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Pulsatile Flow Phantom for Ultrasound Image-Guided HIFU Treatment of Vascular Injuries

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Abstract

A pulsatile flow phantom was developed for studies of ultrasound image-guided High Intensity Focused Ultrasound (HIFU) application in transcatheter hemostasis of injured blood vessels. The flow phantom consisted of a pulsatile pump system with instrumented excised porcine carotid artery, which was imbedded in a transparent agarose gel to model structural configuration of in-vivo tissues. Heparinized porcine blood was circulated through the phantom. The artery was injured using an 18 Gauge needle to model a penetrating injury in human peripheral vasculature. A HIFU transducer with the diameter of 7 cm, focal length of 6.3 cm and frequency of 3.4 MHz was used to seal the puncture. Ultrasound imaging was used to localize and target the puncture site, and monitor the HIFU treatment. Triphasic blood flows present in the human arteries were reproduced, with flow rates of 50–500 ml/min, pulse rates of 62–138 beats/min, and peak pressures of 100–250 mmHg. The penetrating injury of an artery was mimicked successfully in the flow phantom setting, and was easily visualized both optically through the transparent gel and with Power Doppler ultrasound imaging. Hemostasis was achieved in 55 ± 31 s ($n=9$) of HIFU application. Histological observations showed that a HIFU-sealed puncture was filled with clotted blood and covered with a fibrin cap. The pulsatile flow phantom provides a controlled and repeatable environment for studies of transcatheter image-guided HIFU application in hemostasis of a variety of blood vessel injuries.

Keywords

Flow Phantom; Vascular Injury; High Intensity Focused Ultrasound; Acoustic Hemostasis; Image-Guided; Power Doppler; Bleeding Detection

Introduction

Injuries to blood vessels can be caused by trauma (Schackford and Rich 1996) or during surgical procedures (Oderich et al. 2004). Since the late 1980's, incidence of vascular injuries has increased due to an increase in number of assaults, motor vehicle crashes and percutaneous medical procedures (Caps 2000). Furthermore, in recent United States military warfare, up to 70% of all treated injuries are extremity vascular injuries and exsanguination from these injuries is a leading cause of preventable death (Starnes et al. 2006). Patients who present

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definitive signs of vascular injury such as hemorrhage, shock, absent distal pulses, limb ischemia, and/or an expanding pulsatile hematoma require immediate treatment (Britt et al. 2001). The treatment of vascular injuries often consists of ligation and surgical repair (Rich and Rhee 2001). In addition, angiographic embolization has been used for occlusion of injured arteries (Velmahos et al. 2000; Mohr et al. 2003). However, embolization can be applied only in selective cases of vascular injuries since it can lead to distal tissue ischemia (Scalea and Sclafani 2001). Overall, there is a need for development of a non-invasive treatment of peripheral vascular injuries, which may reduce the risks associated with surgery and improve patient care (Lasic et al. 2005), as well as provide a fast life-saving treatment in emergency and battlefield situations.

We have been investigating ultrasound image-guided High Intensity Focused Ultrasound (HIFU) as a method for non-invasive hemorrhage control (Vaezy et al. 2001a). HIFU therapy is capable of delivering cauterization energy deep inside the body, with millimeter accuracy, and with little or no damage to the intervening and surrounding tissues (Chen et al. 1993; Vaezy et al. 2001b). Our preliminary in-vivo studies indicate that HIFU can be used for sealing of 3 mm punctures in porcine femoral arteries (diameter of 5–6 mm) (Vaezy et al. 2006). Further studies will focus on determining the maximal size of punctures in blood vessels that can still be sealed with HIFU technology, and establishing whether this method can be used for sealing of large vessel injuries (punctures of 5 mm in diameter or larger) which are of the highest clinical relevance. Developing HIFU therapy into a non-invasive treatment modality requires precise localization and targeting of the injured sites, and monitoring of the HIFU treatment. Diagnostic ultrasound imaging (e.g., Power and Color Doppler) may be an efficient, real-time, and relatively cheap solution for both bleeding localization and HIFU treatment guidance (Vaezy et al. 2001a). Although arteriography remains the gold standard, recent reports indicate the usefulness of ultrasound in localization of vascular injuries (Britt et al. 2001; Davison and Polak 2004).

