LIVER HEMOSTASIS USING HIGH-INTENSITY FOCUSED ULTRASOUND

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Abstract—Liver hemorrhage, the major cause of death in hepatic trauma, is notoriously difficult to control. We report on the use of high-intensity focused ultrasound (HIFU) to arrest the bleeding from incisions made in rabbit livers. A HIFU transducer, with a spherically curved aperture of 6.34 cm² area, a focal length of 4 cm and a frequency of 3.3 MHz was used. In approximately 94% of the incisions, the hemorrhage was reduced to a slow ooze of blood in less than 2 min. The maximum temperature of liver tissue around the incision area, during HIFU application, was measured to be 86°C. The mechanism of hemostasis, confirmed by histological examination, appears to be coagulative necrosis of a volume of liver tissue around the incision. We believe that acoustic hemostasis, with the unique characteristic of “volume cauterization”, offers a novel method for the management of liver hemorrhage and, thus, has major clinical implications. © 1997 World Federation for Ultrasound in Medicine & Biology.

Key Words: Ultrasound, HIFU, Liver, Trauma, Surgery, Temperature, Coagulative necrosis, Rabbit, Hemorrhage, Acoustic hemostasis.

INTRODUCTION

Uncontrolled hemorrhage of the liver is the primary cause of death in hepatic trauma, with a mortality rate of 10-15% (Beal 1996). Major blood loss resulting in complicating hemorrhagic shock often occurs prior to the patient’s arrival at surgery. After arrival, the surgeon faces a major challenge in arresting severe bleeding due to several factors. First, the liver is the largest internal organ in the body, by weight, consisting on average of 2.7% of the total adult body weight, about 1500 g (Snyder et al. 1975). Second, the liver is highly vascularized, with an average blood flow of about 100 mL/100 mg/min, or about 25% of the resting cardiac output (Rowell 1986). Third, the liver is soft and bears easily, with the ultimate tensile strength of 2.4 g/mm² and the ultimate percentage of elongation of 46%. In perspective, these values are 22% and 72% less than those of the cardiac muscle, respectively (Yamada 1973). As a consequence of these factors, arresting rapid liver hemorrhage or even slow ooze of blood with conventional methods is a time-consuming and difficult task. In addition, liver is particularly susceptible to injury in trauma. The large mass undergoes high deceleration forces on impact (e.g., car accidents) and, because of its low tensile strength, the liver ruptures easily under such stress. Also, the large surface profile of the liver gives it a high probability of being struck by penetrating objects (e.g., gun shots). Consequently, hepatic injury occurs in 30% of penetrating and 15-20% of blunt abdominal trauma (Beitsch 1994). Clearly, better and more rapid ways of treating patients after a traumatic hepatic injury are needed in both civilian and military environments, where rapid assessment and stabilizing treatment is imperative if decreases in morbidity and mortality are to be realized.

We have been interested in the possibility of using high-intensity focused ultrasound (HIFU) to arrest liver hemorrhage. The therapeutic use of focused ultrasound was first proposed in the 1940s (Lynn et al. 1943) and then pursued by Fry and colleagues starting in the 1950s (WJ Fry et al. 1954; WJ Fry et al. 1955). The research...
was aimed at applying focused ultrasound from outside the body to attack tumors deep within the brain without destroying intervening tissue (Barnard et al. 1956). Since this early work, investigation of noninvasive acoustic surgery has continued, as reviewed by a number of authors (FJ Fry 1993; Hill and ter Haar 1995; Sanghvi and Hawes 1994; Crum and Hynynen 1996; Holm and Skjoldbye 1996). Specifically, the use of HIFU to treat liver cancer and benign prostatic hypertrophy has been studied (ter Haar 1995; Gelet et al. 1993; Yang et al. 1992; Damianou and Hynynen 1994; Pratt et al. 1995; Fan and Hynynen, 1996a,b). Currently, we are aware of clinical trials in several countries, including England, for treating liver cancer (Hill and ter Haar 1995), and Japan and Austria for treating benign prostatic hypertrophy (Uchida et al. 1995; Madersbacher et al. 1993). In regard to applications in treating liver and prostate diseases, the vision of acoustic surgery, born earlier this century, is at the forefront of clinical practice.

