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Resection of Abdominal Solid Organs Using High-Intensity Focused Ultrasound

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Abstract

Our objective was to evaluate high-intensity focused ultrasound (HIFU) for minimizing blood loss during surgery by hemodynamically isolating large portions of solid organs before their resection. A high-power HIFU device (*in-situ* intensity of 9000 W/cm², frequency of 3.3 MHz) was used to produce a wall of cautery for sealing of blood vessels along the resection line in surgically-exposed solid organs (liver lobes, spleen and kidneys) of eight adult pigs. Following HIFU application, the distal portion of the organ was excised using a scalpel. If any blood vessels were still bleeding, additional HIFU application was used to stop the bleeding. The resection was achieved in 6.0 ± 1.5 min (liver), 3.6 ± 1.1 min (spleen) and 2.8 ± 0.6 min (kidneys) of HIFU treatment time, with no occurrence of bleeding for up to 4 hours (until sacrifice). The coagulated region at the resection line had average width of 3 cm and extended through the whole thickness of the organ (up to 4 cm). Blood vessels of up to 1 cm in size were occluded. This method holds promise for future clinical applications in resection of solid tumors and hemorrhage control from high-grade organ injuries.

Keywords

High-Intensity Focused Ultrasound; Solid Organ Resection; Hemorrhage Control

Introduction

Significant bleeding during resection of solid organs remains a problem in many patients (Fortner and Blumgart 2001), leading to an increased risk of postoperative complications (Sitzmann and Greene 1994; Weber et al. 2002). Conventional resection techniques consist of a combination of vessel ligation and electrocautery. Adjunctive techniques developed recently include energy-based methods such as microwave coagulation (Satoi et al. 2005), ultrasonic scalpel (Kim et al. 2003; Lee and Park 1999) and radio-frequency ablation (Poon et al. 2005; Weber et al. 2002). In these methods, coagulation necrosis is produced along the resection line, before the part of the organ is excised. The main disadvantage of currently-available energy-based methods is their inability to occlude large blood vessels (diameter of 5 mm or larger). For example, ultrasonic scalpel cannot occlude blood vessels larger than 3 mm in diameter (Lee and Park 1999), while RF ablation cannot occlude vessels larger than 4 mm in diameter

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(Poon et al. 2005). Therefore, large blood vessels usually have to be surgically ligated (Kamiyama et al. 2005; Poon et al. 2005), which can slow down the resection procedure. In the work reported here, our objective was to explore whether high-intensity focused ultrasound (HIFU) can be used as a fast preclotting method for bloodless resection of solid organs, with the ability to occlude blood vessels larger than 5 mm in diameter.

HIFU is based on a localized delivery of a large amount of acoustic energy to a site of interest (e.g., tumor or organ laceration), resulting in coagulation necrosis of tissues and sealing of blood vessels (Vaezy et al. 1999; Yang et al. 1991). HIFU therapy has been shown to be effective in hemostasis of injuries in liver (Cornejo et al. 2004), spleen (Noble et al. 2002) and peripheral blood vessels (Vaezy et al. 1998) in animal studies. However, until now, the application of HIFU for resection of abdominal solid organs (Martin et al. 1998) was impeded by the inability of HIFU devices to deliver large enough energy to occlude blood vessels greater than 3 mm in diameter (Cornejo et al. 2004).

We recently developed high-power (500 W) HIFU devices that are capable of sealing of large blood vessels (up to 1 cm in diameter) and explored whether these devices can be used for resection of abdominal solid organs. A preliminary feasibility study in a pig model, reported here, was performed to determine whether HIFU could provide a method for resection of liver lobes, spleen and kidneys.

Materials and Methods

The animals, domestic pigs weighing 40 – 50 kg, were initially anesthetized with ketamine (35 mg/kg) and xylazine (5 mg/kg) by intramuscular injection. The animals were then intubated and ventilated with oxygen and isoflurane. All procedures were conducted in accordance with the guidelines of the National Institutes of Health for use of laboratory animals with the approval of the University of Washington Institute of Animal Care and Use Committee. Preliminary experiments were performed in livers of three pigs to produce individual lesions with a high-power HIFU device. The high-power HIFU was subsequently used for resection of solid organs in eight pigs: 16 liver lobes (six - left lateral, five - left medial, four - right medial and one - caudate lobe), eight spleens (four distal and four proximal resections) and eight lower poles of the kidney. Pringle maneuver (i.e., compression of the extrahepatic portal vein and hepatic artery) was performed before three (out of 16) liver lobe resections during the HIFU application, to assess the effect of reduced blood flow into the liver on the treatment outcome.

