

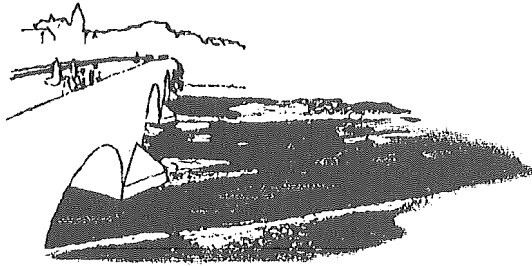
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ABSTRACTS

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Wetzlar, Germany, May 9-11, 2004

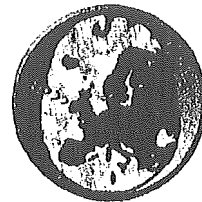
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37 Session VII: Venous System and Animal Models

Therapeutic Ultrasound in A Rat Middle Cerebral Artery Stroke Model -A Safety Study-

Saguchi T 2), Gerriets T 3,4), Walberer M 3,4), Bachmann G 4), Kaps M 3), Furuhashi H 1)

1) ME Lab. and 2) Dep. of Neurosurgery, Jikei Univ. School of Medicine, Tokyo, Japan, 3) Dep. of Neurology, University Giessen 4) Dep. of Radiology - Experimental Neurology Research Group, Kerckhoff-Klinik Bad Nauheim, Germany

Background and purpose: Safety of transcranial ultrasonication (TUS) to an ischemic and reperfused brain was examined in a rat model of middle cerebral artery occlusion (MCAO).

Methods: The origin of the right MCA was occluded in 22 male Wistar rats using a silicone-coated nylon thread (occluder). Neurological evaluation was performed at 80 minutes, 4 hours and 24 hours after MCAO. Reperfusion was induced at 90 minutes after MCAO by withdrawing the occluder into the right common carotid artery. The animals were randomized into two groups:

1) sham operation (n=11) and 2) ultrasonication (n=11).

Continuous wave ultrasound (490 kHz; 0.8 W/cm²) was applied to the affected hemisphere. Magnetic resonance angiography was performed at 4 hours to verify reperfusion. MRI was performed at 4 hours and 24 hours to determine lesion volume on T2-weighted imaging and to quantify T2-relaxation time.

Results: No significant differences were seen between the two groups regarding neuro-

logical score, lesion volume and T2 relaxation time.

Conclusions: Transcranial therapeutic ultrasound (490 kHz, 0.8 W/cm²) did not cause any side-effects in this in-vivo stroke model.

38 Session VII: Venous System and Animal Models

Alternating Low Frequency Ultrasound-Enhanced Thrombolysis with Monitoring by Power M-Mode Doppler

Shimizu J, Nakano M, Hattori Y 1), Ikegami M 2), Saguchi T, Abe T 3), Matsuyama H 4), Furuhashi H 1), Moehring MA, Voie AH, Spencer MP 5)
1) ME Lab, Jikei Univ. School of Med., Tokyo, Japan, 2) Dept. of Pathology, 3) Neurosurgery, Jikei Univ. School of Med. Tokyo, Japan 4) Faculty of Engineering, Sophia Univ., 5) Spencer Technologies, Inc., Seattle, WA, USA

This work aims at implementation and testing of transcranial ultrasonic thrombolysis using a novel probe combining low frequency therapeutic ultrasound for enhancement of t-PA thrombolysis, with diagnostic power M-mode Doppler (PMD). We explored thrombolysis with insonation in the rabbit femoral thrombo-embolic model using this newly developed 500kHz/2MHz combination probe.

Material and Method: The combination probe has two modes. It emits therapeutic ultrasound (US) for enhancement of thrombolysis at 500kHz (T-beam), and diagnostic Power M-mode Doppler (PMD) for monitoring of the blood flow at 2MHz (D-beam). The beams are alternated by an automatic switching circuit (T-beam active for two_@minutes alternating with D-beam active for 30 seconds). This alternating cycle beams is repeated four times and after that, D-beam is active for 5 minutes. This 15 minute protocol is repeated 4 times. 13 rabbits were used for this study. The thrombin clots were produced bilaterally in the animal model. A transit-time ultrasonic flow meter proximal to the clot and a laser flow meter distal to the clot were used to measure blood flow. 1.2mg of alteplase (tPA) was administered intravenously from the right jugular vein, and D-beam (2MHz, 0.04W/cm²) and T-beam (500 kHz, 0.16W/cm²) were applied through an acoustic stand off material to the right clot.

