平成１４年度 研究概要

（研究目的）

本研究開発の目的は、本邦死因の第３位、要介護老人の４割を占め、突然死や重篤な後遺症が社会問題をも惹起する脳血管障害の6～7割を占める脳梗塞の治療法として、急性期における新治療用「経頭蓋超音波血栓溶解装置」を開発し、以って探索的臨床研究を展開することを行い新脳梗塞治療法を確立することである。目的としている。本開発の基礎技術は平成11年～13年度に亘り、厚生科学研究費高度先端医療研究事業での基礎研究の成果である。特許ともなった原理は脳血栓塞栓患者に血栓溶解剤を静注または動注すると同時に、経頭蓋的に超音波照射し、脳塞栓の早期溶解、急速血流再開通を達成し、虚血耐性に脆弱な脳神経系を救出するものである。開発装置はこの血栓溶解超音波治療法に加え、経頭蓋超音波診断画像法を付与し、塞栓部血流動態を監視しながら、同部位へ治療用ビームを電子走査で標的照射させることを特徴とする。本年度は以下の具体的目標を遂行した。(A)「経頭蓋超音波脳血栓溶解装置」の要素技術開発(1)治療用超音波ビームの二次元走査の実現(2)治療用および診断用の超音波ビームの一体化(3)診断装置と治療装置の一体化制御(4)超音波プローブの頭部固定具の設計・検討(B)動物実験による探索的臨床研究のための安全性評価(C)ヒト遺体による頭蓋内音響作用の検討

（研究方法）

本研究の前段は「経頭蓋超音波脳血栓溶解装置」の開発が中心となる。この部分は臨床適用装置とするものであるので日立メディコが中心となり、日立中央研究所および東京慈恵会医科大学ME研究室が参画して実施した。また、動物実験やヒト遺体を用いる研究は慈恵医大グループが中心となって行った。本年度の各具体的目標毎の方法を示す。(A)「経頭蓋超音波脳血栓溶解装置」の要素技術開発(1)治療用超音波ビームの二次元走査の実現治療用500kHz連続波超音波を二次元走査させるため、PZT振動子の一次元配列を作り、試作した。これを電子走査し、そのビームが配列方向に自由に向けられることをシュリーレン法で写真撮影し確認した。(2)治療用および診断用の超音波ビームの一体化同一のプローブから治療用500kHz連続波超音波と診断用2.5MHzパルス波を一定時間毎に切換えて発射するインターミッテント照射を実現するため、コンピュータ・シミュレーションによって形成される音場分布、その検出感度および製造工程の難易度を検討した。診断用のDビーム、治療用のTビームを発射する振動子配列を積層型（重量型）と並列型とで比較した。(3)超音波診断装置を治療装置の一体化制御経頭蓋カラードプラ装置と治療用の装置を一体化し、診断画像上に標的塞栓部を描出し、塞栓部位の血流動態を監視しながら、同標的部へ治療ビームをインターミッテント照射するための電子回路的な一体型制御法を試作した。同時に治療用の駆動系を診断装置内に格納可能とする小型化を実施した。(4)超音波プローブ頭部固定具の検討治療用超音波ビームは長時間に亘って経頭蓋照射することになるので、プローブを頭部に固定し続

ける必要があり、そのためのプローブ保持具を設計した。この保持具は超音波プローブにおける発熱をペルチェ効果で冷却したときの放熱部も備えることとした。これをヒト適用型の三次元コンピュータグラフィックス（CG）で描出し、多面的に検討することとした。(B)動物実験による探索的臨床研究のための安全性評価ラットの脳梗塞モデルは、ナイロン糸の先端をシリコンでコーティングして、塞栓する小泉のモデルを作成して実験に供した。塞栓は同ナイロン糸を外頚動脈から逆行性に中大脳動脈根幹部に挿入した。塞栓作業は麻酔下で行ったが、塞栓の程度はレーザー血流計で監視した。また、同塞栓糸を引き抜くことで血流は再開通するが、この時間も含め連続血流監視をレーザー血流計で行った。実験モデルとしては、塞栓時間を調整し、塞栓中および血流再開通時にも治療用超音波照射を行った。その後覚醒させ、24 時間後に脳を摘出し、病理学的評価を行った。(C)ヒト遺体による頭蓋内音響作用の検討ヒト頭部ファントムを用いても、臨床試験を開始する場合には最終的にヒトと同様の構造体での評価が求められる。それ故ヒト遺体を用いて実験することを倫理委員会で承認を得て実行した。倫理委員会へは計画書および生前同意などの必要書類を提出した。ヒト遺体頭部一側に微小孔をあけ、対側から治療用ビームを発射したときの同ビーム中心軸の温度上昇と音圧を特注製造した 20 チャンネル温度計とハイドロホンとで測定することとした。またこの値と、低出力治療用ビームを用い、健常成人の超音波伝達特性を得て、これを校正値として頭蓋内音響分布を推定することとした。

（結果と考察）

(A)「経頭蓋超音波脳血栓溶解装置」の要素技術の実現(1)治療用ビームの二次元走査電子アレイ走査によって治療用ビームが約 90°の幅で走査できることをシュリーレン法で確認した。これにより、例えば側頭部にプローブを固定した場合、治療用ビームを顔面側から後頭部側のかなりの範囲をプローブを機械的に動かすことなく走査し、標的照射が可能になることを確認した。(2)診断用・治療用のビーム一体化コンピュータ・シミュレーションの結果、振動子配列の 2 方式において音響感度がほぼ同じになることを確認した。それ故、実際に製作し、その結果をもって実用化に適した方法を選択することとなった。T ビームと D ビームをインターミッテント照射可能となることが明らかになった。超音波プローブが一体化されるという見通しを得たことで、小さなエコーウィンドウに対しても方法の適用範囲が広がった。(3)診断装置と治療装置の一体制御治療用 T ビームのインターミッテント照射における照射休止期間に診断用 D ビームを発射し、経頭蓋カラードプラ像の得られるように、診断装置側の信号制御系に、治療系の制御を同期化し、動作確認をした。また、診断装置（市販）の一部に制御系回路が組み込まれることを確認した。これによって、全く一体型で全体のサイズが現行診断装置と余り変わらないシステムとなり得ることが確認された。(4)超音波プローブの頭部固定具の検討長時間側頭部にカラードプラ断層用セクタスキャンプローブを保持し続ける強度があり、人体に合致する 2 つを CG で確認した。(B)動物実験による探索的臨床研究のための安全性評価現在動物実験データを蓄積中で、統計学的評価は充分に行えないが、次の点がある程度明らかとなった。(1)虚血時に超音波照射を行っても、梗塞領域を変えること

