Non-invasive Diagnosis of Liver Clinical Condition by Real-time Tissue Elastography and Shear Wave Measurement : Get More Accessible by One Probe

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Ultrasound Elastography is considered to be useful for non-invasive assessment of liver fibrosis, and can be classified into two main groups, shear wave imaging and strain imaging, according to the excitation method used and physical quantity measured. Hitachi Aloka Medical, Ltd. has recently developed a shear wave elastography technology and offers the strain imaging method using a convex probe. Its shear wave elastography, named Shear Wave Measurement (SWM), provides the display of a unique reliability indicator named VsN, which enables the operator to easily judge whether a measured Vs value is correct or not. Additionally, Real-time Tissue Elastography[*1] (RTE) supported by a convex probe facilitates examinations in obese patients. Combinational Elastography, the concept of using both shear wave elastography and strain imaging to gain a better understanding of the clinical condition of liver, is now achievable with one probe. It can be said that non-invasive diagnosis of the clinical condition of the liver has become more accessible.

Key Words: Shear Wave Measurement, Real-time Tissue Elastography, Convex Probe, Combinational Elastography

1. Introduction

It is very important to understand the stage of liver fibrosis and the level of inflammation both in a treatment plan setting and for predicting the prognosis of viral and other diffuse liver diseases. Liver biopsy is considered as the gold standard but it has problems relating to its invasiveness (pain and bleeding) and the possibility of bias due to sampling error.

Recently, ultrasound elastography has been reported as an effective method for evaluating the level of hepatic fibrosis noninvasively. The possibility of using elastography for evaluating liver cancer risk has also been studied.[1,2] Other publications suggest that liver stiffness significantly varies under the influence of inflammation, jaundice and congestion.[3–6] Many devices capable of ultrasound elastography are available, featuring measurements of different physical parameters and using different excitation methods (generation of the physical phenomena for measurement). The appropriate method should be selected after carefully studying these different features (Table 1).

Table 1: Classification of Ultrasound Elastography

Techniques are classified by the excitation method and physical quantity measured. RTE: Real-time Tissue Elastography; VTI: Virtual Touch Imaging; VTQ: Virtual Touch Quantification; SWE: Shear Wave Elastography.

Cited from, with some modifications, Shiina JSUM Ultrasound Elastography Practice Guidelines. J Med Ultrasonics 2013 and Shiina T., Kudo M. et al: WFUMB Practice Guideline on Ultrasound Elastography. UMB2015.

Physical quantity measured / Excitation method	Strain imaging	Shear wave imaging
Manual compression (vibration, heart beat)	Strain elastography	
	- RTE: Hitachi Aloka Medial - Elastography	
ARFI (Acoustic Radiation Force)	ARFI imaging	Point shear wave elastography
	- VTI	- SWM: Hitachi Aloka Medical - VTQ - ElastPQ
		Shear wave elastography
		- SWE
Mechanical impulse		Transient elastography
		- FibroScan

2. Shear Wave Imaging

Shear waves propagate faster in harder substances than in softer ones. The equation $E = 3\rho Vs^2$ (E: elastic modulus [kPa], ρ: density [kg/m^3] , Vs: shear wave propagation velocity [m/s]) can be applied using the assumption that body tissues are uniform. So, tissue stiffness can be calculated by measuring the propagation velocity of shear waves. Some devices generate shear waves in the liver tissue by vibration of the probe itself, other devices do it by generation of a focused ultrasound pulse. Measurement results are displayed as liver stiffness (elastic modulus), Vs values or color mapping. The method that calculates liver stiffness by measuring Vs is termed Shear Wave Imaging. Liver stiffness or Vs values gradually increase with the progression of liver fibrosis, and are regarded as effective for staging liver fibrosis, hepatic cirrhosis in particular. It has been shown in chronic hepatitis C and B that a higher incidence of liver cancer is related to higher liver stiffness values.[1,2]

3. Shear Wave Measurement (SWM)

Shear Wave Imaging is the method currently most studied for liver fibrosis assessment. This method is now available on the HI VISION Ascendus[*2] (Hitachi Aloka Medical), performed using a convex probe and called Shear Wave Measurement (SWM). Similar to other elastography techniques, the patient lies on his/her back and lifts the right arm. The right lobe of liver is imaged through a right intercostal space while the patient holds their breath in natural respiration. Shear waves are generated from a focused ultrasound pulse once the measurement button has been pressed, and the Vs value is displayed within approximately 2 seconds. The 1cm x 1.5cm region of interest (ROI) needs to be positioned carefully below the liver capsule and where there are no large vessels included in the ROI. This helps to generate a sufficient quantity of shear waves from uniform push pulses. SWM is an elastography technique that measures the Vs value at a point, and is classified as a point shear wave elastography method.

