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Bubble Generation by Standing Wave in Water Surrounded by Cranium with Transcranial Ultrasonic Beam

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Low-frequency ultrasound, typically less than 1 MHz, is suitable for enhancing thrombolysis because it penetrates the cranium effectively. However, intracerebral hemorrhages after transcranial insonation in clinical trials at 300 Hz have been reported. In this study, acoustic bubble formation in a standing wave with a 617 kHz ultrasonic beam in water surrounded by a contoured piece of a human cranium was detected by ultrasound B-mode imaging. This bubble formation was indirect evidence that standing-wave formation led to cavitational adverse effects in brain tissue at the place of reflection by transcranial insonation at a relatively low ultrasonic frequency. A way of suppressing cavitation after bubble formation was also investigated. The efficiency of nucleation of bubbles was highly dependent on pulse duration at a constant total acoustic power. The obtained result suggests that inertial cavitation can be suppressed while preserving the efficiency of thrombolysis by temporally changing the acoustic condition before resonant bubble formation. [DOI: 10.1143/JJAP.44.4625]

KEYWORDS: cavitation, transcranial ultrasound, thrombolysis, standing wave

1. Introduction

Dissolution of the thrombus as soon as possible after an ischemic stroke, typically within three hours, is crucial in reducing the risk of ischemic neuronal injury. A number of reports have stated that ultrasound can enhance the effect of thrombolytic drugs such as the tissue plasminogen activator (tPA) and urokinase.[1–11] Alexandrov *et al.* found that a significantly higher rate of recanalization with tPA was observed in acute-ischemic-stroke patients who were monitored with transcranial Doppler (TCD) at 2 MHz than in those who were not; they concluded that ultrasound including TCD could enhance the thrombolytic activity of tPA.[12,13] As regards thrombolysis enhancement, the use of ultrasound at a relatively low frequency, typically lower than 1 MHz, which can penetrate the skull bone more efficiently, was also studied.[10,11]

Some clinical results on intracerebral hemorrhages after transcranial sonication at 300 kHz have been reported.[14] Although the temporal average of the acoustic power was 0.7 W/cm^2, which seems to be too low to cause cavitational bio-effects by simple progressive waves, some intracerebral hemorrhages occurred, and several hemorrhage spots were areas that were not exposed directly. The intensity threshold of cavitation is known to be highly dependent on whether the acoustic field is a simple progressive mode or has some standing-wave components. Standing waves are known to reduce the cavitation threshold and be formed relatively easily at a lower ultrasonic frequency for the same tissue. It may therefore be hypothesized that the ultrasound beam was reflected by the cranium, produced a standing wave field, induced cavitation, and caused the hemorrhage.

The bio-effects of cavitation have been observed in a standing wave field at a much lower acoustic amplitude than in a progressive wave field.[15] This is because acoustic cavitation can be induced more easily in a standing wave field than in a progressive wave field. The mechanism behind this can be hypothesized as follows (as shown in Fig. 1). A microbubble in a fluid in an acoustic field is subjected to a kinetic buoyance proportional to the product of the acoustic pressure gradient and the bubble volume. For a microbubble smaller than the resonant size, the bubble volume is smaller in a positive half cycle of acoustic pressure than in a negative one. Accordingly, the acoustically induced translatory motion of the microbubble toward the pressure antinode of a standing wave field during the negative half cycle exceeds the motion away from the

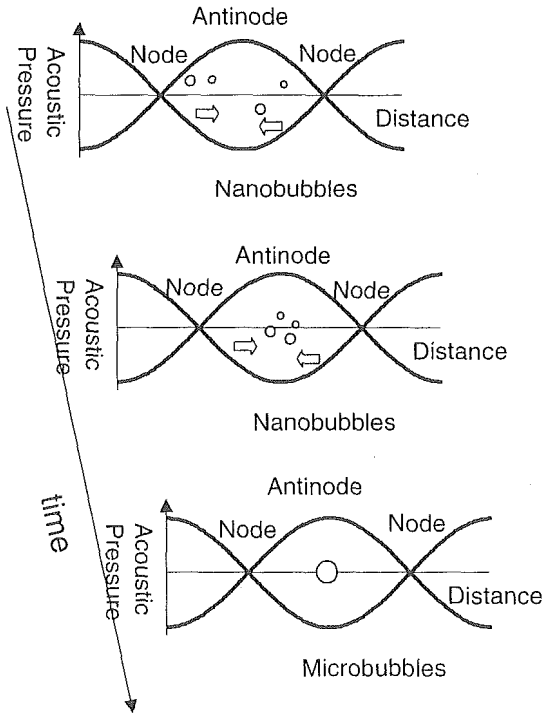

Fig. 1. Bubble-formation mechanism in a standing wave.

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antinode during the positive half cycle. As a result, the microbubble migrates toward the antinode, where its size will increase quickly by merging with other migrated microbubbles and by relatively efficient, rectified diffusion at an acoustic pressure at the antinode.[16] As soon as the microbubble reaches the resonant size, it may abruptly collapse, even at a relatively low acoustic amplitude, causing huge mechanical stress and high temperature, which is called collapse or inertial cavitation. The induction of cavitational damage to biological cells by standing waves was reported by Kerr *et al.*[15]

It was reported that standing wave formation was optically observed in water surrounded by a contoured piece of a human skull.[17] To suppress the possibility of inducing cavitational adverse effects on the brain tissue by transcranial therapeutic ultrasound while utilizing the efficient penetration through the skull bone, it may be important to study the formation of standing waves and bio-effects caused by such an acoustic field. To confirm the possibility of the cavitation induced by the standing wave, acoustic bubble formation was investigated by ultrasound imaging.

2. Materials and Methods

Figure 2 shows the optical setup to obtain schlieren images of the ultrasonic fields.[18,19] It consists of a water tank, a light source, a pinhole, a pair of high-quality optical lenses, a ring knife edge, and a charge-coupled-device (CCD) camera. An ultrahigh-pressure mercury lamp was used as the light source. The entire optical system was constructed by Mizojiri Optical (Tokyo, Japan). The lenses had a diameter of 15 cm and a focal length of 150 cm. The diameter of the ring knife edge was 0.5 mm. The light from the source passes through the first lens, the water tank, and the second lens, and is detected by the CCD camera. The ring knife edge prevents the nondiffracted component of the light from reaching the camera. Only the components diffracted by the spatial change in the refractive index of water form an image on the CCD. Longitudinal acoustic waves, which produce a spatial change of density in water, can thereby be imaged. Two schlieren images with and without insonation were taken and digitized at the same optical setup, and the latter digitized image was subtracted from the former. The effect of optical scattering by small particulates in water was eliminated thereby in the subtracted schlieren image.[20]

A prototype sector-scan phased-array transducer contained in a polymer-resin housing, was fabricated and used for the schlieren experiment. It has an acoustic aperture of 24.5 × 16 mm and an array of 48 PZT (lead zirconate titanate) transducer elements in the longer axis. The PZT transducer with a matching layer, overlaid with an acoustic lens working in its shorter axis, has a central frequency of 770 kHz and a relative bandwidth of 80%. Each PZT element of the transducer was driven by an individual amplifier of a prototype computer-controlled 48-channel amplifier. The focal length and the beam angle were controlled by a PC.

An air-backed circular PZT transducer (C213, Fuji Ceramics, Shizuoka, Japan) with a diameter of 24 mm held in an aluminum housing was used for the bubble-detection experiment. This air-backed transducer was driven at a resonant frequency, 617 kHz, by an amplifier (ENI 2100L, ENI, NY, U.S.A.) that was controlled by a function generator (model 195, Wavetek, U.S.A.). The absolute acoustic power from the air-backed transducer was measured by measuring the radiation force as reported in our previous work.[21] The acoustic intensity on the focal plane was estimated from the acoustic power and the beam width, which was assumed to be the same as the aperture. The pulse duration was changed from 1 to 10 ms at the same duty ratio, 10% as shown in Fig. 3, so that the temporal average of the total acoustic power was kept constant at 0.25 W/cm^2.

