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Substantial fluctuation of acoustic intensity transmittance through a bone-phantom plate and its equalization by modulation of ultrasound frequency

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ABSTRACT

For safe and efficient sonothrombolysis therapies, accurate estimation of ultrasound transmittance through the human skull is essential. The present study clarifies uncertainty surrounding this transmittance and experimentally verifies the equalization of transmittance through the modulation of ultrasound frequency. By changing three factors (ultrasound frequency, the thickness of a bone-phantom plate, and the distance between a transducer and a bone-phantom plate), we measured the intensity of ultrasound passing through the plate. Two activating methods, sinusoidal waves at 500 kHz and modulated waves, were compared. When we changed (1) the distance between a transducer and a bone-phantom plate and (2) the thickness of the bone-phantom plate, ultrasound transmittance through the plates substantially fluctuated. The substantial fluctuation in transmittance was observed also for a cut piece of human temporal skull bone. This fluctuation significantly declined for the modulated wave. In conclusion, modulation of ultrasound frequency can equalize the transmittance with an approximately 30–65% fluctuation drop and an approximately 40% fluctuation drop for a bone-phantom plate and for a cut piece of skull bone, respectively. By using modulated waves, we can develop safer and more effective sonothrombolysis therapies.

1. Introduction

Advancements in therapies for acute ischemic strokes are critical in present-day medicine. Among the available therapies, administration of a recombinant tissue plasminogen activator (rt-PA) is the first choice, and its effectiveness has been proven [1]. However, high ratios of symptomatic intracerebral hemorrhages (4–7%) in the rt-PA-injected patients constitute the treatment's most serious adverse effects [1–3]. Reduction of this hemorrhage ratio is strongly desirable. Furthermore, higher therapeutic efficiency resulting in improved prognosis is no less desirable. For these aims of reduction and improvement, one of the most feasible methods is sonothrombolysis in which irradiation with ultrasound enhances the thrombolytic activity of rt-PA specifically at the irradiation site [4–6]. When the enhancement is successfully obtained, a reduction in rt-PA doses is possible, thus helping decrease the hemorrhage ratio.

Sonothrombolysis has been actively studied, and several clinical trials have been conducted. In a CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA) clinical test [4] with 2 MHz ultrasound, the recanalization rate was improved. In the prognosis after 3 months, however, a statistically significant improvement was not obtained. One of the possible reasons for the 3-month – prognosis result is apparently a problem of low transmittance of 2 MHz ultrasound through the skull. Consequently, a technology to obtain high ultrasound transmittance is favored in sonothrombolysis, not only for 2 MHz but also for other frequencies of ultrasound. A TRUMBI (Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia) trial with 300 kHz ultrasound was stopped prematurely because of an unexpectedly high ratio of cerebral hemorrhages [7]. The reason was not elucidated; however, it was speculated that locally intense spots arose owing to standing waves, which result from the multi-reflection of ultrasound at the inner surface of skulls [7,8].

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To improve the effectiveness and safety [9] of sonothrombolysis, several groups have developed therapeutic devices such as an array transducer composed of both therapeutic and diagnostic ultrasound elements [10], a high-intensity-focused ultrasound probe navigated by MRIs [11–13], and a computer-aided multiple transcranial head frame [14]. For all sonothrombolysis-equipment developments including the above-mentioned examples, estimation of transmittance through human skulls is the most fundamental and important factor for equipment-system designs. For clinical applications, uncertainty of the transmittance is undesirable. If the transmittance is unexpectedly high, the acoustic intensity in the brain will be higher than the anticipated intensity, consequently increasing the risk of cerebral hemorrhages. Likewise, if the transmittance is unexpectedly low, the enhancement effect of thrombolysis will be that much smaller. We believe that the correct estimation of transmittance is one of the most important factors for the effective development of sonothrombolysis therapies. Transmittance varies depending on many factors such as frequency of ultrasound and thickness of bone [15–19]. In particular, White et al. reported interesting frequency-dependent fluctuation behaviors of ultrasound transmittance through the human skull both in calculations and measurements [19]. However, the human skull is not an appropriate measurement sample with which effects of various skull parameters (e.g., thickness, density, sound speed) on ultrasound transmittance are systematically analyzed, because the skull possesses considerably complex structures and various bone thicknesses at different points. In this paper, we use a bone-model plate possessing a representative density of human bone. With this bone plate, we try to systematically analyze transmittance behaviors of ultrasound by varying both the plate parameters and the irradiated ultrasound parameters. In our model, the derivation of which is described later, the transmission of ultrasound fluctuates cyclically according to changes of frequency and plate thickness.

