Ultrasound-Guided Attenuation Parameter

LOGIQ™ E10 and LOGIQ E10s

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) is growing worldwide with the increase in obesity.[1] Among the many forms of NAFLD, non-alcoholic steatohepatitis (NASH) has attracted attention, as it can progress to liver cirrhosis and hepatocellular carcinoma due to hepatocyte apoptosis, inflammation and fibrosis.[2] Traditionally, liver biopsy has been the gold standard for the diagnosis and assessment of hepatic steatosis. However, this method has some problems such as sampling error and inter-pathologist variability.[3] In addition, the invasive nature of the procedure creates a risk of complications. More recently, MR proton density fat fraction (PDFF) has been accepted as a non-invasive reference standard, but limited access and high cost prevent widespread use, especially with respect to regular follow up exams.

The liver echogenicity on ultrasound B-Mode is widely used for the detection of hepatic steatosis. However, this technique does not enable a quantitative assessment since liver texture or brightness may vary depending on the imaging parameters used or the examiner's technique. Therefore, an objective ultrasound quantification method is desired for steatosis grading in current and potential NASH patients. Recently, a novel non-invasive tool that utilizes attenuation of the sound wave was developed. However, it may be susceptible to multi-reflection artifacts from subcutaneous tissues as well as disruptive structures such as vessels or diaphragm since the measurement area is not guided by imaging.[4]

This paper describes Ultrasound-Guided Attenuation Parameter (UGAP), a real-time, image-guided method of measuring the attenuation of the sound wave. The principles of the method as well as the clinical evaluation results are presented.

Ultrasound Attenuation

When the ultrasound wave propagates in an organ, such as the liver, it is gradually weakened due to diffusion, scattering and absorption. Known as sound attenuation, this results in less signal returning to the ultrasound transducer, causing the image to get darker with depth. If an image of a healthy liver has uniform image brightness over depth, it is because of the time-gain compensation (TGC) capability of the ultrasound scanner, which applies a different gain for each depth (Figure 1). In the case of fatty liver, the presence of many lipid droplets in the hepatocytes becomes the dominant factor of the attenuation, sometimes causing insufficient echo signals in the deeper area.

The amplitude of ultrasound wave u propagating in the x direction is expressed as $u=u_0e^{-\alpha x}$, where u_0 is the amplitude at x=0 and α is attenuation rate. Since the sound attenuation increases nearly proportional to the frequency (ranging between 1 MHz to 10 MHz), the attenuation rate can be approximated by $\alpha = \alpha_0 f$, where α_0 is the attenuation coefficient (dB/cm/MHz) and f is frequency in [MHz].[5] Attenuation rate and attenuation coefficient are used primarily to evaluate ultrasound attenuation in human tissues.

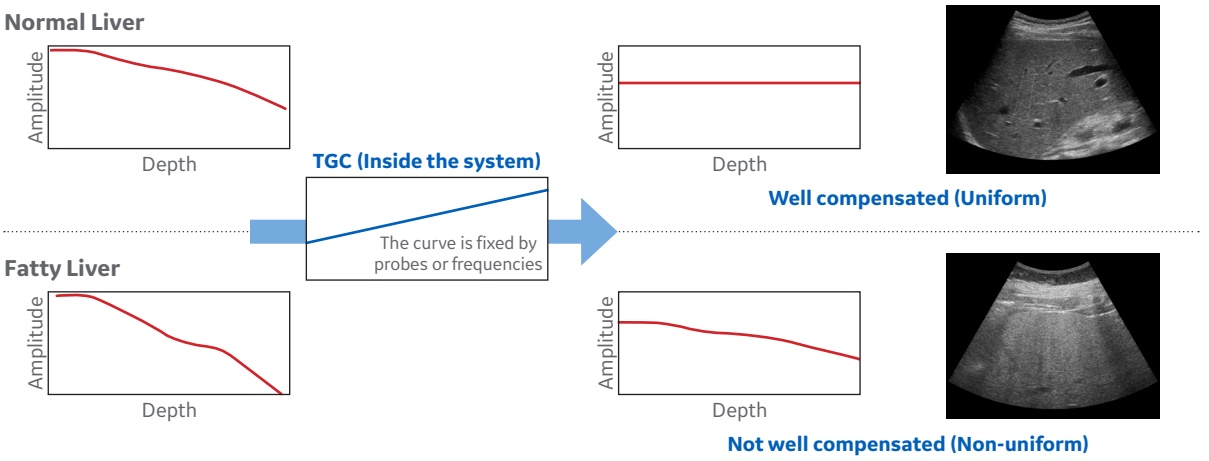

Figure 1. Ultrasound attenuation compensation by TGC.

