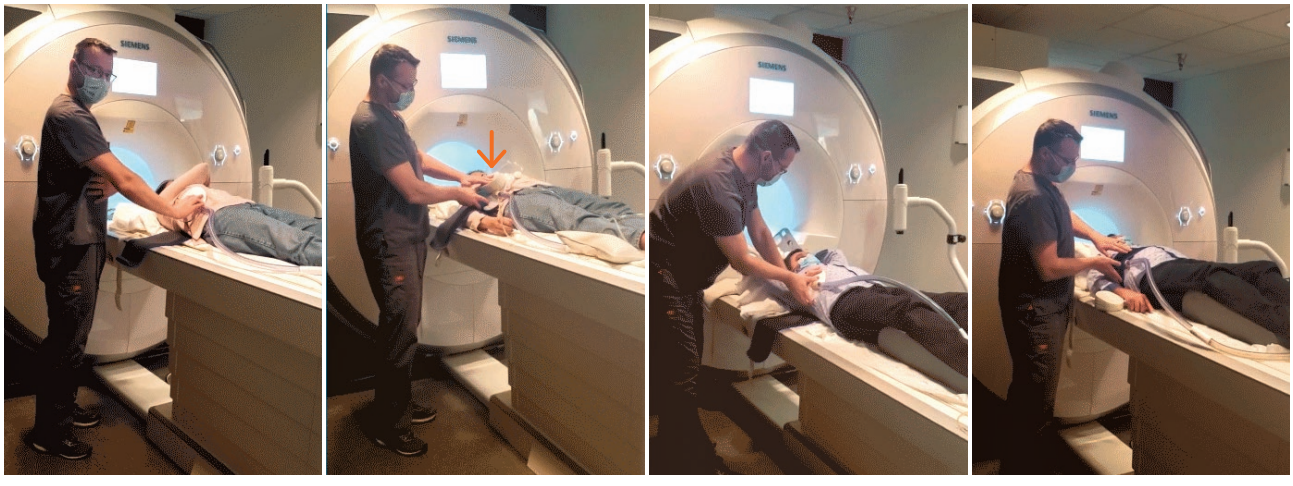
To enable the performance of reliable human liver MRE, the passive driver is placed on the upper abdomen centered at the fifth intercostal space but lateral to the midclavicular line as shown in Figure 1. While positioning the passive driver it is necessary to make sure that the driver's flat surface area is fully in contact with the body close to the liver.

To maintain the passive driver in one fixed position throughout the imaging session, it is necessary to immobilize it with a dedicated elastic belt firmly while ensuring the subjects' comfort to breathe normally. To improve contact between the subject and the passive driver it is advisable to use extra cushioning material such as a sponge or clothing materials (as shown in Figure 2) in between the passive driver and the belt to tightly hold the driver against the body. This enables mechanical waves to be delivered to the region of interest uniformly throughout the imaging session. Finally, it is important to ensure that the passive driver is connected tightly to the active driver via plastic tubing so that there is no air leakage. It may be advantageous to connect the remaining tubing only after the subject has been moved into the scanner.

After placing the driver, it is important to verify that the driver is positioned correctly, i.e., centered in H-F direction with respect to the liver. If collected at end expiration localizer images of sagittal and axial views like those in Figure 3 will show the placement of the driver. The indentation on the sagittal view indicates that the driver is placed at the center with respect to the liver. Similarly, the axial view will show the indentation anterior to the liver. If the position of the driver is not correct, then the driver must be adjusted with respect to these landmarks.

Sequence optimization and image acquisition

The Siemens Healthineers MRE product consists of two sequence options, a GRE based sequence with an optional rapid acquisition mode (see Figure 4) and a sequence based on single-shot spin-echo echo planar imaging (SE-EPI). Both sequences acquire 2D axial slices in the center of the liver at end-expiration with through-slice motion encoding and include a fractional encoding option to shorten TE (Figure 4). The SE-EPI MRE acquisition is more efficient and should be the default acquisition where possible. The primary benefit of SE-EPI is that multiple slices are acquired in a single 11–13 seconds breath-hold and the SE-EPI component makes the sequence more robust to susceptibility that occurs with liver iron loading or with higher field strengths. Fat saturation is very important for SE-EPI; SPAIR-strong is the preferred fat suppression setting for this sequence. GRE MRE requires multiple breath-holds (one per slice), however, in some situations such as where implants exist and lower radio frequency flip angles are necessary, or if referencing previous GRE MRE studies, it can be the sequence of choice. Standard imaging parameters for the two sequences are shown in Table 1 and the standard Siemens Healthineers protocol tree for