Preliminary experiments were performed to assess HIFU treatment times needed to produce full-thickness individual lesions in the liver in-vivo. Ten lesions were produced. HIFU application times were 30 s or 60 s, depending on the liver thickness.

In the subsequent solid organ resection experiments, Color Doppler ultrasound (L10-5 imaging probe, HDI 1000, Philips, Bothell, WA, USA) was used to observe blood vessels before and after HIFU treatment. During the HIFU treatment, a reflector (polystyrene insulation foam, 18 cm × 9 cm × 2.4 cm, Foamular 250, Owens Corning, Toledo, OH, USA) was placed at the posterior surface of the organ (Fig. 1), to allow compression of the organ between the reflector and HIFU device. Compression was performed to reduce or stop blood flow in the organ blood vessels and minimize heat-sink action of blood, thus facilitating formation of HIFU lesions and vessel occlusion. The foam reflector also served to increase the delivered acoustic power at the treatment site by reflecting ultrasound energy back to the solid organ (Murat et al. 2004; Lafon et al. 2007).

HIFU treatment times for full-thickness lesions were 30 s or 60 s as determined in the preliminary experiments. Spacing between the treatment spots and total number of treatments

for producing a contiguous wall of cautery was judged by the operator, based on tissue discoloration due to necrosis and color Doppler inspection. HIFU transducer was moved manually between the treatments. After producing a necrotic wall, distal portion of the organ was excised. If any of the blood vessels were oozing or bleeding after the resection, additional treatment using a solid cone HIFU device (Martin et al. 2003) was applied to seal the vessels. A flow chart of the treatment procedure is shown in Fig. 2. The resected organs were monitored for rebleeding until sacrifice (1–4 h after the treatment). Dimensions of necrotic regions and occluded blood vessels were measured at necropsy.

A 500-W single channel electronic system, consisting of a custom-made driving unit (IC-706MKIIG transceivers, ICOM, Osaka, Japan) and a high-power amplifier (Ameritron, ALS-500 M, Starkville, MS, USA), was developed and used to drive the HIFU transducer (Sonic Concepts, Bothell, WA, USA), which had a diameter of 7 cm, focal length of 6 cm and operating frequency of 3.3 MHz. This HIFU transducer was chosen due to its availability in our laboratory and ability to sustain high input electrical powers. The transducer coupling to the tissue and cooling was achieved via inflatable water pillow (~ 3.5 cm thick) (Fig. 1), connected to a circulation pump with in-line degassing. The water pillow coupling, which was recently developed in our laboratory, allowed continuous application of high powers for several minutes without damaging the transducer. The pillows were custom-made from 0.05–0.07 mm thick polyurethane films, had approximately the same size as the transducer surface and became inflated with water circulation. Tubing inserted into the pillow allowed degassed water to be pumped through the pillow at a rate of 200 mL/min and remove heat from the transducer surface. A thin layer of mineral oil was placed between the pillow surface and HIFU transducer to provide good acoustic coupling and prevent formation of air pockets which could lead to transducer damage.

The acoustic pressure field map was obtained using a needle hydrophone (TNU001A, NTR Systems, Seattle, WA, USA) and used to measure the width (0.4 mm) and length (3 mm) of the HIFU focus (from the –3 dB contours). The electrical power used during our experiments was 380 W, which was the maximal power that the power amplifier could deliver for 60 s without going into an overheat mode. The corresponding acoustic power was 228 W (transducer efficiency of 60 %). The acoustic power was measured by using a reflective radiation force balance (UPM-DT-10, Omhic Instruments, Easton, MD, USA). The free-field ultrasound intensity was obtained by dividing the acoustic power with the focal area. This intensity was derated with the tissue attenuation coefficient (of 0.15 Np/cm/MHz (Christensen 1988)) to obtain *in-situ* intensity of 9000 W/cm². The solid cone HIFU device, used in additional treatments after organ resection, consisted of a 5.5 MHz transducer, equipped with a custom-made solid titanium conical applicator (Martin et al. 2003). The focus of this device was at 10 mm from the tip of the applicator, with *in-situ* intensity of approximately 3500 W/cm².

