IMAGE-GUIDED ACOUSTIC HEMOSTASIS

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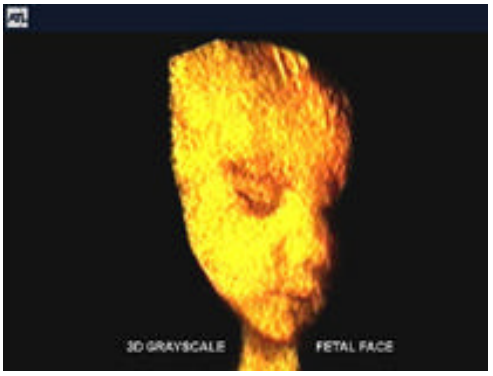
ABSTRACT

The use of ultrasound in medicine has shown remarkable gains in recent years, with non-invasive diagnostic imaging devices capable of visualizing, in real-time, even the small tissues and features of the human anatomy. More recently, however, the concept of using High Intensity Focused Ultrasound (HIFU) for therapy has gained renewed interest. We report on our preliminary studies of the combined use of diagnostic ultrasound imaging devices to detect and localize sites of internal bleeding, and of HIFU devices to induce coagulative necrosis and its resultant hemostasis.

INTRODUCTION

Diagnostic Ultrasound: In recent years, there have been significant advances in the imaging capability of medical ultrasound devices. With improved computing power, new signal processing techniques, and the use of contrast agents, remarkable anatomical detail can be revealed (See Fig. 1).

Fig. 1. An example of the remarkable capabilities of diagnostic ultrasound devices to provide images of anatomical features. This image of the face of a fetus can be acquired in 3-D and then rotated to reveal specific details of normal and abnormal development. Acoustic images such as this, acquired entirely non-invasively, are comparable to early developments in conventional optical photography. (Photo courtesy of ATL Ultrasound)



Therapeutic Ultrasound: Because of its unique properties in soft tissue, medical ultrasound can be brought to a tight focus at a distance from its source (See Fig. 2). If sufficient energy is radiated within the ultrasound beam, cells located in the focal volume can be rapidly heated while intervening and surrounding tissues are spared. Surrounding tissues are unaffected in the unfocused portion of the ultrasound beam because the energy is spread over a correspondingly larger area and associated heating is minimized. Whereas ultrasound intensities on the order of 0.1 Watts/cm^2 are employed in diagnostic imaging applications, intensities in excess of 1,000 Watts/cm^2 are typical in high-intensity focused ultrasound (HIFU) applications. At the focal point, these high intensities result in large, controlled temperature rises within a matter of seconds.

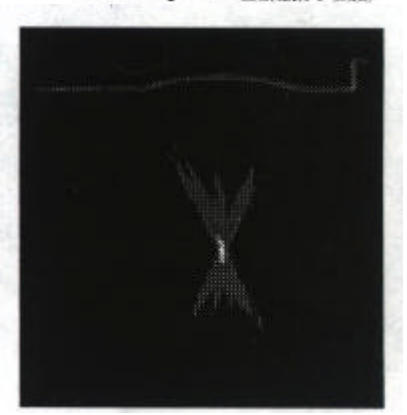
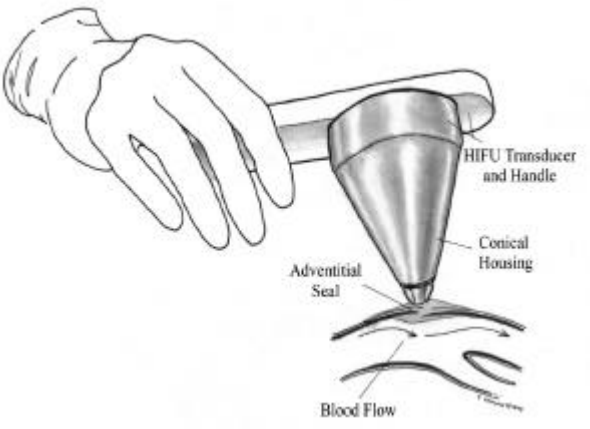


