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Enhancement of Focal Ultrasonic Treatment by Microbubbles

マイクロ気泡による集束超音波治療の高効率化

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1. Enhancement of Ultrasonic Bioeffects by Microbubbles

Ultrasound has moderate tissue attenuation and absorption coefficients at a wavelength reasonably smaller than a human body for penetrating intervening tissues while maintaining the ability to focus energy into small volumes to be treated. This smallness of the focal spot is its great advantage in that it can provide a high geometrical selectivity and, at the same time, its serious disadvantage in that it can significantly slow down the the treatment. Some new approach is needed to significantly improve the throughput.

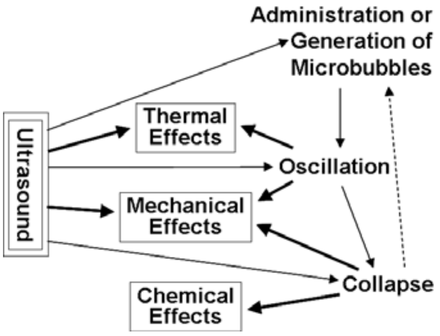

Fig. 1 Bioeffects of ultrasound and their enhancement by microbubbles.

Bioeffects of ultrasound, which can potentially be used for such a kind of treatment, are shown in Fig. 1. In the existence of microbubbles, the ultrasonic vibration amplitude is enhanced in their vicinity by orders of magnitude, and both mechanical and heating effects can be thereby accelerated. Furthermore, sonochemical effects can be induced when a microbubble collapses. In this paper, the acceleration of heating[1] is chosen as an example of such ultrasonic bioeffects enhanced by microbubbles.

2. Theoretical Prediction

Microbubbles, subjected to ultrasonic pressure at near their resonant frequency, convert a significant amount of acoustic energy to heat through their volume oscillation. This type of energy conversion has two mechanisms: viscous heating and a pressure-volume hysteresis loop. The acoustic power converted to heat by the former mechniasm, which is dominant at the therapeutic level of ultrasonic intensity, was calculated by numerically solving a modified Rayleigh-Plesset equation and plotted in Fig. 2. This result predicts that the ultrasonic absorption by tissue is enhanced by twice in the existence of approximately 8 microbubbles in 1 mm^3 of tissue[1].

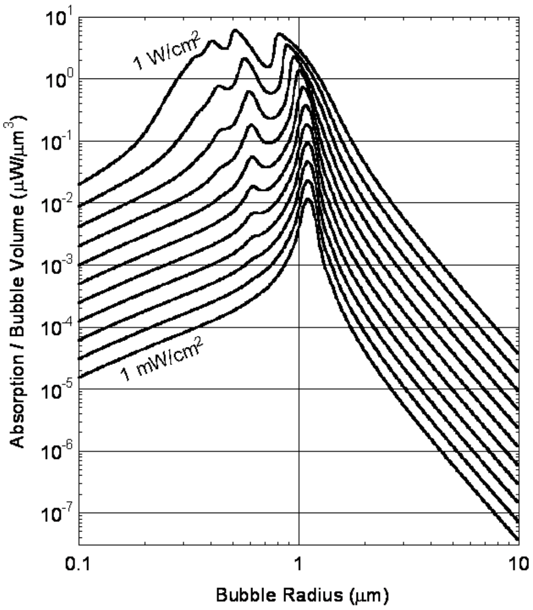

Fig. 2. Theoretically predicted ultrasonic abosorption by microbubble at 3 MHz. Ultrasonic intensity is varied as a parameter from 1 mW/cm^2 to 1 W/cm^2 in a geometric series.

3. *In Vivo* Enhancement by Encapsulated Microbubbles

In vivo experiments of ultrasonic heating enhanced by encapsulated microbubbles, Optison™ (Amersham Health), a suspension of microspheres of human serum albumin with perflutren, C_3F_8, were performed using a prototype dual element PZT transducer at 3.2 MHz (Fuji Ceramics) with a spherical curvature radius of 35 mm and an aperture of 40 mm × 20 mm, in combination with a small imaging probe at 6.5 MHz (EUP-F331, Hitachi Medical).

A 0.25-mm diameter, sheathed thermocouple (Sukegawa Electric) was inserted into the renal

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cortex kidney tissue of an anesthetized rat, at which ultrasound was focused. Optison (0.2 ml/kg) was systemically administered through a jugular vein.

The temperature change in the kidney due to three-time exposure at an ultrasonic intesnsity of 290 W/cm^2 for 10 s is plotted in Fig. 3. The temperature rise due to HIFU immediately after was higher than before the injection by 4-5 times[1].

