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Development of non-invasive method for assessment of hepatic steatosis

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ABSTRACT

Steatosis is a critical feature of liver disease and is considered to play a pivotal role in the progression of nonalcoholic fatty liver disease, as well as being a surrogate marker of metabolic syndrome. The purpose of this study was to develop a non-invasive diagnostic method for assessment of liver steatosis. It is well known that ultrasonic velocity depends on materials and temperature. For example, the ultrasonic velocity in water is 1530 m/s at 37 °C and 1534 m/s at 39 °C, while that in fat is 1412 m/s at 37 °C and 1402 m/s at 39 °C. On this basis, we thought that the percentage of fat in hepatic steatosis could be assessed by detecting changes of ultrasonic in the liver, caused by warming. In order to confirm the effectiveness of this method, we obtained the ultrasonic velocity changes of tissue phantom including lard oil and the liver of living rabbit by ultrasonic warming, and then succeeded in 2-D imaging of ultrasonic velocity changes of the phantom and the liver of living rabbit. We named this the ultrasonic velocity-change method. The experimental results show the possibility that hepatic steatosis could be characterized using our novel, non-invasive method.

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1. Introduction

Liver steatosis results from the accumulation of fatty droplets in the hepatocytes. There are several causes, such as alcohol consumption, viral hepatitis and metabolic dysfunction. Liver steatosis is a reversible, benign condition and a common abnormality occurring in approximately 30% of the general population in the United States [1]. However, in many cases, steatosis can be associated with inflammation (i.e. steato-hepatitis), which may result in liver fibrosis and can progress to cirrhosis, liver failure and hepatocellular carcinoma [2]. Recently, hepatocellular carcinoma also has been recognized as a complication of liver steatosis and emerging evidence suggests that cardiovascular disease may also be more common in patients with steatosis, even when adjusted for traditional risk factors [3,4]. Liver biopsy is regarded as the gold standard for the assessment of steatosis. However, its use in clinical practice is limited because of its invasiveness. Therefore, various imaging methods, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (MRS), have been used for the non-invasive evaluation of steatosis. US commonly detects changes in the liver parenchyma as increased echogenicity compared to the kidney and is the most frequently used tool in clinical practice. The sensitivity of US ranges from 60% to 94%, with a specificity between 88% and 95% [5–7]. The major drawbacks of ultrasonography are operator dependency and are affected considerably by increasing body mass. The sensitivity improves to 80% when liver fat exceeds 30%, but drops to 50% in morbid obesity or when the liver fat content is below 20% [8–10]. CT provides a better estimation of liver fat. Estimation of liver fat content is based on the comparison of hepatic and splenic attenuations and can predict moderate to severe degrees of steatosis with greater sensitivity when steatosis is above 33% of the liver parenchyma [11]. Both US and CT are considered qualitative tests, best suited to detect liver steatosis but not to quantify the amount of fat or to be used to follow disease progression or patients' responses to treatment. On the other hand, MRS has a very good correlation with the amount of liver fat estimated by liver biopsy [12]. The lower limit of MRS is considered to be 5% of the liver wet weight as hepatic triglycerides content [13]. MRS usually can be performed within 20–30 min but is currently limited to academic centers.

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The purpose of this study was to develop a non invasive and inexpensive diagnostic method for assessment of liver steatosis. It is well known that the ultrasonic velocities of various materials have inherent values and vary with temperature. For example, the ultrasonic velocity in water is 1530 m/s at 37 °C and 1534 m/s at 39 °C, while that in fat is 1412 m/s at 37 °C and 1402 m/s at 39 °C. The rate of change of the ultrasonic velocity in water is +2 m/s at 37 °C and that in fat is −4 m/s at the same temperature [14,15]. The ultrasonic velocity increases in muscle and internal organs with a high percentage of water content, but decreases in fatty tissue. On this basis, we thought that the fat in hepatic steatosis could be assessed by detecting ultrasonic velocity change of the liver caused by warming. In order to confirm the effectiveness of this method, we obtained the ultrasonic velocity changes of tissue phantom including lard oil and the liver of living rabbit by ultrasonic warming, and then succeeded in 2-D imaging of ultrasonic velocity changes of the phantom and the living rabbit liver. We named this the method ultrasonic velocity-change method. We wished to confirm whether this method can provide a quantitative evaluation when the liver fat content is between 5% and 20%. The experimental results showed the possibility that the assessment of hepatic steatosis could be achieved using our novel and noninvasive imaging method.