Fig. 2. Visualization of the focused, high-intensity ultrasound beam using a Schlieren technique. The ultrasound transducer (source) is at the top, and has a curved interface so as to produce geometrical gain. In this particular case, with proper transducer quality control, a cigar-shaped focal volume with dimensions on the order of a 2-3 millimeters in diameter and 5-7 millimeters in length can be created. By creating an array, with many elements, even smaller focal volumes can be created. (Image courtesy of Claudio Zanelli)

It has been demonstrated in numerous preliminary *ex vivo* and *in vivo* studies [1-4] that HIFU can be successfully used to close blood vessel punctures and lacerations in animals. Many of these studies have been published or are in press, and include: (a) the treatment of punctured, surgically exposed vessels using visual targeting [1], (b) the treatment of longitudinally incised, surgically exposed vessels using visual targeting [3], and (c) the treatment of surgically exposed, punctured vessels using Doppler-guided targeting [2]. Figure 3 illustrates the technique generally used in our investigations.

Fig. 3. Vascular and capillary bed hemostasis was achieved by applying the tip of the HIFU applicator to the visible bleeding site and manually moving it around the area to be treated. A water-filled cone is used as an acoustic conduction path between the ultrasound transducer and the tissue. This technique was also employed for treating vessel punctures, both with and without Doppler guidance. An ideal design would incorporate a transducer array that would allow electronic targeting and steering of the beam, and would incorporate a solid cone for the acoustic conduction path.



RESULTS:

We describe briefly an overview of our most recent results.

Vascular Hemostasis—Punctured Vessels: Because of coronary heart disease, over 5 million catherizations are performed each year in which invasive catheters are positioned within the coronary arteries to perform balloon angioplasty or other therapeutic procedures. In addition, trauma victims often die because of internal bleeding from severed or torn arteries and veins. Thus, we sought to develop a HIFU-based system that would seal breaches in the vascular system.

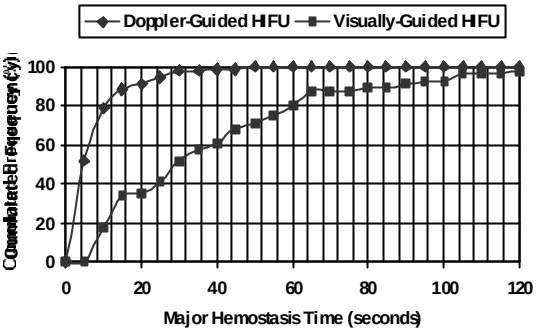
In our first series of experiments, vessels were punctured with 14 and 18-gauge needles (the 14 gauge for the larger vessels) to produce moderate to profuse bleeding in pigs. We examined femoral arteries and veins, axillary arteries, carotid arteries and jugular veins. The vessels ranged in size from 2-10 mm in diameter. In four swine, 57 punctures were treated using visual targeting of the HIFU beam [1]. In this case, we visually aimed the HIFU transducer at the presumed site of the wound (the transducer obscured the exact location), and administered HIFU when the likely site was covered by the transducer.

In each trial, we measured the time until both major hemostasis AND complete hemostasis were obtained. We defined major hemostasis time as the point at which the majority of bleeding had been stopped and only oozing was observed. Complete hemostasis was defined as the point at which all bleeding had terminated. All vessels were successfully treated with an average major hemostasis time of 43 ± 39 seconds and a complete hemostasis time of 62 ± 48 seconds. Although we found these results quite satisfying, we sought to reduce the time required to induce hemostasis.

To improve our targeting accuracy and reduce the time to achieve hemostasis, we investigated the use of Doppler ultrasound for wound-site targeting. In three pigs, 89 trials were conducted using Doppler

ultrasound to guide the treatment [2]. Pulsed Doppler was used in combination with the HIFU transducer with the range gate set at the focal depth of the transducer. The probe was moved over the site of the punctured vessel until a Doppler sound was obtained, indicating that the focus was co-located on the jet of the hemorrhaging artery. At this point, the Doppler unit was disengaged by a foot switch and the HIFU drive system was engaged, applying HIFU to the targeted site by the therapy transducer. After about 1 to 5 seconds of exposure, the HIFU application was terminated and Doppler was again engaged to interrogate the bleeding site. Fig. 4 provides an indication of the success of our therapy.