Ultrasound Attenuation Evaluation Method by UGAP

Principle of Measurement

As shown in Figure 1, measuring the attenuation slope would provide insight into liver attenuation. However, the sound profile in the real signal is not so simple, since it is curved as shown in Figure 2 (A). This complexity is caused by a focused sound beam from transmission as well as reception conditions. To cancel out or compensate for this complexity, several methods have been reported.[6] UGAP performs the compensation based on a Reference-Phantom Method (RPM)[7] (Figure 2). The profile of the echo amplitude for a tissue-mimicking phantom is measured in the depth direction and stored in the ultrasound system as a reference. In this case, a frequency of 3.5 MHz is used. This industry-standard phantom includes glass bead particles for attenuating materials and the attenuation coefficient is known. In the UGAP mode, the transmission and reception conditions are fixed to the same values as were used on the reference phantom, and the acquired echo profiles of the target (liver) are compensated by the reference data. As a result, the compensated sound profiles represent only decay caused by attenuation. If the compensated sound profile is flat, the attenuation is the same as the reference phantom.

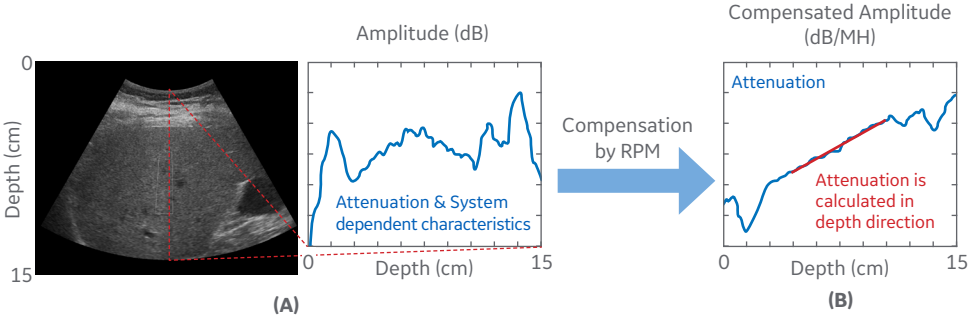

Figure 2. Compensation of ultrasound signal to enable UGAP measurement.

Measurement Algorithm

Although the system-dependent sound profile is compensated, there are still problems in performing a successful measurement. For example, structures such as large vessels and diaphragm may deform the slope profile. Or, multi-reverberation in the subcutaneous fat may generate artifacts into the liver parenchyma. Or, information needed to determine the slope may be diminished if the attenuation is very large. To avoid these problems, UGAP includes an automated measurement algorithm to find and then analyze the optimum measurement range. The start point of the range is determined by analyzing linearity and discontinuity of the echo profile close to the liver surface, thereby avoiding the multi-reverberation artifacts. In addition, the algorithm automatically detects and avoids depths where the signal-to-noise ratio (SNR) is insufficient. This enables the algorithm to employ the deepest usable end point. The diaphragm is also automatically excluded. Finally, the angle of the slope is measured across this optimum range to provide a representative attenuation coefficient. Because this measurement takes place on the raw data of a frozen or recalled image, it is not dependent on gain or other post processing settings. The goal of these automations is to make the UGAP measurement less dependent on the ROI position and more robust across various liver sizes and conditions.

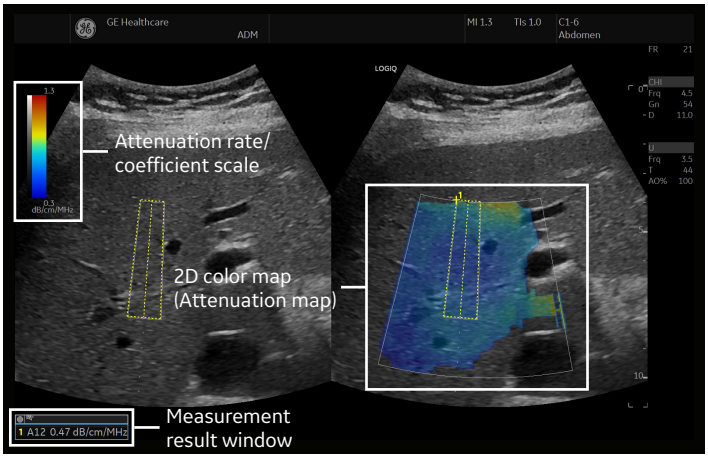

Figure 3. Example of B-Mode/Color dual display format.