A characteristic of the acoustic lesions created by HIFU in livers is that they are effectively self-cauterized. Lesion tissue shows coagulative necrosis, with little or no flow of blood from the healthy normal region to the affected tissue (Chen et al. 1993; ter Haar and Robertson 1993). This result suggests the use of focused ultrasound for cauterizing. Three published papers have described the successful use of HIFU to occlude blood flow in intact arteries in vivo (Delon-Martin et al. 1995; Hynynen et al. 1996a,b). However, there is no documented successful application of HIFU to cauterize a bleeding fresh wound.

We became interested in using ultrasound to produce hemostasis in the hope that such methods would ultimately provide a lifesaving treatment during the so-called "golden hour," a brief grace period after a severe injury in which proper therapy can save the life of the injured. An acoustic hemostasis method, capable of extending the incision and treatment processes were repeated. The site to be treated. The targeting and duration of exposure was controlled while visually monitoring the results. Two time-points in the experiment were measured: 1. The time for reducing the profuse bleeding to a slow oozing of blood was defined as the major hemostasis time; 2. The time for arresting the bleeding entirely was defined as the complete hemostasis time. In most experiments, after hemostasis was achieved at one incision site, another lobe of the liver was exposed and the incision and treatment processes were repeated. The depth and length of the incisions were measured after the HIFU treatment.

A total of 27 incisions and HIFU treatments were conducted in the animals. Control incisions were made in 4 instances, in 4 different rabbits. The 4 control incisions were allowed to bleed for 2, 3, 4 and 10 min. after which

**METHOD**

The HIFU transducer had an aperture of 6.34 cm² that was spherically curved to produce a focus at 4 cm. It was operated at 3.3 MHz, continuous mode, producing an acoustic power of 65 watts, measured with an absorber-type radiation force balance (Sonic Concepts, Woodinville, WA). This power was produced by apply-
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Fig. 1. The sequence of the experiment: (a) The incision and its profuse bleeding; (b) the HIFU transducer in action; and (c) the arrest of hemorrhage and completion of the HIFU treatment.

HIFU was applied to arrest the hemorrhage, except in the last case. In the last case, the animal was euthanized at the 10-min time-point, and the untreated liver incision region was used for histological examination. Representative tissue samples were obtained from treated and untreated regions for histological examination. The samples were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin.

Thermal measurements were performed in the HIFU treatment of 14 incisions, made in the livers of 2 rabbits. A Chromega/Constantan thermocouple with 0.005-inch diameter wires was used for temperature measurements. The linear response of the thermocouple was verified in a water bath from 30°C to 100°C. The response times were determined by rapid immersion in 80°C and 0°C water (i.e., temperature elevation and drop from the room temperature, 25°C). The response times, defined as the time between the immersion and the plateau of the final temperature, were 50 ms and 100 ms for the temperature elevation and drop, respectively. These response times are much faster than all of thermal responses to treatment recorded in the liver. The thermocouple was inserted in the liver parallel to the surface, so that the thermal junction was approximately 5 mm deep. The position of the thermocouple was fixed using superficial sutures in the liver and the skin. An incision was made at a distance of 1–2 mm from the junction of the thermocouple, and HIFU was applied to stop the bleeding. The thermal measurements continued for the duration of the HIFU treatment.

All animals were alive at the end of experiment, when they were euthanized with an overdose of the same anesthetic mixture, followed by a 2-mL KCl saturated solution within 2 min.

RESULTS

Figure 1 shows the sequence of the acoustic hemostasis experiment. Profuse bleeding of the liver in the water tank occurred immediately after the incision was made (Fig. 1a). The intense acoustic field induced acoustic streaming in the water surrounding the incision area (Fig. 1b). The streaming often moved the blood away from the bleeding site, thus permitting a clear visualization of the area to be treated. The HIFU treatment was stopped when the hemorrhage was completely arrested (Fig. 1c). The treatment produced a discoloration of the tissue around the incision from its natural maroon to a gray-tan color, appearing necrotic or "cooked". The mean ± standard deviations of the length and depth of the incisions were 16.1 ± 4.87 mm and 4.2 ± 1.94 mm, respectively.