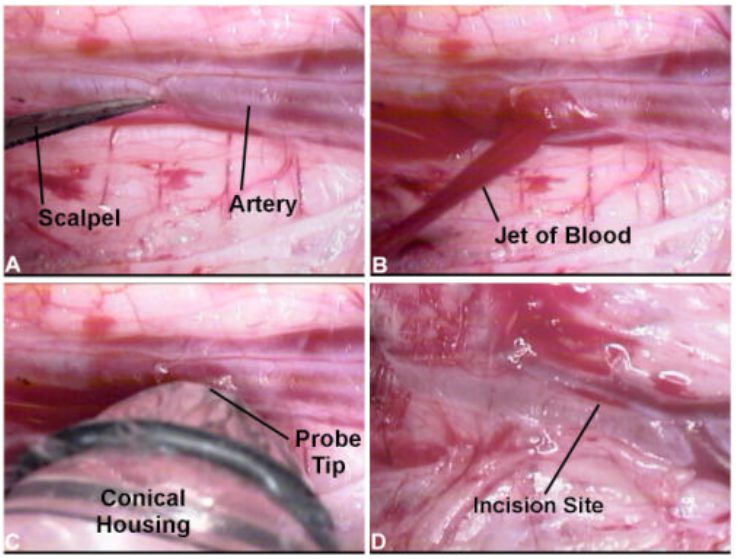
Fig. 4. The statistical cumulated frequency of the major hemostasis times for the Doppler-guided treatment compared to a similar puncture treatment, but with only visual-guidance [1,3]. The use of Doppler [2] resulted in a marked reduction in the time required to achieve hemostasis because the applicator was accurately aimed at the exact location of bleeding. We believe that a targeting approach using Doppler guidance, perhaps combined with image-guidance, has enormous promise for the treatment of vascular wound sealing.



Vascular Hemostasis—Incised Vessels: In another study [3], we examined the ability of HIFU to seal relatively major cuts and lacerations in vessels. Because the lateral dimension of the cut (~ 1 cm) was often larger than the transducer focus, it was necessary to mechanically translate the transducer focus back and forth over the wound site. In a group of 4 pigs, longitudinal incisions of 2-8 mm length were produced in the vessels [3]. A total of 76 incisions were treated by vision-guided HIFU. We also explored a technique of rapidly scanning the HIFU beam using a mechanical vibrating device. The objective was to distribute the heating effect of HIFU over a wider region than the diameter of the beam at the focus (~ 1 mm). In the treatment of incised vessels, bleeding was completely stopped by HIFU in 91% of the incisions, while major hemostasis was achieved in all trials. The mean times to achieve major and complete hemostasis were 17 ± 15 and 25 ± 19 seconds, respectively.

We demonstrated to our satisfaction that HIFU could rapidly and successfully seal punctures and lacerations in blood vessels in a matter of seconds. Once the arteries and veins were punctured, blood jetted from the wound with considerable velocity. The HIFU beam, when applied directly over the jet, stopped the flow because of a combination of applied pressure from the applicator and the acoustic streaming generated by the HIFU beam; as a result, the wound was rapidly sealed. Figure 5 provides a rather graphic demonstration of the effectiveness of the HIFU technique in vascular hemostasis.

Fig. 5. This figure shows a dramatic demonstration of the capability of HIFU to induce acoustic hemostasis in vascular wounds. In this figure, a 0.5 cm cut was made in the femoral artery of a pig; the frame in the upper right shows that a strong jet of blood was emitted from this cut. The application of HIFU to this particular cut induced complete hemostasis in less than 10 seconds. Note from the frame in the lower right that the damaged area appears to be entirely sealed. We also determined from our histology studies that the inner wall of the vessel was not damaged. We believe that the low sound absorption in blood, and its flow, protects the interior of the vessels. Note also that this HIFU probe design visually obscures the bleeding site. Application of the HIFU focal area to the appropriate site is accomplished by trial and error.