To achieve a controlled experimental setup for testing of ultrasound image-guided HIFU devices, we developed a flow phantom that can mimic a peripheral vascular injury. The flow phantom provided a repeatable and robust environment for the feasibility testing of ultrasound-guided HIFU application, allowing optimization of this method before its application in an in-vivo setting. In comparison to flow phantom studies, in-vivo studies are confounded by a limited control over physiological parameters. Also, the natural physiological and anatomical differences between animals and physiological differences in the same animal over the course of the experiment (i.e. change in the blood pressure and heart rate) make it difficult to perform a well-controlled in-vivo study. However, only in-vivo animal model can mimic the complexity of bleeding from traumatic vascular injuries (Luo et al. 2006; Panetta et al. 1992). For example, the anatomy of the injured region often changes due to the expanding hematoma (Shayne et al. 1994). This dynamic environment may represent a challenge for both bleeding detection and HIFU hemostasis due to the injured blood vessels being displaced from its original location, which cannot be modeled in a stationary flow phantom setting. Therefore, a final evaluation of image-guided HIFU devices has to be performed in-vivo, after the preliminary in-vitro feasibility and optimization studies are completed.

Flow phantoms usually consist of a pump that circulate fluid, a channel through which fluid flows, and a tissue-mimicking phantom that surrounds the channel (Dabrowski et al. 2001; Peopping et al. 2002; Rickey et al. 1995). Flow phantoms can be designed to allow accurate reproduction of complex vascular geometries, easy modeling of flow properties using mathematical simulations, and good mimicking of thermal and/or acoustic tissue properties (Law et al. 1989; Peopping et al. 2002; Vella et al. 2003; Rickey et al. 1995). These phantoms have been used previously in ultrasound research, for example in determination of accuracy of B-mode and Doppler ultrasound imaging (Rickey et al. 1995; Walker et al. 2004), assessment

of new ultrasound imaging methods (Potdevin et al. 2004), and studies of flow in diseased blood vessels (Peopping et al. 2002).

There is a significant variation in the construction of flow phantoms, depending on their application (Dabrowski et al. 2001; Peopping et al. 2002; Rickey et al. 1995). When the exact flow through the phantom must be known, a rigid tube is often used to form the channel, providing a known and inflexible geometry. Studies using acrylic, heat-shrink tubing (Rickey et al. 1995), dialysis tubing (Potdevin et al. 2004), polyester resin (Frayne et al. 1993), and quartz (Law et al. 1998) have been reported. However, all of these materials have high attenuation and acoustic impedance and introduce an impedance mismatch between the channel and tissue/blood mimicking material (Law et al. 1998), leading to reflection and other artifacts. Using a more flexible material such as latex or silicone rubber may reduce the impedance mismatch and provide a better approximation of the elasticity of a real vessel, but such materials still have the acoustic impedance significantly different from the tissue acoustic impedance and may cause shadowing artifacts (Law et al. 1998; Rickey et al. 1995). Another option is to mold the channel out of a tissue mimicking material (i.e. have a wall-less channel) (Rickey et al. 1995). This solution eliminates attenuation and impedance mismatch problems and allows for production of channels of various geometries. However, using a wall-less design can limit flow through the phantom, since high flow rates have been shown to cause a rupture in the surrounding tissue-mimicking phantom material (Peopping et al. 2002). Excised blood vessels have also been used in flow phantom studies to ensure that the channel has the complexity of the human vessel wall and approximates well in-vivo mechanical properties of the vessels (Dabrowski et al. 1997; Dabrowski et al. 2001). However, problems associated with using real blood vessels include lack of availability, short shelf life, and sample variability. Fixation of the vessels in formaldehyde can increase their shelf life (Dabrowski et al. 2001); however, this procedure changes the mechanical vessel properties by making them more rigid.

Ideally, the fluid flowing through the phantom should match the viscosity, speed of sound, attenuation, and backscattering of human whole blood. To achieve this, one approach is to use an artificial blood mimicking fluid. For example, machine cutting fluid (Dabrowski et al. 2001; Frayne et al. 1993; Rickey et al. 1995) or glycerol (Law et al. 1989; Peopping et al. 2002; Ramnarine et al. 1998) can be mixed with water to increase its viscosity and density. Also, small particles such as cellulose (Law et al. 1989) or nylon (Dabrowski et al. 2001; Peopping et al. 2002; Ramnarine et al. 1998; Rickey et al. 1995) can be added to water to increase scattering. These fluids can provide a reasonable approximation of the physical and acoustic properties of real blood (Ramnarine et al. 1998). Another approach is to use blood derivatives, since whole blood is not appropriate because of its tendency to clot. Blood derivatives such as hardened red blood cells suspended in saline (Law et al. 1989) or anticoagulated porcine blood with removed platelets and white blood cells (Lin et al. 1999) have been used previously. In our studies, the whole porcine blood used in the phantom had to be heparinized to prevent clotting. This blood can be used as a model of human blood for the patients that are anticoagulated or coagulopathic (Abramson and Niles 1999).