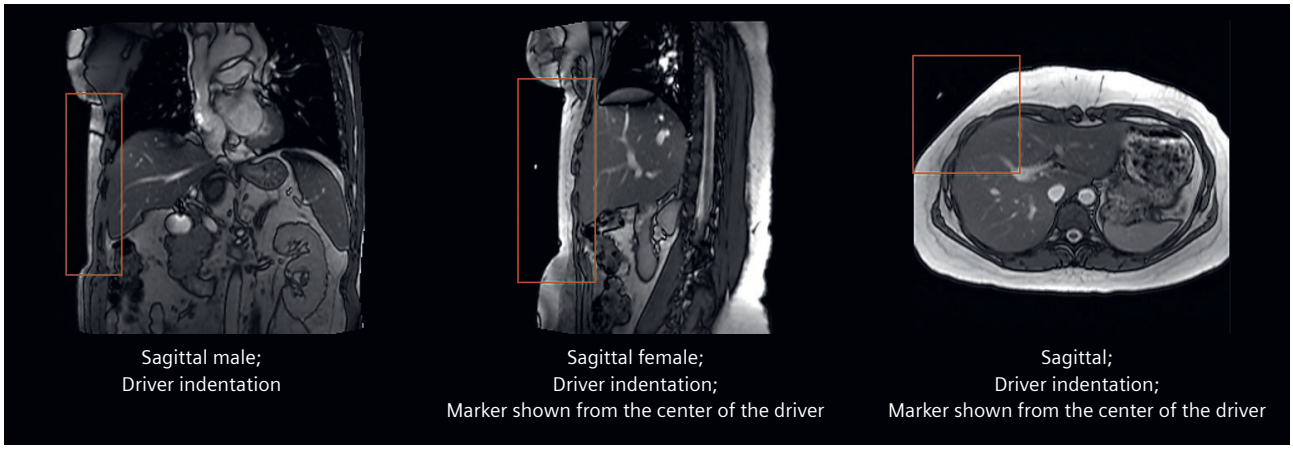


2 Demonstration of MRE setup and driver placement for liver imaging, using the dedicated elastic belt, plus cushioning material (arrow).
Watch the videos on https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/body-pelvis/mr-elastography

MR Elastography is shown in Figure 5. As previously mentioned, an MRE protocol can be added either at the beginning (pre-contrast) or the end (post-contrast) of a measurement program.

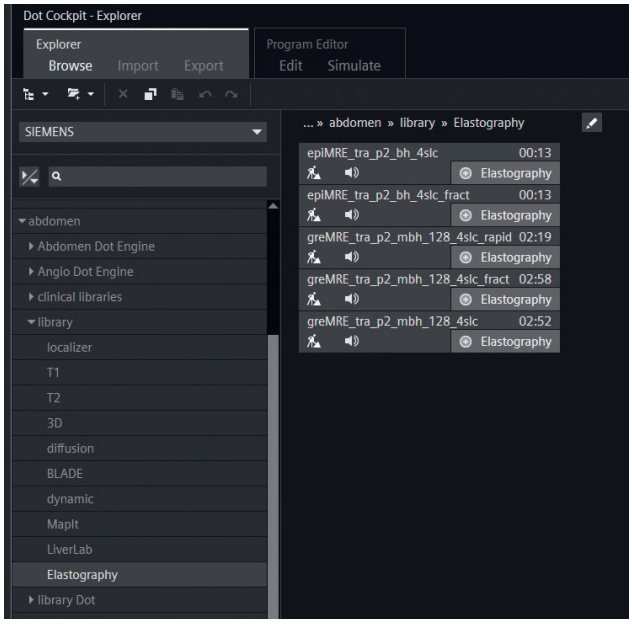
The mechanical excitation frequency is fixed at 60 Hz, and the amplitude of the active driver is typically set to 40%, which will work well, irrespective of body habitus, in 85% of the patients. If the current driver amplitude should lead to either too much or too little motion encoding, some control over the motion encoding strength is possible using the Gradient mode UI parameter, since the amplitude of the motion encoding gradient (MEG) will scale with it: It is lower for Normal and higher for Fast Gradient mode.

The active driver is activated ("triggered") via the sequence, and automatic breath-hold commands can be used. Make sure that both MRE and the localizer are acquired in end-expiration.