Results: The initial pre-thrombolytic state showed no flow waveform. The waveform changed into a small spike pattern synchronized to the heart beat at the beginning of thrombolysis. The blood flow became rapid and the waveform changed to a large spike pattern with the progression of thrombolysis. Finally the waveform showed a blood flow pattern with the large spike pattern at the end of recanalization. The recanalization ratio of US side is 5/13 (38.5%) and no-US is 4/13 (30.8%). The average time of recanalization cases are 15.6min (US) and 26.5min (no-US) (p=0.133). Although this is not statistically significant, a tendency for faster recanalization of the side receiving US is suggested.

Conclusions: This investigation demonstrates work in progress regarding alternating Doppler monitoring and low frequency therapy in the context of ultrasound enhanced thrombolysis, and is anticipated to contribute to effective primary treatment in acute embolic stroke therapy.

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Standing-Wave Formation in Water Surrounded by Cranium Radiated From 500 kHz Ultrasonic Sector Probe

Azuma T 1), Kawabata K 1), Umemura S 1), Ogihara M 2), Asahusa K 2), Kubota J 2), Sasaki A 2), Nakano M 3), Abe T 3), Furuhashi H 3)

1) Central Research Laboratory, Hitachi, Ltd., Kokubunji, Tokyo, Japan, 2) Hitachi Medical Corporation, Kashiwa, Chiba, Japan and 3) Medical Engineering Laboratory, Jikei University School of Medicine, Tokyo, Japan

The use of ultrasound at a relatively low frequency, typically lower than 1 MHz, which can penetrate a skull bone more efficiently, are suitable to enhance the effect of thrombolytic drugs such as tissue plasminogen activator. Acoustic cavitation can cause adverse biological effects through inducing huge mechanical stresses and generating chemically active species. The generation of cavitation is affected not only by acoustic intensity and frequency, but also other conditions of an acoustic field, especially standing wave formation. In this study, standing-wave formation in water surrounded by a contoured piece of

a human cranium with a transcranial ultrasonic beam at 500 kHz was optically observed using Schlieren imaging. The ultrasonic beam was generated from a prototype sector-scan phased-array transducer, which can transmit ultrasound beam in various angles, with a fixed transducer position on the skull bone. The standing waves patterns were clearly seen near the places of reflection in the Schlieren images at certain beam angles. No standing wave patterns were detected in the basically the same setup with a commercial sector-scan phased-array transducer at 2 MHz. These suggests that standing waves can also be formed in the brain tissue near the place of reflection by transcranial insonation of a human brain at a relatively low ultrasonic frequency, typically less than 1 MHz, and further suggests the possibility of inducing the intracerebral hemorrhages through cavitation in brain tissue thereby. In order to suppress standing wave formation, modulations in ultrasonic frequency, amplitude, and beam angle should be studied to achieve efficient transcranial thrombolysis. This work was supported in part from the Research on Advanced Technology program of the Japanese Ministry of Health, Labor and Welfare.

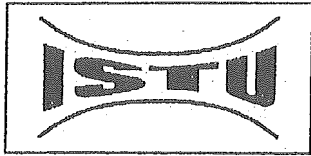
Dual Frequency Bilaminar Transducer for Ultrasound-Enhanced Transcranial Thrombolysis with Doppler Monitoring

Azuma T 1), Umemura S 1), Ogihara M 2), Kubota J 2), Sasaki A 2), Furuhashi H 3)

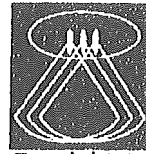
1) Central Research Laboratory, Hitachi Ltd., 2) Hitachi Medical Corporation, and 3) ME Laboratory, Medical Science Jikei University School of Medicine, Tokyo, Japan

