Dear Professors, Hu, Kang, and Pyrsopoulos,

I sincerely appreciate your kind managements allowing me to transfer my manuscript from *World Journal of Gastroenterology* to your journal, *World Journal of Hepatology*. I proofread along with each comment as shown in the below as a point-by-point response and indicated the corrections with underlines in the revised version of “WJH72023_TxtMarked_Suda”.

I hope this transfer of the revised version makes my manuscript published in your prestige journal, *World Journal of Hepatology*.

Sincerely,

**A point-by-point response to the Referees’ comments:**

*Reviewer: 1*

In the article entitled: "Gravity assistance enables liver stiffness measurement to detect liver fibrosis under congestive circumstance", the authors Suda T et al. describe in detail.....

The Table and the Figures are informative. The English language, however, needs much polishing. I think the article is interesting and provides an innovative and practical idea. It may be published in the WJG after some modifications, as indicated in my comments below.

**Major Comments:**

1. (Page 6, Line 9): In the RESULTS section of the Abstract, data and their respective level of significance are missing. It is imperative to be added.
A1. Along with the reviewer’s comment, the data and their respective level of significance were added in the revised version. Because the data presentation becomes too complex to show in the context of the abstract with respect to the difference between SpSWE and LdSWE, Fibrosis-4, and platelet counts, they are added in the corresponding figure legends for each instead of in the abstract.

2. (Page 6, Line 26): The effect of gravity is expected to be less pronounced at the upright or even at the sitting position. Have the authors measure liver stiffness at these positions?

A2. Thank you for the reviewer’s suggestive comment. Unfortunately, however, measuring liver stiffness at the upright or at the sitting position is technically difficult to get reproducible results, because it is hard for patients to keep those positions without strain especially for elderlies. We do not have substantial amount of data for liver stiffness at these body positions. I am sorry.

3. (Page 7, Lines 16-18): This sentence must be modified. Liver congestion may be less prominent at the left lateral decubitus position because the inferior vena cava is released from liver pressure. However, liver congestion is not expected to be completely eliminated. Of course, the resulting LSM will be closer to real liver fibrosis, but still may carry some residual elements of the venous congestion.

A3. Thank you for your thoughtful comment. The sentence was modified to reduce restrictive expression as follows. “Here we report a simple strategy of liver stiffness measurement to identify clues to liver fibrosis even under congestion.”

4. (Page 11, Lines 24 & 26): Please give also the equivalent in kPa values.

A4. The velocity of m/sec (Vs) was converted to Young's modulus of kPa (E) by adopting the formula: \( E = V_s^2 \times 2 \times (1+\gamma) \times \rho \), where \( \gamma \) and \( \rho \) are assumed to be Poisson coefficient of 0.5 and tissue density of 1, respectively. The calculated values in kPa were added to the corresponding velocities in the text and tables in the revised version.

5. (Page 12, Lines 11): Authors should clarify whether they refer to inter- or intra-observer CV, at the same examination or at different sessions.
I am sorry, but we did not evaluate the inter- or intra-observer variation. In the revised version, following descriptions were added in “Shear Wave Elastography Measurements” and “Statistical analysis” paragraphs, respectively.

“SWE was measured in the cohort consisting of 298 or 41 cases by 7 ultrasonographers or 2 medical doctors, respectively, who had conducted SWE measurements every day for more than 2 years or ultrasonography of the abdomen for more than 2 decades and SWE measurements for more than 3 years.”

“The inter- or intraobserver variation was not evaluated.”

6. (Page 13, RESULTS): One would expect to see first a Table with the overall view of the 2D-SWE measurements of the 3 groups in the supine and the left lateral decubitus position. In addition, besides giving only p-values, authors should provide the medians (IQR) (or means ± SD) of the respective parameters, as well.

A6. The summary table of shear wave elastography was added in the revised version as a Table 2. The data in both m/sec and kPa and their respective levels of significance were added in the tables, text, and corresponding figure legends of the revised version.

7. (Page 13, Lines 21): Please give the critical value of “stiffness” in m/sec and kPa.

A7. The values of stiffness were described not only in m/sec but also in kPa over the entire manuscript including tables in the revised version.

8. (Page 13, Lines 24-25): The cardiothoracic ratio is not a good indicator of congestive heart failure (CHF) (see: Future Cardiol 2015;11:171, J Royal Soc Med 2015;108:317). Authors should have had selected a parameter with higher sensitivity for CHF, as for eg. the cardiac ejection fraction, the centripedal or bidirectional blood flow in the hepatic veins, or something similar.

A8. Thank you for your expertise. Unfortunately, we did not routinely check hepatic venous flow or other indicators with higher specificity for congestive heart failure, because the patients enrolled in this analysis were not expected to be suffering from heart diseases.

The report that the reviewer referenced made conclusion that cardiothoracic ratio as determined by chest radiograph is sensitive but not specific
and has a strong negative predictive value for identifying left ventricular dilation as 83.3% sensitivity, 45.4% specificity, 43.5% positive predictive value and 82.7% negative predictive value. In our cohort, the number of cases showing cardiothoracic ratio of larger than 50% were 11 out of 35 ∆2dSWE-positive cases and 6 out of 37 ∆2dSWE-negative cases revealing no significant difference of frequencies between two groups with p value of 0.17 (Fisher's exact test). If the aforementioned positive and negative predictive values are taken into consideration, the number of cases showing cardiothoracic ratio of larger than 50% were 9 out of 35 ∆2dSWE-positive cases (11x43.5%+(35-11)x(100%-82.7%)) and 8 out of 37 ∆2dSWE-negative cases (6x43.5%+(37-6)x(100%-82.7%)). The frequencies between two groups were still not significantly different either with p value of 0.78.

We believe that the cardiothoracic ratio is still meaningful for our purpose even if it may not be generally a good indicator of congestive heart failure as the reviewer indicated. In the revised version, the result of Fisher’s exact test using original number of cases was inserted. The statistical method was additionally described in the material and method section.

9. (Page 14, Lines 6-8): Do you have any measurements of the IVC diameter in the sitting or the upright position? If yes, please mention its changes in the Discussion section.
A9. I am sorry. We did not check them in these body positions.

10. (Page 15, Lines 26): Figure 5 could be omitted.
A10. The Figure 5 was omitted in the revised version.