Bleeding from surface capillaries (< 0.5 mm in diameter) of the incision was arrested almost immediately (a few s) after the application of HIFU. More time was required to stop the bleeding from larger vessels (0.5–2.5 mm in diameter) in the incision. In approximately 94% of the incisions, major hemostasis was achieved in a time less than or equal to 2 min of continuous application of HIFU (Fig. 2). The average ± stan-
The standard deviation of the major hemostasis time was $1.4 \pm 0.69$ min. We found that, in 7 cases, after achieving major hemostasis additional application of HIFU was necessary for complete hemostasis. The additional HIFU application appeared to be required by those incisions that included a large cut vessel (i.e., larger than 2.5 mm in diameter). In approximately 80% of the incisions, complete hemostasis was achieved in a time less than or equal to 3 min of continuous HIFU application (Fig. 3).

Figure 4 shows a representative plot of temperature vs. time in an incision during HIFU application to stop the bleeding. The plot shows 3 major temperature elevations, each followed by a cooling period. Each peak occurred when the HIFU focal point passed by the thermocouple. The maximum temperature was reached within 1–2 s of HIFU application. The range of the maximum temperature elevation, in 14 thermal measurements, was 59–86°C. The range of the cooling time from the peak temperature to the baseline of 40°C was 40–60 s.

Figure 5 is a photograph of the liver sample used for histological examination. Region 1, from a control incision made 10 min before euthanasia, was used as a normal liver sample, and region 2, from a HIFU-treated incision, was used as a treated liver sample. On light microscopic examination, the untreated liver exhibited normal architecture with no evidence of cell injury or necrosis (Fig. 6A). The HIFU-treated region was non-uniform in appearance (Fig. 6B). There were scattered, well-demarcated zones of coagulative necrosis, alternating with small foci of cavitation and tissues containing only minimal histologic alteration. The zones of coagulative necrosis had distorted hepatic architecture with detachment of individual hepatocytes, although the cytoplasmic borders were preserved (Fig. 6C). The nuclei were dark and condensed (i.e., pyknotic), indicative of coagulative necrosis, and the cytoplasm was deeply stained. Portal tracts were similarly affected by the ther-
Fig. 6. Photographs of histological sections (magnification bars equal 200 (μm): A. Untreated liver, showing intact architecture and no evidence of necrosis. A portal tract in the center of the field shows normal architecture of vein, artery, and the bile duct. B. treated liver showing coagulative necrosis (left half of field, arrows) with disruption of hepatic architecture, detachment of individual hepatocytes, and smudged, pyknotic nuclei. Also seen are foci of cavitation that contain erythrocytes (arrowhead 1) or are empty (arrowhead 2). C. coagulative necrosis in the treated liver involving a portal tract (center of the field) and adjacent hepatocytes; D. liver tissue adjacent to the HIFU-treated region, showing intact architecture with sinusoidal congestion (arrowheads). A central vein is in the center of the field (arrow).

Discussion

The mechanism of acoustic hemostasis appears to be coagulative necrosis due to an elevation in the temperature of the liver tissue in the focal region of HIFU. The coagulative necrosis appeared to cause a collapse of blood vessels (sinusoids and vessels up to 2 mm in diameter), leading to hemostasis. Our thermal results show clearly that HIFU produces a temperature elevation in tissue, confirming the well-documented thermal effect of HIFU (FJ Fry 1993; ter Haar 1995; Lele 1977). The histological results also confirm that the HIFU treatment of the liver was predominantly due to thermal injury, as evidenced by the presence of coagulative necrosis. These findings are comparable to those of the other investiga-
Fig. 7. Photographs of histological sections showing vessel walls (delineated by arrowheads) in the normal and treated liver (magnifications bars equal 100 μm). A. The wall of a normal larger portal vein branch; B. normal central vein; C. the wall of a HIFU-treated portal vein branch. The cells of the tunica media are discohesive and have pyknotic nuclei; D. a central vein in the HIFU-treated region, displaying coagulative necrosis of the vessel wall and the surrounding hepatocytes.

tors (Yang et al. 1992; Sibille et al. 1993; Susani et al. 1993), and are similar to the histological changes seen with other types of thermal injury, such as electrocautery. These results suggest that HIFU-induced hemostasis may be applicable when the normal hemostatic mechanisms are either too slow (major liver trauma or during liver resection) or are not functioning properly due to platelet or coagulation factor deficiencies.