When one measurement from a series is exceptionally out-of-range, the accuracy of that value could be questioned. However, if no dispersion of the measurement results is displayed, the result would be regarded as correct, despite the fact that all of the measurements could be inaccurate. The greatest feature of SWM is the display of the reliability of the measurement results. SWM samples multiple points inside the ROI in one measurement, and displays the median as the result. The distribution of Vs values is presented as a histogram, and the interquartile range (IQR) is also shown. Thus, the dispersion of measured values can be checked at a glance. Additionally, measurements significantly out-of-range and values from disturbed waveforms are excluded from the calculation of the median Vs value. The ratio of accurate samples used in the calculation is quantified and displayed as VsN (Figure 1).

We measured Vs on 186 patients with hepatic disease using SWM and 3 other different Shear Wave Imaging devices to compare the measurement results. The Vs values from the 4 devices showed a high correlation (Figure 2). When there was a large difference of Vs values (dispersion) between the 4 devices, Δ Vs [the difference of inter-equipment Vs values] was compared to the VsN. We found a sharp increase in the value of Δ Vs above 0.75m/s when VsN was less than 60. Further, when the distance between the skin and liver capsule exceeded 2cm, the number of VsN values below 60 increased (Figures 3 & 4). Therefore, we conclude that the reliability of the measurement is high if VsN is 60 or above. If, conversely, VsN is less than 60, the measurement values may not represent the true stiffness of the liver.

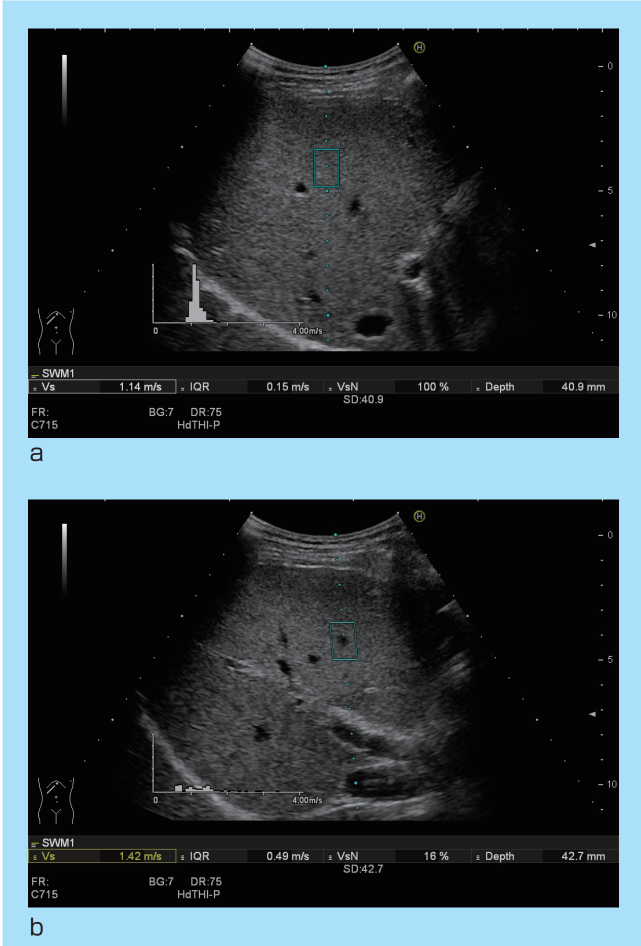

Figure 1: Shear Wave Measurement Examples

When the measurement is appropriate, the histogram shows a normal distribution with a high peak, and IQR is low. Most of the measurement values are considered accurate and VsN takes a high value (a). When the measurement is inappropriate (e.g. large vessels are present in the ROI), the histogram lacks a peak, IQR is high and VsN is low (b).