11. (Page 18, Lines 12): Authors should add a comment on the possible shortcomings of their study.
A11. Thank you for your thoughtful comment. The following discussion was inserted at the last paragraph of the discussion section. “One limitation of our study is the relatively smaller number of cases and selection bias. The limited number of enrollments may have caused inadequate assessment of the biological variability. In particular, the efficacy as a prognostic indicator of liver stiffness measurements
in supine and left decubitus postures has to be validated in a cohort of congestive heart diseases to guide decisions with respect to the burden of liver diseases. Although the significance of our hypothesis was supported by FIB4 and platelet counts of surrogates for liver fibrosis, there is no standardized indicator for liver fibrosis in congestive hepatopathy referred to in a validation study. A longitudinal observation would be necessary. Furthermore, the gravitational effects on the liver architecture were proposed but not visualized or quantified in this study. To obtain direct evidence, SWE should be measured at two body positions coupled with a quantitative evaluation of structural deformation of the liver.”

Minor Comments:
1. (Page 1, Line 8): circumstances.
2. (Page 5, Line 8): ...is prolonged...
3. (Page 5, Line 12): Regular measurements...
4. (Page 5, Line 24): 2D-shear wave elastography (2D-SWE)
5. (Page 6, Line ): Please refer always to "2D-SWE".
6. (Page 7, Line 13): ...there are...
7. (Page 9, Lines 24 & 27): The words "hypothetically" and "hypothetical" can be omitted.
8. (Page 13, Lines 19): ...was lower...
9. (Page 15, Lines 20):...at higher...

A-min. Thank you for your thorough reviewing. I appreciated. All suggestions were corrected in the revised version except for #2, #7, and #9.

In terms of #2, English Editing Service corrected that “has been prolonged”. For #7, I believe that it is better to keep "hypothetically" and "hypothetical" in our context. Because 3 groups of normal, congestion, and congestion with fibrosis have not been proven by histology and/or other definitive measures. The sentence raising #9 issue includes typo, which has been corrected.

Reviewer: #2
Q. Font style and font style must be same.
A. I believe I have adjusted font style throughout the manuscript. However, if still
Reviewer: #3

The presented manuscript titled “Gravity assistance enables liver stiffness measurement to detect liver fibrosis under congestive circumstance” is an interesting approach…. At this point I have a list of concerns, that I hope You will be able to address:

1. In the Patients section you declare, that 2D-SWE was performed in 298 cases of patients (cohort #1). Then you state that 41 cases of cohort #2 were performed with virtual touch quantification method. In the Shear Wave Elastography Measurements you declare, that 2 devices were used for this group: pSWE with ACUSON S2000 and 2dSWE by Aplio 500. If my understanding is correct, those two cohorts were diagnosed with different devices and different methods. What was the reason for that? As it is already proven there is a significant difference between the vendors and elastography methods in results as well as error ratios. How did you address this problem?

   A1. Yes, we used 2dSWE in the cohort #1 and pSWE in the cohort #2, respectively. Because when we started shear wave elastography measurements, only pSWE was available, we used pSWE. After that the machine in which 2dSWE measuring function was implemented was appeared to be available. We realized that 2dSWE measurements have higher reproducibility, then we introduced them in our clinic.

   As the reviewer concerned that there is no standard way to normalize SWE values that were measured using different technologies. A direct comparison should be avoided among SWE values that were measured using different technologies. In this study, however, we separately analyzed cohort #1 and cohort #2 for the different purposes. The values in cohort #1 should not be analyzed with the values in cohort #2 and vice versa. On the other hand, the fundamental property observed in cohort #1 must be true in cohort #2 and vice versa.

   We believe it is scientifically reasonable to make the discussion in the study for cohort #1 on the basis of the relationship between liver stiffness and interstitial tissue pressure, which was observed in cohort #2.

2. What was the number and experience of ultrasonographers performing the elastography examinations? Did you calculate their compliance? What was the
examination protocol?

A2. I am sorry, but we did not evaluate the inter- or intra-observer variation. 2dSWE was measured in cohort #1 by 7 ultrasonographers as I acknowledged. They all had experienced 2dSWE measurements every day for more than 2 years at the beginning of this study. pSWE was measured by 2 medical doctors, who had experience of ultrasonography for abdomen more than 2 decades and of pSWE measurements for more than 3 years at the time when the study started. The information was added in the Materials and Methods section.

In terms of the examination protocol, the following description was inserted in the Materials and Methods section of the revised version. “SWE was measured thrice in each segment (posterior, anterior, medial, and lateral) with a transient breath hold at a neutral cycle after one-night of fasting followed by a 30-min or longer rest while the patient was in the supine position. A region of interest (ROI) was set between 1 and 5 cm beneath the liver capsule. In the case of 2dSWE measurements, the size of the ROI was approximately 30 mm x 30 mm square, and 3 measurements were achieved in each ROI by placing an acquisition circle 2 mm in diameter after confirming the proper propagation of shear waves in a “wavefront” style display.”

3. What was the percentage of non-diagnostic measurements? What measurement quality parameters have been used and with what cut-offs?

A3. As I mentioned in the Results section, only the cases, in which the difference between SpSWE and LdSWE is greater than the robust coefficient-of-variation, were incorporated in the main analyses in this study. This is because to make sure that we can focus on the effects of postural change on 2dSWE values. All measurements were recorded, but the case, in which variation of SWE values obtained from twelve sites were larger than the effects of postural change on SWE, was excluded from further analyses. The quality is assured in this study by selecting not each measurement value, but each case based on the variation of SWE values. %CVR values were added in the Table 1 as an average ± standard deviation.

4. In Patients section you declare that fatty liver disease was diagnosed by US on the
basis of liver hyperechogenicity and presence of at least two additional findings. Did you obtain the quantitative information in the form of the liver/kidney b-mode ratio? How were the vascular blurring and deep-attenuation of echo-beam evaluated? Did you in any way evaluate the liver fat (for example attenuation, sound speed, fat fraction etc.)?

A4. In this study, SWE was not measured for the purpose to evaluate pathophysiology of liver diseases including NAFLD. We did not obtain the quantitative information in terms of liver fat content.

5. What were the inclusion and exclusion criteria for this work, as they are not clearly stated?
A5. 2dSWE was measured all consecutive cases, who were subjected to 2dSWE measurements for the evaluation of various diseases. There was no specific inclusion or exclusion criteria. It was additionally described in Materials and Methods section of the revised version.