A human skull (adult male, Mongoloid) was contoured and used in the schlieren experiment. Figure 4 shows the contoured piece of cranium assembled together with the other parts of the whole skull. The height of the contoured piece was 25–30 mm, which was larger than the diameter of the array transducers. The cranial piece was suspended in degassed water in the tank with its contour planes perpendicular to the optical axis of the Schlieren system. The ultrasound array transducer was attached to the outer surface

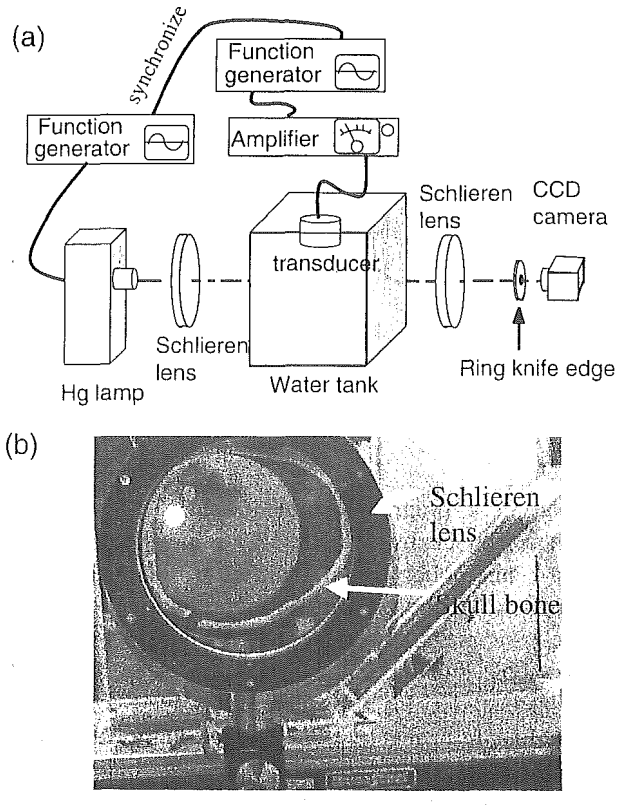

Fig. 2. Optical setup.

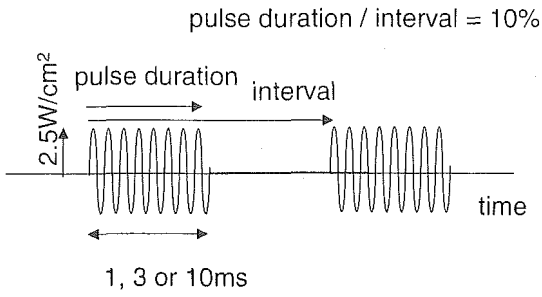

Fig. 3. Pulse sequence for air-backed PZT transducer.

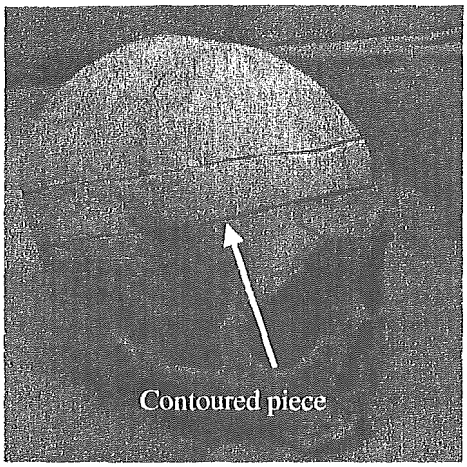

Fig. 4. Cranium used in experiment: contoured piece of cranium and whole skull bone.

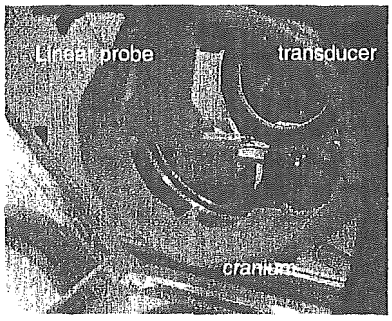

Fig. 5. Experimental setup for obtaining ultrasonic B-mode image of bubble formation.

of the cranial piece in the position where the ultrasonic penetration was maximal. The position was close to the ditches in the cranium, along which vessels run on the brain surface.

Figure 5 shows the setup for obtaining ultrasonic B-mode images of bubble formation in the standing-wave condition. The B-mode images were obtained using an EUB-8500 ultrasonic. scanner with a linear array probe, EUP-L53S (Hitachi Medical Corp., Tokyo, Japan). The imaging probe was operated at an ultrasonic frequency of 9 MHz. To obtain a high enough sensitivity to detect small bubbles, the linear imaging probe was set inside the cranium, as shown in Fig. 5. The air-backed PZT transducer was also set inside the cranium, in order to ensure that the acoustic power in the cranium is similar to that was found to induce intracerebral hemorrhages in the clinical trial.[22]

3. Results

Figure 6 shows a subtracted schlieren image obtained with the array transducer driven at 600 kHz. This drive frequency was similar to that of the air-backed transducer for the bubble-detection experiment described in the next paragraph. A stripe pattern is clearly seen near the place of reflection. The stripes near the place of reflection are approximately parallel to the inner surface of the cranium, and the spacing of the stripes is approximately half of the wavelength, indicating that the stripes seen in Fig. 3 are the

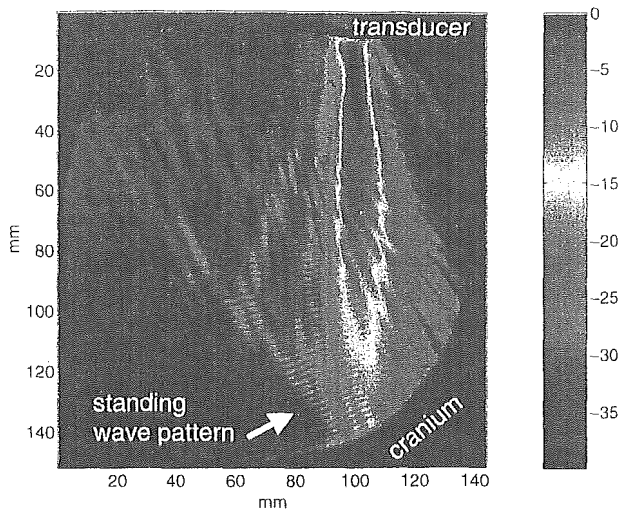

Fig. 6. Schlieren image in cranium.