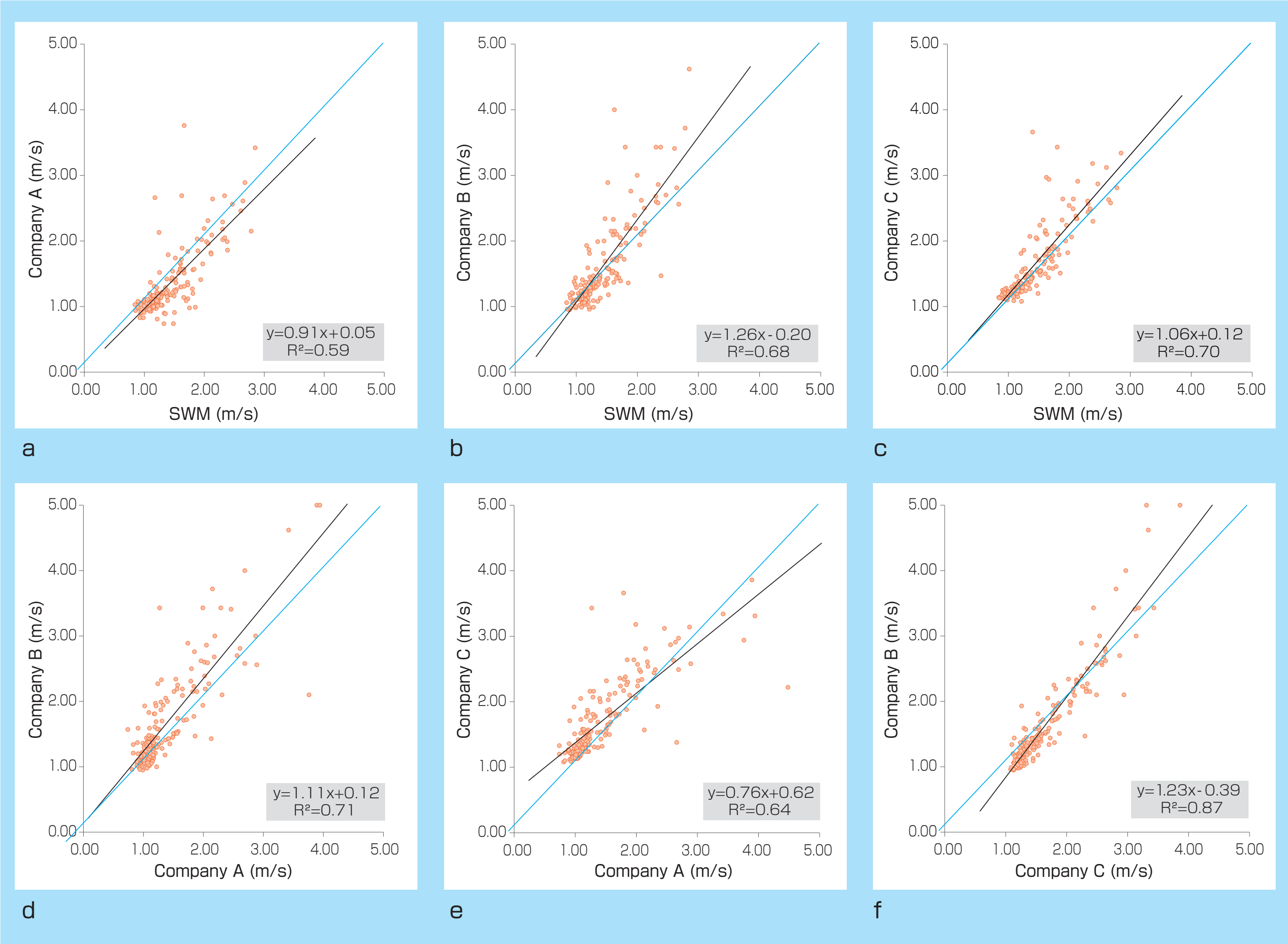

Figure 2: Correlation of Vs value Measured by Different Devices

SWM showed good agreement with other equipment measuring shear wave velocity.
SWM – Company A (a), SWM – Company B (b), SWM – Company C (c), Companies A – B (d), Companies A – C (e), Companies C – B (f)