6. In Table 1 you present the Hepatocellular carcinoma group of patients. It is proven, that liver focal changes can increase the measurement values in their vicinity. How this problem was addressed? Additionally diffused HCC can be non-detectable in ultrasound? were there any cases included in this work? What methods of verification did you apply?
A6. When we measure 2dSWE, a proper propagation of shear wave was confirmed in “wavefront” style display. It is easy to understand if ROI was placed where shear wave propagation is affected by the nodule of HCC. We avoided to measure 2dSWE within the sphere of HCC influence. In terms of diffuse type of HCC, none of patients we enrolled so far developed diffuse type of HCC more than 2 years after 2dSWE measurement in this study.

7. Did you exclude any underlying liver diseases in the cohort #2 patients? There is no characterization of the cohort #2 in your work, Table 1 presents only cohort #1? could you please provide full information on this group?
A7. The cohort #2 consists of 41 cases (male 19 cases, female 22 cases, median age was 5.5 years old (IQR: 1.7 – 61.0 years old)), in which pSWE measurements
were achieved before and after open-heart surgery. Ten valvular disorders and 31 congenital heart diseases included aortic stenosis an/or insufficiency, pulmonary stenosis and/or insufficiency, tricuspid stenosis and/or insufficiency, mitral stenosis and/or insufficiency, left or right ventricular outflow tract obstruction, atrioventricular septal defect, atrial septal defect, ventricular septal defect, single ventricle, double-chambered right ventricle, double outlet right ventricle, corrected transposition of the great arteries, complete transposition of the great arteries, aortic valve right coronary apex deviation, total anomalous pulmonary venous drainage, Tetralogy of Fallot, and so on. No patients were treated or followed for chronic liver diseases. We confirmed HBsAg negativity, anti-HCV antibody negativity, and no alcohol abuse. I believe the information of heart diseases in detail are redundant from the focus of this manuscript. The least information was added in the revised version.

8. What was the time period between the SWE and cardiac surgery? As it is proven that invasive procedures can elevate the liver stiffness due to congestion? how this problem was addressed?

A8. As it was mentioned in the legend of supplementary figure 1, pSWE was measured within a week after open-heart surgery. What we would like to know is that SWE was positively correlated with the pressure at inferior vena cava. The reason of increase or decrease of inferior vena cava pressure does not affect on our conclusion.

9. Why there was no correlation to golden standard, the liver biopsy?

A9. As I mentioned in the introduction section, the heterogeneity of fiber deposition is quite large in congestive hepatopathy. That is why the liver biopsy could not be golden standard to evaluate liver fibrosis under congestive circumstances. Furthermore, the life-threatening risk of liver biopsy is increased under congestion. The liver biopsy should not be recommended to patients with congestive hepatopathy.

10. As this work is claimed to be a retrospective one? is it a standard procedure to evaluate liver stiffness in your center in left decubitus position? If that is the issue,
for what reason and according to what guidelines?

A10. No. 2dSWE is not routinely measured in left decubitus position in our hospital. When it is difficult to clearly visualize some area of the liver in ultrasound study such as left medial segment, however, it is standard procedure to change body position so as to make manipulation easy. Therefore, the review boards of our institute and university judged that 2dSWE measurements in left decubitus position is simple extension of a regular study.
Observational Study

Gravity assistance enables liver stiffness measurements to detect liver fibrosis under congestive circumstances.

Suda T et al. A gravity-assisted evaluation of liver stiffness

Takeshi Suda, Ai Sugimoto, Tsutomu Kanefuji, Atsushi Abe, Takeshi Yokoo, Takahiro Hoshi, Satoshi Abe, Shinichi Morita, Kazuyoshi Yagi, Masashi Takahashi, Shuji Terai

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Author contributions: Each author is a main contributor to the following points. TS: study concept, study design, analysis and interpretation of data, and writing the manuscript; AS, TK, and TY: analysis and interpretation of the data; TH, SA, SM, and MT: acquisition of the data; KY: study supervision; MT: critical revision.
Supportive foundation acknowledgment: This study was supported for data collection and statistical analyses by a grant from the Niigata University Medical and Dental Hospital (Clinical research support project/2013) to Takeshi Suda.

Institutional review board statement: In this study, two different cohorts were employed for liver stiffness measurements: cohort #1 (298 cases with various liver diseases) and cohort #2 (41 cases receiving cardiac surgery). The review boards of the Uonuma Institute of Community Medicine and Niigata University Medical and Dental Hospital approved both studies.

Informed consent statement: The review boards of Uonuma Institute of Community Medicine and Niigata University Medical and Dental Hospital did not require informed consent in the studies for cohorts #1 and #2 because these studies were retrospective studies using medical records and no additional invasive examinations were conducted for the study.

Conflict-of-interest statement: Takeshi Suda, Ai Sugimoto, Atsushi Abe, Tsutomu Kanefuji, Takahiro Hoshi, Satoshi Abe, Shinichi Morita, Takeshi Yokoo, Kazuyoshi
Yagi, Masashi Takahashi, and Shuji Terai declare that they have no conflicts of interest. There is no relationship that should be disclosed in association with this study. The authors have nothing to disclose in relation with this manuscript.

Data sharing statement: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

STROBE statement: The guidelines of the STROBE Statement have been adopted.

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Research background:
Congestive hepatopathy, an abnormal state of the liver as a result of congestion, has become a prognostic determinant by insidiously proceeding toward end-stage liver disease without effective biomarkers in patients with congestive heart diseases as survival has been prolonged owing to surgical and medical improvements. Although liver stiffness is generally a useful surrogate marker for liver fibrosis, which is a universal prognosticator in any type of chronic liver disease, regular measurements of shear wave elastography cannot qualify liver fibrosis in cases of congestion because congestion makes the liver stiff without fibrosis. A noninvasive biomarker is demanded for the managements of patients with congestive heart diseases.

Research motivation:
When it is difficult to clearly visualize some area of the liver in ultrasound study, we ask patients to change body postures from supine to such as left decubitus position. At that time, we realized that shear wave elastography values substantially changed in some case. We hypothesized that the effects of congestion and fibrosis on liver stiffness may be dissociated by measuring shear wave elastography in different body positions.

Research objectives:
This study aims to establish a strategy that enables the evaluation of fibrous accumulation in the liver with respect to architectural rigidity under congestive circumstances by measuring shear wave elastography.

**Research methods:**

Two-dimensional shear wave elastography was measured in the supine and left decubitus positions in 298 consecutive cases as they were subjected to an ultrasound study for various liver diseases. To clarify the relationship between liver stiffness and interstitial tissue pressure, virtual touch quantification of point shear wave elastography was measured before and after cardiac surgery in a different cohort consisting of 41 cases. Regions of interest were placed at twelve sites, and the median and robust coefficient of variation were calculated. The liver stiffness values and clinicopathological data such as cardiothoracic ratio and the Fibrosis-4 Index were statistically analyzed.