It is known that ultrasound can enhance thrombolysis with tissue plasminogen activator (tPA). An optimum control of the tPA injection and the therapeutic sonication requires simultaneous blood flow monitoring. The optimal frequency for ultrasound-enhanced thrombolysis and ultrasonic Doppler monitoring are different; typically 500 kHz and 2 MHz for the former and the latter, respectively. In order to use temples for the acoustic window for transcranial ultrasound, the total aperture size for monitoring and therapy is very limited. In order to generate 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 the model, the imaging and therapeutic arrays used PZT ceramic with a centre frequency of 2 MHz and 500 kHz, respectively. Several different thicknesses of the frequency selective isolation layer made of epoxy resin were tested. The results showed that the isolation layer 50 micro-meters thick 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 based on this analysis. B-mode and color flow images of phantoms 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 in the permissible range. The transmission efficiency of the therapeutic array should be also discussed, since the low efficiency of the therapeutic array may require cooling equipment. This Research is supported by Japanese Ministry of Health, Labor and Welfare.

ISTU 2004, Kyoto, Japan



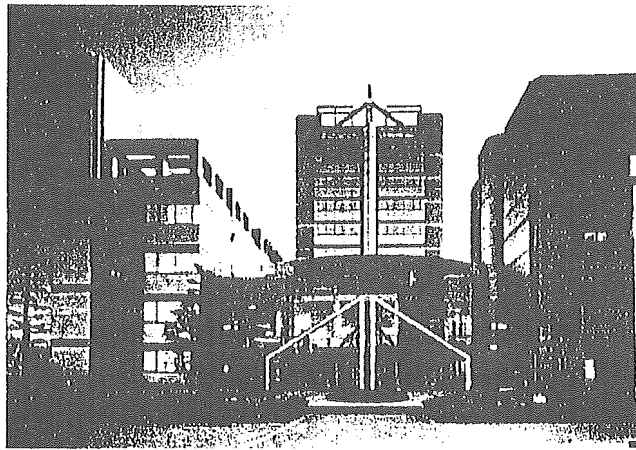
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Schlieren Imaging of Therapeutic Field in Water Surrounded by Cranium Radiated from
Ultrasonic Sector Transducer for Thrombolysis

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²Jun Kubota, ²Akira Sasaki, ³Jun Shimizu and ³Hiroshi Furuhata

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The use of ultrasound at a relatively low frequency, typically lower than 1 MHz, which can penetrate a cranium more efficiently, is suitable to enhance the effect of thrombolytic drugs. Acoustic cavitation can cause adverse biological effects through inducing huge mechanical stresses and generating chemically active species. The generation of cavitation is affected not only by acoustic intensity and frequency, but also other conditions of an acoustic field, especially standing wave formation. In a standing wave field, a microbubble migrates toward the antinode of the standing wave, where it will increase its size by merging with other migrated microbubbles. 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. In this study, standing-wave formation with a transcranial ultrasonic beam at 500 kHz in water surrounded by a sliced piece of a human cranium was optically observed with a Schlieren imaging system. The ultrasonic beam was generated from a prototype phased-array transducer, which can transmit an ultrasound beam in various angles, with a fixed transducer position on the cranium. A stripe pattern caused by standing waves was clearly seen near the place of reflections on the inner side of the cranial piece. No standing wave patterns were detected in the basically the same setup with a commercial phased-array transducer at 2 MHz. These suggests that standing waves can be formed also in the brain tissue near the place of reflection by transcranialinsonationofahumanbrainatarelativelylowultrasonicfrequency, typically less than 1 MHz, and further suggests the possibility of inducing the intracerebral hemorrhages through cavitationinbraintissue thereby. Modulationsinultrasonicfrequency, amplitude, and beam angle are being studied to suppress standing-wave formation and will also be discussed. 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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 佐々木 明²⁾, 古幡 博³⁾, 河合 良訓³⁾