は少ないと考えられること(2)急速血流再開通のためか、再灌流障害と考えられる出血例が認められること(3)通常使用予定の 3～4 倍の強力超音波に対しても大きな変化はなく、病理学的にほぼ同等なこと現在蓄積中の虚血時並びに再灌流時における超音波照射のデータをさらに充実させ、臨床試験の事前検討データとして確実なものとする必要がある。(C) ヒト遺体による頭蓋内音響作用の検討 20 チャンネルのニードル型温度計および直径 1φ のハイドロホンを作成し、米国試験機関で絶対値校正を行った。 現在ヒト遺体データを積み上げるべく努力している最中である。D.考察全く無侵襲的な「経頭蓋脳血栓溶解装置」の基本的要素技術の開発を概ね終了し、実用化に向けての道筋が明らかとなった。この装置は、実時間的に脳血流動態を監視しながら、脳血栓を同一プローブから出される治療用低周波超音波で急速溶解するものである。そのため、二次元走査の可能な治療ビームに関する技術、診断と治療の機能を一体化した複合超音波装置の基本は完成した。しかし実用化し臨床応用するには、診断・治療一体化プローブの製作試験という大きな問題があり、最適化のために次年度の課題となった。また、プローブ保持用の機具も次年度試作・評価を行わねばならない課題である。技術面でのこのような課題は残されているが、本質的課題は解決前であり、患者 QOL への配慮などの頁に臨床現場的課題へも迫りつつあると考える。一方、超音波の及ぼす脳神経系への影響は既に正常例（ラット）では問題ないことを証明済みである。また、虚血 3 時間についても評価済みで、病理学的悪化は認められていない。しかし、現在虚血時間・再開通タイミングを変えたときの影響を検討中で、その成果は次年度になる。本装置の根本的適用障害にはならないものと考えられる。さらに、ヒト遺体を用いたデータ蓄積は次年度へ続く課題である。

（結論）

経頭蓋超音波脳血栓溶解装置の要素技術を概ね完成し、臨床応用への技術的障害はなくなりつつある。残された課題は、製造法上の評価を踏まえた診断・治療一体化プローブ特別評価、頭部固定具の試作・検討だけである。一方、前臨床試験としての虚血・再灌流時の超音波作用の影響およびヒト遺体を用いた頭蓋内音響評価は次年度に亘って積み上げる必要のあるものである。以上、本年度はその当面の目的を達成し、飛躍的な成果を得ることができた。

平成１５年度 研究概要

（研究目的）

脳梗塞は本邦死因第３位を占める脳血管障害の6～7割を占め、非致死的であっても重篤な後遺症を招き、さらには要介護老人の数割の原因となる医学的社会的重要な課題である。この脳梗塞の治療法は発症超早期の血栓溶解による血流再開通を第一選択とするが、現行血栓溶解剤適用には、発症後 3～６時間以内(病態と薬剤の種類によって異なる)の適用時間限界、溶解までの所要時間の長さ、容量性副作用の存在などの問題がある。血栓溶解時間の短縮、投与量の軽減そして投与可能な時間の延長を経頭蓋超音波照射で実現しようとするものである。本研究は、超急性期血栓溶解療法中に同一プローブにより経頭蓋的に血栓溶解用の超音波と脳内動脈血流の監視用超音波を発射する治療診断一体型の「経頭蓋超音波脳血栓溶解装置」を開発する。同時に超音波を併用することの脳神経系に対する安全性を評価し、安全かつ有効な超音波脳血栓溶解法の前臨床試験を行う。最終年度では、様々な脳梗塞の病型に対する本脳血栓溶解療法の有用性を探索的に臨床研究し、臨床適用可能な超急性期超音波脳血栓溶解療法への道を開くことを目的としている。この研究は基礎研究成果として経頭蓋照射超音波の種類、その有効性に関する in vivo 実験による実証及びその基本特許化に基づいて発展させたものである。15 年度は、前年度の検討を踏まえて、次の点を目的とした。（１）経頭蓋超音波脳血栓溶解装置の設計・製作・評価（２）経頭蓋超音波脳血栓溶解療法の安全性評価（主に in vivo 実験）

（研究方法）

１）「経頭蓋超音波脳血栓溶解装置」の設計・製作をした。

（１）治療・診断一体化プローブ　血栓溶解効果が易くかつ安全な超音波は周波数 400～600kHz帯である。ただし、キャビテーション発生危険率に4倍の安全係数をかけmechamical index MI≦0.25 とし、かつ温度上昇を示す thermal index TI≦2 として脳内温度上昇を 2℃以下とした場合。開発では 500kHz を選定。標的性を高めるため、治療用の脳血栓溶解ビーム（T ビームと略）を±45°のスキャン走査可能にするため、16 素子の PZT 振動子配列を設計・製作した。一方血流監視・診断用の経頭蓋カラー・ドプラ断層法（TC-CFI）用には、2MHz、64 素子のセクタ走査ビーム（D ビーム）を採用した。T ビームと D ビームを同一プローブ内に置いて設ける手法として、T/D ビーム用振動子配列を並べる並置型と両者を重ねる積層型とを作り、性能比較を行い、T ビーム、D ビームの放射特性の良好なものを採用することとした。

（２）T/D ビーム交互照射制御　T ビームと D ビームを交互発射するインターミッテント照射法とし、各照射時間は選択可能な制御システムとした。

（３）音場特性試験　変型シュリーレン法を用いて T ビームスキャン幅、音場強度を確認。またファントムを用い、D ビーム像を既製市販装置と比較評価した。

（4）監視用Dビーム像のヒトによる評価　Dビーム像は通常の超音波カラー・ドプラ像に相当するので、開発プローブを用いてヒト経頭蓋カラー・ドプラ断層像を測定し、既製市販装置の像と比較評価した。

（5）プローブの頭部固定具　健常5例に固定具を用いてプローブを固定し、姿勢を変えてその安定性を評価した。

2）安全性評価実験

（1）頭蓋内音場分布測定　頭蓋骨で減衰が少ない低周波超音波は頭蓋内に残存する割合が高いので、頭蓋内の音場分布をシュリーレン法で評価した。

（2）サル頭部を用いた安全性評価実験　サル麻酔下に開発した装置を用いて経頭蓋的超音波インターミッテント照射を行い、その神経病理学的評価を行った。(健常サル8例中、照射例3例、非照射例5例)

（3）ラット脳梗塞再灌流モデルによる梗塞領域ＭＲＩ評価実験　ラット虚血モデルにおいて再灌流時の経頭蓋超音波照射（500kHz）照射がもたらす障害拡大の有無を0.8W/cm2についてMRIの拡散強調画像及びT2強調画像で評価した。単純虚血再灌流例11例、超音波照射例11例。

（4）ペンシル型D/Tビームによる血栓溶解効果　家兎股動脈両側塞栓モデルに対し、経頭蓋ドプラパワーモード法（TCD-PMD）で監視しながら間欠的に500kHz一方向性(non-scan)ビームを照射し、tPA投与下での再開通時間を比較評価した。13例。

（5）神経保護薬と超音波の共存性実験　神経保護薬フリーラジカルスカベンジャー（エダラボン）投与下のマウスの培養スライス標本に超音波を照射したことによる神経細胞の死細胞数を比較評価した。PI染色により、エダラボンの単純・併用及び正常各6例、また、in vivo実験としてラット脳梗塞モデルを作成し、適用する実験を進めた。

（結果と考察）

1）開発した装置（経頭蓋超音波脳血栓溶解装置）は所期の性能を満足した。すなわち、シュリーレン法ではTビームのセクタスキャン能力が、並置型でも積層型でも大差なく、小型化した積層型を開発の中心に置くこととした。また積層型プローブによるファントム像及びヒト頭蓋カラー・ドプラ像共に市販製品との間に大差なく、画像としての血流監視・塞栓部探索能力の充分なことを確認した。