**Research results:**

The inferior vena cava diameter was significantly reduced in left decubitus (Ld) position in subjects with higher 2-dimensional shear wave elastography (2dSWE) value in Ld (LdSWE) than the 2dSWE value (SpSWE) in supine (Sp) (p=0.007) but not in those with lower LdSWE values (p=0.32). Among 81 patients, in whom SpSWE was increased or decreased in Ld beyond the magnitude of robust coefficient-of-variation, all 37 with normal SpSWE had a higher LdSWE than
SpSWE (Normal-to-Hard), whereas in 44 residual subjects with abnormal SpSWE, LdSWE was higher in 27 subjects (Hard-to-Hard) and lower in 17 subjects (Hard-to-Soft) than SpSWE. SpSWE was significantly correlated with the difference between 2dSWE values in Sp and Ld (Δ2dSWE) only in Hard-to-Soft (p<0.0001). Δ2dSWE was larger in each lobe than in the entire liver. When Hard-to-Hard and Hard-to-Soft values were examined for each lobe, fibrosis-4 or platelet counts were significantly higher or lower only for Hard-to-Soft versus Normal-to-Hard cases.

**Research conclusions:**

With the help of gravity during body postural changes, the impacts on architectural rigidity and interstitial tissue pressure are dissociated when measuring liver stiffness. Because a rigid liver is resistant to structural deformation, stiff-liver softening in left decubitus position suggests fiber accumulation of the liver. In this report, a simple strategy of liver stiffness measurement is proposed to identify clues to liver fibrosis even under congestive circumstances.

**Research perspectives:**

Because there is no standardized indicator for liver fibrosis in congestive hepatopathy, a longitudinal observation would be only the way to validate the efficacy of liver stiffness measurements in supine and left decubitus postures as a decision guidance strategy with respect to the burden of liver diseases in a cohort of congestive heart diseases. Furthermore, synergistic studies that measure shear
wave elastography and quantify structural deformation of the liver in different body positions will help understand the physiological components and mechanisms defining liver stiffen.
ABSTRACT

BACKGROUND
As survival prolongation has been prolonged owing to surgical and medical improvements, liver failure becomes a prognostic determinant in patients suffering from congestive heart diseases. Congestive hepatopathy, an abnormal state of the liver pathology as a result of congestion, insidiously proceeds toward end-stage liver disease without effective biomarkers evaluating the pathological progression. Regular measurements of shear wave elastography cannot qualify liver fibrosis, which is a prognosticator in any type of chronic liver diseases, in cases of congestion because congestion makes the liver stiff without fibrosis. We hypothesized that the effects of congestion and fibrosis on liver stiffness can be dissociated by inducing architectural deformation of the liver to expose structural rigidity.

AIM
To establish a strategy measuring liver stiffness in as a reflection of architectural rigidity under congestion.

METHODS
Two-dimensional shear wave elastography (SWE2dSWE) was measured in the supine (Sp) and left decubitus (Ld) positions in 298 consecutive cases as they
were subjected to an ultrasound study for various liver diseases. Regions of interest were placed at twelve sites, and the median and robust coefficient-of-variation were calculated. Numerical data were compared using the Mann-Whitney U or Kruskal-Wallis test followed by Dunn's post-hoc multiple comparisons. The inferior vena cava (IVC) diameters onat different body positions were compared using the Wilcoxon matched pairs signed rank test. The number of cases with cardiothoracic ratios greater than or not greater than 50% was compared using Fisher's exact test. A correlation of SWE2dSWE between different body positions was evaluated by calculating Spearman correlation coefficients.

RESULTS

The IVC diameter was significantly reduced atin Ld in subjects with higher SWE at2dSWE values in Ld (LdSWE) than SWE-atin Sp (SpSWE) (p=0.007, (average ± SD) 13.9 ± 3.6 vs. 13.1 ± 3.4 mm) but not in those with lower LdSWE, values (p=0.32, 13.3 ± 3.5 vs. 13.0 ± 3.5 mm). In 81 subjects, SpSWE was increased or decreased in Ld beyond the magnitude of robust coefficient-of-variation, which suggests that body postural changes induced an alteration of liver stiffness significantly larger than the technical dispersion. Among these subjects, all 37 with normal SpSWE had a higher LdSWE than SpSWE (Normal-to-Hard, SpSWE - LdSWE (Δ2dSWE): (minimum – maximum) -0.74 – -0.08 m/sec), whereas in 44 residual subjects with abnormal SpSWE-Ld-SWE, LdSWE was higher in 27 subjects (Hard-to-Hard, -0.74 – -0.05 m/sec) and lower in 17 subjects (Hard-to-Soft, 0.04–0.52 m/sec) than
SpSWE. SpSWE was significantly correlated with the difference between SpSWE and LdSWE (Δ2dSWE) only in Hard-to-Soft. (p<0.0001). Δ2dSWE are was larger when compared in each lobe than when compared in the entire liver. When Hard-to-Hard and Hard-to-Soft values were examined for each lobe, Fibrosis-4 or platelet counts were significantly higher or lower only for Hard-to-Soft versus Normal-to-Hard cases.

CONCLUSION
Gravity alters the hepatic architecture during body postural changes, causing outflow blockage in hepatic veins. A rigid liver is resistant to structural deformation. Stiff-liver softening in the Ld position suggests a fibrous liver.

Key words: Shear wave elastography; Inferior vena cava diameter; Congestive hepatopathy; Liver fibrosis; Body positions; Fibrosis-4 index

Core tip:
Medical progress ironically makes the liver a prognostic determinant in patients with congenital heart diseases because there is are no effective biomarkers to evaluate pathological progression in congestive hepatopathy. A canonical liver stiffness measurement cannot screen for fibrous liver under congestion because congestion itself makes the liver stiff without fibrosis. Here, we report a simple strategy of liver stiffness measurement to find fibrous, identify clues to liver fibrosis.
even under congestion. The basic data presented in this report provide insights not only for the clinical application of liver stiffness in patients with congestive heart diseases but also for the physiological components and mechanisms underlying liver stiffness.
INTRODUCTION

