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Review

The potential applications of high-intensity focused ultrasound (HIFU) in vascular neurosurgery

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ABSTRACT

This review assesses the feasibilty of high-intensity focused ultrasound (HIFU) in neurosurgical applications, specifically occlusion of intact blood vessels. Fourteen articles were examined. In summary, MRI was effective for HIFU guidance whereas MR angiography assessed vessel occlusion. Several studies noted immediate occlusion of blood vessels with HIFU. Long-term data, though scarce, indicated a trend of vessel recanalization and return to pre-treatment diameters. Effective parameters for extracranial vascular occlusion included intensity ranges of 1690–8800 W/cm^2, duration <15 seconds, and 0.68–3.3 MHz frequency. A threshold frequency-intensity product of 8250 MHz W/cm^2 was needed for vascular occlusion with a sensitivity of 70% and a specificity of 86%. Complications include skin burns, hemorrhage, and damage to surrounding structures. With evidence that HIFU can successfully occlude extracranial blood vessels, refinement in applications and demonstrable intracranial occlusion are needed.

1. Introduction

High-intensity focused ultrasound (HIFU) is gaining recognition as a minimally invasive technique for the treatment of liver cancer, benign prostatic hypertrophy, prostate cancer, bladder cancer, and benign and malignant lesions of the kidney and breast.[1] After Delon-Martin et al. successfully occluded femoral arteries and veins in rats with HIFU in 1995, attention turned to its use for vascular occlusion.[2]

To better define its role in vascular neurosurgery, including for obliteration of vascular malformations or devascularization of large tumors, our literature review summarizes use of HIFU for occlusion of noninjured blood vessels. Evidence is presented by topics relevant to neurovascular applications, including technique, imaging guidance, occlusion results, occlusion assessment, hemorrhage, and complications. We speculate how this technology might find application in vascular neurosurgery.

1.1. Principles of HIFU

Ultrasound is a pressure wave at a frequency above the threshold of human hearing (~20,000 Hz). It is produced by passing an electrical current through quartz or ceramic materials (such as, barium titanate, lead zirconate titanate) causing them to resonate; this resonance is referred to as the piezoelectric effect. Ultrasound waves can be targeted to produce an elliptical focus. The potential for medical use exists because this focusing allows precise delivery of energy and its harmless passage through intervening structures.

Most of the medically-relevant effects of ultrasound are associated with its thermal effects (Fig. 1). Ultrasonic heat generation depends on the intensity (W/cm^2), duration of exposure, extent of focusing, and attenuation (dB/cm/MHz) of the treated tissue. With the highest attenuation, bone can produce heat rapidly. The mechanical effects of ultrasound can apply pressure to the acoustic field and can result in streaming of fluids; these effects are less biologically relevant.

The phenomenon of cavitation associated with ultrasound describes the formation of gas bubbles within fluid after a threshold acoustic pressure is reached. These bubbles can cause either mechanical effects on surrounding tissues by their formation and collapse, or thermal effects as ultrasound absorption increases at that site. Ultrasound at intensities sufficient enough to cause cavitation causes more rapid heat production.

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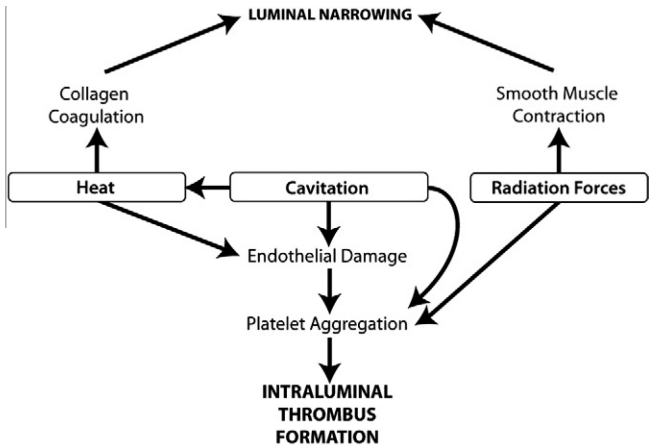

Fig. 1. Schematic of the mechanism of vessel occlusion with high-intensity focused ultrasound.

1.2. Mechanism of vascular occlusion

To identify the potential of HIFU in the treatment of vascular lesions, understanding the mechanisms of HIFU-induced vascular occlusion is essential. These mechanisms likely involve a combination of vessel constriction caused by the denaturization of collagen, intravascular coagulation initiated by endothelium disruption, and vessel contraction due to mechanical forces of ultrasound.