3 Localizers illustrating the driver placement for an optimized MRE liver examination. Positioning the driver center to the liver facilitates uniform propation of waves in the region of interest. (An MR visible fiducial has been added to the passive driver in this case showing the center of the passive driver in these images.)

4 Example parameter card for a GRE MRE protocol in Rapid mode (TR 25 instead of 50 ms, petrol highlight). Shortening the TE below the gap in the range bar (orange highlight) would activate fractional motion encoding (which may boost signal at the expense of sensitivity, but this is only recommended for cases with short T2*).



5 The Siemens Healthineers protocol tree for Elastography representing all MRE options: epiMRE with and without fractional encoding, and greMRE in its standard, rapid and fractional encoding configuration.

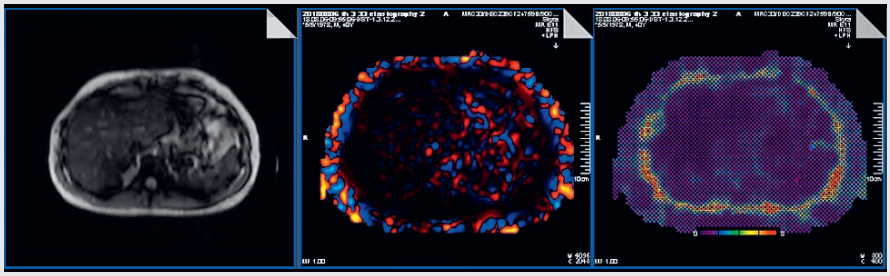
Parameter	SE-EPI MRE	GRE MRE
FOV	420 mm (x 100%)	420 mm x 70–100%
TR	1000–1200 ms	25[a] or 50 ms
TE	47 ms or lower[b]	21 ms or lower[b]
Slice thickness	8 mm, 25% gap	10 mm, no gap
Acquisition matrix	100 x 100%	128 x 80%
Bandwidth	2170 Hz/pixel	399 Hz/pixel
Gradient Mode	Normal, Fast[c]	Normal, Fast[c]
GRAPPA factor	2	2
GRAPPA reference lines	24 GRE/separate	12 integrated
Fat saturation	SPAIR – strong	none
Other key settings	Prescan Normalize, Adaptive Coil Combination	

Table 1: Typical sequence parameters for MRE.
[a] Selecting a TE of 25 ms will put the GRE MRE sequence into "Rapid" mode [14] (see Figure 4).
[b] Selecting TE lower than the gap in the sequence UI (see Figure 4) will cause the motion encoding gradients to be shortened to 65% of full ("fractional" encoding [15]); this is beneficial for short T2 / T2*, but will also reduce motion encoding, so it is only recommended for problem-solving.
[c] The gradient mode will influence the motion encoding via the MEG amplitude; start with Normal, and if there is not enough motion encoding, go to Fast.
Protocols (.exar1 files) are available for download at https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/body-pelvis/mr-elastography

Insert 2: Trouble shooting

No waves or inadequate waves in the liver (Figure 6)

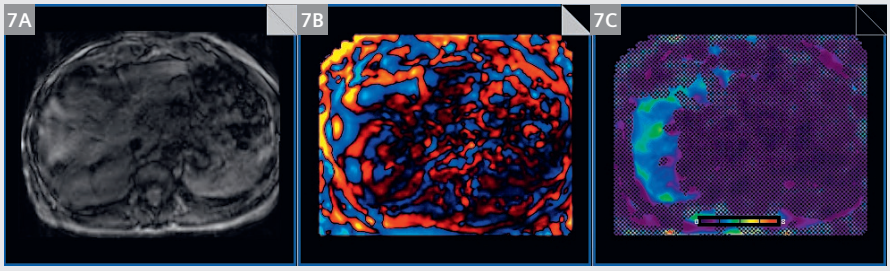
1. Check tubing for disconnection and pneumatic pressure leakage. Make sure that the passive driver diaphragm (flat surface) is not damaged.
2. Make sure the passive driver has a good contact with the subject's body and is positioned correctly as shown in Figure 2.
3. Make sure the active driver is turned on and not in standby mode.