2）各種安全性試験によって次の成果を得た。（1）頭蓋内では低周波超音波の減衰が少なく、対側の頭蓋骨で反射し、それが再反射する形で、超音波伝播経路が広いこと、反射点近傍では定在波が立つことが明らかとなった。(2)正常なサルに対してはTビームによる出血、浮腫などの発生、神経細胞異常のないことを神経病理学的に確認した。（3）虚血再灌流ラット脳に対して、超音波による増悪効果のないことを神経学的評価及びMRI評価で確認した。（4）2MHzと500kHzの併用は血栓溶解時間をやや早くすることを家兎股動脈塞栓モデルで確認した。（5）神経保護薬エダラボンと超音波の複合作用のないことをマウス脳培養スラ

イス標本で確認した。

本年度の成果として、経頭蓋超音波脳血栓溶解装置を開発し、所期性能の確認及びサルによる安全性の確認事例を通し、次のような新たな脳血栓溶解療法の道の開けつつあることを示した。脳梗塞発症後超急性期の血栓溶解剤投与とともに併用する本法を用い、血流状態・再灌流状態を監視しながら、塞栓部に向けて低周波超音波ビームで標的照射し得る治療・診断一体化超音波システムが完成し得ること、また、その再灌流状態の実時間的監視によってtPA 投与量の最適化を実現し得ること、さらに安全性の確保を得つつあることを示した。世界的には TCD による血流監視が tPA 投与による開通率の向上を招くことが臨床的に実証されている。しかし、その超音波周波数は診断用の 2MHz であり、本研究で扱う治療用超音波(500kHz)のような効率的血栓溶解効果は望めないものである。開発した装置のような 2 次元ビームスキャン走査による標的性、カラー・ドプラ診断表示による梗塞領域の俯瞰性などは世界を凌駕する脳血栓溶解技術である。なお、頭蓋内での定在波の消去（開発装置はその能力を含んでおり、特許申請済み)、他の脳虚血状態下の評価を今後実施し、次年度最終年度の探索的臨床研究に向けた倫理委員会承認用の安全性実験成績を積み上げる予定である。

（結論）

経頭蓋超音波脳血栓溶解装置を開発し、その所期能力は充分に満たされ、臨床的活用のできることの見通しを得た。また、経頭蓋超音波脳血栓溶解療法の安全性を in vitro、in vivo 実験で確認し、探索的臨床研究を展開する基盤をある程度築き上げた。これらにより、最終年度の前半に安全性評価を追加し、倫理委員会の承認を得て、臨床研究を行い得ると結論された。

平成１６年度 研究概要

（研究目的）

前年技術的に完成した「経頭蓋超音波脳血栓溶解装置」を元に、有効性の確認、音響学的安全性、さらに同装置の超音波条件による医学生物学的安全性を in vivo 動物実験で確認することを目的とした。また、探索的臨床研究の展開することを目的とした。

（研究方法）

【有効性確認】血栓塞栓型モデル（シリンジ活用、狭窄率 95％）を tPA 溶液で充填し、ヒト新鮮血血栓で塞栓状態とし、開発プローブで超音波照射し、再開通時間を観察した。【音響学的安全性】超音波照射法としてバースト波 300KHz、0.72W/cm2　Ispta、と開発装置の連続波 500KHz、0.72 W/cm2　Ispta とを音響学的に比較した。キャビテーション発生状況についてはシュリーレン法で確認した。[医学生物学的安全性]血液脳関門、神経保護薬併用についてラット脳塞栓モデルで病理組織学的に評価した。特に開発装置の臨床使用状況を模擬し、健常霊長類（マカカ族）を用いて経頭蓋超音波照射の安全性を病理組織学的に評価した。

（結果と考察）

（１）有効性：開発装置は tPA 単独の溶解率 63.8％から 91.6％へ増高した。（２）音響学的安全性：Istpa が同じでもバースト波の duty cycle が長いと発生したキャビテーションの可能性が高まり、また、発生したキャビテーションが消失しにくいことをヒト頭蓋骨照射で確認した。（３）医学生物学的安全性：開発装置の最大超音波照射条件で脳梗塞状態が悪化させられないことを組織病理学的、免疫学的に示した。２）梗塞／再灌流モデルにおいて、神経保護薬の薬効を超音波は阻害しなかった。３）健常霊長類の脳に対し、開発装置の超音波条件は何らの損傷を惹起しないことを神経病理学的、免疫学的に明らかとなった。ただし、本脳血栓溶解療法は、血栓溶解剤との併用を前提とした。しかし、tPA の国内承認が得られていないため、探索的臨床研究は実行し得なかった。

（結論）

経頭蓋超音波脳血栓溶解装置を開発、その有効性、安全性を in vitro、in vivo 実験で確認し、安全で有効な急性期脳血栓溶解療法になり得ることを確認した。

Ⅲ. 資料

DUAL FREQUENCY ARRAY TRANSDUCER FOR ULTRASONID-ENHANCED TRANSCRANIAL THROMBOLYSIS

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Abstract – It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA). A blood flow monitoring is required for an optimum control of the tPA injection and the therapeutic sonication. In order to transmit 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. An epoxy resin isolation layer with 50 micro-meters reduced the amplitude of the unwanted response at 2 MHz by 13 dB, while it reduced the amplitude of the therapeutic waves at 500 kHz only by 2 dB.

I. INTRODUCTION

It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA) [1]. A blood flow monitoring is essential to optimize the amount of tPA bolus and the duration and magnitude of therapeutic sonication. Ishibashi et al. found that an ultrasonic frequency of approximately 500 kHz was most suitable for recanalization of a rabbit's artery through a human temporal bone [2]. In a higher frequency range, heat damage is not ignored. In a lower frequency range, the damage in brain caused by cavitation effects may be not ignored.

However, the frequency of 500 kHz is too low for ultrasonic blood flow imaging. Therefore, respective use of two frequencies for ultrasound-enhanced thrombolysis and ultrasonic imaging would be ideal. A diploe layer in a skull bone disturbs propagation of ultrasound waves [3]. But a temple includes thin or no diploe layer, and can be used as an acoustic window. Because of this reason, the total aperture size for the transcranial therapy with ultrasound monitoring should be limited to the size of a tmeple.

In this study, the structure of a probe consisting of a therapeutic array and an imaging array overlaid on it, was investigated. By using this structure, ultrasonic waves at two frequencies for imaging and therapy can be transmitted through the same aperture. Numerical simulations were used to estimate the oscillation modes in the two arrays; the impulse response in the imaging array and the transmission efficiency of the therapeutic array.

II. FREQUENCY SELECYIVE ISOLATION LAYER

In order to ensure independent oscillatory motions of the two arrays, between these two arrays, a frequency selective isolation layer was inserted. 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. The

thickness and acoustic impedance of the layer was optimized for this function.

The model for numerical simulation was shown in figure 1. The 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. Requirements for this layer were the isolation at 2 MHz and the transparence at 500 kHz. If thickness of the isolation layer was quarter of the wavelength at 2 MHz, two imaging pulses, which reflected at the front and back of the isolation layer, were synchronized, and the amplitude of synthesized pulse increased. On the other hand, this thickness was so thin for therapeutic waves that it did not disturb that propagation. In order to confirm this idea, several different materials and thicknesses of the isolation layer were tested. The pitches of the imaging and therapeutic array were 0.3 mm and 1.2 mm, respectively. Since these pitches were different, several imaging elements were located on one therapeutic element. In this case, isolation layer must stop cross-talk over several elements, the cross-talk was also investigated.