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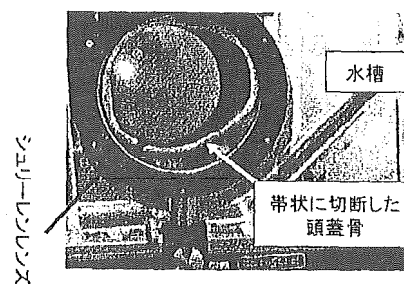
数100kHz域の超音波の印加によりtPA (tissue plasminogen activator) 等の血栓溶解剤の効果が増強することが、動物実験により明らかにされている¹⁾。しかし、超音波の強度があるレベルを超えると、キャビテーション作用などにより、脳組織に損傷を与える可能性がある。キャビテーションは進行波よりも定在波によって、より生じやすいことが知られている。このため、頭蓋内の超音波音場の様子を把握することは重要であるが、これまで観測が行われたことがなかった。特にDaffertshoferらにより、300kHzの経頭蓋骨超音波照射治療において、脳内で出血が生じた事例が報告されており、頭蓋内超音波音場を把握することの必要性が高まっている。今回、図1 (a) に示すように、頭蓋骨を带状に切断し、切断面の法線方向と光軸を平行にして、頭蓋骨を水中に固定。頭蓋骨の外側から500kHzの超音波を照射する配置により、頭蓋内水中音場のシュリーレン測定を行なった。図1 (b) にシュリーレン像を示す。トランスデューサから頭蓋骨を透過した超音波は、反対側の骨の内側で、一回目の反射をしており、この反射部分近傍において定在波パターンが観測された。またこの反射波は更に、別の場所で反射して、元の入射波と、頭蓋の中央近傍でビームが交差して、干渉パターンが生成していることも観測され、シュリーレン法によって、頭蓋内超音波音場が複雑な様相を示すことが解った。定在波音場の生成からキャビテーションの生成に至るには一定の時間が必要である。ビームの走査や、周波数変調、パルスシーケンスなどにより、定在波の生成を抑制し、キャビテーション生成の確率を低減することが可能と考えられる。発表においては、現在開発中のドップラモニタリング付アレイ型治療用超音波

プローブを用いた、各照射方式による音場への影響に関する評価結果に関しても議論を行なう。

文 献

- [1] T. Ishibashi, M. Akiyama, H. Onoue, T. Abe and H. Furuhata, Stroke, vol. 33, pp.1399-1404, 2002.

(a) 実験配置



(b) シュリーレン像

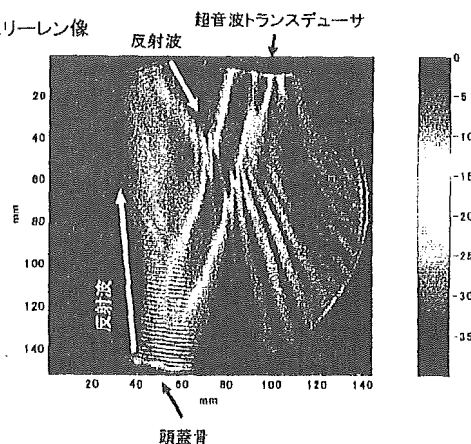


図1 頭蓋骨内超音波音場のシュリーレン観測

Schlieren images of acoustic field in skull bone

Takashi AZUMA¹⁾, Kenichi KAWABATA¹⁾, Shinichiro UMEMURA¹⁾, Makoto OGIWARA²⁾, Jun KUBOTA²⁾, Akira SASAKI²⁾, Hiroshi IIURUHATA³⁾, Yoshinori KAWAI³⁾

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Keywords: biological effect, cavitation, acoustic, Schlieren image

07-3

血栓溶解治療用トランスデューサから照射される頭蓋内超音波音場のシュリーレン観測

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慈恵会医科大学ME研究室³

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佐々木明², 古幡博³

Schlieren Observation of Therapeutic Field in Water Surrounded by Cranium Radiated from Ultrasonic Transducer

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Hitachi Medical Corporation Kashiwa Japan², ME Lab.,
Medical Science Jikei University School of Medicine Tokyo
Japan³

Takashi Azuma¹, Kenichi Kawabata¹, Shinichiro Umemura¹,
Makoto Ogihara², Jun Kubota², Akira Sasaki²,
Hiroshi Furuhashi³

【目的】数100kHz域の超音波照射により血栓溶解剤の効果が増強することが、動物実験により明らかにされている[1]。このとき、キャビテーション作用による組織損傷を避ける必要があるが、定在波音場では気泡が定在波の腹に集積し、キャビテーション核になるため、進行波に比べ、キャビテーション閾値が低下する。このため、頭蓋内音場を把握する必要がある。【方法】シュリーレン法は波の伝播に伴う媒質の屈折率変化を可視化する方法である。頭蓋骨を鉢巻状に切断し、切断面の法線方向と光軸を平行にして、頭蓋骨を水中に固定。頭蓋骨の外側から500kHzの超音波を照射、頭蓋内水中音場を可視化した。【結果】頭蓋骨内で超音波は、反対側の骨の内側で反射、反射部近傍にて定在波パターンが観測された。定在波の生成からキャビテーションに至るまで数サイクル以上の超音波照射が必要なので、時間変調などの方法でキャビテーション抑制を検討する必要があることが解った。【謝辞】本研究の成果の一部は厚生労働省のトランスレーショナルリサーチの補助金を受けて実施したものである。