The survival of children and adolescents undergoing the Fontan procedure continues to improve as various modifications of this operation have been applied since 1968\(^1\)-\(^3\). In conjunction with technological advancements in the pathophysiological evaluation of the liver, the frequency of encountering the spectrum of liver disease is increasing in patients with heart diseases. The frequency of nonalcoholic cirrhosis is reported to be greater than 4% among hospital admissions of patients with a single functional ventricle, whereas it is approximately 0.3% of hospitalizations for patients without congenital heart diseases\(^4\). The pathophysiology is termed congestive hepatopathy, which is not restricted to the postoperative condition of the Fontan procedure but arises from chronically elevated hepatic venous pressures secondary to biventricular or isolated right-sided heart failure. Low cardiac output itself may also accelerate fibrosis pathways by reducing circulating blood flow to the liver. To determine a specific patient’s prognosis, screening and management strategies (including candidacy for isolated heart or combined heart-liver transplantation), the detection of fibrous progression in the liver is critical. Unfortunately, there is a growing awareness that fibrosis biomarkers, such as serum tests, fibrosis calculators, and liver stiffness, are not reliable in congestive hepatopathy\(^5\)-\(^7\). Even liver biopsy is unlikely to stage fibrosis and predict clinical outcomes accurately because the heterogeneity of fiber deposition is quite large in congestive hepatopathy\(^5\).
Liver stiffness is a useful surrogate marker in viral hepatitis and alcoholic and nonalcoholic fatty liver diseases to assess the degree of fibrous accumulation in the liver,[8-11] which is a good prognostic indicator irrespective of the etiologies for chronic liver diseases. Because liver stiffness is directly measured in the liver as a physical property, this value is fundamentally spared from systemic disparity. Based on its noninvasive nature, the value can be repeatedly measured from various sites, especially in shear wave elastography using an acoustic radiation force impulse technology or in magnetic resonance elastography. On the other hand, the clinical feasibility may be limited in magnetic resonance imaging, as many patients with congestive hepatopathy have non-magnetic resonance compatible cardiac devices. Furthermore, congestion itself increases liver stiffness and causes overestimation of the amount of fibrosis, as it was reported in transient elastography.[12]

This study aims to establish a strategy that enables the evaluation of fibrous accumulation in the liver with respect to architectural rigidity under congestive circumstances by measuring shear wave elastography. After assessing the impacts of interstitial tissue pressure on shear wave elastography, the effects of body postural changes on the diameter of the inferior vena cava (IVC) and liver stiffness were evaluated. Based on the different reactions of shear wave elastography upon changing body positions, the patients were hypothetically divided into three groups: normal liver, congestive liver, and congestive liver with...
fiber accumulation. The Fibrosis-4 index (FIB-4) and its constituents were compared among groups to endorse the significance of hypothetical classification. The possibility to dissociate fibrosis from underlying congestion using a gravity aid to induce architectural deformity of the liver is discussed.

**MATERIALS AND METHODS**

*Patients*

Two-dimensional shear wave elastography (2dSWE) was measured in both the supine and left decubitus positions in 298 consecutive patients, who were subjected to 2dSWE measurements for the evaluation of various diseases, including nonalcoholic fatty liver disease (NAFLD). The patients’ characteristics are summarized in Table 1. All studies were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. Routine blood biochemistry was measured in the clinical laboratories of our hospital, where a quality control of each test was regularly performed every day. NAFLD was diagnosed based on the criteria proposed by the Asia-Pacific Working Party on NAFLD[13]. Fatty liver was diagnosed by abdominal US as defined by an increased echogenicity of the liver along with the presence of any two of the following three findings: liver-kidney contrast, vascular blurring, and deep attenuation of echo-beam[14].

To clarify the relationship between liver stiffness and interstitial tissue pressure, virtual touch quantification of point shear wave elastography was
measured before and after cardiac surgery in a different cohort consisting of 41 cases (19 males and 22 females, 5.5 (1.7–61.0) years old (median (interquartile range))) with disorders, including 10 valvular and 31 congenital heart diseases. No patients were treated or followed for chronic liver diseases. HBsAg negativity, anti-HCV antibody negativity, and no alcohol abuse were confirmed. Physical properties with respect to cardiac function were evaluated using ultrasound, chest X-ray, and cardiac catheterization. The data are shown in supplementary digital content Figure 1 and referenced in the discussion section.

The review boards of the Uonuma Institute of Community Medicine and Niigata University Medical and Dental Hospital approved the study measuring liver stiffness in our main cohort consisting of 298 cases with various diseases in two body positions and another cohort of 41 patients undergoing cardiac surgery, respectively. These studies did not require informed consent because they were retrospective studies using only medical records or noninvasive imaging examinations.

Shear Wave Elastography Measurements

Shear wave elastography (SWE) evoked by acoustic radiation force impulse was measured as point shear wave elastography using an ACUSON S2000 ultrasound system (Siemens Healthcare, Erlangen, Germany) or as 2dSWE using an Aplio 500 (Canon Medical System Corporation, Ohtawara, Japan). SWE was
measured thrice in each segment (posterior, anterior, medial, and lateral) with a transient breath hold at a neutral cycle after one-night of fasting followed by a 30-min or longer rest while the patient was in the supine position. A region of interest (ROI) was set between 1 and 5 cm beneath the liver capsule. In the case of 2dSWE measurements, the size of the ROI was approximately 30 mm x 30 mm square, and 3 measurements were achieved in each ROI by placing an acquisition circle 2 mm in diameter after confirming the proper propagation of shear waves in a “wavefront” style display. When 2dSWE was measured at two body positions, the measurements were performed again in the liver at 12 sites in the left decubitus position. SWE was measured in the cohort consisting of 298 or 41 cases by 7 ultrasonographers or 2 medical doctors, respectively, who had conducted SWE measurements every day for more than 2 years or ultrasonography of the abdomen for more than 2 decades and SWE measurements for more than 3 years.