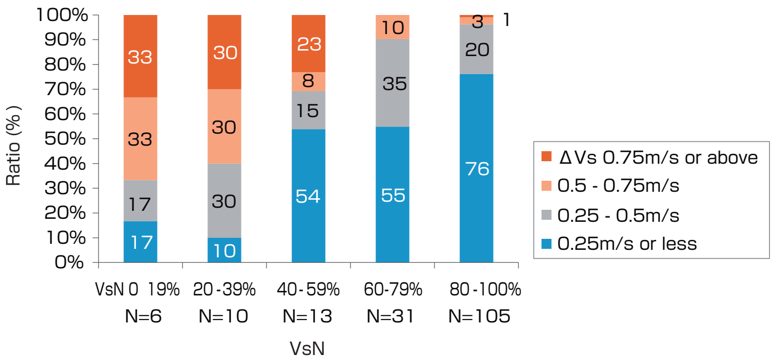

Figure 3: Relation between VsN and Δ Vs

If VsN falls to less than 60, the difference of Vs measurement between devices (Δ Vs) increases, showing that a correct measurement is difficult.

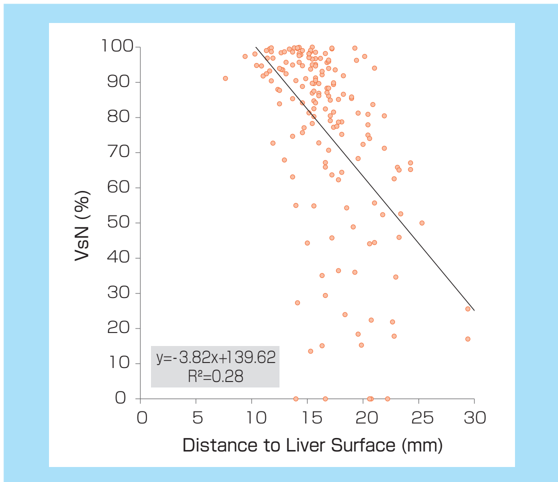

Figure 4: Relation between Distance from Skin to Liver Capsule and VsN

When the distance between the body surface and liver capsule exceeds 2cm, VsN tends to fall to less than 60.

4. Strain Imaging

RTE is a method that displays the relative strain of tissues as a color map in real time, the so-called Strain Imaging technique. When a tissue is subjected to an external force, harder areas of the tissue show relatively less strain than softer parts. The RTE technique measures displacements in the ROI and calculates strain by spatial differentiation.

The harder areas are displayed in blue and the softer areas in red, with intermediate areas shown in green. The real-time color map uses 256 gradations. When RTE is performed in patients with diffuse chronic liver disease such as chronic hepatitis C, the low strain area (%blue) increases and becomes more complex in shape as hepatic fibrosis advances.

Such relative strain changes in chronic liver disease represent the progression of hepatic fibrosis[7] and have been described using several independent image features: MEAN (average value of average strain) gradually decreases as fibrosis progresses while SD (standard deviation of average strain) increases gradually. AREA (area of low strain region in blue) also gradually increases. A multiple regression equation for liver fibrosis index (LFI) for objective diagnosis of the degree of hepatic fibrosis has been derived based on these and other image feature values and compared to liver biopsy diagnosis data from chronic hepatitis C cases (used as training data). LFI is automatically calculated using the measurement tool in the ultrasound system.[8] LFI gradually increases with the progression of fibrosis with significant differences between the stages. AUROC for fibrosis diagnosis using LFI of F4, ≥F3 and ≥F2 takes a high value of 0.800, 0.865 and 0.846, respectively.[9)–11)] Additionally, RTE images are considered to faithfully reflect the level of fibrosis with no significant influence from inflammation, jaundice or congestion.

RTE was originally developed for the examination of the thyroid and mammary glands, so a linear probe, EUP-L52, whose frequency bandwidth is 3 to 7MHz was used. But, this probe is not always optimal for liver examinations due to its high frequency. Penetration is not adequate especially for patients with large amounts of subcutaneous and visceral fat and fatty liver, with these parts often displayed in blue, mistakenly leading to an overestimation of fibrosis. For correct diagnosis, an ROI has to be selected that contains low subcutaneous fat to avoid insufficient penetration, and multiple reflections and blood vessels have to be excluded from the ROI; a technique which requires practice.