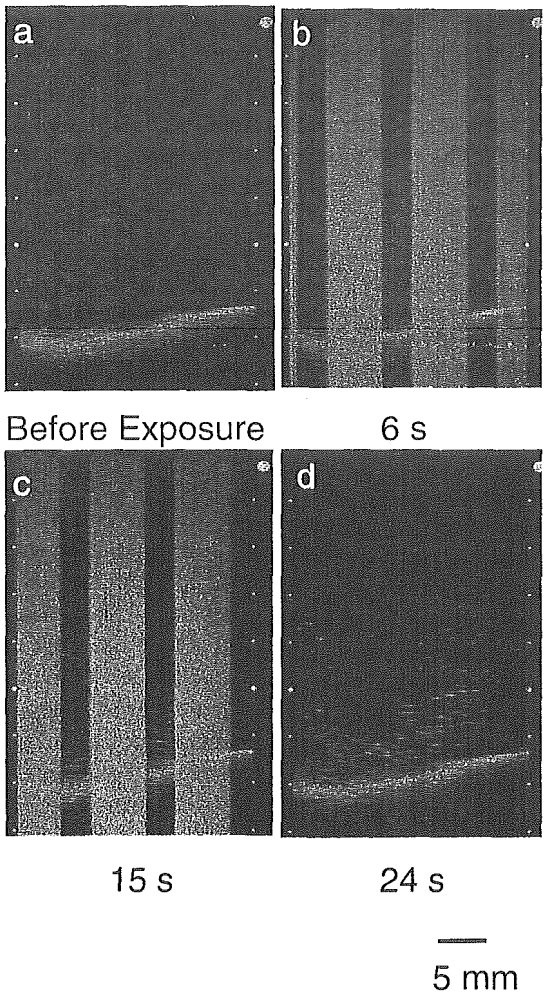

Fig. 7. B-mode image at pulse duration of 10 ms.

pattern of the standing waves formed near the place of reflection.

Figure 7 shows B-mode images at a pulse duration of 10 ms and a duty ratio of 67%. Images taken just before the exposure (a), 6 and 15 s after the start of the exposure (b and c), and just after completion of the exposure (d) are shown. The object seen at the bottom of each image is the cranium.

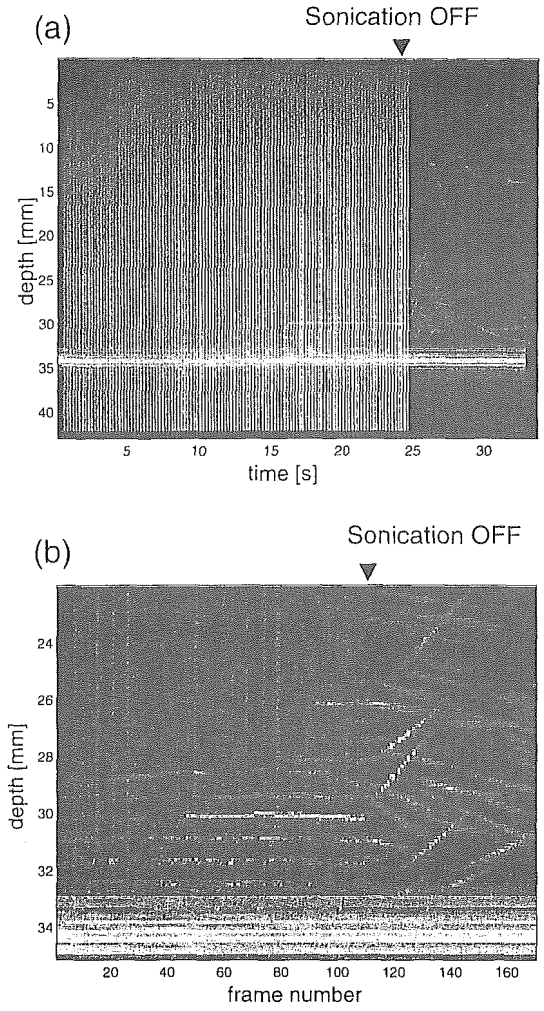

Fig. 8. M-mode image at pulse duration of 10 ms.

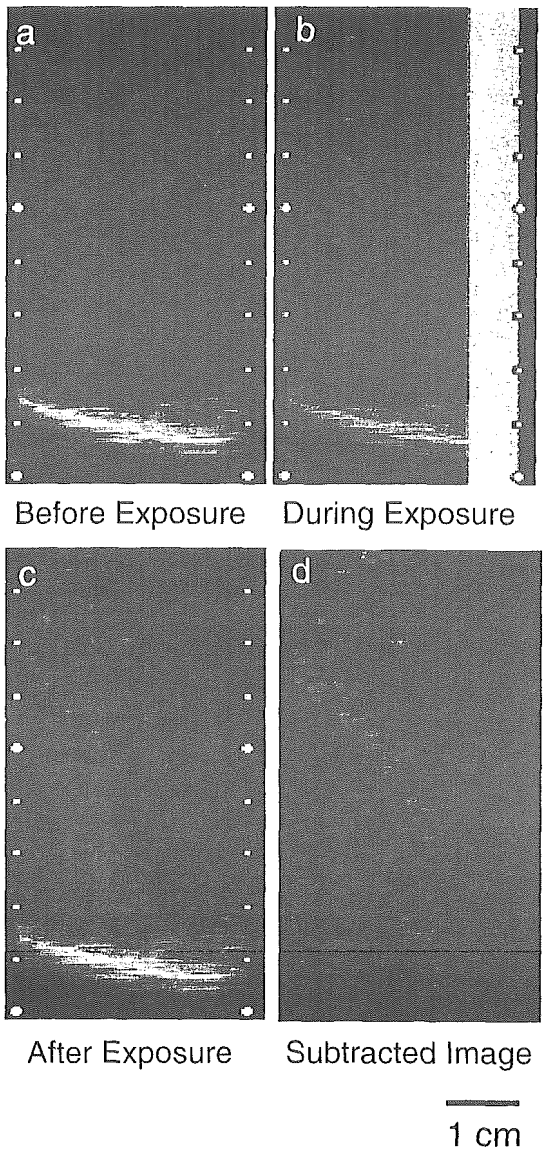

Fig. 9. B-mode image at pulse duration of 10 ms.

The air-backed PZT transducer was set above, so it is not seen in these pictures. The white stripe patterns shown in Figs. 7(b) and 7(c) are the electric and the acoustic noise caused by the exposures from the air-backed PZT transducer at 617 kHz. Approximately 10 s after the start of the exposure, clouds of bubbles were ultrasonically observed in openings between the white-stripe patterns. These bubble clouds did not move during ultrasonic exposure, but moved upward after the exposure was stopped. From one of the rasters in the B-mode images, M-mode images were constructed as shown in Fig. 8. Figure 8(b) shows an image constructed by eliminating the rasters disturbed by exposure noise, seen as white stripes in Fig. 8(a). In Fig. 8(b), the cranium is seen at a depth of 35 mm and the echoes scattered by bubbles are seen above the cranium. The positions of bubbles were stable during the sonication at 617 kHz, and moved upward because of their buoyancy after the sonication was stopped. The spacing between the stripes was 0.8 mm. This is close to half the wavelength (1.24 mm) multiplied by the cosine of the angle between the imaging plane and the 617 kHz ultrasound beam, approximately 40 deg.

The pulse duration dependence of the efficiency of bubble nucleation was investigated at a constant total acoustic power. Figure 9 shows the result of bubble detection at a pulse duration of 10 ms and a duty ratio of 10% with the same setup as that used in the experiment shown in Fig. 7. Images taken just before the exposure (a), 40 s after the start of the exposure (b), and just after the end of the exposure (c) are shown. The object seen at the bottom of each image is the cranium. To increase the sensitivity for detecting bubble clouds, subtraction was performed between the images before and after the exposure, and the result is shown in Fig. 9(d). Some bubble clouds are seen at a pulse duration of 10 ms. Figure 10 shows the result of bubble detection at a pulse duration of 3 ms with the same setup and at the same total acoustic power as that used in the experiment shown in Fig. 9. Images taken just before the exposure (a), 40 s after the start of the exposure (b), and just after the end of the exposure (c) are shown. The object seen at the bottom of each image is the cranium. Subtraction was performed between the images before and after the exposure, and the result is shown in Fig. 10(d). Some bubble clouds are also seen at a pulse duration of 3 ms. Figure 11 shows the result of bubble detection at a pulse duration of 1 ms with the same setup and at the same total acoustic power as that used in the experiment shown in Figs. 9 and 10. Images taken just