Results

Our preliminary experiments showed that 30 s treatments were sufficiently long to produce full thickness lesions in the liver regions that were 1–2 cm thick, while 60 s treatments could produce full thickness lesions in the regions that were 2–4 cm thick. The liver lesions had diameter of 2.8 ± 0.3 cm and length of 3.7 ± 0.3 cm, after 60 s of treatment. Occluded large blood vessels (>3 mm in diameter) were observed inside the lesions, indicating that it may be feasible to use high-power HIFU for resection of large solid organs.

Figure 3 shows a sequence of ultrasound scans along a HIFU-treated liver lobe, starting in the proximal region with respect to the HIFU wall of cautery and ending in the distal region. Patent blood vessels (arrows, Fig. 3) can be seen in the proximal region (S1, Fig. 3). At the site of

HIFU treatment (S2, Fig. 3), a hyperechoic region can be observed, indicating a necrotic lesion (Yuen 2001). In the distal region (S3, Fig. 3), no patent blood vessels were usually observed.

In resection experiments, multiple treatments were performed to form overlapping HIFU lesions along the resection line. The resection line was located at 12–13 cm from the tip of the lobe (Fig. 4a), where the lobes were 3 ± 1 cm thick. The resection was achieved in 287 ± 54 s of high-power HIFU application (Table 1). With Pringle maneuver applied, the high-power HIFU application times were 252 ± 18 s (three lobes treated). In 14 of 16 treatments, additional application of a solid cone HIFU device for 133 ± 55 s was needed to seal remaining bleeding blood vessels. Table 2 shows the number of vessels that were still bleeding after resection as a function of the lobe size and HIFU application time. The size of occluded blood vessels (measured at necropsy) was 5 ± 2 mm (average $\pm$ standard deviation), with the maximum size of 1 cm. The width of the necrotic liver region was 3.3 ± 0.5 cm (Fig 4b and 4c). No bleeding from the resected regions (Fig. 4d) was observed for up to 4 hours (until sacrifice).

Figure 5a shows the positions of the distal and proximal resection lines in the spleen, at 12–15 cm and 27–30 cm from the tip of the spleen, respectively. The thickness of the spleen was 1–1.5 cm. The resection was achieved in 208 ± 63 s of high-power HIFU application (Table 1). The size of occluded vessels was 2.8 ± 1.7 mm, with splenic artery being 2–2.5 mm and splenic vein being 4–5 mm. One or two vessels were still oozing after proximal resections and were sealed using a solid cone HIFU device for 40 ± 4 s (Table 1). The width of the necrotic region was 2.5 cm on average (Fig. 5b and 5c). Figure 5d shows a dry wound, with no bleeding from the resected proximal region of the spleen.

Lower poles of the kidneys were removed after 162 ± 29 s of high-power HIFU application. In one kidney, additional application of a solid cone device was needed for 60 s to seal residual bleeding from the renal artery. The thickness of the kidney at the place of resection was 2.5 cm. The width of the necrotic region was 2.6 ± 0.5 cm (arrow, Fig. 6a). The size of the occluded vessels was 2.8 ± 1.7 mm. No bleeding was observed after the treatment (Fig. 6b).

Figure 7 shows sealed blood vessels in the HIFU-treated regions of different solid organs. Gross appearance of vessels inside the HIFU-treated liver is shown in Fig. 7a. Liver vessels were sealed with a plug consisting of coagulated blood, as observed under light microscopy (Fig. 7b). An artery and vein in the HIFU-treated region of the spleen are shown in Fig. 7c and Fig. 7d, respectively. The opposite sides of the vessel walls of the artery (of less than 0.2 mm in size) appeared to adhere to each other (arrow, Fig. 7c). The vein was occluded with coagulated blood (arrow, Fig. 7d). Figure 7e shows an example of a sealed artery in the HIFU-treated region of the kidney. This artery was also sealed with coagulated blood.

Discussion

Our results show that HIFU can be used to minimize blood loss during surgery, by producing a wall of cautery before the removal of a part of highly-vascularized solid organ. Occlusion of large blood vessels (> 5 mm) usually presents a considerable challenge for currently-used cauterization methods (Harold et al. 2003; Kamiyama et al. 2005), since high blood flow rates convect away the deposited thermal energy and large elastic forces of the vessel wall keep these vessels open. However, in our current study, HIFU was shown capable to seal blood vessels of up to 1 cm in size, at various depths inside a solid organ. Our hypothesis is that the occlusion of large blood vessels was achieved by both depositing large acoustic power and collapsing the vessel walls (by compression) to counteract the heat-sink action of blood flow.