III. RESULTS

Figure 2 showed mode shapes of transducers. When the imaging array was driven, only the driving element vibrated and other imaging elements and therapeutic elements did almost not vibrate. When the therapeutic array was driven, imaging elements located on the driving element vibrated all together. These results showed both the imaging and the therapy mode worked as designed.

Figure 3 showed the impulse responses of the imaging transducer with the isolation layer (a) and without the isolation layer (b). Without the isolation layer, an unwanted response was observed about 2 μsec after the main pulse. The amplitude of the unwanted response is 0.7 times that of the main pulse. The duration between the main pulse and the unwanted response was approximately same as the round-trip propagation time in the therapeutic array. On the other hand, the unwanted response was disappeared with the isolation layer.

Figure 4 showed the cross-talk with adjacent elements. By using the isolation layer, each element in the imaging array could be driven independently. The isolation between two arrays ensured independent oscillatory motions in the imaging array.

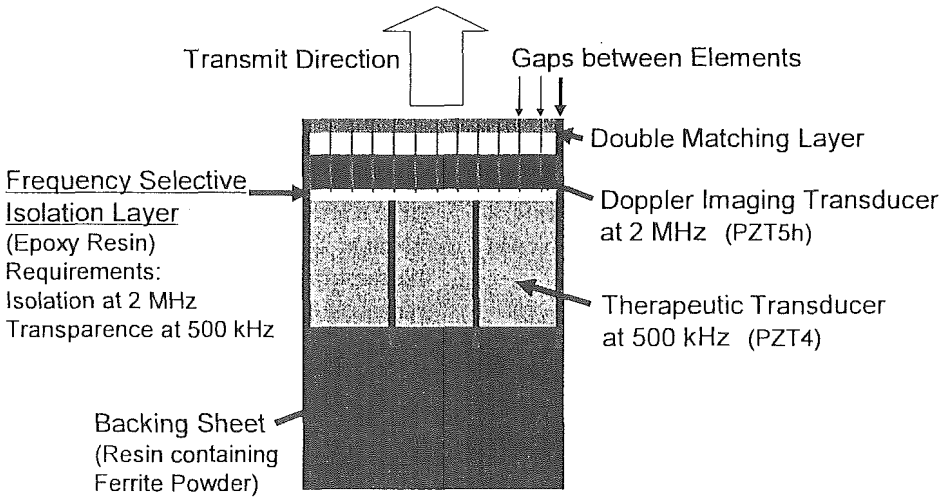

Figure 1: Double-Piezoelectric-Layer Transducer with Frequency Selective Isolation

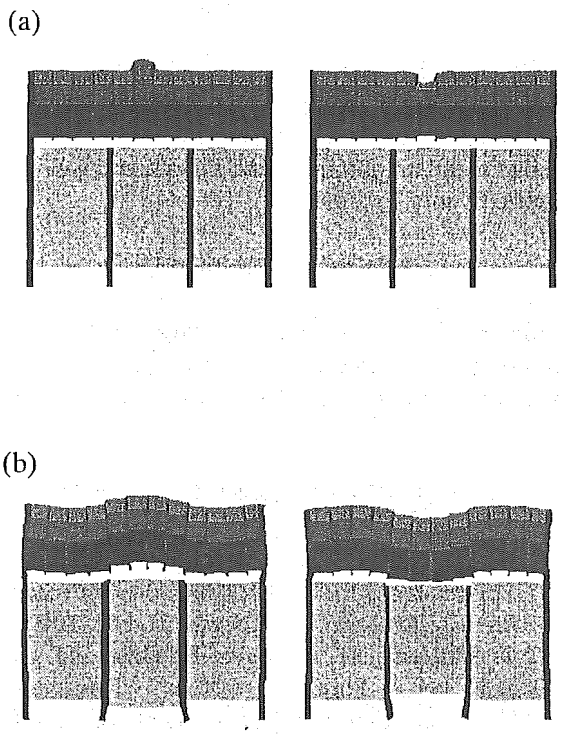

Figure 2: Mode shapes for excitation of Doppler imaging transducer at 2 MHz (a) and Therapeutic Transducer at 500 kHz (b).

IV. Discussion

For several different materials of isolation layers, peak amplitudes of unwanted temporal response were shown in Figure 5. Each material of isolation layers were that is used for an acoustic lens, an epoxy resin, a polymer piezoelectric material without poling, a resin containing ferrite powder, a ceramic containing epoxy resin and a PZT ceramic respectively. This graph was normalized by value of the PZT ceramic case. This result showed that unwanted temporal responses depended on acoustic impedance of isolation layers strongly.

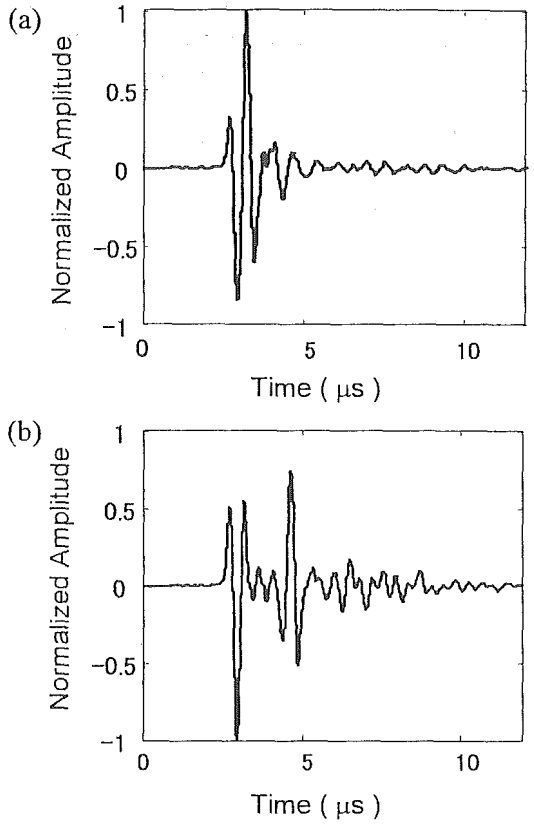

Figure 3: Impulse responses of imaging transducer with isolation layer (a) and without isolation layer (b).

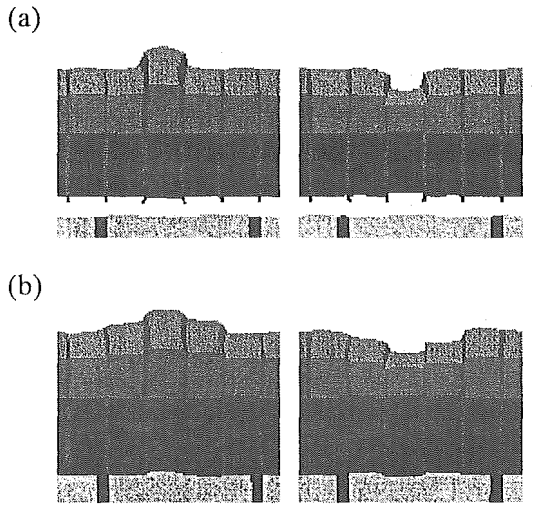

Figure 4: Cross talk with adjacent elements with isolation layer (a) and without isolation layer (b).