Collagen denaturation plays a pivotal role in vascular occlusion. Collagen, which constitutes 28% of arterial walls, begins to denature from 62 to 67 °C; denaturation involves a transition from a crystalline form to a gelatinous form seen histologically as the separation of connective tissues and loss of birefringence.[3]

In their 1994 study using an argon laser to induce hyperthermia of post-mortem human aortas, Agah et al. found that the rate process for thermal damage to arteries was similar to that of the denaturation of collagen.[3] With progressive temperature increases, the percentage of denatured collagen proportionately rose, coinciding with the increasing histological disruption of the vessel. The authors concluded that collagen denaturation was the primary mechanism of thermal damage to arteries.[3] This mechanism was supported by the HIFU studies by Fujiwara et al. showing arterial occlusion at peak temperatures reaching 97 °C but not at temperatures between 46 and 48 °C.[4]

Intraluminal thrombosis induced by HIFU, which was first observed by Delon-Martin et al., occurred adherent to the treated portion of the vessel that extended throughout the lumen in varying lengths.[2] The authors concluded that thrombus adherence was possibly caused by disruption of the endothelial lining that then led to platelet activation by collagen exposure. This cascading effect was further supported with *in vitro* studies by Poliachik et al. who demonstrated platelet activation and aggregation by HIFU at intensities that cause cavitation.[5] They attributed the mechanism of platelet activation to the mechanical shearing from the HIFU-induced cavitation or acoustic streaming.

Providing additional insight into the mechanism of arterial constriction, Ishikawa applied HIFU to an artery at four different intensities.[6] They measured vessel constriction by monitoring peak systolic velocities (PSV); these velocities showed no statistically significant increase at the lowest intensity but did increase at 1080 W/cm.[2] However, peak temperatures (54.3 °C) in these arteries were less than that required for collagen denaturation; histological examination subsequently revealed no changes in the arterial walls. The author observed no evidence of vacuolar degeneration and found the elastic fibers of the tunica media were intact. With no evidence of collagen coagulation, they then concluded that vessel contraction can also occur due to the mechanical effects of HIFU.[7]

In summary, two events lead to vessel occlusion after HIFU application. First, narrowing of the lumen is achieved by thermal-induced coagulation of collagen in the vessel wall and by mechanical forces that cause smooth muscle contraction. Second, intraluminal thrombosis is initiated by endothelial damage.

2. Literature review

Searching PubMed in August 2009 with no date or language restrictions, we used the terms *focused ultrasound* or *HIFU* linked to *arterial, artery, venous, vein, vessel, vascular,* or *occlusion*. Among 177 articles (including references) reviewed, we identified 14 papers that evaluated the effects of focused ultrasound on noninjured blood vessels.

3. Guidance of HIFU

Precise imaging is essential to guide the intracranial application of HIFU. If exposed to high temperatures, delicate neural structures surrounding target vessels will be damaged with disastrous consequences. Of 14 studies on vessel occlusion with HIFU, six used ultrasound for guidance, three used visual inspection, three did not report their method, and two used MRI.

Ultrasound has proven effective for extracranial guidance because it passes freely through soft tissues whereas its attenuation by the skull impedes its precise targeting of intracranial blood vessels. However, MRI is not so impeded by the skull and can delineate small deep brain structures that may surround target vessels. Obviously treatment planning to avoid damage to eloquent areas is invaluable and, for these reasons, MRI appears most suitable for guiding HIFU.

The most clinically applicable MRI system, developed by Hynynen et al., includes a temperature-sensitive MRI scan to direct HIFU, giving instant feedback about the temperature of the target tissue.[8] While initially emitting a low-intensity test sonication in a remote location, the authors then attuned the elevated temperature at this site to the focus of the transducer before delivering therapeutic sonications. This system seems ideal in preventing complications because the operator can monitor surrounding structures for deleterious rises in temperature.

4. Evidence of arterial occlusion

After Delon-Martin et al. first documented vascular occlusion with HIFU,[7] others then documented its effects on intact blood vessels.[4,6–18] After surgically exposing the femoral veins of six rats, Delon-Martin repeatedly applied low-dose sonications to the veins until occlusion was seen and also demonstrated occlusion of two femoral arteries. This study demonstrated that small veins (<2 mm diameter) and arteries could be temporarily occluded.

We identified 14 studies in which successful occlusion was achieved in small diameter arteries (range 0.5–1.0 mm) and veins (range 1.0–1.5 mm) (Table 1). However, intracranial AVMs have larger diameters and thus higher flow rates. Increased flow rates cause heat loss by convection, which prevents the temperature elevation of the vessel wall to that amenable to vessel coagulation. This effect of blood flow acting as an energy sink has been described while applying HIFU to tumors and may pose a problem when applying HIFU to large vessels.[19]

Although HIFU was applied to larger diameter vessels by Yang et al., occlusion of such arteries has yet to be demonstrated.[18] Specifically, they described HIFU effects using a rabbit aorta and inferior vena cava; diameter of the inferior vena cava exceeded 10 mm