Color Mapping for Measurement Guidance

To find the right scan-plane and ROI for measurement, B-Mode and two types of new color-mapped images are available in UGAP mode (Figure 3).

(a) Attenuation map: Displays color-coded local attenuation values for each pixel. When the measurement area (denoted by a trapezoid with a center line in Figure 3) has a uniform color, it is suitable to measure. The color will become inhomogeneous if the area includes a disruptive structure such as a large vessel.

(b) Quality map: Displays a color at pixels where signal quality is sufficiently high to perform a measurement. Even though the B-Mode texture may look homogeneous, a lack of color could be the result of unseen artifacts.

To aid in the acquisition and measurement of UGAP, various display formats are selectable: B-Mode only, B-Mode with color map overlay, and a dual display that shows both images side-by-side. Figure 3 shows an example of the B-Mode/Color map dual display. Examples of the color-coded attenuation for different degrees of steatosis are shown in Figure 4.

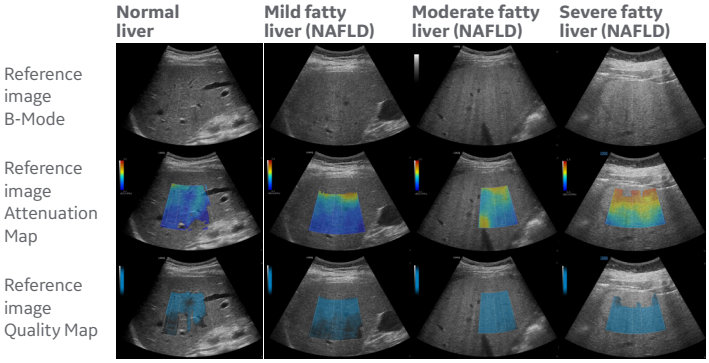

Figure 4. Examples of color-mapped attenuation images at different degrees of liver fat (Courtesy of Prof. Sporea, Victor Babes University of Medicine and Pharmacy of Timisoara).

Evaluation of Steatosis Grade in Chronic Liver Disease by UGAP

This section summarizes the results of a UGAP clinical evaluation for hepatic steatosis cases reported by Iwate Medical University Hospital.[8]

Materials and Methods

A total of 180 consecutive patients with hepatitis C (HCV) or NAFLD-related chronic liver disease (CLD) were enrolled in a UGAP measurement study. Liver biopsy (LB) and Controlled Attenuation Parameter (CAP™) were also performed on the same day. Evaluations were completed for 163 cases, excluding nine cases in which CAP was not measurable and eight cases in which the accuracy of LB was insufficient. Patients' sex, age, etiology, body mass index (BMI) and steatosis grade are shown in Table 1.

Variable	Value
Subject	163
Sex (Male/Female)	92/71
Age (y)	60.7 ± 13.9
Etiology (HCV/NAFLD)	85/78
BMI (kg/m^2)	25.9 (22.4 – 28.4)
Steatosis grade (%)	
S0 (< 5%)	62 (38.0)
S1 (5% – 33%)	63 (38.7)
S2 (33% – 66%)	23 (14.1)
S3 (> 67%)	15 (9.2)

Table 1. Patients' sex, age, etiology, BMI and steatosis grade.

Radiofrequency-based ultrasound echo data (RF data) were acquired by intercostal scan of the right liver lobe (segment V). LOGIQ E9 XDclear™ 2.0 and C1-6-D convex array probe (3.5 MHz) were used in this feasibility study. RF data were transferred to a consumer PC in which UGAP prototype software was running. The measurement position was selected by avoiding large vessels visible in the B-Mode image.