In figure 6, we have plotted the acoustic energy of the unwanted temporal responses of the imaging transducer versus the transmission efficiency of the therapeutic transducer, with the thicknesses of isolation layers as the parameter to be changed. The epoxy resin was chosen for the material of isolation layer. The optimum condition was thinner than the matching condition, quarter of the wavelength at 2 MHz.

Since the acoustic impedance of the isolation layer in this simulation was smaller than optimum value indicated at figure 5, the optimum thickness might be thinner than the matching condition.

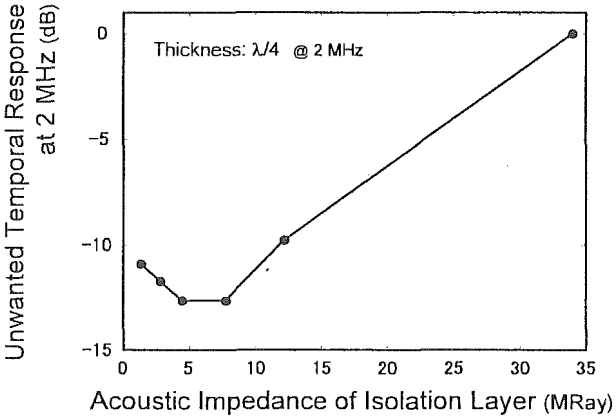

Figure 5: Unwanted temporal response in imaging transducer versus acoustic impedance of isolation layer

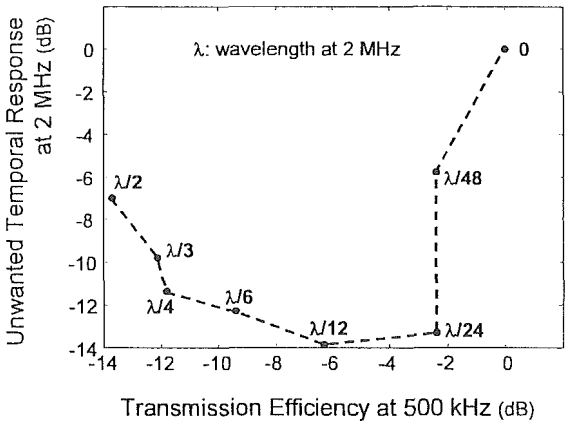

Figure 6: Unwanted temporal response in imaging transducer versus transmission efficiency of therapeutic transducer

V. CONCLUSION

These results showed that the isolation layer with 50 micro-meters reduced the amplitude of the unwanted response at 2 MHz by 13 dB, while it reduced the amplitude of the therapeutic waves at 500 kHz only by 2 dB.

ACKNOWLEDGMENTS

Financial support by Japanese Ministry of Health, Labor and Welfare and cooperation by Dr. Katoh, Dr. Saguchi, Dr. Shimizu, M. Kaburagi and M.Ogiwara are highly appreciated.

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PROTOTYPE DUAL FREQUENCY BILAMINAR ARRAY TRANSDUCER CAPABLE OF THERAPEUTIC EXPOSURE AT 500 kHz AND DOPPLER MONITORING AT 2MHz

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Abstract – It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA). A blood flow monitoring is required for an optimum control of the tPA injection and the therapeutic sonication. In order to transmit ultrasonic waves at two frequencies, one for imaging and the other for therapy, from the same aperture, we proposed 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.

A prototype sector array transducer was designed and constructed based on numerical simulation. B-mode and color flow images of human brains obtained with the prototype were comparable to those of conventional structure transducers with respect to sensitivity and resolution. Schlieren images showed that the sidelobe levels of the therapeutic beam were less than -20 dB when steering angle was limited to 45 degrees in each direction.

I. INTRODUCTION

It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA) [1]. A blood flow monitoring is essential to optimize the amount of tPA bolus and the duration and ultrasonic amplitude of therapeutic sonication. Ishibashi et al. found that an ultrasonic frequency of approximately 500 kHz was most suitable for recanalization of a rabbit's artery through a human temporal bone [2]. In a higher frequency range, heat damages may not be ignored. In a lower frequency range, damages in brain caused by cavitational effects may not be ignored, either. However, the frequency of 500 kHz is too low for ultrasonic blood flow imaging.

The ideal solution for these constraints is respective use of two frequencies for ultrasound-enhanced thrombolysis and ultrasonic imaging. Since a diploe layer in skull bone disturbs propagation of ultrasound waves [3], the effective acoustic window is limited in a temple, having a thin or no diploe layer. Because of this reason, the total aperture size for the transcranial therapy with ultrasound monitoring is very limited.

We proposed a probe structure consisting of a therapeutic array with an imaging array overlaid on it. Numerical simulations ensured that the independent compressive oscillations of the two arrays with a frequency selective isolation layer between these arrays [4]. In this study, we fabricated the prototype probe with the isolation layer. The sensitivity and resolution of imaging arrays were compared to those of the conventional structure probe and the simulation results.

II. FABRICATION OF PROTOTYPE TRANSDUCERS

In order to ensure independent compressive oscillatory motions of the two arrays, between these two arrays, a frequency selective isolation layer was inserted. 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. The thickness and acoustic impedance of the layer was optimized for this function.

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Figure 1 shows the design of prototype transducer. Numerical simulation were 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. The pitches of the imaging and therapeutic arrays were 0.3 mm and 1.2 mm, respectively.

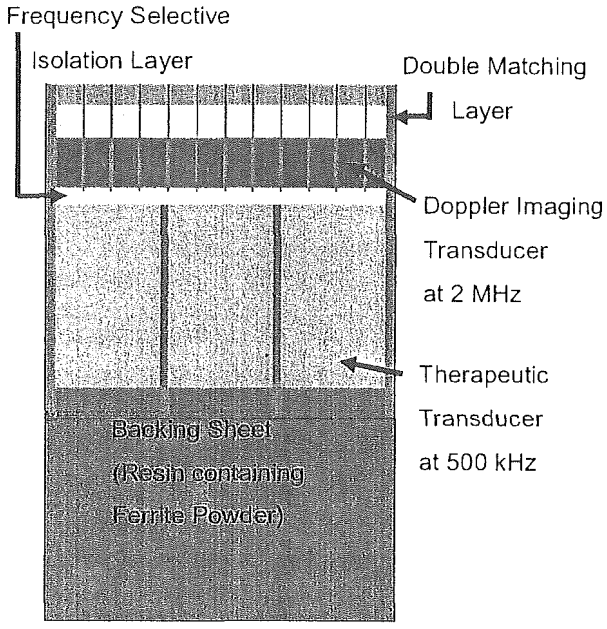

Figure 1 Design of prototype transducer

The thickness and acoustic impedance of isolation layers were optimized based on simulation. The strength of unwanted temporal responses in imaging transducer and the transmission efficiency of therapeutic transducer were evaluated. An epoxy resin 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 100 micro-meter thick epoxy sheet was selected as the isolation layer because of the restriction of fabrication. Figure 2 shows the prototype transducer. The whole size is the same as that of the conventional structure imaging probe at 2MHz.

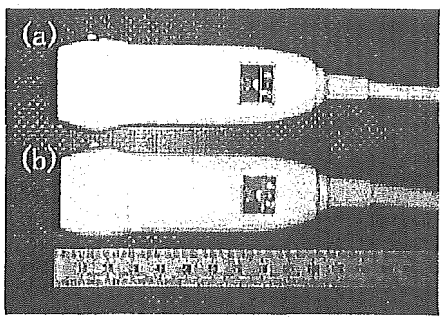

Figure 2 Prototype probe (b) and conventional imaging probe (a).