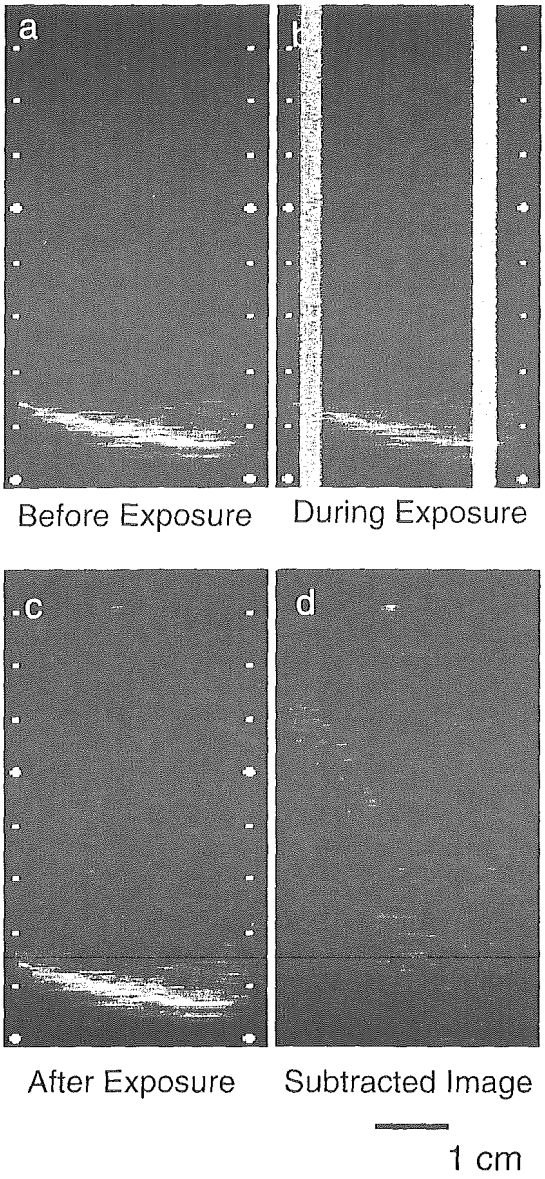

Fig. 10. B-mode image at pulse duration of 3 ms.

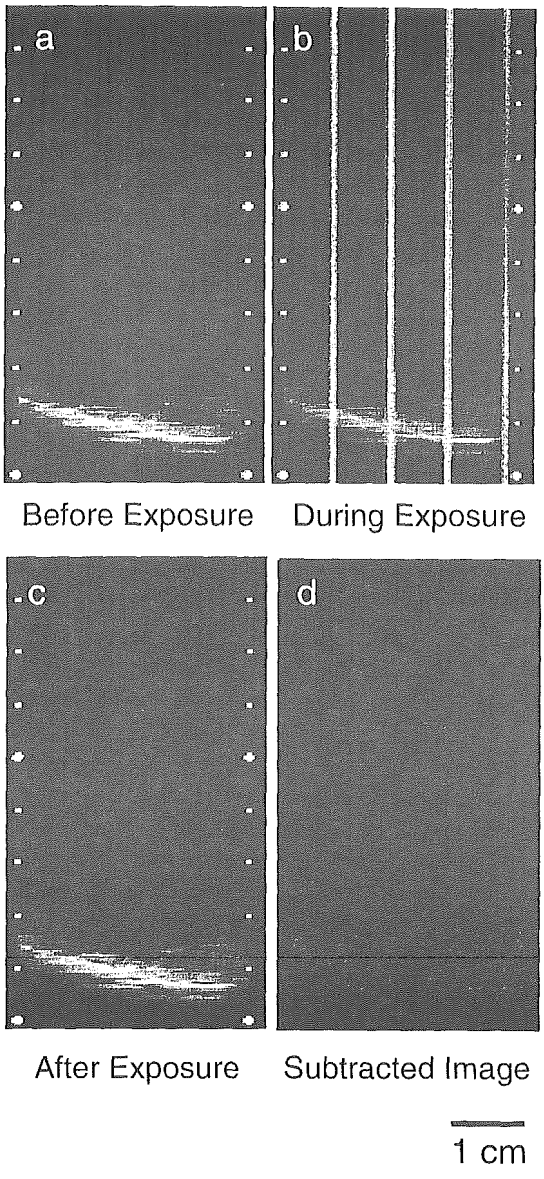

Fig. 11. B-mode image at pulse duration of 1 ms.

before the exposure (a), 60 s after the start of the exposure (b), just after the end of the exposure (c), and the subtracted image between before and after the exposure (d) are shown. No bubbles were detected in B-mode images after a 60-second exposure.

4. Discussion

Standing-wave formation was optically observed in water surrounded by a contoured piece of a human cranium using a transcranial ultrasonic beam. This observation suggests that standing waves will also be formed in the brain tissue by transcranial insonation of a human brain in a similar setup, because the attenuation in brain tissue is small at 500 kHz, typically less than 0.3 dB/cm.[23]

This result further suggests the possibility of inducing cavitational adverse effects on brain tissue by transcranial therapeutic insonation at a relatively low ultrasonic frequency, typically less than 1 MHz, through standing-wave formation near the place of reflection. Daffertshofer *et al.* reported that intracerebral hemorrhages occurred after transcranial insonation at 300 kHz when the instantaneous intensity was 3.5 W/cm^2 in water, and the duty ratio was 20%.[14,22] This intensity was slightly higher than the intensity, 2.5 W/cm^2, at which the bubble formation was observed in our experiment. The sum of insertion and reflection losses through a cranium without the diploe, a temporal bone, was reported to be 3–10 dB.[24] This penetration loss can explain the difference between these two intensities. The observation of the standing-wave formation indicates that standing waves were formed in the brain tissue and induced intracerebral hemorrhages through cavitation. To confirm the possibility of the cavitation induced by the standing wave, we tried to detect acoustic bubble formation using ultrasound imaging. Bubble formation was detected and bubbles gathered at antinodes of the standing wave when the interval between the exposures was short. This result strongly supports our hypothesis that acoustic cavitation is caused by standing-wave formation in the cranium. The efficiency of the nucleation of bubbles highly depends on pulse duration at the same total acoustic power. The observed pulse duration dependence is almost coincident

with the evaluation of cavitation using a sono-chemical approach.[25]

Several groups have discussed that cavitation plays a role in thrombolysis.[7,9] There are two kinds of cavitations, i.e., noninertial cavitation and inertial cavitation. While no report has been made on the basis of certain experimental evidence, noninertial cavitation may enhance thrombolysis through increasing acoustically induced strain in a clot, presumably the fibrin network. Even though suppression of cavitation may reduce ultrasound enhancement of thrombolysis, inertial cavitation has to be avoided because it can cause severe adverse effects by inducing huge mechanical stresses and generating chemically active species. The obtained result suggests that inertial cavitation can be suppressed while preserving the efficiency of thrombolysis by temporally changing the acoustic condition before resonant bubble formation.