The in vivo measurements of the thermal behavior of the liver tissue as a function of HIFU treatment provided several interesting observations. First, the HIFU beam had to be very close to the thermocouple (1–2 mm) to obtain a thermal response. The temperature elevation at the focus seemed to be highly localized, and to dissipate rapidly spatially. This effect may have been due, in part, to the water around the liver, although we have observed a similar effect in recent studies where water did not surround the liver. The thermocouple was located well within the coagulated region by the end of a treatment period, representing a sampling of a point in the tissue that would undergo acoustic hemostasis. The maximum measured temperature during HIFU was found to be 86°C. We believe that this temperature represents the temperature of the liver tissue when the HIFU beam was at or very near the focus, for 1–2 s exposure. Peak temperature recordings below 86°C may have been due to a larger distance between the focus and the thermocouple. There are a number of other factors for consideration (Malcolm and ter Har, 1996), including the relationship between the temperature elevations and the acoustic absorption, the applied intensity at the site, the specific heat of the tissue, and the rate of heat dissipation in tissue and as a result of blood perfusion. After coagulative necrosis starts, all of the above parameters may change, and affect the cooling times observed. Also, the cooling time may vary depending on whether or not the HIFU beam was still in a close distance to the thermocouple, treating adjacent bleeding tissue. Further studies will be needed in the future to elucidate all the thermal
variables involved with in vivo HIFU treatment of the liver.

Although thermal injury appears to be the mechanism responsible for acoustic hemostasis, a mechanical effect of HIFU must also be considered. The mechanical effect of HIFU usually stems from acoustically-induced cavitation activity. Cavitation results from the generation of vapor and gas-filled voids during the negative portions of the acoustic pressure field. The collapse of these voids during the subsequent positive portions of the field can result in enormous concentrations of energy. The intensity threshold for cavitation in excised liver, at 3 MHz, has been reported to be 1300 W/cm² (Chan and Frizzell, 1977), below our estimated spatial peak intensity of 3000 W/cm² at the focus. Except in certain restricted cases (FJ Fry et al. 1995; Crum and Hynynen 1996), excessive cavitation is to be avoided in the use of HIFU for therapeutic applications. At this stage, we are uncertain of the role of cavitation in acoustic hemostasis, and whether its presence is desirable or undesirable.

In the course of HIFU treatment, and as a result of hand movement and deep focusing for optimal hemostasis, the acoustic beam was sometimes focused in tissues underlying the liver, consisting of bowels, skin, and stomach. The HIFU produced a thermal effect (slight discoloration) in the underlying tissues. The effect appeared to be minimal, because the beam had traveled through a layer of liver, to reach the underlying tissue with a reduced intensity. We are currently investigating methods to absorb the acoustic beam as it leaves the other side of the liver to prevent any damage to the underlying tissue. Also, a careful investigation of the side effects and precise, controlled application of HIFU is required (Sibille et al. 1993; Chapelon et al. 1990; Watkin et al. 1996).

We used an approach, in applying HIFU, that consisted of focusing the ultrasound deep in the tissue that is adjacent to the bleeding site and, thus, inducing hemostasis over an extended volume. This is in contrast to conventional cauterization techniques where cauterization is effective just at the surface, usually resulting in concomitant damage of the tissue surface (Tranberg et al. 1986). We believe that "volume cauterization" is the key to our success in this application and is unique to acoustic hemostasis.

SUMMARY

We used HIFU to produce hemostasis in surgical incisions made in rabbit livers. The transducer was spherically curved, with an aperture of 6.34 cm², and a focal length of 4 cm. It was operated at 3.3 MHz, producing a spatial average intensity of about 3000 W/cm². The average time of major hemostasis was 1.4 min.

In more than 80% of the incisions, complete hemostasis was achieved in 3 min or less. The mechanism of hemostasis appears to be coagulative necrosis of the liver tissue. Thermal measurements and histological results confirmed the coagulative necrosis of the treated tissue due to thermal effects of HIFU. The acoustic hemostasis may have significant clinical implications for both trauma and elective liver surgeries.

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