III. Evaluations of Prototype Transducers

Figure 3 is round-trip pulse response of prototype probe. The response from the experiment is indicated by a solid line and that of numerical simulation by a dashed line. The reflector, consisting of an aluminum plate, was placed at 4 cm from each probe. The prototype probe was driven by a pulser-receiver (5900PR, Panametrics) and the data were acquired by a digital oscilloscope (TDS3034, Tektoronics). The acoustical parameters used in simulation are the same as this experimental set-up. The shape of the main pulse acquired in the experiment was similar to that of the numerically obtained pulse response, however the ringing pulse in the experimental result was larger than that of the numerical simulation.

Figure 4a and b are the pulse responses of conventional and prototype probes, and the spectra of these pulse responses, respectively. The amplitude of prototype was 73 % of that of conventional. An unwanted ringing response 2 micro-second after the main pulse was only observed in the pulse response of the prototype probe. The shape of spectrum of prototype was affected by this unwanted ringing, however the sensitivity of the prototype probe at 2MHz is similar to that of the conventional structure imaging probe. Therefore, the sensitivity of transcranial Doppler was confirmed to be

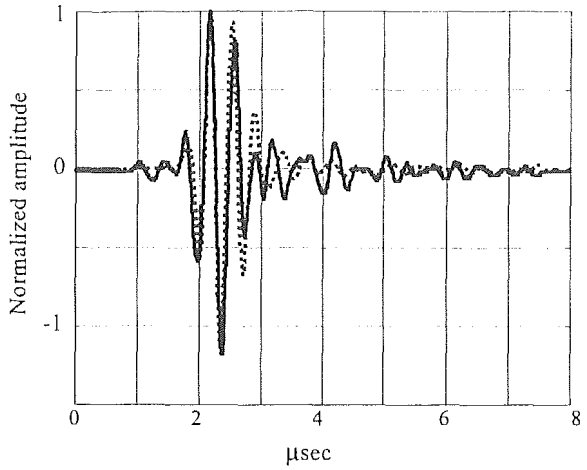

Figure 3 Round-trip pulse response of prototype probe (a) and numerical simulation(a).

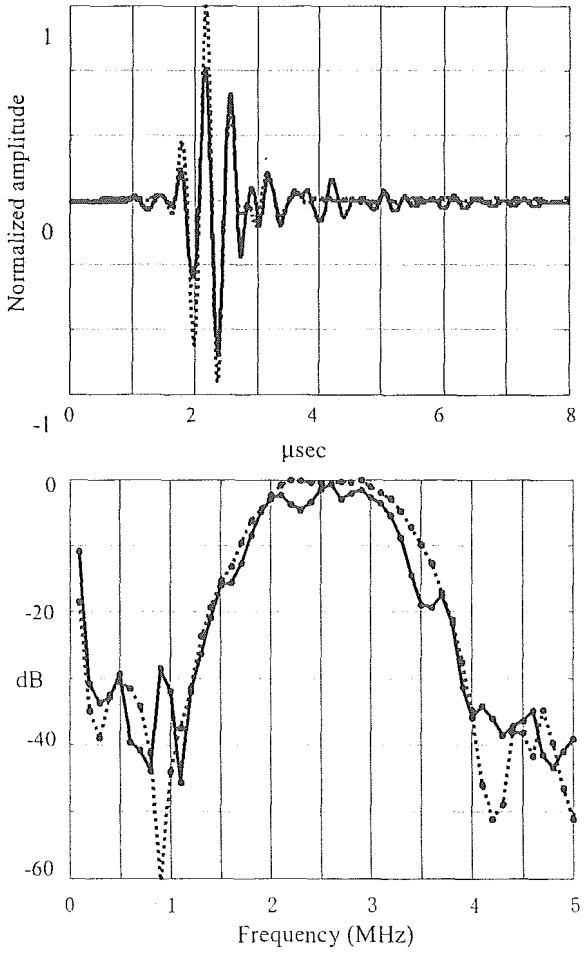

Figure 4 Round-trip pulse response (a) and spectrum (b) of the prototype probe

comparable to those of conventional structure probe.

Figure 5 shows B-mode images of a tissue phantom obtained by the prototype and conventional structure probes. The image captured by the prototype probe is comparable to those of the conventional structure probe with respect to sensitivity and resolution. A color flow image and a Doppler spectrum of human brain obtained by the prototype probe are shown in figure 6.
This image was useful for aiming of the therapeutic beam.

IV. DISCUSSION

The evaluation of the prototype probe demonstrated that the isolation layer worked as designed. This isolation layer has three requirements, 1) the reduction of ringing response, 2) elimination of cross talk between adjacent elements and 3) transparence for therapeutic array. If the thickness of the isolation layer is quarter of the wavelength at 2 MHz, two imaging pulses, reflected at the front and back of the isolation layer, will be synchronized, and the amplitude of transmit pulse will be increased. On the other hand, this thickness was so thin for therapeutic waves that it will not disturb that propagation.

The amplitude of unwanted response in the prototype probe is affected by the difference between ideal and actual thickness of the isolation layer. They were improved by obtaining the isolation layer based on the numerical simulation.

The lateral resolution was affected by the strength of the cross talk between adjacent elements in the imaging array. Figure 5 shows cross talk coupled through the therapeutic array can be ignored, since the lateral resolution of the image obtained by the prototype probe was comparable to that of the conventional probe.

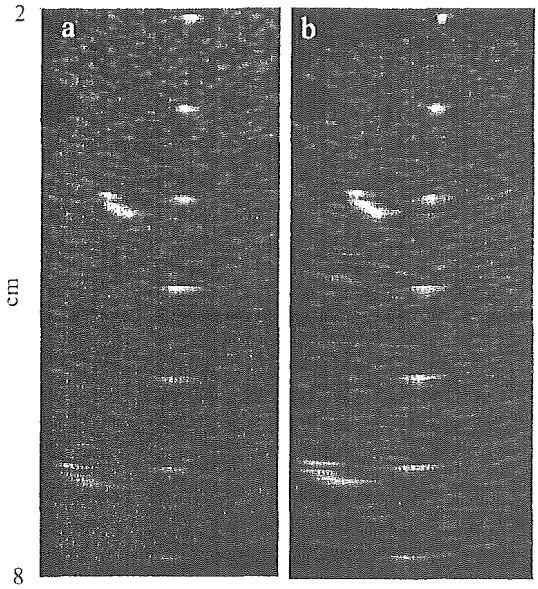

Figure 5 Phantom images captured by conventional probe(a) and prototype probe(b).

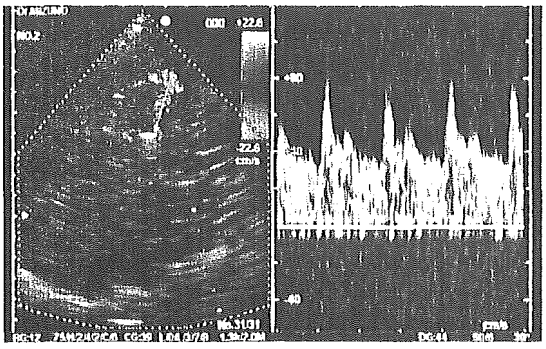

Figure 6 Color mapping and Doppler spectrum of human middle cerebral arterial flow captured by prototype probe.