Acknowledgment

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経頭蓋骨超音波治療のための骨の超音波透過率に関する FDTD 法を用いた基礎検討

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1. 緒言

経頭蓋骨超音波ドプラ法（TCD）は、頭蓋骨内の血流のモニタリング法として有用な方法である[1]。一方で超音波は tPA 等の薬剤の効果を促進することが知られており、古幡らは、これらを組合わせて、血流モニタリング下の血栓溶解治療を提案している。これまで、TCD には 2 MHz 程度、血栓溶解治療には 500kHz 程度の周波数が最適であることが知られており、これらを同時に行うには異なる周波数を送信し得るトランスデューサを開発するか、両方の効果を得る周波数を選ぶかの検討が必要となる。今回我々は FDTD 法を用いて、頭蓋骨の超音波伝播に関する詳細な検討を行った結果を報告する。

2. 頭蓋骨のシミュレーションモデル

まず図１に示す様に、実際の頭蓋骨の大きさを測定した。頭蓋骨は、図２のように場所によって厚さ、形状が異なり、板間層がある場合と板間層が無い場合で、超音波の透過率の周波数特性が大きく異なることが予想される。

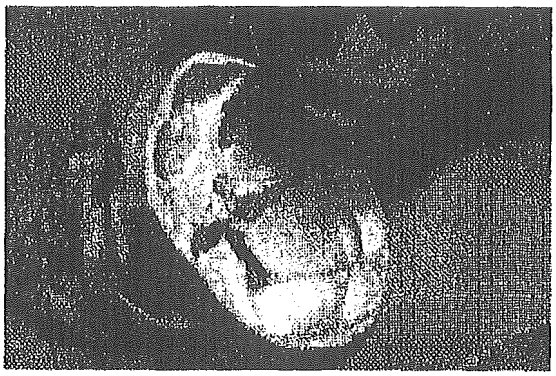

図１　モデルに用いた頭蓋骨

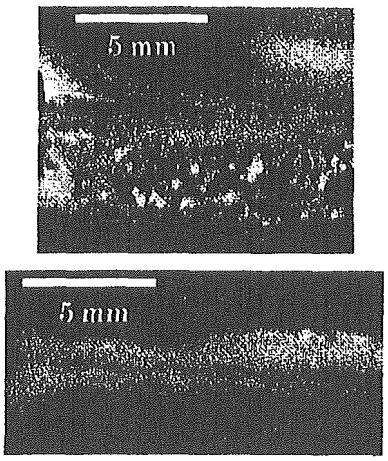

図２　頭蓋骨断面の拡大写真（上図：板間層の有る厚い部分　下図：板間層の効果が無視し得る薄い部分）

板間層が無視し得る程薄い場合は、超音波の透過率、反射率の計算は、厚み共振を考慮することでモデル化は容易である。一方板間層の有る場合は、スポンジ状の骨とその間に存在する骨髄液の混合物の音響的な振るまいを考慮しなくてはならない。

一般に音速が異なる２種類の物質からなる均質な混合物の粗密波音速は、体積変化と体積弾性率 K は逆数の関係にあるから各々の体積弾性率 K_1, K_2 から

$$\frac{1}{K}=\frac{1}{K_1}+\frac{1}{K_2}$$

と、求まり、音速が近似出来る。しかし、このような考え方が成り立つのは、混合物の粒径が波長

Simulation study of ultrasound transmission on skull bone for transcranial ultrasound therapy

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に比べ充分に小さい時のみであり、図２のように波長と同等で、構造がスポンジ状になっている場合には、横波伝播の効果を考慮する必要もあり、この近似法では精度が不充分である。

そこで今回我々は時間領域有限差分法（FDTD法）プログラムであるPZFlex[2]を用いて、板間層有りと無しの場合それぞれの超音波透過特性に関してシミュレーションを行なった。板間層が無い部位は均質な厚さ2mmの骨。板間層が有る場合は、全体で4mm、板間層2mm。穴の大きさは平均値0.24mm、void率50%。骨の密度：3000 kg/m3、縦波音速：3360 m/s、横波音速1120 m/s。透過率の計算には、パルス波を入力し、透過前後での波形をFFTし、その比を取った。パルス波としては、中心周波数2.5MHzのsin波に、波数が３のハニングを掛けた波形を用い、空間差分のセルサイズは20μmとした。

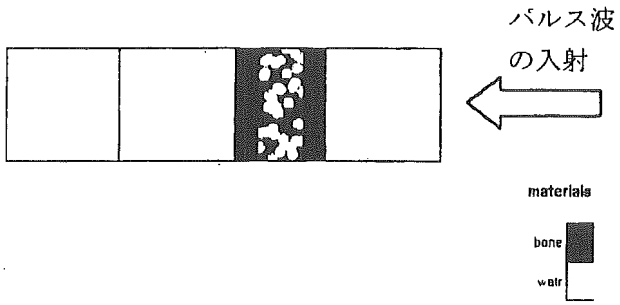

図３　板間層の有る部分のシミュレーションモデル

3. 結果及び考察

図４はパルス波の伝播の示す計算結果である。この図中の黒線の位置での波形のFFTの結果から透過率を求めた結果が図５である。（散乱、屈折の分があるので、FFT後に伝播と直交する方向に平均を行なった。）板間層が無視し得る薄い部分は、850kHz、1.7MHz、2.6MHzなど、厚み共振点のあたりに、透過率の極大点があり、板間層の有る厚い部分では、厚み共振の効果は小さくなり、周波数が上がるにつれてほぼ単調に透過率が減少した。

この結果から、イメージング用の音響窓としては、板間層が厚い部分を避ける必要があり、血栓溶解には板間層があっても低い周波数を用いれば音響窓として用いることができることが解る。

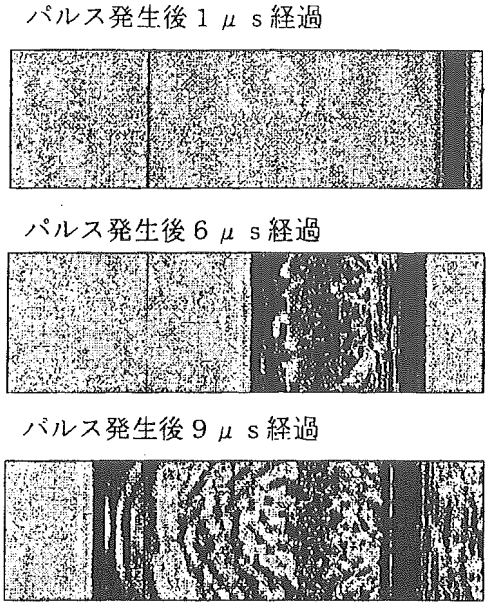

図４　パルス波の伝播を示すシミュレーション結果

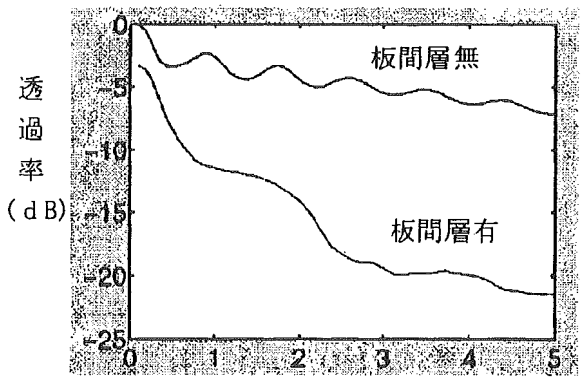

図５　頭蓋骨の超音波透過率のシミュレーション結果

4. 謝辞

今回のシミュレーションモデルの元となった頭蓋骨は慈恵医大の加藤征教授に測定させて戴いたものであり、ここに深く感謝する。

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Analysis of Propagation through Cancellous Bone for Transcranial Ultrasonic Treatment

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Recent advances in biomedical ultrasound are taking transcranial image assisted treatment to its practical stage. In order to achieve accurate transcranial ultrasonic focusing for both imaging and treatment, wave propagation through skull bones has been studied to correct the phase and amplitude aberration induced by them. Pernot et al. performed finite differences simulation based on CT data [1]. They assumed a mixture law of the sound speed in the cancellous bone although the pore size is in a similar order of magnitude with the wavelength. Bosy et al. reported a numerical analysis taking each pore into account [2]. In this study, we first performed finite difference time domain (FDTD) simulation of sound propagation [3] through a dipole, a cancellous layer in a skull bone, in a wide range of the volume ratio of pores in a ultrasonic frequency range of 2-3 MHz. The obtained sound speed was then fit to a mixture law of the α-th power of compliance. The phase can thereby be corrected based on the volume ratio of pores and the thickness of the bone layers, which can be obtained from CT data, without performing time-consuming FDTD simulation through a cancellous bone in prior to each transcranial image assisted treatment.
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Oct. 27～29 2004/Sapporo