To define the cut-off value of 2dSWE suggesting the least fiber accumulation in the liver, 2dSWE was measured in 480 voluntary annual medical checkup visitors who were diagnosed with NAFLD one year prior. Because median 2dSWE values in the 480 visitors fit well on a Gaussian distribution represented by an average of 1.324 m/sec (5.26 kPa) with a standard deviation of 0.0847 m/sec (0.022 kPa, $r^2=0.98$), a cut-off value to distinguish the liver with fiber accumulation was statistically defined and reported as the average plus standard deviation of 1.41 m/sec (5.96 kPa)\textsuperscript{15}. 
Statistical analysis

A robust counterpart to the standard deviation was calculated as follows. First, the median absolute deviation was calculated as the median of the difference in the absolute values between each SWE and the median of 12 measurements; thereafter, a constant factor of 1.4826 was multiplied. Finally, the robust coefficient-of-variation (CVR) was calculated by dividing the robust standard deviation by the median and is expressed as a percentage. The inter- or intraobserver variation was not evaluated. Numerical data from independent cases were compared using the Mann–Whitney U or Kruskal–Wallis test followed by Dunn's post-hoc multiple comparisons between two groups or among three groups, respectively. IVC diameters at different body positions in each case were compared using the Wilcoxon matched pairs signed rank test. A correlation of 2dSWE between different body positions was evaluated by calculating Spearman correlation coefficients. The number of cases with cardiothoracic ratios greater than or not greater than 50% was compared using Fisher’s exact test. The statistical methods of this study were reviewed by Professor Kohei Akazawa from the Department of Medical Informatics, Niigata University Medical and Dental Hospital. All statistical analyses were conducted with GraphPad Prism version 7.0 (GraphPad Software Inc., La Jolla, CA, USA), and two-sided P-values less than 0.05 were considered statistically significant.
RESULTS

Livers with normal stiffness in the supine position harden in the left decubitus position, whereas stiff livers harden or soften.

When 2dSWE was measured for both positions of supine (SpSWE) and left decubitus (LdSWE) positions, the values revealed a significant positive correlation, as shown in Figure 1a (p<0.0001, r=0.68). Because 12 values of 2dSWE in each liver were dispersed on a case-by-case basis, it is reasonable to assume that 2dSWE is substantially affected by changing body positions only when the difference between SpSWE and LdSWE (Δ2dSWE; SpSWE - LdSWE) is greater than the dispersion of SpSWE, which is a robust coefficient-of-variation (CVR). Among 298 cases, LdSWE increased or decreased from SpSWE over the magnitude of CVR in 81 cases (27.2%). These 81 cases can be classified into four groups based on SpSWE normality and positive/negative Δ2dSWE values. For 37 cases in which SpSWE was slower than the upper normal limit of 1.41 m/sec (5.96 kPa, see Methods), Δ2dSWE was negative as shown in Figure 1b in all the cases (Normal-to-Hard: NH), as shown in Figure 1b. On the other hand, in 44 cases with stiff livers in the supine position, Δ2dSWE was negative (Hard-to-Hard: HH) or positive (Hard-to-Soft: HS) in 27 and 17 cases, respectively. The 2dSWE values in each group at different body positions are summarized in Table 2.

To assess the possibility that Δ2dSWE is determined by cardiac function, the cardio-thorax ratio was compared between cases with negative and positive Δ2dSWE. As shown in Figure 1c, the cardio-thorax ratio was
not significantly different between the two groups (p=0.51). The number of cases showing a cardiothoracic ratio larger than 50% was 11 out of 35 Δ2dSWE-positive cases and 6 out of 37 Δ2dSWE-negative cases and was not significantly different between the two groups (p=0.17).

**IVC shrinks in the left decubitus position as the liver hardens but not as the liver softens**

Next, the effects of the body positions on IVC diameter were evaluated irrespective of whether the Δ2dSWE scale was beyond or within the CVR. In the results, the diameter of the IVC in the left decubitus position was significantly reduced compared with that in the supine position in Normal to Hard the cases showing normal liver stiffness in the supine position, as shown in the left panel of Figure 2a (p=0.013). Consistently, the IVC diameter was also shortened in Hard-to-Hard shortened in the cases with a stiff liver in the supine position that hardened further in the left decubitus position (Figure 2a middle panel, p=0.0070). On the other hand, the IVC diameters in the supine and left decubitus positions were not significantly different in Hard-to-Soft the cases with a stiff liver in the supine position that softened in the left decubitus position (Figure 2a right panel, p=0.32).

**Liver stiffness is tightly associated with body postural change in cases in which a stiff liver softens in the left decubitus position, especially in the right lobe**

To understand the implications of the pressure connection between the liver and
IVC, the correlation between SpSWE and Δ2dSWE was evaluated. As shown in Figure 2b, a significant correlation was not observed in Normal-to-Hard the cases showing normal liver stiffness in the supine position (p=0.56) or Hard-to-Hard the cases with a stiff liver in the supine position that hardened farther in the left decubitus position (p=0.88). In contrast, SpSWE and Δ2dSWE revealed a significant positive correlation in Hard-to-Soft the cases with a stiff liver in the supine position that softened in the left decubitus position (p<0.0001, r=0.38), suggesting a direct connection between the IVC pressure and the interstitial pressure of the liver.

When the same relation was separately evaluated in the right or left lobe, as shown in Figure 2c, the correlation was clearly tighter in the right lobe (p<0.0001, r=0.48) compared with than in the left lobe (p<0.0001, r=0.31).

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Gravity unevenly impacts the liver architecture between the right and left lobes

The paradoxical increment/shrinkage of LdSWE/IVC in the left decubitus position indicates that pressure thresholds exist between the hepatic veins and IVC, where outflow blocks would be built under architectural deformation of the liver during postural changes. Given that postural changes may not evenly impact the liver architecture, Δ2dSWE was separately evaluated in the right and left lobes. As shown in Figure 3, larger differences in Δ2dSWE were noted between the right and left lobes in both cases with positive or negative Δ2dSWE values in the entire liver. When Δ2dSWE is positive or negative in the entire liver, Δ2dSWE in a single lobe is reciprocally negative or positive, respectively,
suggesting that the impact of postural change on liver architecture would be detected much easier in a single lobe compared with than in the entire liver.

Softening of the stiff liver in the left decubitus position suggests fibrous progression of the liver.

To infer the relationship between pathological differences of the liver and Δ2dSWE, FIB4 and its constituents, platelet count, age, and alanine aminotransferase, were compared among cases of Normal-to-Hard, Hard-to-Hard, and Hard-to-Soft cases. As shown in Figure 4, FIB4 and platelet counts revealed significantly higher and lower values, respectively, in Hard-to-Soft against than in Normal-to-Hard cases, especially when a texture was not judged in the entire liver but in a single lobe of the right or left (judged in the entire liver, right lobe, left lobe; (FIB4) p=0.04, p=0.006, p=0.01; (platelet counts) p=0.29, p=0.05, p=0.05, respectively). In terms of age and alanine aminotransferase, no significant differences were noted between Hard-to-Soft and Normal-to-Hard cases even when Hard-to-Soft values were determined in each lobe (Figure 5).

No significant differences were noted between the Normal-to-Hard and Hard-to-Hard for any groups in terms of FIB4, platelet counts, age, or alanine aminotransferase, either levels.