V. CONCLUSION

We proposed a dual frequency bilaminar transducer for ultrasound therapy with Doppler image monitoring with frequency selective isolation layer.

The numerical simulation showed that isolation layer reduced the unwanted response in the imaging pulse at 2 MHz by 13 dB, while it reduced the amplitude of the therapeutic waves at 500 kHz only by 2 dB. The actual isolation layer of the prototype probe reduced the unwanted response by 16 dB, while it reduced the amplitude of main pulse of imaging only by 3 dB.

B-mode and color flow images of human brains obtained with the prototype were comparable to those of conventional structure transducers with respect to sensitivity and resolution.

ACKNOWLEDGMENTS

This work was supported in part by the Health and Labour Sciences Research Grants for Translational Research from the Japanese Ministry of Health, Labor and Welfare.

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SCHLIEREN OBSERVATION OF THERAPEUTIC FIELD IN WATER SURROUNDED BY CRANIUM RADIATED FROM 500 kHz ULTRASONIC SECTOR TRANSDUCER

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Abstract – Standing-wave formation in water surrounded by a section of a human cranium, produced by a transcranial 500 kHz ultrasonic beam was observed optically. The ultrasonic beam was generated from a prototype sector-scan phased-array transducer, designed for transcranial enhancement of thrombolysis with tissue plasminogen activator (tPA). The amplitude distribution and the wavefronts of the ultrasonic field were observed in schlieren images. The stripe patterns of the standing waves were seen clearly near the sites of reflection in these images under certain acoustic conditions. No standing wave patterns were detected in the basically the same arrangement with a sector-scan phased-array transducer operating at 2 MHz. These finding suggest that standing waves may be formed in the tissue at the positions of reflection by transcranial insonation of a human brain at a relatively low ultrasonic frequency, typically less than 1 MHz. This suggests further the possibility of inducing cavitational adverse effects in brain tissue.

I. INTRODUCTION

Dissolution of the thrombus as soon as possible after ischemic stroke, typically within 3 hours, is crucial to reducing the risk of ischemic neuronal injury. A number of reports have been made that ultrasound can enhance the effect of thrombolytic drugs such as tissue plasminogen activator (tPA) and urokinase[1,2,3]. Alexandrov et al. found that a significantly higher rate of recanalization with tPA was observed in the acute ischemic stroke patients who were monitored with transcranial Doppler (TCD) at 2 MHz than in those who were not and they concluded that ultrasound including TCD could enhance the thrombolytic activity of tPA[4]. Using of ultrasound at a relatively low frequency, typically lower than 1 MHz, which can penetrate a skull bone more efficiently, was also studied for thrombolysis enhancement [3]. Standing waves are considered to be formed in tissues more easily at such a low ultrasonic frequency, because ultrasonic attenuation, diffraction and scattering in tissues, which disturb standing wave formation, work less than at a higher frequency. Actually, Daffertshofer reported that intracerebral hemorrhages occurred after transcranial insonation at 300 kHz [5].

Cavitational bioeffects have been observed in a standing wave field at a much lower acoustic amplitude than in a progressive wave field [6]. This is because acoustic cavitation can be induced much more easily in a standing than progressive wave field. The microbubble migrates toward the antinode due to the primary Bjerknes force, there it will increase its size quickly by merging with other migrated microbubbles as shown in figure 1. As soon as the microbubble reaches the resonant size, it may violently collapse, easily even at a relatively low acoustic amplitude, causing huge magnitudes of mechanical stress and temperature, which is called collapse or inertial cavitation. The induction of cavitational damage to biological cells by standing waves was reported[6].

In order 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 is important to study the formation of standing waves within a skull. Spatial variations in the optical refractive index of a medium are detected in schlieren images. Raman and Nath [7] showed that quantitative imaging of acoustic fields was possible thereby. This method is suitable for such measurement because it does not disturb the

0-7803-8412-1/04/$20.00 (c)2004 IEEE.

2004 IEEE International Ultrasonics, Ferroelectrics, and Frequency Control Joint 50th Anniversary Conference

acoustic field. In this study, the ultrasonic field formed by transcranial insonation in water surrounded by a contoured piece of a human skull were optically observed as schlieren images.

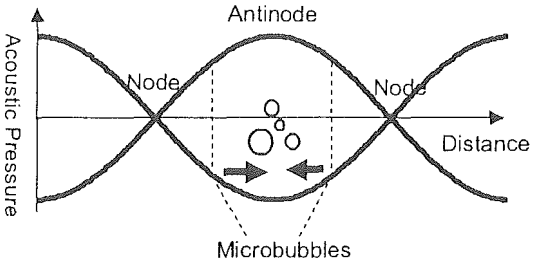

Figure 1 Bubbles-formation in Standing Wave Field

II. Materials and Methods

A prototype sector-scan phased-array transducer was fabricated and used for the transcranial insonation. It has an acoustic aperture of 24.5 mm x 16 mm consisting of an array of 48 transducer elements in the longer axis. The PZT transducer with matching layer has a central frequency of 770 kHz and a relative bandwidth of 80%. For the transcranial insonation at 2 MHz, a commercial sector-scanning type phased array probe for transcranial Doppler imaging (EUP-S50, Hitachi Medical) was used in combination with a commercial scanner (EUB-8500, Hitachi Medical).

Figure 2 shows the set-up to obtain schlieren images of the ultrasonic fields. The lenses were 15 cm in diameter and had a focal length of 150 cm. The light from the source passes through the first lens, the water tank and the second lens and was detected by the charge-coupled-device (CCD) camera. The ring knife edge prevented the nondiffracted component of the light from reaching the camera. Only the components diffracted by the spatial change in the optical density formed an image on the CCD. Longitudinal acoustic waves, which produce the spatial change in water, can thereby be imaged.

Two schlieren images with and without insonation were taken and digitized at the same same set-up and the latter digitized image was subtracted from the former. The effect of optical scattering by small particles in water was eliminated thereby in the subtraction schlieren image.

A light-emitting diode (LED) and an ultra-high-pressure mercury lump were used as the light source in the synchronous and the conventional asynchronous schlieren modes, respectively. Shlieren images of ultrasonic wavefronts, obtained using a high-intensity LED as a synchronous light source [8]. The chip type LED (model NSCG100 GT, Nichia) had an optical output power of 3 mW. It had a peak emission wavelength of 525 nm. A wave generator was used for driving the ultrasonic transducer. In the synchronous schlieren mode, another wave generator was also used for driving the LED. The two generators were either phase-locked to each other or operated with a slight difference in frequency of less than 1 Hz.

A human skull (adult male, Mongroid) was contoured and used in the experiment. The height of the contoured piece was 25-30 mm, which was larger than the short axis of the aperture of the 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 transducer was attached to the outer surface of the contoured piece and located to the position where the ultrasonic penetration was maximal. The position was close to the ditches in the cranium, which had been along vessels on the brain surface. The sector-scan plane of the transducer was set perpendicular to the optical axis.