2. Principle of ultrasonic velocity-change method

In general, biological tissues consist mainly of water and their ultrasonic velocities increase with rising temperature. On the other hand, the velocities of tissues containing fat decrease with rising temperature. The ratio of ultrasonic velocity change is +1.9 m/s in water but it is −4.9 m/s in fat, therefore, it may be possible to quantify the percentage of fat on the basis of the change in ultrasonic velocity with temperature. In the liver, the change in ultrasonic velocity with respect to temperature depends heavily on the percentage of fat [16]. Fig. 1 shows the basic experimental setup for the ultrasonic velocity-change method, which consists of a water tank kept at constant temperature, a block containing fat dispersed in water, the ultrasonic linear array transducer and the warming ultrasonic transducer. The ultrasonic linear array transducer transmits and receives the ultrasonic pulse wave. The ultrasonic pulses emitted from the array transducer are reflected from the various boundaries of different acoustic impedance. As shown in Fig. 1, the echo pulses reflected at the boundaries shift according to the ultrasonic velocity change caused by the local temperature rise [17,18] with the warming ultrasonic transducer.

The echo pulses reflected at the boundary surfaces I and II are received by the same transducer. After warming, the echo pulse becomes faster when it propagates in the water-rich domain and reflects back from boundary surface I ($\Delta\tau_1$), but becomes slower when it propagates in the fat containing domain and reflects back from boundary surface II ($\Delta\tau_2$). Consequently, the difference in shift may be expressed as $\Delta\tau_1 + \Delta\tau_2$. The pulse shift between the bi-border ($\Delta\tau_n$) distinguishes the latter shift ($\Delta\tau_{n-1} + \Delta\tau_n$) from the former ($\Delta\tau_{n-1}$). The round trip time of the echo pulse between the boundaries and the time difference are denoted by τ_n and $\Delta\tau_n$, respectively, so that the velocity change, Δv_n, of the warmed region may be represented by $\Delta vn = v\frac{\Delta\tau n}{\tau n}$, where v is the ultrasonic velocity.

The echo waveform of each acoustic scan line was divided into appropriate sections with the width of the transmitted pulse. The cross-correlation between the corresponding section of the waveform data stored before and after warming was calculated to obtain the time difference, $\Delta\tau$, of the echo pulse shift induced by the temperature change. The ultrasonic velocity-change is constructed from $\Delta\tau$ and τ for each acoustic scan line.

The ultrasonic velocity change Δv by the temperature change ΔT is represented as follows,

$$\frac{\Delta v}{\Delta T} = \left(\frac{\Delta v}{\Delta T}\right)_w \cdot x + \left(\frac{\Delta v}{\Delta T}\right)_f (1 - x),$$

where x is the fat content, $(\Delta v/\Delta T)_w$ is the temperature dependence of ultrasonic velocity in water and $(\Delta v/\Delta T)_f$ is that in fat. As $(\Delta v/\Delta T)$ w and $(\Delta v/\Delta T)$f can be determined in advance, the fat percentage x can be determined from the Δv and ΔT values of the object. Δv can be obtained by the ultrasonic velocity-change imaging method. ΔT is required for the calculation.

3. Experimental verification for effectiveness of the imaging method

3.1. Preliminary experiment using tissue phantom

Before the experiment using living rabbits, we assessed different fat content of the tissue phantoms containing lard oil manufactured by OST Co., Ltd. (Tokyo, Japan). The lard-free phantom was composed of water, agar, talc, thickener and 1-propanol, and the proportions (by weight) of the water, agar, talc, thickener and 1-propanol were 85.54, 1.20, 3.60, 1.20 and, 8.46%, respectively. The lard phantom manufactured by adding sodium dodecyl sulfate and lard to the lard-free phantom. A conventional pulse echo system (5077PR, Olympus) was used to obtain the pulse shift in the lard-free phantom and the phantoms containing 10%, 20% and 30% lard. We measured the ultrasonic velocity in each phantom at 30 °C. Then, we obtained the ultrasonic velocity change for each phantom at various temperatures between 30 °C and 40 °C. Fig. 2 shows that the ultrasonic velocity changes depend on the percentage of fat. Linear approximations of the velocity change rates of the

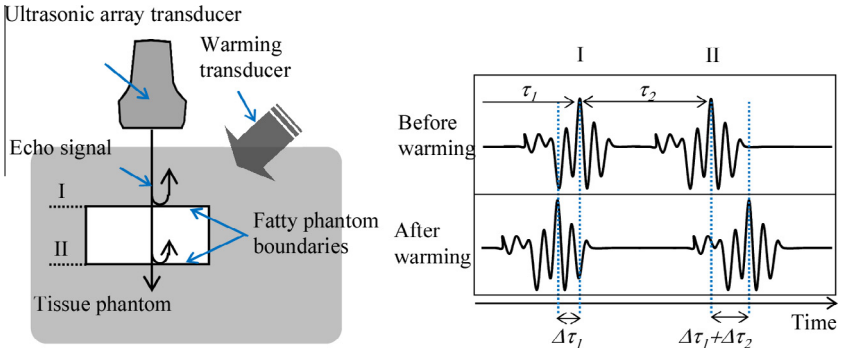

Fig. 1. Principle of the ultrasonic velocity change imaging method. Left, schema of the position of the ultrasonic transducers for imaging and heating. Right, the sequential of pulse shift. I, II: tissue boundaries.

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