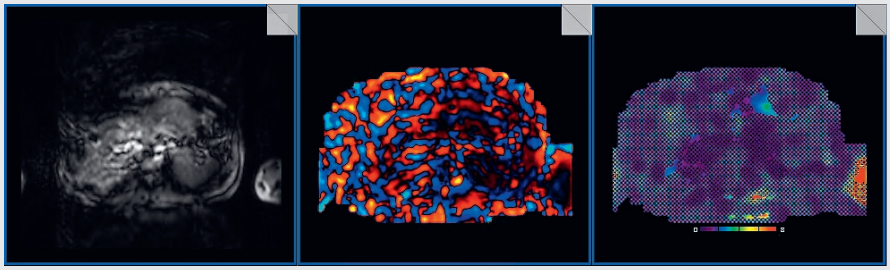
6 Example of a scan without mechanical vibration. The reason could be a disconnected pressure hose, or an active driver in standby mode.

No planar waves (Figure 7, Figure 8)

1. Adjust the driver position lateral to the center of Xiphoid as shown in Figure 1.
2. Check the localizer images as shown in Figure 3 to ensure the driver position is correct. If not adjust the driver position accordingly.
3. Additional care must be taken in imaging women and obese subjects in placing the driver laterally by moving the breast to have adequate planar waves in the liver.



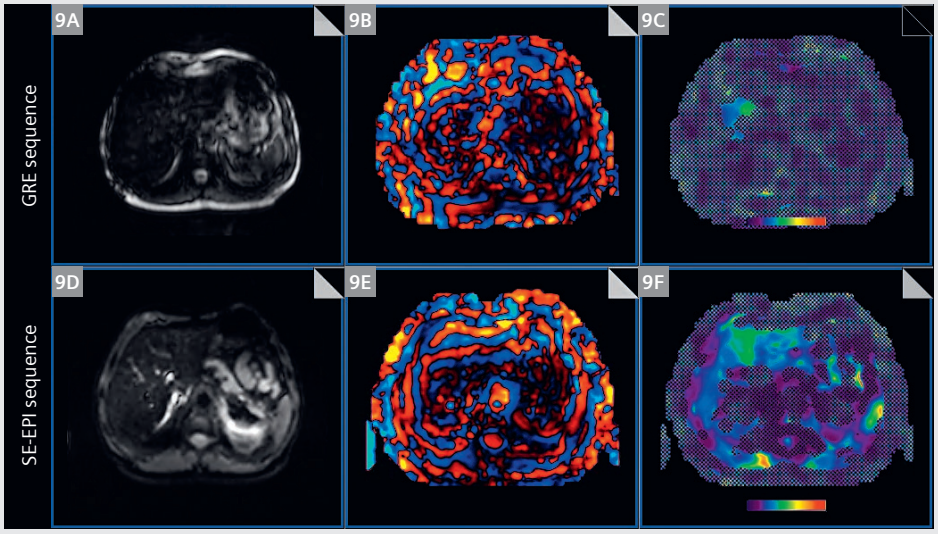
7 Volunteer example at 1.5T with bad placement of the passive driver. **(7A)** Magnitude, **(7B)** wave image with incoherent wave pattern, **(7C)** elastogram with 95% confidence markings.



8 Example of a scan with erroneous driver triggering (Rapid GRE). The reason could be a wrongly set mechanical frequency on the active driver, or a wrongly configured trigger output (optical-to-electrical converter).

Signal loss through transverse relaxation (Figure 9)

The motion encoding gradient between excitation and acquisition in the sequence timing causes echo times to be comparatively long, e.g., ~20 ms for gradient-echo sequences and ~50 ms for SE-EPI sequences. Long echo times in turn make the sequences prone to signal loss if the transverse relaxation times (T2 or T2*) are short, which can be the case at 3T or with hepatic iron overload. Image acquisition parameters should be adjusted for these scenarios. The GRE based MR elastography technique does not perform well on iron overload liver; however, the SE-EPI based technique can be deployed with customized parameter settings [11] to obtain diagnostic quality images.



9 Volunteer example at 3T with R2* ~ 90 s-1, corresponding to a liver iron content of ~1.5 mg/g dry weight. **Top row**: GRE sequence, **bottom row**: SE-EPI sequence. **(9A, D)** magnitude, **(9B, E)** wave image, **(9C, F)** elastogram with 95% confidence markings.