An important finding in this study was that the hemostasis times did not change significantly when the animals were heparinized. This result provides grounds for two important considerations: 1) the HIFU hemostasis mechanism may be independent of the coagulation cascade, and 2) HIFU may have an

accelerating effect on the coagulation cascade, even in the presence of heparin. Again, we observed no statistically significant difference in the hemostasis times of normal vs. heparinized animals.

Another important finding was that there was no damage to the endothelium of the vessel. Microscopic examination of the interior of the blood vessels treated by HIFU showed little or no damage (See Fig. 6a). In fact it appears as if live endothelial cells are present in the interior of the sealed area (See Fig. 6b).

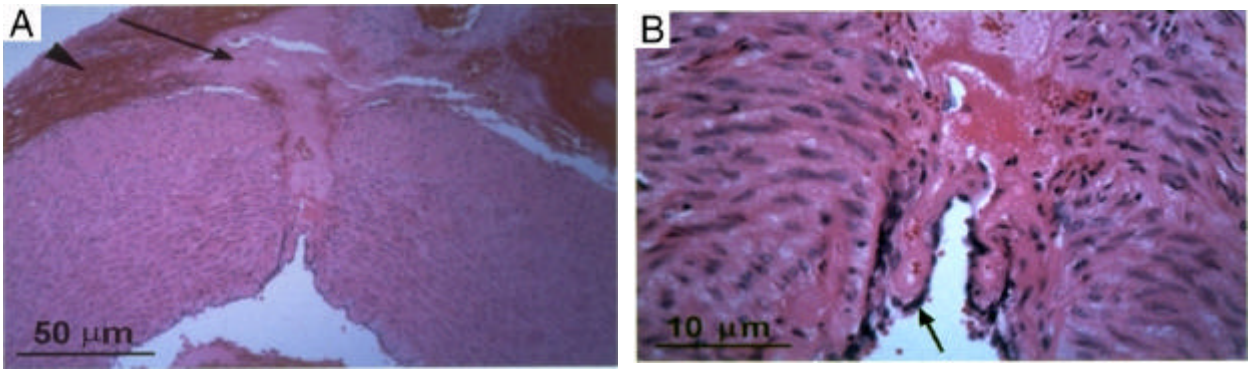


Fig. 6. Microscopic view of segment of punctured artery after HIFU treatment. (A) Note that a fibrin plug has formed and sealed the wound. (B) High power view of the sealed artery shown in (A). The arrow points to live endothelial cells that line the interior of the repaired area.

In an effort to understand why there appears to be little damage to the endothelial wall, we mathematically modeled the acoustic and thermal fields produced by HIFU in the presence and absence of blood vessels, and have determined that this absence of internal damage is predicted by our model [5]. In this model, we examined the temperature fields produced by a focused HIFU transducer with a blood vessel both present and absent. We discovered that the temperature within the blood vessel itself is quite low, compared to that in the tissue surrounding the vessel (See Fig. 7). This result is principally due to the low acoustic absorption in the blood. When flow is introduced in the model, even further reductions in the interior temperature are seen. Thus, when HIFU is applied to a blood vessel, producing hemostasis of a vascular puncture or tear, the interior walls of the vessel are protected from damage by the low acoustic absorption in blood and the cooling effect of the blood flow.