[1] T. Ishibashi, M. Akiyama, H. Onoue, T. Abe and H. Furuhashi, Stroke, vol. 33, pp.1399-1404, 2002.

07-4

500kHz血栓溶解 / 2 MHzドップラ血流画像撮像用積層型アレイトランスデューサの開発

日立製作所中央研究所¹, 日立メデコ²,
慈恵会医科大学ME研究室³

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泉美喜雄³, 佐々木明², 古幡博³

500kHz ultrasound-enhanced thrombolysis / 2MHz Doppler flow imaging bilaminar transducer array

Central Research Laboratory, Hitachi Ltd. Tokyo Japan¹,
Hitachi Medical Corporation Kashiwa Japan², ME Lab.,
Medical Science Jikei University School of Medicine Tokyo
Japan³

Takashi Azuma¹, Shin-ichiro Umemura¹, Makoto Ogihara²,
Jun Kubota², Takashi Kobayashi², Mikio Izumi²,
Akira Sasaki², Hiroshi Furuhashi³

経頭蓋超音波血栓溶解治療においては、治療の効果と出血のリスクはトレードオフの関係にあるため、溶解剤の投与量や超音波照射時間、出力を制御するためには、頭蓋内血流モニタを用いた治療制御が必須である。しかし、治療用の周波数は、温度上昇や機械的作用の観点から数100kHz域が適しており、撮像用には、頭蓋骨透過率と空間分解能の点から2MHzが適している。この大きく異なる二つの周波数を一つの圧電素子の周波数帯域内に含めるのは困難である。音響窓がこめかみに空間的に限定されている経頭蓋超音波照射には、二つの圧電素子を並べることも実用的ではない。我々はこの課題に対し、治療用と撮像用の二つの素子アレイを積層した構造を提案し、試作による動作確認を行った結果を報告する。圧電素子を積層すると、互いの相互作用により、各層の独立動作が困難である。新規に周波数選択性の分離層を各層の間に積層することで、各層の独立動作が可能であることをシミュレーションで見出し、構造の最適化を行った。この構造に沿って従来の撮像プローブと同サイズの試作を行った。治療アレイからは出力0.5W/cm、500kHz、±45度の範囲で電子走査可能なビームが送波可能であり、撮像アレイから、従来の撮像専用アレイと遜色のない血流画像が撮像可能であることを確認した。本研究の成果の一部は厚生労働省のトランスレーショナルリサーチの補助金を受けて実施したものである。

Congress Program and Abstract

ICA 2004

The 18th International Congress on Acoustics
Kyoto International Conference Hall
4-9 April 2004, Kyoto, Japan

Acoustical Science and Technology for Quality of Life

Under the aegis of the International Commission for Acoustics
Organized by : Science Council of Japan
Acoustical Society of Japan
Institute of Noise Control Engineering of Japan
In Cooperation with Japan National Tourist Organization



Therapeutic ultrasound (II)

Chairperson:

Shin-ichiro Umemura - *Central Research Laboratory, Hitachi Ltd., Japan*

Kullervo Hynynen - *Harvard Medical School, USA*

[14:20 - 15:20] Room: Room A

Mo4.A.1 - CONCEPT OF ULTRASOUND CEREBRAL INFARCTION THERAPY EQUIPMENT FOR EARLY DISSOLUTION OF THROMBUS

Jun Kubota¹, Akira Sasaki², Makoto Ogihara¹, Takashi Azuma³, Shin-ichiro Umemura³, Hiroshi Furuhashi⁴

¹*R&D Center, Hitachi Medical Corporation, Japan,*
²*Ultrasound Div., Hitachi Medical Corporation, Japan,*
³*Central Research Laboratory, Hitachi, Ltd., Japan,* ⁴*ME Laboratory, Jikei University School of Medicine, Japan*