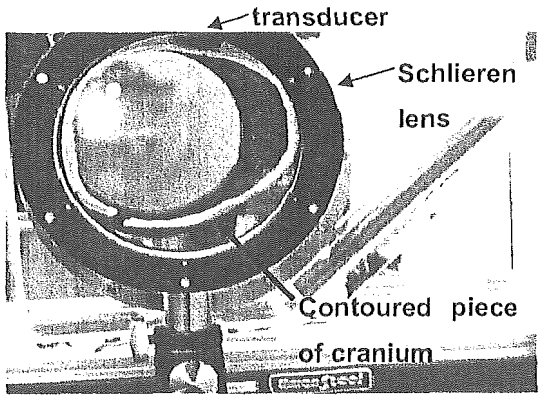

Figure 2 Set-up to obtain schlieren images

III. Results

Figure 3 shows the subtraction schlieren images obtained in the asynchronous mode with the prototype transducer driven at 500 kHz with an electronic focal length of 50 mm at beam steering

angle of 12°. The twice-reflection by the cranium as well as the once-reflection can be seen in some of the pictures. In this pictures, the interference pattern between the penetrated beam from the transducer and the twice-reflected beam is seen. A stripe pattern is clearly seen near the place of the first reflection. Another stripe pattern is also seen near the place of the second reflection.

Figure 4 shows the subtraction schlieren images obtained in the synchronous modes in the same acoustical set-up. The wavefronts are clearly seen in the synchronous image. Especially, the bended wavefronts near the transducer induced by the thickness inhomogeneity of skull bone in the aperture were observed and the interference pattern was observed as the amplitude modulation in wavefronts. The stripes near the place of reflection seen in the asynchronous image are approximately parallel to the wavefronts seen in the synchronous image and the spacing of the stripes is a half of the spacing between the wavefronts. These show that the stripes seen in Figure 3 were the pattern of the standing waves formed near the place of reflection. Figure 5 shows the subtraction schlieren images obtained in the asynchronous mode with the commercial transducer driven at 2.08 MHz with an electronic focal length of 50 mm at beam steering angle of 0°. No stripe patterns are seen in these pictures.

IV. DISCUSSION

Standing-wave formation was optically observed in water surrounded by a contoured piece of a human cranium with transcranial ultrasonic beam. This suggests that standing waves will also be formed in the brain tissue by transcranial insonation of a human brain in a similar set-up, because the attenuation in brain tissue is small at 500 kHz, typically less than 0.3 dB/cm [9].

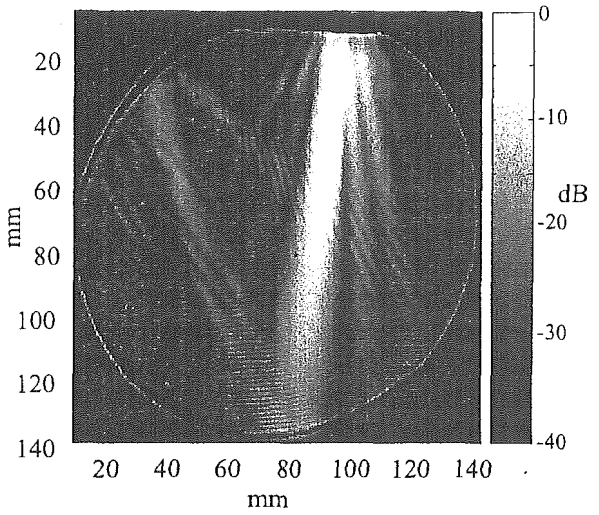

Figure 3 Asynchronous schlieren images at 500 kHz

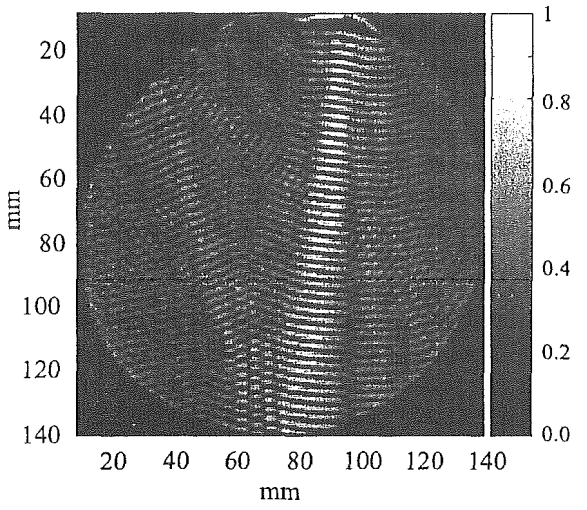

Figure 4 Synchronous Schlieren images at 500 kHz

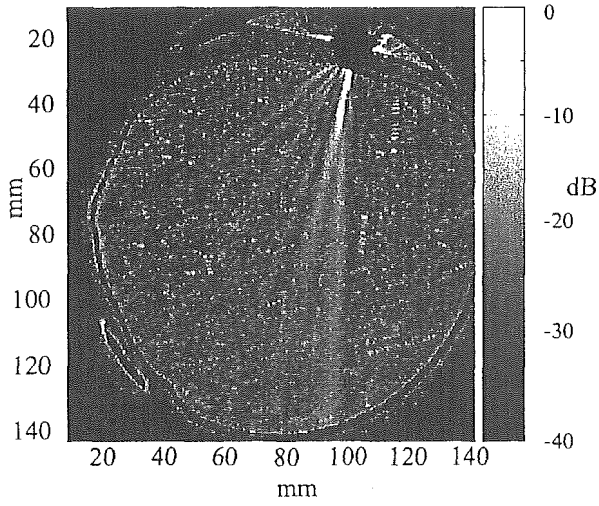

Figure 5 Asynchronous schlieren images at 2 MHz

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. Our study may indicate that standing waves were formed in the brain tissue and induced the intracerebral hemorrhages through cavitation.

Several groups discussed that cavitation played a role for thrombolysis. There are two kinds of cavitations i.e. stable cavitation and collapse cavitation. While no report has been made based on a certain experimental evidence, stable cavitation may enhance thrombolysis through increasing acoustically-induced displacement in the clot. Even though suppression of cavitation may reduce ultrasound enhancement of thrombolysis, collapse cavitation has to be avoided because it can cause severe adverse effects through inducing huge mechanical stresses and generating chemically-active species.

The results in Figure 6 show that standing wave formation was not observed at an ultrasonic frequency of 2 MHz. Considering the attenuation in brain tissue at 2 MHz is a few times higher than at 500 kHz, the possibility of forming standing waves in the brain tissue by transcranial insonation at 2 MHz is expected to be much less than at 500 kHz. However, using an ultrasonic frequency of 2 MHz instead of 500 kHz to reduce the possibility of inducing cavitation during therapeutic insonation may not be a practical choice, because the attenuation through the cranial bone at 2 MHz is higher than 500 kHz by more than 20 dB.

Other ways to suppress standing-wave formation such as modulation in ultrasonic frequency, amplitude and beam angle should be studied in order to achieve efficient transcranial thrombolysis while minimizing the possibility of inducing adverse effects.

ACKNOWLEDGMENTS

This work was supported in part by the Health and Labour Sciences Research Grants for Translational Research from the Japanese Ministry of Health, Labor and Welfare. The authors gratefully acknowledge Prof. Y. Kawai (Department of anatomy in Jikei University School of Medicine) for help in the usage of human skull bone and Dr. Saguchi and Dr. Shimizu (Department of Neurosurgery in Jikei University School of Medicine) for discussion about transcranial ultrasound therapy.

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