DISCUSSION
It has been reported that the IVC diameter and area decreased significantly from the right lateral to the supine position and further to the left lateral position in a healthy population\textsuperscript{[16]}. The height of the IVC relative to the right ventricle, compression of the IVC between the liver and spine, different levels of venous return and/or splanchnic blood pooling are thought to cause postural differences in IVC size\textsuperscript{[16,17]}. Consistently, the IVC diameter was significantly reduced in cases with normal liver stiffness when the body positions were changed from supine to left decubitus in our cohort. Liver stiffness is clearly correlated with IVC pressure/diameter in the supine position, as shown in Supplemental Figures 1a and 1b. Thus, if the pressure is equilibrated between the IVC and hepatic veins during body position changes, liver stiffness should be reduced in the left decubitus position. However, our study clearly revealed that IVC diameter and liver stiffness exhibited paradoxical changes. The liver hardened, whereas the IVC diameter was reduced. These findings suggest that a pressure threshold exists between the IVC and hepatic veins at in the left decubitus position in livers with normal stiffness. Given that intra-abdominal organs relocate along with the postural change\textsuperscript{[18]}, it is reasonable to assume that the hepatic veins are vented and twisted against the IVC in the left decubitus position, establishing an outflow block. Furthermore, it is anticipated that a rigid liver is less deformed after a body position change. A minimal outflow block keeps the efflux from the liver to the IVC and obviates the shrinkage of the IVC. Therefore, we hypothesized that a stiff liver in the supine position would soften in the left decubitus position if
substantial fiber accumulation was present. Otherwise, the liver will further harden (Supplemental Figure 2).

Because IVC pressure strikingly affects liver stiffness\cite{12}, as shown in Supplemental Figures 1a and 1b, the correlation of liver stiffness before and after changing of the IVC pressure strongly indicates a direct connection between the IVC and hepatic veins (Supplemental Figure 1c). Along with the body position changes from the supine to left decubitus position, a significant correlation between SpSWE and $\Delta$2dSWE was only observed in cases with a liver that softened in the left decubitus position. These results strongly support the notion that pressure thresholds generally exist between the IVC and hepatic veins in the left decubitus position, but fewer pressure differences are noted between the IVC and hepatic veins in cases with a stiff liver that softens in the left decubitus position. Furthermore, the correlation coefficients were substantially different between the lobes. In addition, $\Delta$2dSWE revealed large differences between the right and left lobes. These values are reciprocally negative and positive, suggesting that poor venous drainage in the left decubitus position heterogeneously occurs in the liver and is compensated through the area where gravity generates less impact. It is well known that if the flow volume is reduced from the portal vein, the arterial flow instantly compensates, and vice versa\cite{19}. In a similar way, if venous drainage is hindered in a certain area, congestion is avoided by opening latent vascular connections toward the outside of the burden area, as noted in the case of Budd-Chiari syndrome\cite{20}.
The different anatomical connections between the IVC and hepatic veins are one reason for the uneven impacts of gravity on the lobes among cases\textsuperscript{[21]}. Given that liver stiffness is measured in two different body positions, it is assumed that a separate evaluation of each lobe should have a higher probability to detect the different architectural rigidities. In fact, higher probabilities were calculated when the groups for the comparison of FIB4 were assessed in each lobe. One limitation of our study is the relatively smaller number of cases and selection bias. The limited number of enrollments may have caused inadequate assessment of the biological variability. In particular, the efficacy as a prognostic indicator of liver stiffness measurements in supine and left decubitus postures has to be validated in a cohort of congestive heart diseases to guide decisions with respect to the burden of liver diseases. Although the significance of our hypothesis was supported by FIB4 and platelet counts of surrogates for liver fibrosis, these findings should be histologically reconfirmed in a future study. The efficacy as a prognostic indicator of liver stiffness measurements in supine and left decubitus postures also has to be validated in a cohort of congestive heart diseases for guiding decisions with respect to the burden of liver diseases. There is no standardized indicator for liver fibrosis in congestive hepatopathy referred to in a validation study. A longitudinal observation would be necessary. Furthermore, the gravitational effects on the liver architecture were proposed but not visualized or quantified in this study. To obtain direct evidence, SWE should be measured at two body positions coupled with a quantitative evaluation of structural
CONCLUSION
In this report, a strategy was proposed to measure shear wave elastography that enables evaluation of architectural deformity under congestive circumstances. With the help of gravity, the impacts on architectural rigidity and interstitial tissue pressure are dissociated when measuring liver stiffness. The basic data presented in this report provide insights not only for the clinical application of liver stiffness in patients with congestive heart diseases but also for the physiological components and mechanisms defining liver stiffness.

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REFERENCES


5 Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol* 2015; **28**: 932-943 [PMID: 25793895 DOI: 10.1038/modpathol.2015.40]


13 **Farrell GC**, Wong VW, Chitturi S. NAFLD in Asia--as common and important as in the West. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 307-318 [PMID: 23458891 DOI: 10.1038/nrgastro.2013.34]


51: 1797-1800 [PMID: 15532829]


Figure legends

Figure 1

Body position effects on liver stiffness

a) Two-dimensional shear wave elastography (2dSWE) values that were measured in the supine and left decubitus positions revealed a significant positive correlation (p<0.0001, r=0.68). The black continuous and dotted lines reveal the best hit and 95% confidence band in the equation of least squares. b) The cases in which 2dSWE increased or decreased in association with changing body positions beyond the magnitude of robust coefficient-of-variation can be classified into 3 groups: normal 2dSWE (Normal-to-Hard: NH) or abnormal 2dSWE that increased (Hard-to-Hard: HH) or decreased (Hard-to-Soft: HS) on the left decubitus position in the left decubitus position. The difference in 2dSWE between supine and left decubitus positions (supine – left decubitus) was negative in NH (-0.23 ± 0.15 m/sec) and HH (-0.25 ± 0.14 m/sec) but was positive in HS (0.21 ± 0.12 m/sec). c) The cardiothoracic ratio was not significantly different between the patients with abnormal 2dSWE in the supine position, which further hardened or softened in the left decubitus position (*, p=0.51), 47.3 ± 8.0 vs. 45.7 ± 6.1%. The horizontal bars in b) and c) indicate the average (bold) and standard deviation.