CAP was measured with FibroScan® 502 touch (EchoSens, Paris, France) and M probe (3.5 MHz), also by intercostal approach to the segment V. CAP value was used only when liver-stiffness measurement (LSM) achieved more than ten valid shots, a success rate of at least 60% and an interquartile range <30% of the median LSM value.[9]

An ultrasound-guided LB was performed using a 14-G biopsy needle with a 22 mm core length in all patients. LB samples shorter than 15 mm were excluded. Steatosis was categorized based on Brunt grading[10] as follows: S0 < 5%, S1 = 5% – 33%, S2 = 34% – 66% and S3 = ≥ 67%. BZ-X700 Microscope System (Keyence Corp., Osaka, Japan) and BZ-H3 C Hybrid Cell Count Software (Keyence) were used to automatically determine the ratio of fat droplet area to hepatocyte area in the biopsied specimens, which was termed the percentage steatosis.

Results

The relationship between UGAP and steatosis percentage and the relationship between UGAP and CAP are shown in Figure 5 (A) and Figure 5 (B), respectively. A significantly strong correlation was confirmed between UGAP and percentage steatosis, Spearman's rank correlation coefficient was 0.777 ($p < 0.001$). A significant correlation was confirmed also between UGAP and CAP, the correlation coefficient was 0.648 ($p < 0.001$).

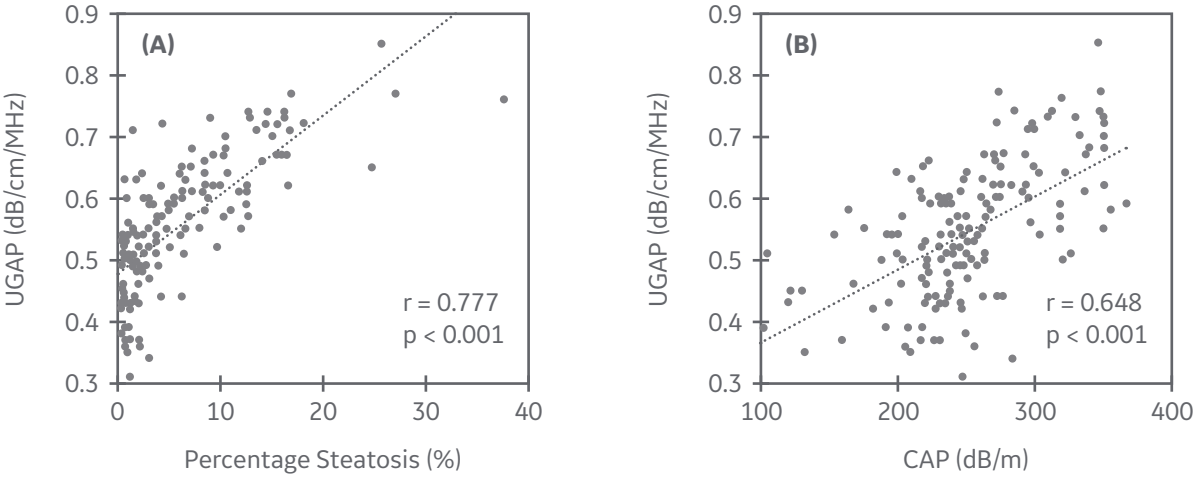

Figure 5. Relationship between (A) UGAP and % Steatosis based on LB and (B) UGAP and CAP.

UGAP values in each steatosis grade are shown in Figure 6. The average values of UGAP in S0, S1, S2 and S3 steatosis were 0.49, 0.56, 0.66 and 0.72 dB/cm/MHz, respectively, as UGAP increased with increasing steatosis grade. Using the Mann-Whitney U-test, a significant difference was confirmed between S0 and S1 ($p < 0.01$), and S1 and S2 ($p < 0.01$).

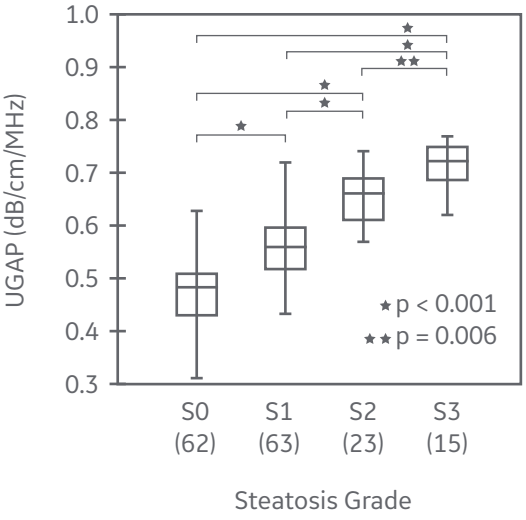

Figure 6. Measured UGAP values in each steatosis grade.