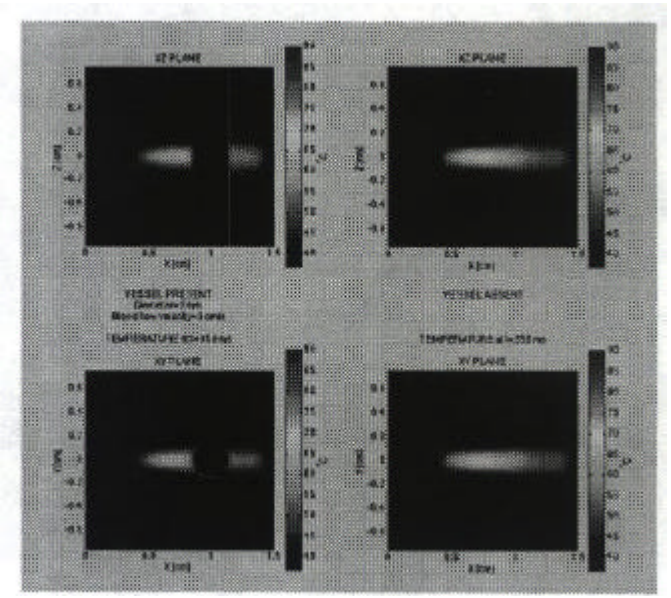


Fig. 7. Temperature fields produced by a focused HIFU transducer with a blood vessel both present and absent. The temperature bar is shown on the right of the figure. The figures on the left show that the temperature within the blood vessel itself is quite low, compared to that in the tissue surrounding the vessel. This result is principally due to the low acoustic absorption in the blood. When flow is introduced in the vessel, even further reductions in the interior temperature are seen. Thus, when HIFU is applied to a blood vessel, producing hemostasis of a vascular puncture or tear, the interior walls of the vessel are not normally damaged.

Wounds to the vascular system are the most dangerous when they involve large blood vessels, but blunt trauma often involves gross damage to the capillary bed, which results in oozing of blood from the damaged area, which may be quite large. Thus, we sought also to use HIFU to induce hemostasis over a large volume of traumatized organ tissues, particularly the highly vascularized organs as the liver and the spleen.

Liver Hemostasis: We modeled liver trauma by first surgically exposing the liver and then performing a variety of insults to it. Our first HIFU experiments were in injuries to rabbit liver injury [6] and the success of these initial studies has resulted in evolving our studies to larger animals. Liver injuries were made in anesthetized animals (10 rabbits and 4 pigs). In rabbits, the injuries consisted of 27

incisions in livers (approximately 15 mm long and 4 mm deep). In pigs, the injuries were 5 incisions (approximately 4 cm long and 7 mm deep), 6 punched holes (4 with 1.1 cm diameter, and 2 with 2.5 cm diameter), 2 complete tears of a tip of liver lobe (approximately 5 x 6 cm wide and 1.5 cm thick), and a stellate laceration (about 8 fractures, 5-7 cm long and 5-10 mm deep). All pigs were heparinized. HIFU was applied within 1 minute of injury, using either a 3.3 MHz (rabbits) or a 5 MHz (pigs) high power transducer. The rabbit experiments were performed while the liver was submerged in a water tank for acoustic coupling. The pig experiments were performed on a surgical table, with the 5 MHz probe equipped with a conical coupler, filled with degassed water. The transducers were maneuvered such that the focal spot of the ultrasound beam was placed visually where hemostasis was needed. The transducer was then manually scanned along the injured surface. For the 5 MHz transducer, this meant that the tip of the conical coupler was moved over the bleeding sites. All treatments were performed while active bleeding was occurring (i.e., we did not clamp the portal triad or other vessels to temporarily stop bleeding.)

Complete hemostasis was achieved, on the average, in less than 3 minutes for rabbit liver lacerations, in 74 seconds for pig liver laceration, and in 54 seconds for pig liver holes. The tears and stellate lacerations required about 4-7 minutes of HIFU application over the raw surface, in the cracks of the fractures, and on the persisting bleeding sites (usually the hepatic veins). The treated liver generally appeared white as illustrated in Fig 8 (see arrows). Histological analysis demonstrated coagulative necrosis of liver tissue, causing sinusoidal and vascular collapse due to tissue structure deformation. Suturing of the persistently bleeding hepatic veins was performed in one location for each lobar tear. As with our previous experience with vessels, heparinization of the animals had no effect on the hemostasis times.