Postprocessing and evaluation

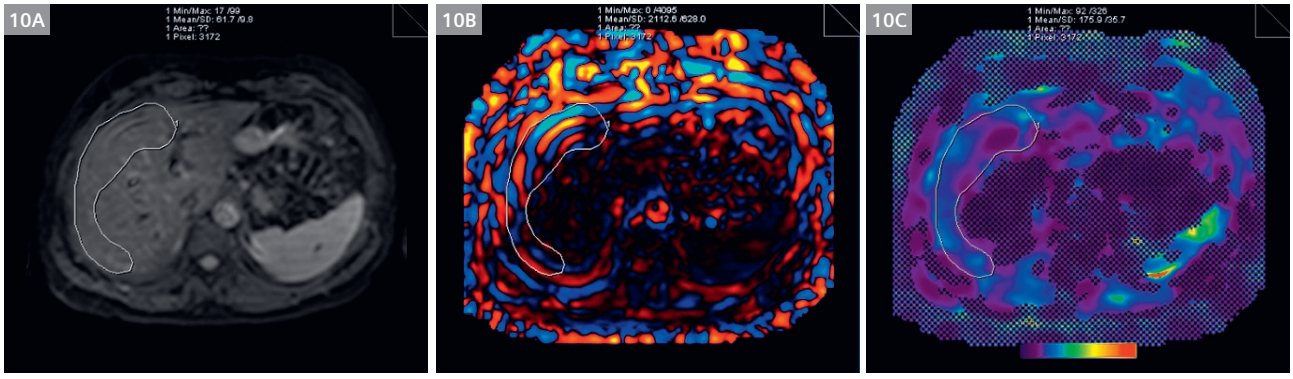
The phase difference images are processed for the standard MRE option using an inline implementation of Resoundant's MMDI inversion algorithm to generate the stiffness maps called elastograms. Stiffness is calculated as the magnitude of the complex shear modulus [18]. The output further contains the original magnitude and phase difference images, and additional computed output: confidence map, stiffness map with confidence markings, and finally colored interpolated wave images. The confidence map is based on the wave quality, i.e., which includes wave signal-to-noise-ratio (SNR) wave amplitude and shape. Then, the stiffness map uses a 95% threshold of the confidence map (shown as unhatched area) to determine the regions to trust within the liver parenchyma and report the stiffness values. Figure 10 shows an example of output series obtained in one healthy volunteer.

The image quality of the data should be analyzed further to determine if any motion artifacts exist which are typically a result of improper breath-hold. The artifacts appear in the magnitude image as blurring or ghosting in the phase encoding direction. Additionally, the wave images (colored images of the output from the scanner) are also qualitatively analyzed to determine discernible waves propagating in the liver as connected wave fronts as shown in Figure 10.

The stiffness map is generated using a color scale from 0–8 kPa; a grayscale reading of 100 corresponds to 1 kPa. Note that all colorized maps are natively grayscale images displayed using a color lookup table; hence, they can be windowed, and ROI measurements can be made directly from them[1].

For repeatable measurements, a large region of interest is drawn in the liver parenchyma excluding the hatched region, avoiding the large vessels and at least 1 cm in from the edge of the liver. Note that the cross-hatched regions contain pixels of value zero, so they must not be included in ROI measurements. If in doubt, propagate ROIs to the stiffness map without cross-hatching. Make sure that the wave images show planar wave propagation in the selected region and avoid areas close to the liver edge and the left lobe. Divide ROI mean values by 100 to report the mean stiffness value in kPa. Hot spots in the stiffness maps that occur under the MRE driver or at the liver periphery are typically due to over driving or wave reflections respectively and should be avoided when drawing the ROIs. However, it is acceptable to include small artificial hot spots in the center region of the parenchyma as these may not change the mean stiffness value significantly. In Figure 10, it can be observed that planar waves penetrate throughout the liver and the stiffness map shows sufficient coverage of the liver to report the mean stiffness. Table 2 shows typical stiffness values used to stage liver fibrosis [19]; a meta-analysis [20] reported slightly different values. We advise the user to consult the scientific literature for latest studies which best match their clinical environment.

Stiffness values are generally independent of field strength. However, increased sensitivity to susceptibility effects such as iron overload cause signal loss in the liver parenchyma to be more prevalent at higher field strengths.



10 Scan results (SE-EPI) from a healthy volunteer. **(10A)** Magnitude, **(10B)** wave image, **(10C)** stiffness map with 95% confidence mask overlay; note the color bar indicating the color map distribution across the 0–8 kPa range. Planar wave propagation can be inferred from the uninterrupted wave pattern in the ROI. The manual free-hand ROI contours select regions of high wave quality while observing anatomical placement and the confidence mask.