第25回

超音波エレクトロニクス

基礎と応用に関するシンポジウム

講演論文集

25th

平成16年10月27日～29日　札幌

主催：超音波シンポジウム運営委員会
共催：応用物理学会
協賛：映像情報メディア学会，海洋音響学会，超音波工業会，電気学会，電子情報通信学会，
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日本分光学会，日本分析化学会，日本分析機械工業会，IEEE UFFC Society Japan Chapter

Proc. Symp. Ultrason. Electron., Vol. 25, (2004) pp. 401-402
27-29 October, 2004

経頭蓋超音波用 2MHz/0.5MHz 積層型アレイトランスデューサ

Laminated Array Transducer for Trans Cranial 2/0.5MHz Ultrasound

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Makoto Ogihara, Jun Kubota, Akira Sasaki (Hitachi Medical Corp.)
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1. はじめに

脳血管障害は，癌，心臓疾患に次いで死者数の多い疾患であり，その中でも脳梗塞患者は脳血管障害の6～7割を占めている．また、死に至らなくても脳虚血時間が長くなるに伴い，障害・麻痺の発生する危険性が増大するため，脳血栓を早期に溶解，急速再開通させることが重要となる．現在，血栓溶解剤投与時においてドップラモニタリングにより治療時の血栓溶解効果が高まる事が知られている．そこで我々は虚血耐性に脆弱な脳神経系を救出するため，血栓溶解剤投与と共に，経頭蓋的な治療用超音波の血栓部位への局限照射を併用し，脳血栓の早期溶解、急速再開通するための次世代の超音波脳血栓溶解療法として，超音波による診断と治療を同時に行う「経頭蓋超音波脳血栓溶解装置」を開発している．

2. 治療/診断装置

本システムは，送波アンプ，診断装置，超音波プローブ，診断装置，アンプの制御用ＰＣからなる．同一超音波プローブによる治療(T)・診断(D)の 2 周波超音波の出力を行うため，治療/診断用(T/D)超音波をPCにより制御し交互に照射する系とした．また，振動子は狭い音響窓を有効に使えるように，治療用・診断用振動子を積層させる構造とした．

また治療用Ｔビームにおいても照射方向を偏向させることができるため，本システムでは診断画像上で治療部位を指定し，その部位に自動的にＴビームを照射することが可能となる．これらより，中大脳動脈を中心に 1 次元モニタでボリューム探索を行う現状の TCD に対し，脳血管全域をカラー断層像で探索し治療用超音波を血栓部位に限局照射することで高い溶解効果と安全性を兼ね備えたシステムとなる．

照射する超音波周波数は，D 用には通常と同様 2 MHz を，T 用には生体安全性を考慮して，0.72 W/cm^2 の超音波パワーにおいて TI 値 2 以下，MI 値 0.25 以下となる 0.5 MHz を用いている．

3. 治療/診断複合型積層プローブ

このような仕様を満たすために試作したプローブの構造図を **Fig.1** に示す．

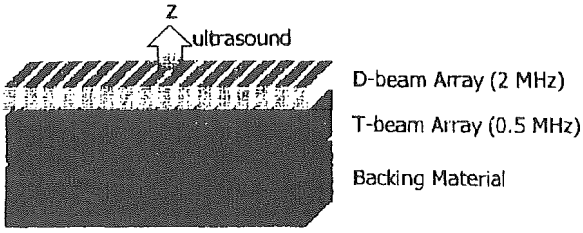

Fig.1 Structure of the Laminated Array Transducer

バッキング材の上に治療用(T: 0.5 MHz)の振動子，さらにその上に診断用(D: 2 MHz)の振動子を積層させる構造とした．試作した治療診断複合型積層プローブの外観は既製品のセクタ型プローブと同等のもので口径は 20mm 程度となり，狭い頭蓋骨の音響窓にも十分対応可能な口径の治療/診断複合型プローブとなった．

既製品の診断用プローブと試作した T/D 複合プローブの画像比較を行った結果を **Fig.2** に示す．B モード，カラードプラ及びドプラソノグラムを観察した結果，脳血管，拍動の様子が両者で観察でき，試作した T/D 複合プローブは診断能，S/N 比とも既製品と比較しても遜色ないものとなった．

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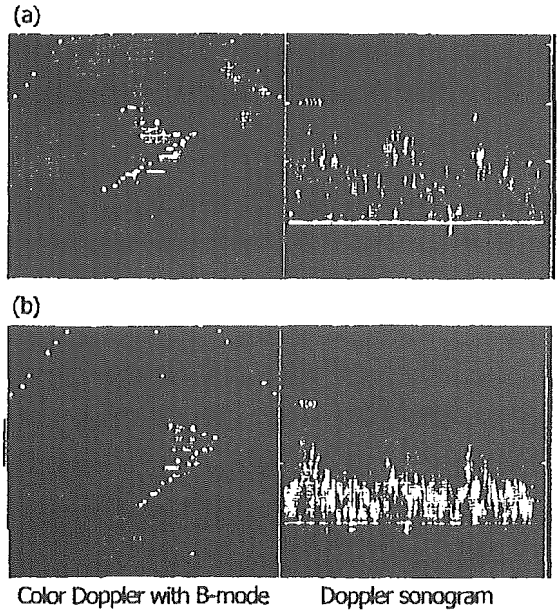

Fig.2 US images of product probe (a) and T/D combined probe (b)

治療/診断を積層させた形状の振動子を圧電振動解析有限要素法(PZFlex)を用い解析を行った結果の一例を Fig.3 に示す．シミュレーションではＴビーム用アレイの有無によるＤビームの出力超音波を比較している．

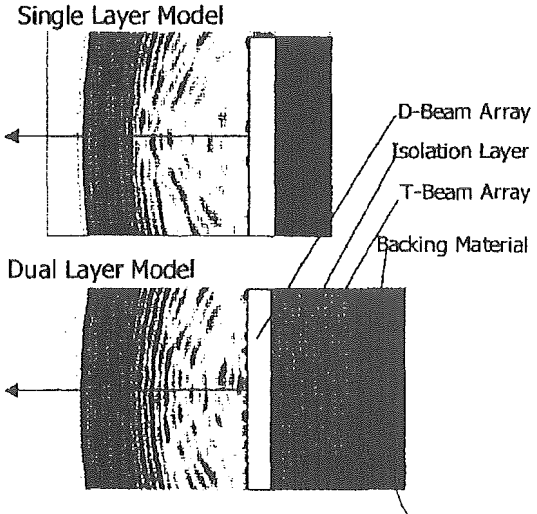

Fig.3 Comparison of the computer simulation results of single layer model and dual layer model

シミュレーション結果から両者の出力波形は差異がほとんど見られないことがわかる．今回試作したT/D 複合型積層プローブにおいて，T 用振動子が診断画象に影響を与えていないことがわかる．