We develop equipment for cerebral infarction therapy, which is comprised that ultrasound is illuminated on embolized part of a brain trans-cranially with injection of thrombolytic agent. Minimizing the thermal and mechanical bio-effect of therapeutic ultrasound, its frequency band is selected between 500-800kHz, where Thermal Index, that indicates an increase of tissue temperature, $TI = < 2$, and Mechanical Index (MI), that $MI = 1$ indicates threshold of possibility of causing cavitations in human body, equal to or less than 0.25. The equipment emits therapy and diagnostic beams alternately whose output level and intermittent duty ratio are controllable through modulation. The results of computer simulation and basic experimental data of therapy/diagnostic compound transducers, which are nearly equally work as separate transducers, are described. It is expected that the system lower the fatality rate of the stroke patients, improve the prognosis, and contribute to decrease health care cost.

Concept of Ultrasound Cerebral Infarction Therapy Equipment for Early Dissolution of Thrombus

Jun Kubota 1), Akira Sasaki 1), Makoto Ogihara 1), Takashi Azuma 2), Shin-ichiro Umemura 2), Hiroshi Furuhashi 3)

1) Hitachi Medical Corporation, Kashiwa, 2) Central Research Lab., Hitachi, Ltd., Kokubunji, 3) The Jikei University, Tokyo, all in Japan
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Abstract

We develop equipment for cerebral infarction therapy, which is comprised that ultrasound is illuminated on embolized part of a brain trans-cranially with injection of thrombolytic agent. Minimizing the thermal and mechanical bio-effect of therapeutic ultrasound, its frequency band is selected between 500-800kHz, where Thermal Index, that indicates an increase of tissue temperature, $TI < 2$, and Mechanical Index (MI), that $MI = 1$ indicates threshold of possibility of causing cavitations in human body, equal to or less than 0.25. The equipment emits therapy and diagnostic beams alternately whose output level and intermittent duty ratio are controllable through modulation. The results of computer simulation and basic experimental data of therapy/diagnostic compound transducers, which are nearly equally work as separate transducers, are described. It is expected that the system lower the fatality rate of the stroke patients, improve the prognosis, and contribute to decrease health care cost.

Cerebrovascular accident (CVA) is the third largest cause of death in Japan. Cerebral infarction (CI) dominates 70% of the CVA, and often leaves allopahsis or paralyses after the recovery, and might increase the number of elderly people who need nursing care. We develop equipment for CI therapy, that make up over 60% of cerebrovascular disorder, from which large number of people die every year, the next to cancer and cardiovascular disease. The equipment is comprised that ultrasound is illuminated on embolized part of a brain trans-cranially with injection of thrombolytic agent so that blood clot in cerebral artery should dissolve in early time from the injection, be rapidly recanalized, and relieve cerebral nerve system that is destructible from ischemia. To treat CI, it is the first choice to dissolve thrombi or emboli that is the principal cause in a few hours from sideration. It is said that the earliest disobliteration will promise good prognosis Furuhashi et al.[1][2] published in vitro and vivo experiment results. This study aims to develop a trans-cranial ultrasonic cerebral thrombolysis system to study usefulness of the technique clinically applicable for various disease pattern of CI explanatorily.