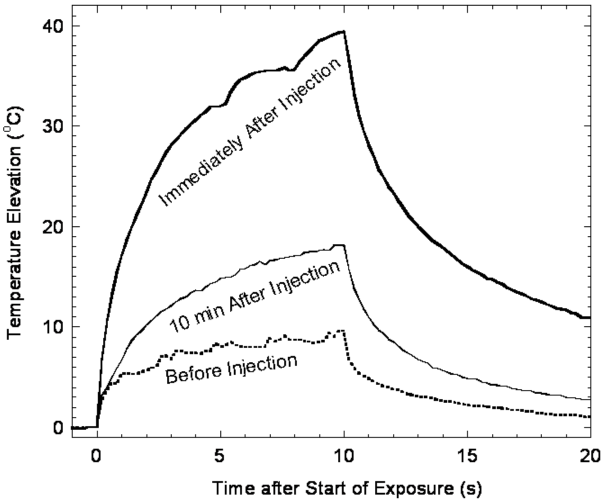

Fig. 3. Murine kidney tissue temperature with HIFU exposure at 290 W/cm^2 before and after intravenous injection of Optison (0.2 ml/kg).

Significant enhancement of ultrasonic tissue heating with a safe dose of a microbubble agent was demonstrated. However, microbubbles need be localized to the tissue to be treated because most of the ultrasonic energy will otherwise be attenuated before it reaches the target tissue.

4. Tissue-Selective Phase-Change Nano-Droplet

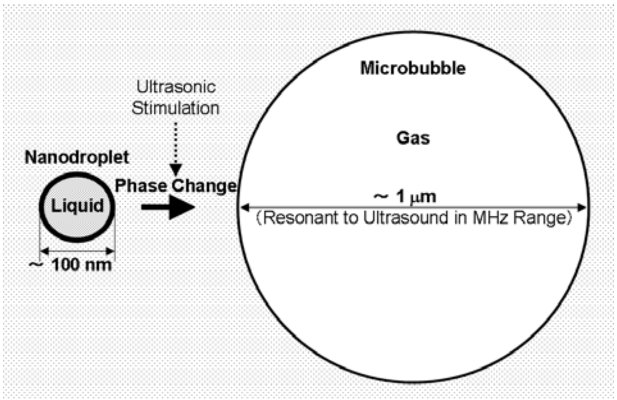

Fig. 4. Phase-change of nano-droplet to microbubble for tissue selective acceleration of ultrasonic heating.

The delivery of microbubbles to the target tissue as phase conversion nano-particles can satisfy this need. As schematically shown in Fig. 4, a liquid particle approximately 100 nm in radius, which has the EPR effect to accumulate in tumor tissues because of the size, can potentially be phase-changed to a gas bubble approximately 1 μm in radius, which efficiently absorbs ultrasonic energy in a MHz range also because of the size.

Nano-droplets, 170 nm in mean diameter, containing a mixture of perfluoro-n-pentane (n-PFP) and perfluoropentane, stabilized with dipalmitoylphosphatidylcholine coating, demonstrated phase-change by stimulation with an ultrasonic pulse at 1-10 W/cm^2 in the MHz range. The intensity threshold for phase-change decreased as the n-PFP concentration increased[2].

In this approach, the synergistic selectivelty between the molecular selectivity by the nano-droplets and the geometric selectivity by the ultrasonic focusing is expected. However, the approval process for clinical use will not be simple.

5. Generation of Microbubbles by Extremely High Intensity Focused Ultrasonic Pulses

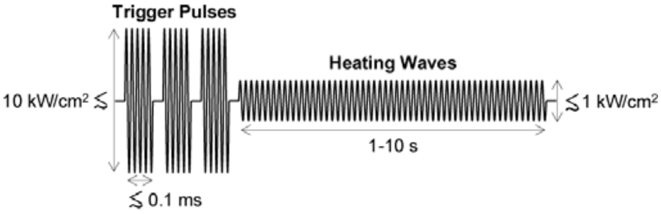

Fig. 5. Transmission sequence for enhancing ultrasonic heating by ultrasonically generated microbubbles.

The approval process will be much simpler if the microbubbles, enhancing the treatment, are generated in tissue solely by ultrasound. Focused ultrasound pulses at an extremely high intensity, higher than the order of 10 kW/cm^2, are needed for such a purpose. The shorter pulse length is better to keep the generated microbubbles localized. A typical transmission sequence is shown in Fig. 5. Significant acceleration in coagulation in excised chicken breast tissue as well as in polyacrylamide gels was demonstrated with focused array transducer at 1 MHz[3].

5. Conclusion

The enhancement of high-intensity focused ultrasound treatment by microbubbles has such a great potential that it is worthy of further study.

References

1. S. Umemura, K. Kawabata, K. Ssaki: IEEE Trans. UFFC **52** (2005) 1690.
2. K. Kawabata, N. Sugita, H. Yoshikawa, T. Azuma, S. Umemura: Jpn. J. Appl. Phys. **44** (2005) 4448.
3. Y. Inaba, S. Yoshizawa, S. Umemura: Jpn. J. Appl. Phys. **49** (2010) 07HF22.