Figure 2

Alteration of the inferior vena cava (IVC) diameter and liver stiffness after changing body positions
a) The IVC diameter was significantly reduced in patients with normal two-dimensional shear wave elastography values (2dSWE) in the supine position (Normal, *, p=0.013, 13.1 ± 3.7 vs. 12.4 ± 3.5 mm) or patients with abnormal 2dSWE in the supine position, which further hardened in the left decubitus position (Harden, **, p=0.0070, 13.9 ± 3.6 vs. 13.1 ± 3.4 mm). However, the diameter was not reduced in patients with abnormal 2dSWE in the supine position, which softened in the left decubitus position (Soften, #, p=0.32, 13.3 ± 3.5 vs. 13.0 ± 3.5 mm). The horizontal bars in each plot indicate the average (bold) and standard deviation. Sp and Ld indicate the supine and left decubitus positions, respectively. b) 2dSWE in the supine position revealed a significant positive correlation with the difference of 2dSWE between the two body positions only in the Soften group (black open circle) (p<0.0001, r=0.38) but not in the Normal (grey gray diamond) and Harden (grey gray closed circle) groups. c) In the Soften group, 2dSWE values in the supine position were plotted against the difference in 2dSWE between the supine and left decubitus positions in the right or left lobe. A Spearman's correlation coefficient of 0.48 in the right lobe (Rt) was higher than 0.31 in the left lobe (Lt). The black continuous and dotted lines reveal the best hit and 95% confidence band in the equation of least squares between 2dSWE values in the supine position and the difference in 2dSWE for two body positions in b) and c).

Figure 3
Reciprocal variation of liver stiffness difference between lobes

In both cases, with positive (left column) or negative (right column) differences of two-dimensional shear wave elastography values (2dSWE) between two body positions in the entire liver (All), the difference varies less (positive: -1.52 ± 7.91 m/sec, negative: -17.04 ± 10.71 m/sec) or more (positive: 12.38 ± 9.55 m/sec, negative: -1.46 ± 9.39 m/sec) in the right lobe (Rt) compared with the entire liver (gray or black, respectively, positive: 6.13 ± 6.18 m/sec, negative: -7.57 ± 5.98 m/sec) and reciprocally more (positive: 9.74 ± 8.03 m/sec, negative: -0.08 ± 9.11 m/sec) and less (positive: -2.51 ± 8.85 m/sec, negative: -12.05 ± 13.56 m/sec) in the left lobe (Lt) compared with the entire liver (positive: 4.86 ± 3.68 m/sec, negative: -8.06 ± 8.02 m/sec). The upper and middle panels represent cases where the difference in 2dSWE for the entire liver is within or beyond the magnitude of robust coefficient-of-variation, respectively. In the bottom panel, the results in the upper and middle panels are combined. The circle and horizontal bars in each plot indicate the average and standard deviation, respectively.

Figure 4

Figure 4 (Change graphs from median with IQR to average with SD)

Fibrous progression of the liver was suggested in the Soften group

Fibrosis-4 (FIB4, top panel) and its constituent of platelet counts (bottom panel) were compared among 3 groups in which two-dimensional shear wave elastography values (2dSWE) increased or decreased in association with
changing body positions beyond the magnitude of robust coefficient-of-variation; normal in the supine position (Normal-to-Hard: NH), abnormal and increased (Hard-to-Hard: HH) or decreased (Hard-to-Soft: HS) in the left decubitus position. The group was classified based on the difference in 2dSWE values in the entire liver (left column) or each lobe of right (middle column) or left (right column). A significant difference in FIB4 (entire: $p=0.04$, $1.29 \pm 0.87$ vs. $1.89 \pm 1.16$, right: $p=0.006$, $1.29 \pm 0.87$ vs. $2.12 \pm 1.22$, left: $p=0.01$, $1.29 \pm 0.87$ vs. $1.91 \pm 1.07$) and platelet counts (entire: $p=0.29$, $25.7 \pm 7.6$ vs. $22.1 \pm 7.7 \times 10^4$/mm$^3$, right: $p=0.05$, $25.7 \pm 7.6$ vs. $20.2 \pm 5.7 \times 10^4$/mm$^3$, left: $p=0.05$, $25.7 \pm 7.6$ vs. $21.0 \pm 7.3 \times 10^4$/mm$^3$) was observed between Normal-to-Hard and Hard-to-Soft. The probabilities were higher when the group was determined in each lobe. The horizontal bars in each plot indicate an average (bold) and standard deviation.

**Figure 5**

**Higher value of fibrosis 4 in Soften is not due to aging or liver cell damage**

Fibrosis 4 constituents, age (top panel) and alanine aminotransferase (ALT, bottom panel), were compared among 3 groups in which two-dimensional shear wave elastography values (2dSWE) increased or decreased in association with changing body positions beyond the magnitude of robust coefficient-of-variation; normal in the supine position (Normal to Hard: NH) or abnormal and increased (Hard to Hard: HH) or decreased (Hard to Soft: HS) in the left decubitus position. The group was classified based on the difference in 2dSWE for the entire liver (left
Supplemental Figure 1

Relationship between interstitial tissue pressure and liver stiffness in patients with heart diseases

a) Inferior vena cava (IVC) pressure or diameter that was preoperatively measured during a cardiac catheterization or ultrasound study, respectively, revealed a significant positive correlation with point shear wave elastography (pSWE) (p<0.0001, r=0.63 or p<0.0001, r=0.59, respectively). The black continuous and dotted lines reveal the best hit and 95% confidence band in the equation of least squares between IVC pressure/diameter and pSWE. b) pSWE was measured within a week after a cardiac surgery and was significantly decreased in cases in which the IVC diameter was shortened after surgery (*, p=0.014). The difference in pSWE before and after surgery (after − before) for cases in which the IVC diameter was shortened or not shortened after surgery was -0.31 ± 0.42 m/sec or 0.32 ± 0.30 m/sec, respectively. The horizontal bars in each plot indicate an average (bold) and standard deviation. c) A significant negative correlation was noted between pSWE values before surgery (pre pSWE) and the difference in pSWE values before and after surgery (p<0.0001, r=-0.81). The black continuous and dotted lines reveal the best hit and 95% confidence band in the
equation of least squares equation between the pSWE and pSWE difference.

Supplemental Figure 2

Structural rigidity of the liver detected by means of gravity

Gravity alters the hepatic architecture during body postural changes, causing outflow blockage in the hepatic veins and diameter reduction in the inferior vena cava and diameter, finally increasing the liver stiffness. Because a rigid liver is resistant to structural deformation, stiff-liver softening in the postural change from the supine to the left decubitus position suggests a fibrous liver.