In our previous in-vivo studies, immediate clamping/compression of the liver, using a padded surgical clamp, was used as a method to minimize bleeding and enhance deposition of HIFU thermal energy for the purpose of hemostasis of large veins after the portion of the liver was

cut off (Martin et al. 1998). Hemostasis of a bleeding liver cross-section area of 20 cm² required 4.7 min of HIFU application with clamping, whereas a 15 cm² area treated without compression required 14 min of HIFU application time. The application of clamping in solid organ resection with high-intensity ultrasound was first reported by Murat et al. (2004). In this study, partial nephrectomy of porcine kidneys was achieved with the application of unfocused ultrasound transducer (intensity of 26 W/cm², frequency of 3.8 MHz) and a brass reflector. The kidney was clamped between the transducer and reflector, and vascular clamping of the vessels entering the kidney was also performed. A complete resection was achieved in 7 out of 8 kidneys in 6.6 min of HIFU application time.

We initially performed several liver lobe resections after Pringle maneuver was applied or without Pringle maneuver, to determine the difference between these treatments. Since Pringle maneuver did not appear to be advantageous in terms of HIFU application time and the number of vessels oozing or bleeding after the resection, it was abandoned in the later treatments. Therefore, HIFU may have an advantage over other methods of resection (energy-based or surgical) in which Pringle maneuver is often a necessary step (Beal 1996; Pachter et al. 1996), carrying a risk of ischemia to healthy liver tissues. The safe limit of warm ischemic time of the human liver was reported to be less than 30 min (Lu et al. 2004), which puts time constraints on the current liver resection methods.

In our current studies, maximal resection blood loss (which does not account for blood remaining in the resected portion of the solid organ) was estimated to be less than 1% of overall blood volume during liver lobe resections and less than 0.2% of the blood volume during kidney and spleen resections. In comparison, during lobectomies performed with standard surgical techniques in patients, the resection blood loss was reported to be 10–14% of the blood volume (Choi et al. 2005). In addition, the resection blood loss in patients was also 10–14% for right hepatectomy during resection with saline-linked radio-frequency dissecting sealer (Poon et al. 2005) and 4% on average during laparoscopic hepatectomy with a combination of ultrasound coagulating shears and electrocautery (Kamiyama et al. 2005). The results of our study indicate that HIFU application may offer a reduction of blood loss during solid organ resections, as compared with standard surgical or energy-based techniques.

The liver lobe resection was achieved within 7 min in our experiments. In comparison, in surgeries performed in patients, the resection time was 95 min (range 45 to 180 min) during liver lobe resection using RF ablation (Poon et al. 2005), 181 ± 45 min using a combination of ultrasound coagulating shears and electrocautery (Kamiyama et al. 2005) and approximately 400 min using standard surgical techniques (Choi et al. 2005). Splenectomy was performed within 5 min in our experiments as compared with 12 min needed for splenectomy of the ovine spleen using RF ablation (Haghighi et al. 2005). For the kidney treatment, our average time of 3 min was the same as the resection time previously reported for kidney resection using RF ablation (Pareek et al. 2005) and 2.2 times faster than the time needed for the resection of kidneys using unfocused high-intensity ultrasound transducer (Murat et al. 2004; Lafon et al. 2007), all in a porcine model.

Our current studies showed that HIFU can be successfully used to produce full-thickness coagulated regions in the solid organs that are up to 4 cm thick. However, human liver thickness can be up to 3 times greater than the thickest regions of the porcine liver (caudate lobe) that were resected in our studies. Thus, it is necessary to perform further experiments to determine the limits of thickness of the solid organs that can be resected using high-power HIFU application.

In our previous studies, long-term (up to 60 d) safety of HIFU application was shown in hemostasis treatments of lacerations in the rabbit liver (Vaezy et al. 2004) and spleen (Noble

et al. 2002). In these studies, blood analysis showed no significant difference in serial hematologic or coagulation measures between HIFU-treated and sham groups. ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels increased immediately post-treatment and returned to normal values by d 7. At 60 d post-treatment, scarring as well as liver and spleen tissue regeneration at the treatment site were observed. Similar healing and tissue repair mechanisms are expected to be observed after HIFU application in the resection of the liver lobes, spleen or kidney.