A convex probe, EUP-C715, whose frequency bandwidth is 1 to 5MHz (140mm or greater depth penetration) has recently become available which improves penetration significantly. The diagnostic capability is also improved because the observation area is enlarged in both the depth and lateral directions, enabling a more easy selection of the examination area. With the convex probe, examination is easier in patients with thick subcutaneous fat, high-level obesity and fatty liver; patients which are difficult to examine with a linear probe (Figure 5). LFI data measured with linear and convex probes shows a high correlation, indicating that conventional measurement results can now be more readily obtained by all operators. (Figure 6).

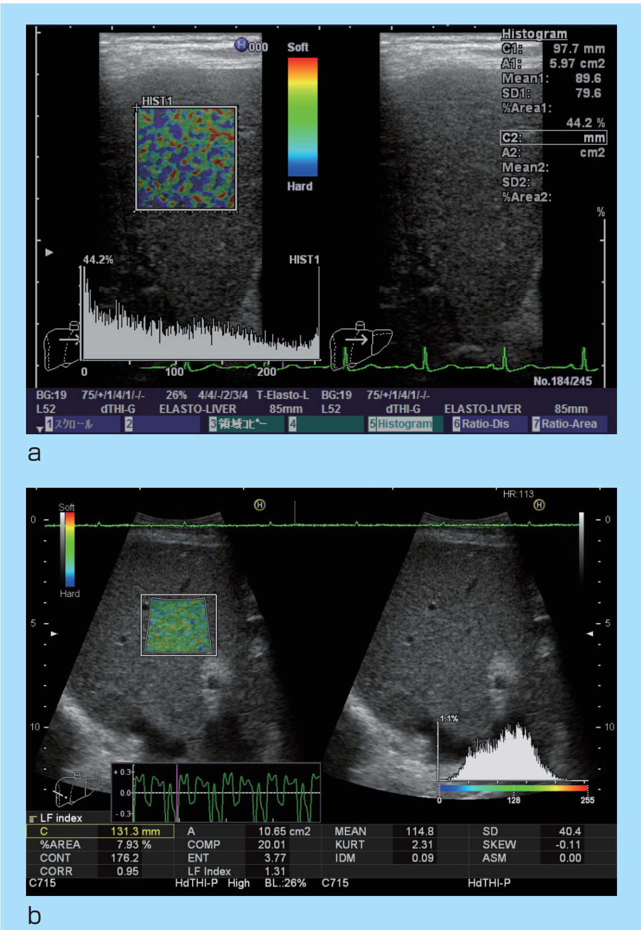

Figure 5: Real-time Tissue Elastography with Linear and Convex Probes

In patients with thick subcutaneous fat, the RTE image can be obscured by a blue coloring due to insufficient penetration with the linear probe, often preventing adequate evaluation (a). When using a convex probe, the wider FOV and improved penetration facilitates RTE measurement (b).

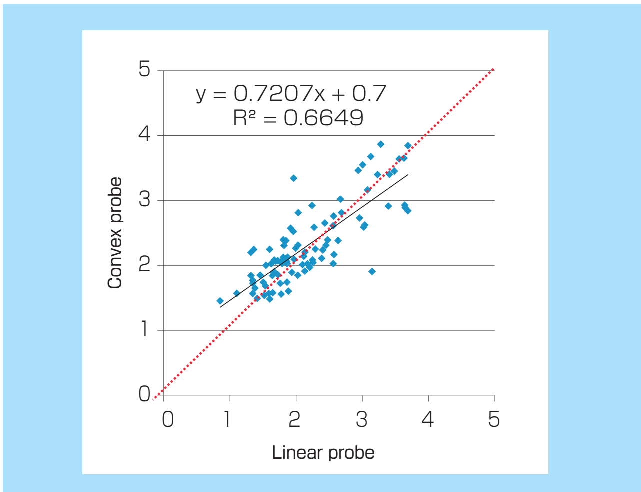

Figure 6: Comparison of Liver Fibrosis Indices Measured with Convex and Linear Probes

Similar LFI values were obtained with convex and linear probes.

5. Combined Approach to Elastography

Vs values measured with Shear Wave Imaging vary significantly under the influence of not only fibrosis but also inflammation, jaundice or congestion. On the other hand, changes in the relative strain in chronic liver disease examined by RTE reflects only the progression of liver fibrosis and the measurement is seldom affected by these factors.