Receiver operating characteristics (ROC) curve of UGAP and CAP for diagnosis of S1 or higher, S2 or higher and S3 steatosis are shown in Figure 7: (A): ≥S1, (B): ≥S2, (C): S3. Area under the ROC curve (AUROC), 95% confidence interval (95% CI) and cutoff value of UGAP are shown in Table 2. The AUROCs of UGAP for the prediction of S1 or higher, S2 or higher and S3 steatosis were 0.900 (95% CI: 0.834 – 0.967), 0.950 (95% CI: 0.894 – 0.993) and 0.959 (95% CI: 0.920 – 0.999), respectively. The AUROCs of CAP for the prediction of S1 or higher, S2 or higher and S3 steatosis were 0.829 (95% CI: 0.743 – 0.914), 0.841 (95% CI: 0.728 – 0.953) and 0.817 (95% CI: 0.703-0.932), respectively.

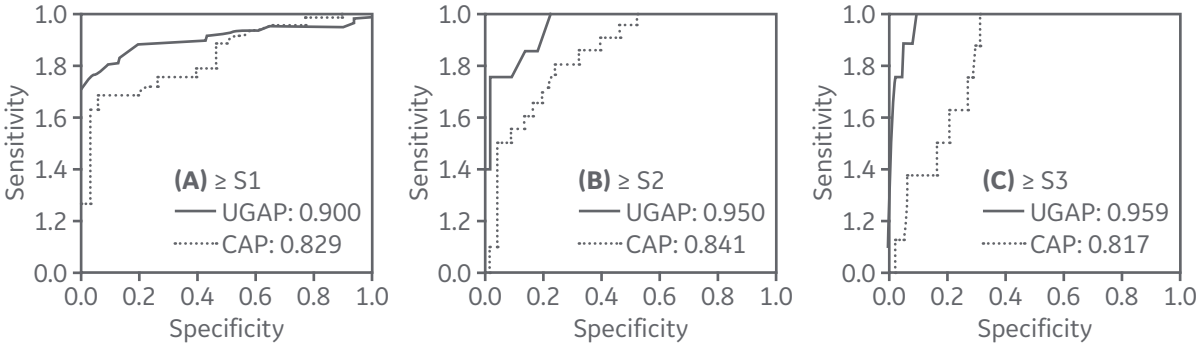

Figure 7. ROC of UGAP and CAP for diagnosis of steatosis grade (A) ≥S1, (B) ≥S2 and (C) S3.

	UGAP		
	≥ S1	≥ S2	S3
AUROC (95% CI)	0.900 (0.834 – 0.967)	0.950 (0.894 – 0.993)	0.959 (0.920 – 0.999)
Attenuation coefficient cutoff value (dB/cm/MHz)	0.53	0.60	0.65
Attenuation rate cutoff value (dB/m)	186	210	228

Table 2. AUROCs, 95% CI and cutoff values of UGAP for the prediction of ≥S1, ≥S2 and S3 steatosis.

Discussion

In this study, the accuracy of UGAP for discriminating steatosis grade in patients with CLD was evaluated. A significantly strong correlation was confirmed between UGAP and percentage steatosis ($r = 0.777$, $p < 0.001$). The AUROCs of UGAP for the prediction of S2 or higher and S3 steatosis were 0.950 and 0.959, respectively. This compares favorably to the performance of CAP (S2 or higher: 0.841, S3: 0.817).

With respect to the ability to discriminate S1 or higher, the accuracy of abdominal ultrasonography was somewhat reduced with an AUROC of 0.900. This diagnostic performance also compared favorably to CAP (S1 or higher: 0.829).

UGAP had high diagnostic accuracy in detecting hepatic steatosis in patients with CLD.

Conclusion

UGAP is a new, non-invasive method for measuring a patient-specific, quantitative attenuation parameter that is well correlated to liver biopsy for discriminating hepatic steatosis among patients with CLD. The B-Mode image provides an anatomical guide while the attenuation and quality maps provide an attenuation quality guide. This combination provides extensive user assistance for proper placement of the UGAP measurement ROI. Lastly, automated algorithms optimize the results within the specified measurement ROI. As such, UGAP is an easy and fast tool that, in combination with 2D shear wave elastography, has the potential to aid in the initial diagnosis and follow-up care of CLD patients.

References

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