In summary, the development of high-power HIFU devices and application of organ compression allowed fast production (within several minutes) of a wall of cautery and subsequent resection of a solid organ with a minimal blood loss. This method holds promise for future clinical applications in resection of solid tumors and hemorrhage control of high-grade injuries in solid organs. Our future studies will focus on the optimization of HIFU parameters (duty cycle, intensity, frequency, transducer f-number, and application time) to produce sealing of large blood vessels with minimal damage to the surrounding healthy tissues and on the long-term safety of this application.

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Fig. 1. Solid organ resection using HIFU. a) Schematic of the experimental set-up. b) Application of high-power HIFU device in the resection of a liver lobe. The organ was compressed between the HIFU device and a reflector.

Fig. 2.
Flow chart of the treatment protocol.

Fig. 3.

Ultrasound images of a representative HIFU-treated liver lobe. (S1) Patent blood vessels (arrows) in the proximal region of the liver lobe. (S2) HIFU treatment site can be observed as a hyperechoic region (outlined, arrow). (S3) Liver lobe distally from the treatment site shows no patent blood vessels. Straight dashed line outlines the posterior surface of the liver lobe (in S2 and S3).

Fig. 4. Liver resection. a) Appearance of left lateral (LL), left medial (LM) and right medial (RM) lobes before the HIFU treatment. Dashed line shows the place where HIFU device will be positioned. b) Anterior view of a wall of cautery (arrow) in the LL lobe. c) Posterior view of a wall of cautery (arrow). d) Cross-sectional view of the resected liver lobe, *in-vivo*.

Fig. 5. Spleen resection. a) Appearance of spleen before resection. Dashed lines show distal and proximal locations where resection will be performed. b) Anterior view of the necrotic region (arrow) in the proximal region of the spleen. c) Posterior view of the necrotic region (arrow) in the proximal region of the spleen. d) *In-vivo* spleen after resection in the proximal region.

Fig. 6. Resection of a lower pole of the kidney. a) Appearance of the HIFU-treated kidney immediately before the resection. Necrotic region (arrow). b) Resected kidney *in-vivo*. No bleeding was observed after lower pole of the kidney was removed.

Fig. 7.

Appearance of sealed blood vessels. a) Gross appearance of vessels in the HIFU-treated region of the liver (arrows). b) Histological appearance of a sealed liver artery. Coagulated blood can be observed inside the artery (arrow). c) An artery inside the HIFU-treated region of the spleen. The adhesion of opposite sides of the arterial wall appears to be present (arrow). d) A sealed vein inside the HIFU-treated region of the spleen. The vein appears to be filled with coagulated blood (arrow). e) Appearance of a sealed artery in the kidney (arrow).

Table 1
HIFU application for resection of different solid organs. Data are given as mean $\pm$ standard deviation.

	Number of treated organs	HIFU time for producing a wall of cautery [s]	Additional HIFU time to seal remaining bleeding vessels [s]	Overall HIFU application time [min]	Delivered acoustic energy [kJ]
Liver lobes	16	287 $\pm$ 54	133 $\pm$ 55 (14 cases)	6.0 $\pm$ 1.5	74 $\pm$ 18
Spleen	8	208 $\pm$ 63	40 $\pm$ 4 (4 cases)	3.6 $\pm$ 1.1	48 $\pm$ 16
Kidneys	8	162 $\pm$ 29	60 (one case)	2.8 $\pm$ 0.6	38 $\pm$ 8

Number of blood vessels that were bleeding after the liver lobe was cut along the wall of cautery. No dependence was observed between the number of bleeding vessels (given as median [range]) and the lobe size or HIFU application time. The last two columns show the approximate width and thickness of the lobes.

Table 2

Liver lobe	Number of lobes treated	HIFU time for producing wall of cautery [s]	Number of bleeding vessels	Lobe width [cm]	Lobe thickness [cm]
Left lateral	6	302 ± 54	1 [0–2]	9	2.5
Left medial	4	281 ± 40	2.5 [1–3]	7	2
Right medial	5	270 ± 73	2 [2–3]	7.5	3.5
Caudate	1	300	2	6	4