Therefore, the level of inflammation, jaundice and congestion can be estimated by simultaneously performing Shear Wave Imaging and Strain Imaging (Combinational Elastography) and analyzing the difference in the data between these 2 techniques. This interpretation method is described using the case of a 27-year old male suffering from acute hepatitis B. Mild enlargement of the liver and a small volume of ascites were found in B-mode examination, and the ALT was increased to 1290IU. Jaundice and congestion were not found. LFI was 1.2 before treatment, equivalent to an estimated fibrosis stage of F1. In Shear Wave Imaging, on the other hand, liver stiffness by FibroScan[*3] was 8.8kPa, which is equivalent to F3. The divergence is most probably due to the influence of inflammation because the patient had no jaundice or congestion. We may consider that, assuming F1 is in the approximate range of 3 to 4kPa, that 3 to 4 out of the 8.8kPa before treatment is accounted for by the influence of fibrosis and the remaining 4 to 5kPa reflects the influence of inflammation. Actually, liver stiffness gradually decreased with decreasing ALT and recovered to 3.8kPa after 6 weeks. The divergence between the shear wave and strain imaging results had also disappeared (Figure 7).

Combinational Elastography using the Vs measurement obtained by Shear Wave Imaging, with evaluation using RTE at the same time is useful for correctly assessing the clinical condition of the liver.

Development of the SWM technique and RTE with a convex probe has made it possible to perform Combinational Elastography in series following the normal ultrasound examination, using the one probe. Non-invasive diagnosis of liver disease has become more easily accessible using ultrasound elastography.

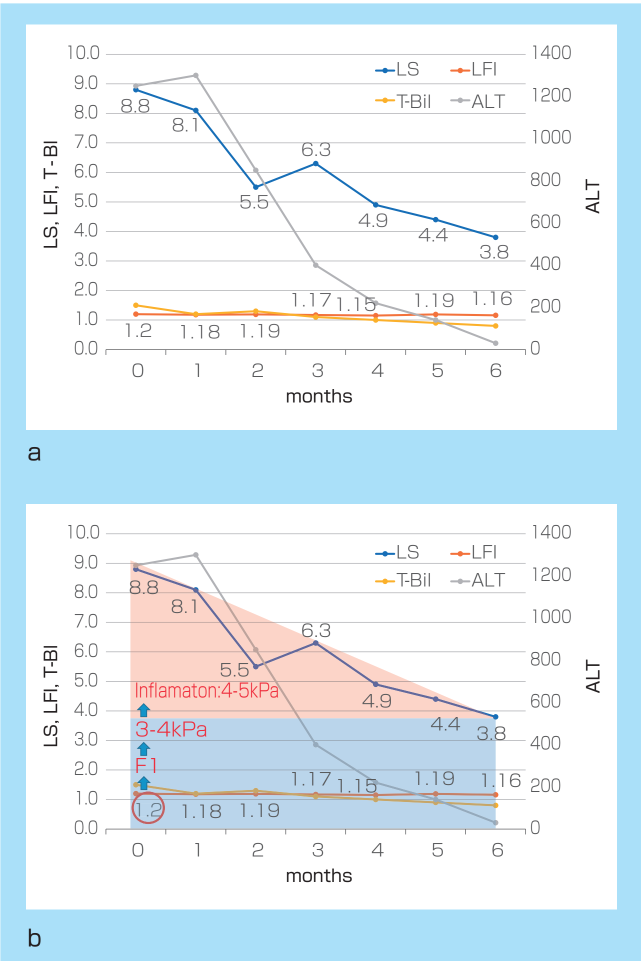

Figure 7: Treatment Course and Interpretation in an Example Case

ALT improved quickly as a result of treatment. Likewise, liver stiffness also improved. T-Bil and LFI remained at the same level throughout treatment (a). Blue-shaded area is considered to reflect fibrosis and the red-shaded area inflammation (b).

6. Acknowledgment

We would like to express our gratitude to those people in Hitachi Aloka Medical with whom technical matters related to evaluation of clinical usefulness of this function have been discussed repeatedly in all stages from prototyping to availability on-board the ultrasound machines.

*1 Real-time Tissue Elastography and *2 HI VISION Ascendus and Ascendus are registered trademarks of Hitachi Medical Corporation.
*3 FibroScan is the trademark of ECHOSENS.

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