In the past, fluctuations in ultrasound transmittance have not been considered large enough to influence sonothrombolytic therapy's safety or effectiveness. Some previous works reported phase shift of ultrasound with frequency change through a phantom plate [20] or human skull [21] (model calculation). We hypothesize that fluctuations are, in fact, much larger than previously considered, and that the fluctuations significantly affect sonothrombolysis effectiveness and safety. Therefore, we have performed relevant calculations by using a simple model of a bone-phantom plate, and experimentally measured ultrasound transmittance by changing the ultrasound frequency and thickness of the bone-phantom plate.

Many previous studies concerning ultrasound transmission have not investigated the distance between a transducer surface and bone. Clement et al. [22] observed a phase shift of ultrasound through human skull when they moved a transducer. In this case, the authors simultaneously changed both the transducer's location and the distance between the skull surface and the transducer. No published study has conducted a systematic analysis regarding the distance between a transducer surface and bone has not been done. Because water shows similar properties as tissue in terms of density and sound speed, the aforementioned distance can be treated as the thickness of human skull's surrounding skin. Ultrasound reflected at the bone-surface travels back to the transducer and is reflected at the transducer surface, and then, propagates toward the bone again. Owing to interference between the reflected ultrasound and the non-reflected one, transmittance may fluctuate. Therefore, we varied the distance between the transducer surface and the bone-phantom plate in addition to the ultrasound frequency and the plate thickness.

Furthermore, because this undesirable fluctuation results from ultrasound-related reflection and interference, we expect that modulation of ultrasound frequency, which disrupts ultrasound regularity, equalizes the fluctuating transmittance. We have, moreover, experimentally verified this hypothesis. Previously, we used ultrasound modulation [23–25] to reduce standing waves, which constituted a possible cause of cerebral hemorrhages in the TRUMBI trial [22,26,27]. In the current study, we expect that modulation of ultrasound not only can reduce standing waves but also can equalize the fluctuating transmittance of ultrasound through human skulls.

2. Materials and methods

2.1. Experimental setup

We used a transducer (a special-order product; Ueda Japan Radio Corporation, Ueda, Nagano, Japan; Fig. 1A presents a photo of the transducer) possessing a nominal frequency of 500 kHz and a broad bandwidth from 357 kHz to 665 kHz (6-dB down). This transducer was made of 5-mm-thick porous piezoelectric material, and its matching layer was made of SA16 (an epoxy resin). No backing was added. The surface of the transducer formed a flat disk shape whose diameter was 24 mm. A signal from a generator (AFG3102; Tektronix, Beaverton, OR, USA) was amplified with an amplifier (HSA4101; NF Corporation, Yokohama, Kanagawa, Japan) and introduced to the transducer. When we activated the transducer at 500 kHz in water, the wavelength of the ultrasound was approximately 3 mm, and the focused point was 47 mm away from the transducer's surface. (The value of this focused point was calculated according to Eq. (A).)

$$\frac{D^2}{4\lambda} - \frac{\lambda}{4}, \quad (D : \text{transducer diameter}, \lambda : \text{wavelength}), \tag{A}$$

For a model of human temporal skull bone, we used a bone-phantom plate (a special order product; Ueda Japan Radio Corporation, Ueda, Nagano, Japan). The plate size was 50 mm × 70 mm, and the plate thicknesses ranged from 0.6 mm to 4.4 mm at 0.2 mm intervals. Photos of a 2-mm-thick plate are shown in Fig. 1B and C. The plate's surface was placed parallel to the flat disk surface of the transducer. Although thickness of human temporal bone varies from one person to the next, the thicknesses of bone plates lie within a range related to the human temporal bone (3.1 ± 0.9 mm (the average ± S.D.) reported by Wijnhoud et al. [28]. The sound speed of the bone-phantom plates was 2884 m/s (measured according to the ultrasonic pulse method), and its density was 1664 kg/m^3 (measured according to the Archimedes' method). These values are comparable to the human skull bone [16]. The absorption rate of the plate was 0.402 dB/mm/MHz (the average value measured according to the transmission method at 2, 3, 4, and 5 MHz), which was approximately half of a value (0.7 dB/mm/MHz) of human skull bone at 0.56 MHz [29].

A cut piece of human temporal skull bone (3.5 cm × 8.0 cm, Fig. 1D) was purchased through the General Science Corporation Import Company (Tokyo, Japan) from Ets du Docteur Auzoux (Paris, France) on March 2006.

We measured ultrasound intensity passing through the bone-phantom plate with an acoustic intensity measurement system (AIMS) (Onda Corporation, Sunnyvale, CA, USA) equipped with a needle hydrophone having an active tip of 0.4 mm in diameter (HNC-0400; Onda Corporation, Sunnyvale, CA, USA). Special-order calibration was made in a wavelength range from 250 kHz to 1 MHz with 50 kHz intervals in addition to the standard calibration from 1 MHz to 10 MHz. The measurement was conducted with an average acoustic intensity of 200 μsec measurement period. By changing three factors (the frequencies of ultrasound, the thicknesses of the bone-phantom plate, and the distances between the