次に，Ｄ用振動子を透過したＴビームの音場分布を長軸，短軸それぞれ測定した結果を Fig.4 に示す．

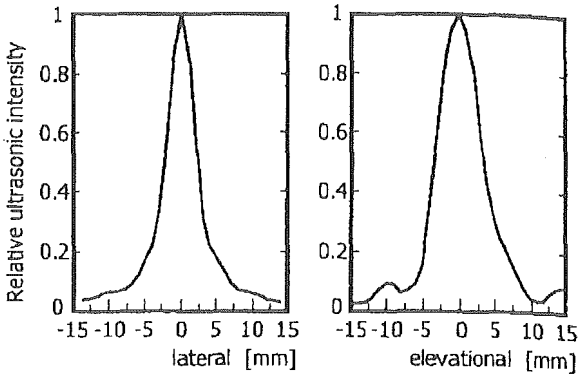

Fig.4 Beam pattern on the focal plane (z = 28 mm)

半値幅：短軸＝7.5 mm、長軸＝4 mm であり，パワー密度は 0.72 W/cm^2 以上となった．このことから，治療を行う超音波として十分な効果を得られる出力が得られている．また，治療用超音波は±45° の範囲内で任意の角度に偏向でき、また焦点距離も制御できることを確認した．

本システムでは治療用ビームがセクタスキャン型であること，治療/診断のプローブが一体となっていることから，診断画像上の任意の部位に治療ビームを照射し，かつドップラ波形により再開通状態を観察できる治療/診断複合型の治療装置となった．

4. 結論

治療・診断用の振動子の積層化により，頭蓋骨の音響窓に適合した小口径の治療/診断複合型プローブを試作した．診断用ビーム(Sector D-Beam)の経頭蓋的な画像の取得，治療用ビーム(Phased-Array T-Beam)の偏向の確認を行ったことで，治療/診断両ビームを交互に照射するシステムを実現し，診断画像上の血栓への限局照射を可能とした．

謝辞

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O7-5

フリーラジカルスカベンジャー薬剤投与時における超音波血栓溶解療法の安全性評価 －in vitro実験による検討－

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Safety evaluation of transcranial ultrasonic thrombolysis with free radical scavenger

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【目的】急性脳塞栓症などに適用されるtissue plasminogen activator（tPA）の血栓溶解効率は超音波照射によって増強される。これを利用した超音波併用脳血栓溶解療法を開発中である。さらにフリーラジカルスカベンジャー" Edaravone"の使用頻度が高い臨床状況を考慮して、Edaravone投与時に適用する超音波脳血栓溶解療法の安全性をin vitro実験によって評価した。

【方法】マウス脳器官培養スライス及びヒト神経芽細胞腫SK-N-MC細胞を用いた。Edaravone投与単独，超音波照射単独，両者併用と何もしない対照群の4群を設定し、スライスに関してはn = 6，SK-N-MC細胞に関してはn = 2とした。超音波は周波数500 kHz，出力0.3 W/cm^{2}の正弦連続波とした。照射時間は2分間照射30秒休止を4回繰り返した後5分間休止するセットを4セットで計1時間とした。Edaravoneは6μMで使用した。スライスについてはpropidium iodide（PI）染色により28日間に渡って細胞死を評価した。またSK-N-MC細胞に関してはアポトーシスを起こした細胞数をTUNEL法及びFACSにより評価した。

【結果】Edaravone投与単独，超音波照射単独及び両者併用の全群について、スライスに対する傷害性は認められなかった。またSK-N-MC細胞に対するアポトーシス誘導も認められなかった。

【結論】本研究で検討した治療用超音波照射条件では有意な副作用は認められなかったが、さらに確認の実験を行う必要がある。

O7-6

超急性期脳梗塞治療に向けた経頭蓋超音波脳血栓溶解装置の試作

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窪田純[1]，荻原誠[1]，佐々木明[1]，東隆[2]，梅村晋一郎[2]，阿部俊昭[3]，清水純[4]，古幡博[4]

Trial production of the equipment which dissolves cerebral thrombosis by transcranial ultrasound for treating acute cerebral infarction

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Jun Kubota[1], Makoto Ogihara[1], Akira Sasaki[1], Takashi Azuma[2], Shin-ichiro Umemura[2], Toshiaki Abe[3], Jun Shimizu[4], Hiroshi Furuhata[4]

【背景】Translational研究開発の一環として超急性期脳梗塞治療のための経頭蓋超音波脳血栓溶解装置を開発中である。これは脳血栓・塞栓症患者に血栓溶解剤投与と併用し、塞栓部に超音波照射することで脳血栓の早期溶解、急速再開通を行うものである。

【開発内容】脳組織内での出血のリスクを低減するため、治療超音波（T）ビームの照射方向を調整し、照射範囲を患部周辺に限定する。使用するTビームは、熱的及び機械的生体影響を最小とするため、超音波による体温上昇の指標となるTI値をTI≦2、かつ、キャビテーション閾値の1/4となるMI≦0.25を満たし最大の許容出力余裕を得る周波数として約500kHzを採用した。再開通状態の監視を行うため、Tビーム照射と画像診断（D）とを交互に実施する系とし、照射されるTビームの出力レベルと間欠時間との制御を行うシステムとした。一方、Dビームは通常のTCDと同等の2MHzとし、頭蓋骨の限られた音響窓を有効に活用して限局照射するため、T/D両ビームの電子制御用の振動素子アレイを積層することによって音響窓を共有する構造とした。

【結果】試作した超音波装置プロトタイプを用い、vitro及び健全動物試験を通じ、システムとして所期の目的を達成した。今後、安全性確認後、臨床適用を目指す。本研究は、厚生労働省科学研究費補助金「基礎研究成果の臨床応用推進事業」によって実施された。

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サテライト・ハンズオンセミナー：6月3日(木)

開催場所
石橋文化センター

The 23rd Annual Meeting of the Japan Academy of Neurosonology
June 3-4,2004,Kurume

PROGRAM and ABSTRACTS

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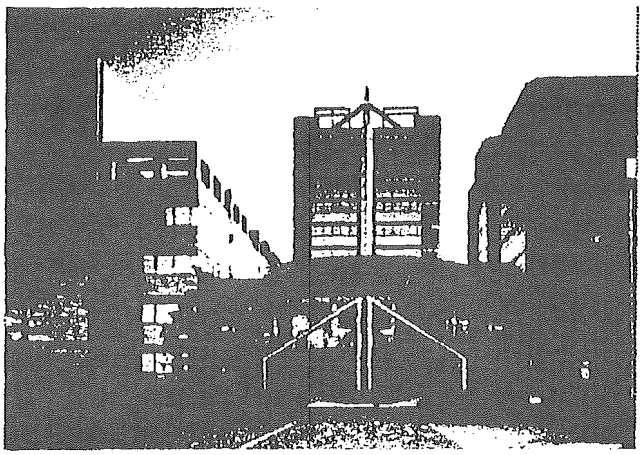

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ISTU4 abstract

Development of Transcranial Ultrasonic Thrombolysis System for Ischemic Stroke Treatment

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[Background] Transcranial ultrasonic thrombolytic system is under development, for acute ischemic stroke (AIS) therapy during hyperacute phase. The system has a great potential for early recanalization in a thrombo-embolism by combining thrombolytic agent with transcranial ultrasonication.

[Development] In order to avoid the risk of intracranial hemorrhage, the direction of therapeutic ultrasonic (T) beam is targeted only at an area around the embolic artery. Not to mention, in order to minimize mechanical and thermal adverse bioeffects, T beam frequency is selected 500kHz under the condition of MI≦0.25 and TI≦2 at a suitable acoustic intensity on less than the maximum regulation level of the conventional diagnostic ultrasonic equipment. The transcranial diagnostic (Doppler or color flow imaging) (D) beam at 2MHz is used for monitoring the recanalization. The system irradiates both T- and D-beam by turns in the signal control subsystem. This alternate irradiation is performed by a single probe, which includes two laminated phased array transducer elements for the T/D beams. The system is also designed to avoid the standing wave which generates bubbles via cavitation effect in the brain since MI value is spatially partly intensified to larger than 1.0 because of interference.