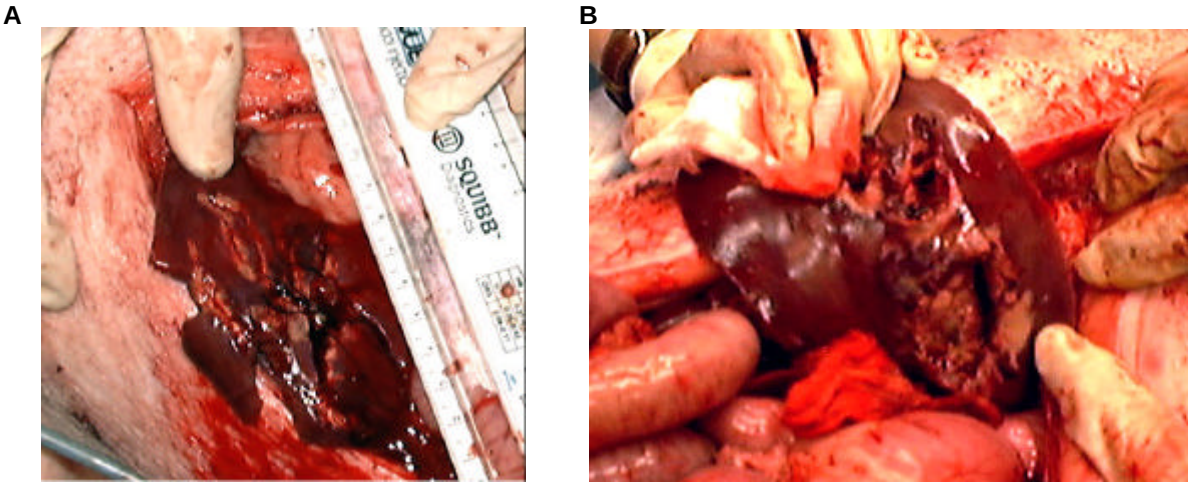


Fig. 8. Use of HIFU to cauterize severe trauma injury to liver of pig. (A) A stellate laceration; (B) holes of various dimensions; note that the treated areas are lighter in color and demonstrate that little additional bleeding is occurring after HIFU treatment. Even with this severe trauma, we were able to achieve complete hemostasis in less than 7 minutes.

We are continually impressed with our success in obtaining hemostasis, especially in the cases of extreme trauma to the tissues. We believe that this success is due to the unique capability of ultrasound to penetrate deep into tissues—thus, we achieve “volume cauterization”, unlike most other cauterization devices that produce only “surface cauterization”. This mechanism is effective even in the presence of experimental coagulopathy by heparinization.

Spleen Hemostasis: We initially tried applying 3.5 MHz HIFU to the experimental spleen injuries but had limited success in inducing hemostasis. More recently, however, we have used a 5 MHz HIFU transducer with good success. Two studies were conducted: the first examined the treatment of small splenic lacerations representing approximately grade I injury [7]. In the first study, a total of 39 incisions in 5 anesthetized pigs were investigated. The method of HIFU application consisted of a manual scanning of the HIFU transducer over the incision, at a rate of approximately 1 mm/s. Control of bleeding was usually achieved after the first pass. Using a 5-MHz HIFU transducer, we were able to control and to completely stop bleeding from splenic incisions, 25-50 mm in length and 2-8 mm in depth, in 28 ± 13 and 55 ± 22 seconds, respectively. Additional HIFU application was sometimes required to stop all bleeding. We discovered that if we produced a thin, lightly cauterized, surface layer that we call an “emulsification paste”, we could stop the parenchymal bleeding even when the animals were well heparinized. In the second study, we produced severe injuries of pig spleen. Bleeding from large lacerations, approximately 1 cm deep and 8 cm long, was stopped within 2-3 minutes of HIFU application. Also, bleeding from large holes, up to 3 cm in diameter were stopped using HIFU

application.

Image-guided Transcutaneous Acoustic Hemostasis. The ultimate goal of our envisoned effort is to develop a non-invasive, transcutaneous device that would terminate all forms of bleeding in a human patient. To accomplish this goal, it will be necessary to develop a device that can *image* the bleeding location so that low flow rate bleeds can be detected and targeted; only then can subsequent application of HIFU induce hemostasis. "Image-guided therapy" promises revolutionary advances in modern surgery, with its strong emphasis on minimally invasive techniques.