1. Introduction

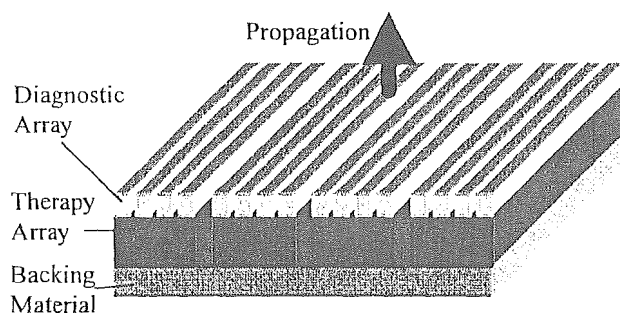


Fig.1 Structure of the Dual-frequency Transducer

2. System configuration

As a fundamental concept, we propose a monitoring to dissolution feedback therapy method, combining medication decrease and side-effect suppression. To realize it, therapy and diagnosis combination probe is needed, since the acoustic window apertures are restricted to two to three cm square in the cranial bone. Therapy transducer needs a large aperture to transmit 500 kHz beam to a limited region of infarction, and diagnostic transducer also needs a large aperture to acquire precise images with 2 MHz beam. Transmitting circuit drives the transducer to emit 500 kHz T-beam of less than 0.72 W/cm² in intensity, and 2 MHz D-beam of the same intensity level intermittently. The system also has a feature of two-dimensional deflection of the beam to confine the irradiating region. Fig.1 shows the configuration of the therapy-diagnostics laminated probe where the D-beam transducer is formed over the T-beam transducer held on a backing material.

2.1. Simulation

Fig.2 shows the simulation model of the complex transducer, which is made up of materials of the backing material, the therapy transducer (array), separating layer, diagnostic transducer (array), and two matching layers.

Both the D/T-laminated and D-beam single layer array vibrating system are simulated, using PZFlex piezo-mechanical finite element analysis code, driving single element of the array.

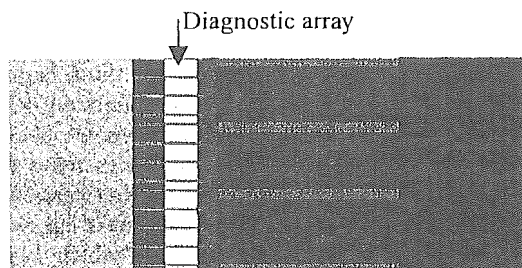


Fig.2 Piezo-acoustic analysis of the dual frequency transducer

2.2. Basic experiments

Normal single layer array works as Fig. 3, when a single element of the array is driven by a continuous wave of 2 MHz, where wave front from a common point source can be seen, as an instantaneous propagating mode of operation.

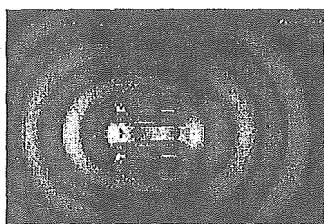


Fig.3 Simulated wave front emit from a single element of a single layer diagnostic transducer

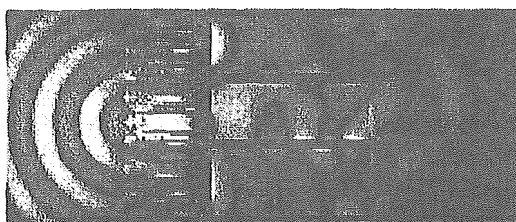


Fig.4 Simulated wave front emitted from a diagnostic element of the dual frequency transducer

The complex dual frequency array operates as Fig. 4 when a single element of the D-beam array is driven by cw of the same frequency. Wave front is different propagating in the backing direction, meanwhile it is almost the same as the single layer array when propagating in front.

On the other hand, the same array operates as Fig. 5, when a single element of the T-beam array is driven. While the limitation of irradiation angle from the point source is shown, when comparing the wave front propagating from front face and backing side, it suggests that it is possible to deflect T-beam to somewhat large angle direction from the front face.

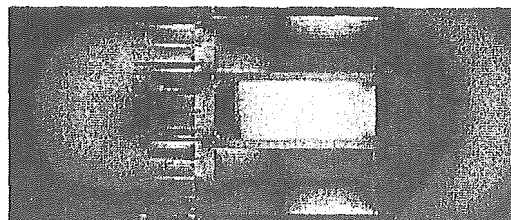


Fig.5 Simulated wave front emitted from a therapy single element of the dual frequency transducer

3. Results and discussion

T-beam propagation pattern through and in the cranial bone is observed in water with Schlieren technique although not shown here. Interference pattern is observed in the vicinity of the opposite concave reflection plane. That suggests the standing wave may build up, and could generate bubble via cavitation effect in the brain where Mechanical Index is as high as one regionally and stationary.

4. Conclusions

Therapy and diagnostic dual frequency multi layer ultrasound transducer is developed for Cerebral Infarction therapy by simultaneous use of trans-cranial ultrasound and thrombolysis agent, monitoring blood recanalization by TC color flow imaging. Preliminary experiments suggest that more sophisticated driving technique is needed than simple continuous wave.

5. Acknowledgements

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6. References

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