[Results] The fundamental function and performance of the developed system has been verified from in vitro and in vivo animal experiments. The newly developed compound probe provided the same precise image as the commercialized single diagnostic phased array probe. T-beam of the compound probe has supplied the maximum acoustic intensity designated by the regulation for the diagnostic equipment although the cooling system cools down excessive temperature rise.

[Conclusion] As it is anticipated from the results, the developed system has proved to be useful equipment for treating the AIS patients, and in addition, its further safety evaluation will be required for the T/D system in clinical applications.

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77-A029　　血栓の早期溶解を目指した診断治療複合超音波プローブの原理試作

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【はじめに】脳血管障害は，癌，心臓疾患に次いで死者数の多い疾患であり，そのうち脳梗塞疾患は6-7割を占める．我々は脳血栓塞栓症患者に血栓溶解剤静注投与と併用して経頭蓋的に超音波照射し，脳血栓の早期溶解，急速再開通を行うことで虚血耐性に脆弱な脳神経系を救出するシステムの開発を行っている．

【超音波脳梗塞治療装置】本システムは経頭蓋超音波診断レベルの血流画像を取得し再開通監視を行うことにより，脳血管の再開通状態を確認し，溶解剤投与量を制御することができ，更に治療超音波（T）ビームの照射方向を3次元的に制御し照射範囲を患部周辺に限定することにより，脳組織内での出血に対する危険を避けることを可能とする．Tビームには，熱的及び機械的生体影響を最小とするため診断レベルでの超音波の体温上昇の指標であるTI値をTI≦2，かつ，キャビテーション閾値であるMI=1の1/4となるMI≦0.25の両者を満たす周波数帯域である300-800kHzを採用した．また，再開通状態の監視を行うためTビーム照射と画像診断（D）とは交互に実施する系とし，照射されるTビームの出力レベルと間欠時間との制御を行うシステムとした．一方，Dビームは通常のTCDと同等の2MHzとし，頭蓋骨の限られた音響窓を有効に活用して限局照射するため，T/D両ビーム用のトランスデューサは振動素子アレイを積層とすることによって音響窓を共有する構造とした．

【積層型プローブの試作】本研究では，超音波治療システムについて，特にシミュレーション予測に基づいてプロトタイプを試作したので報告する．試作したプローブの外観をFig. 1に，アレイの構造をFig. 2に示す．厚さの異なる2枚の振動子（T及びD用）がバッキング材の上面にT，Dの順で積層されている．また，Fig. 3では今回試作したプローブにおいて超音波を表面より50mmの距離に収束させた際の音場分布を長軸，短軸それぞれ測定した結果を示す．半値幅はそれぞれ11.8mm，17.4mmとなり，所期の動作を確認した．

本装置の臨床応用により，脳梗塞患者の死亡率低減，予後の改善，更には医療費削減への寄与が期待される．〔本開発は一部，厚生労働科学研究費補助金（基礎研究成果の臨床応用推進研究事業H14－トランス－016）による．〕

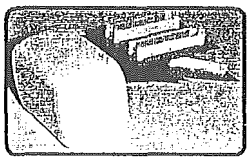

Fig.1 Photo of the T/D Combination Probe

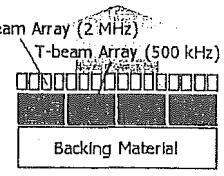

Fig.2 Structure of the Dual-frequency Transducer

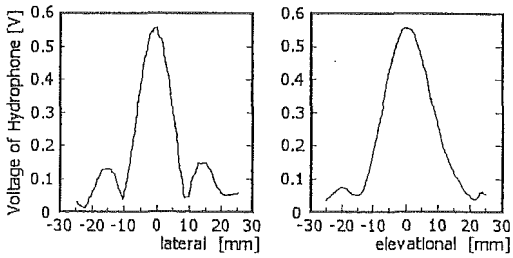

Fig.3 Beam pattern on the focal plane of z = 50 mm

Trial production of diagnostic and therapeutic compound ultrasonic transducer for early dissolution of thrombosis

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Keywords: probe, ultrasonography·transcranial

Seventh Congress of the Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB 2004)

ABSTRACTS

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Utsunomiya Tobu Hotel Grande
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The Shinkyo Bridge over the Daiyagawa River in Nikko National Park
(Photo courtesy of Japan National Tourist Organization)

AOS19-3

Dual Frequency Array Transducer with Bilaminar Structure for Ultrasound-Enhanced Transcranial Thrombolysis

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It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA). An optimum control of the tPA injection and the therapeutic sonication require a blood flow monitoring. Ishibashi et al. reported that an ultrasonic frequency of approximately 500 kHz was most effective for recanalization of a rabbit's artery through a human temporal bone. However, this frequency is too low for ultrasonic blood flow imaging. Therefore, respective use of two frequencies for ultrasound-enhanced thrombolysis and ultrasonic imaging would be ideal. Since only a temple is the available acoustic window for transcranial ultrasound, the total aperture size for imaging and therapy is very limited. In order to expose ultrasonic waves at two frequencies for imaging and therapy from the same aperture, we propose a probe consisting of a therapeutic array with an imaging array overlaid on it. Between these two arrays, a frequency selective isolation layer was inserted to ensure independent oscillatory motions of the two arrays. The function of this layer is expected to reflect the waves from the imaging array and allow the waves from the therapeutic array to pass through. Numerical simulation was performed using a finite element code, PZFlex. In this model, the imaging and therapeutic array used PZT ceramic with a center frequency of 2 MHz and 500 kHz, respectively. The imaging array had two acoustic matching layers. Several different thicknesses of the frequency selective isolation layer made of epoxy resin were tested. These results showed that the isolation layer with 50 micro-meters reduced the amplitude of the imaging pulse waves at 2 MHz reflected at the therapeutic array by 13 dB, while it reduced the amplitude of the therapeutic waves at 500 kHz only by 2 dB. A prototype array transducer was constructed according to this analysis. Its experimental results; the pulse responses of the imaging layer, the Schlieren beam patterns radiated from the each layer and the tissue phantom images taken by the imaging array will be presented. This Research is supported by Japanese Ministry of Health, Labour and Welfare.

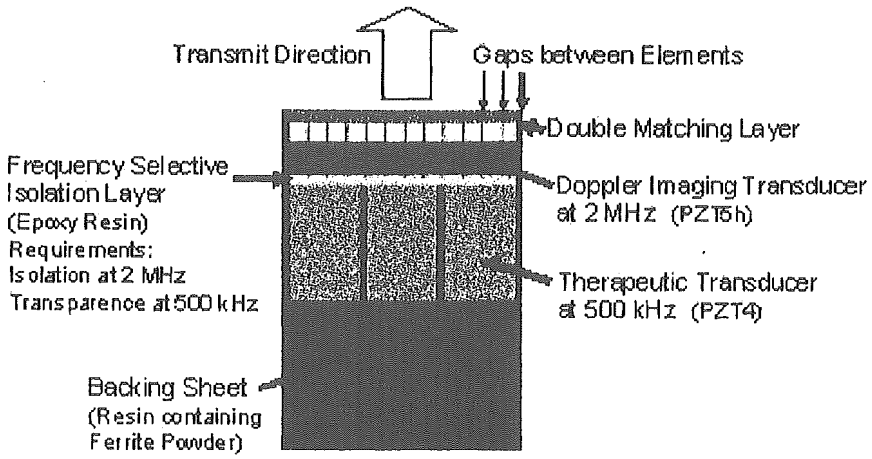

Figure 1: Double-Piezoelectric-Layer Transducer with Frequency Selective Isolation