We are pleased to report [8] that we have demonstrated "proof-of-principle" for this major objective, as shown in Fig. 9 below. It is clear from this figure that our efforts at system integration are still preliminary, and indeed the engineering development of this basic idea is a major challenge. Fig. 9, however, also illustrates several important concepts. First, in Figs. 9A and 9B, we show the geometrical arrangement of the imaging and therapy systems, and the catheter used to induce the wound to the artery. In Fig. 9C, a Color Doppler image of the bleeding artery that was perforated by the catheter is shown (unfortunately, in this publication, only black and white images are possible). The bright red region (or the region shown by the arrow) indicates the flow of blood from the wound. This image was obtained by driving the scanning transducer (scanhead) of a commercial ultrasound unit in a Doppler mode. Fig. 9D shows our preliminary success in performing image-guided therapy. In this figure, we synchronized the imaging and therapy transducers in order to obtain an ultrasound image of the region near the wound. This image is thus a visualization of the HIFU focal region, where lesions will be produced. As indicated by the label, a hyperechoic region indicating the HIFU focal region is visible. We believe that the high temperature produced at the focus by the HIFU transducer causes a mild form of cavitation, which results in gas evolution from the tissue, and thus generates this bright spot. Using this information, we can "guide" the HIFU focus to the site of the vessel wound, and apply therapy at the appropriate site. Because ultrasound imaging and therapy are performed in real-time, we can "monitor" the treatment at the bleeding site, as shown in Fig. 9E. This allows us to determine, indeed verify, that the blood has been confined within the artery and transcutaneous acoustic hemostasis induced. Fig. 9F shows that we have performed successful transcutaneous acoustic hemostasis on this animal. It is obvious that this approach has enormous potential, not only for achieving acoustic hemostasis, but also for treating disease. For example, many carcinomas are diagnosed with ultrasound, and are thus clearly visible on diagnostic ultrasound scans. One can envision image-guided treatment of these tumors, with real time monitoring of the progress of the therapy.

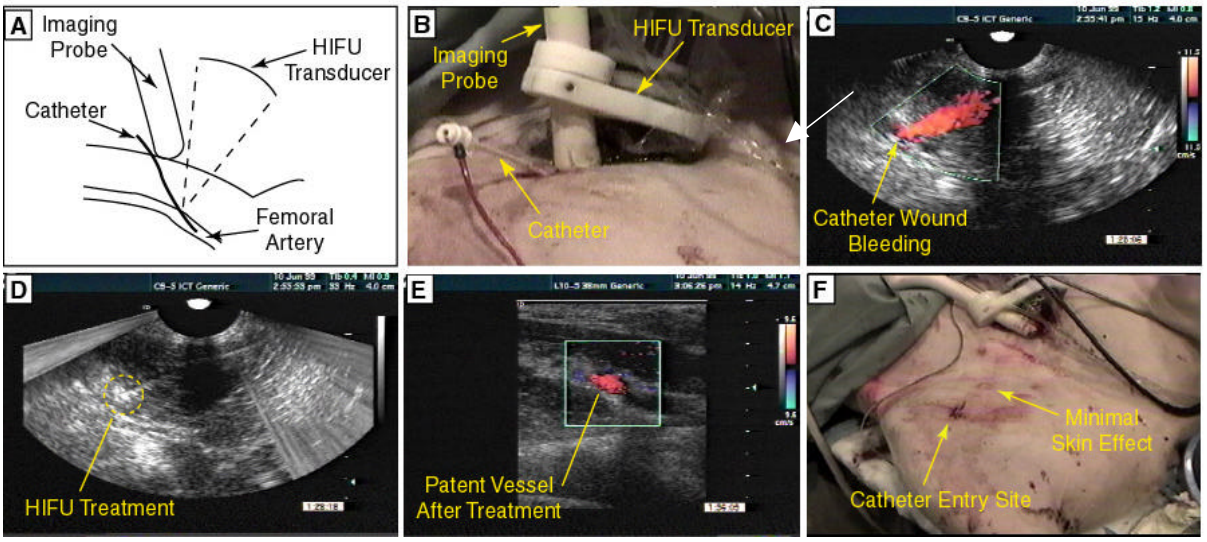


Fig. 9. Demonstration of transcutaneous, image-guided, acoustic hemostasis. See text for details.

SUMMARY:

We have demonstrated that the concept of image-guided acoustic hemostasis has enormous potential in the treatment of a variety of medical conditions involving trauma.

ACKNOWLEDGMENT:

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