[1]*Some PACS systems may not be able to retain these properties. Depending on syngo MR software version, there may be transfer/export settings to manage this.*

F0	F1	F2	F3	F4
3.00 ± 1.12 kPa	3.11 ± 0.82 kPa	3.87 ± 1.85 kPa	4.78 ± 1.89 kPa	6.52 ± 2.34 kPa

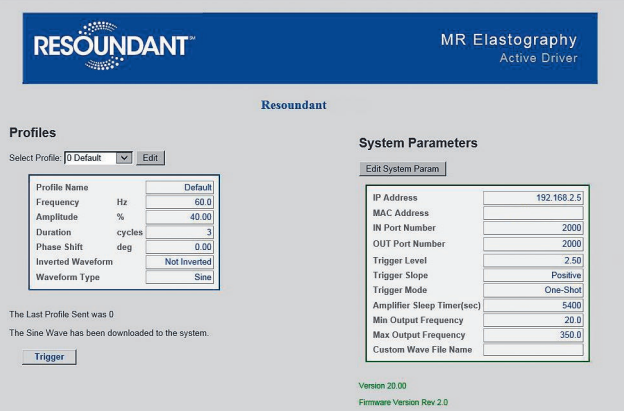
Table 2: Mean ± standard deviation values of MRE-derived liver stiffness for different fibrosis stages from 289 patients according to [19].

Insert 3: Setup and configuration

The hardware part of the MRE option is set up by a service engineer. Settings of the active driver can typically be configured once and remain unchanged thereafter. Details can be found in the operator manual [16]; some of them are given here for reference.

Figure 11 is a screenshot of the active driver's configuration page which can be accessed via a web browser and Ethernet connection, which may be a special research configuration[2]. The number of cycles per trigger is set to 3 for both GRE and SE-EPI MRE sequences as they are each designed to trigger the active driver every 50 ms. In pediatric patients[3] or in the 15% of adult patients with very large or very small body habitus, it can be beneficial to change the driver amplitude.

Note: If you have an older driver with earlier firmware (< version 2.0 as shown in the lower right-hand corner of the configuration screen), the driver frequency will need to be set to 60.1 Hz in order to sync correctly with the incoming triggers from the sequence. Additionally, the driver has a sleep timer configured in the lower part of the right-hand column on the configuration page. After the preset amount of time, the amplifier will go to sleep and no longer respond to triggers. To wake up the unit either depress the Trigger button on the configuration page or manually cycle the power on the unit. Without this sleep timer, damage to the driver can occur, greatly limiting its lifespan.



11 Screenshot showing the MRE active driver setting card (Resoundant Inc, Rochester, MN, USA) containing all necessary parameters for either MRE sequence at the proper frequency and amplitude.

[2]Please work with your MR Collaborations scientist and your service engineer if this special configuration is necessary at your site.
[3]MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

Summary and take away points

It was the intent of this article to give Siemens Healthineers MRE users, both new and experienced, guidance on how to consistently perform MRE with high-quality results. The content is weighted heavily on achieving a good patient setup with proper passive driver positioning. We have found that driver positioning can be highly variable in practice and is a major contributor to non-diagnostic MRE exams. Using the described workflow, however, it was shown that achieving measurable areas from 65% to 85% of liver coverage, our definition of a successful exam, is possible. Further, reproducibility of the results not only depends on patient setup and scanning workflow, but also on standardized image interpretation, quality checks, and ROI measurements. Therefore, the guidance provided includes these topics as well.

Once the MRE option is set up and configured correctly (see Insert 3), and the workflow for scanning, reading, and reporting is established, the procedure should be kept

unchanged to achieve low variability between examinations. In Insert 1 we summarize a best-practice workflow that includes some elements that may not be commonly considered. With its additional hardware and patient setup, the MRE acquisition has some inherent complexities not present in other MR imaging applications. Optimal wave propagation can depend on multiple factors ranging from hardware functionality to setup to exiting patient pathology. To address some of the more common scenarios we have provided a troubleshooting guide as Insert 2.

Finally, it should be noted that the current standard MRE solution is tailored to breath-hold liver applications by only acquiring a low number of slices and only encoding a single (through-slice) motion direction. This implicitly makes simplifying assumptions of in-plane, planar wave propagation without reflections. This also makes localized stiffness readings, e.g., by liver segment, less reliable. Thus, this "2D" standard solution cannot easily be transferred to other organs in the abdomen, or to other body regions. There exist prototypes with contiguous coverage of larger regions and "3D" motion encoding in all three spatial directions [12], as well as dedicated applications in other body regions [13].

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