The flow phantom, reported here, utilized circulating heparinized blood and blood vessels imbedded in an optically and acoustically transparent gel, and could mimic physiological conditions of human peripheral blood vessels. This phantom was similar to the phantom reported by Dabrowski et al. (2001), except that our setup utilized blood (instead of blood mimicking fluid), thus allowing assessment of the ability of HIFU to produce blood coagulation at the site of injury. Our experimental setup enabled reproducible production of vascular injuries and controlled studies of bleeding detection and ultrasound image-guided HIFU hemostasis. In these studies, Power Doppler was used to localize the injuries during HIFU treatment, and to determine vessel patency after the treatment. Our objective was to determine

whether Doppler-guided HIFU treatment can be used for non-invasive localization and sealing of puncture wounds in blood vessels, while preserving vessel patency.

Materials and Methods

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. Adult domestic pigs (weighing approximately 70 kg) were sedated via intramuscular injection of Acepromazine (0.4 mg/kg) and Ketamine (20 mg/kg), and then anesthetized using an intravenous injection of Ketamine (20 mg/kg) and Xylazine (2.5 mg/kg) dosed to effect, to allow placement of an endotracheal tube. Following intubation, the animals were ventilated with oxygen and isoflurane (1–3%) to maintain anesthesia. Blood and carotid arteries were harvested after in-vivo studies (performed on porcine solid organs) were completed. Heparin (200 units/kg) was injected prior to harvesting to prevent blood clotting (Abramson and Niles 1999). Catheters were placed in aorta and/or vena cava, and 1 liter of blood was withdrawn. The carotid arteries (diameter of 4–6 mm) were excised immediately after the animal was euthanized (with an injection of Euthasol, 1 ml per 4.5 kg of animal weight, followed by 20 ml of concentrated KCl). The carotid artery was chosen (instead of extremity vessels such as femoral artery) since it provides a relatively long vessel length (approximately 6 cm) with no side branches which is advantageous for the instrumentation of the artery in the flow phantom. The heparinized blood and the arteries (stored in saline) were refrigerated for up to 5 h before use.

A detailed schematic of the pulsatile flow phantom setup with imbedded artery and circulating blood is shown in Fig. 1. The blood flow was produced by a solenoid actuated metering pump (E-plus, Pulsafeeder, Punta Gorda, Florida, USA). The volume of the flow pump reservoir was 800 ml. A plenum, made from a 25 ml serological pipette capped with a stopcock, served as a damping column and was used to control the velocity and pressure waveforms of blood by adjusting the levels of air in the plenum. The pipette was first partially filled with fluid and then the stopcock was closed, leaving some air trapped at the top. When the pump produced a pulse, the pressure in the tubing become greater than the pressure of the air at the top of the column. Thus fluid flowed into the column and compressed the air. The compression of the air stored some of the energy from the pulse. As the pressure in the tubing dropped at the end of the pulse, the air expanded, pushing some of the fluid from the column back into the flow phantom. The resulting action was dampening of blood pressure waveforms.

The pump provided control of pulse rate, stroke volume, and systolic and diastolic blood pressure. The pulse rate was calibrated by counting the number of pulses in a minute. The flow rate for a set stroke volume and pulse rate was determined by measuring the volume of fluid that was ejected from the pump in a minute. The peak (systolic) pressure was predominantly controlled by the volume of air in the plenum, while the diastolic pressure was predominantly controlled by the amount of constriction before the blood re-entered the reservoir. Increasing the constriction increased the diastolic pressure. Changes in the blood velocity followed similar behavior to blood pressure changes. Temporal waveforms of pressure and velocity were observed using a pressure transducer instrumented in the flow phantom and Pulsed Doppler ultrasound imaging (L10-5, HDI 3000, Philips, Bothell, WA, USA). The Pulsed Doppler interrogation window was localized in the center of the artery lumen and included the whole width of the artery.

Heparinized whole blood was circulated through the excised carotid artery instrumented in the flow phantom. The artery was placed inside a gel box (Fig. 1) and sutured to the removable tubing connectors inserted in the plastic tubing with an inner diameter of 6.4 mm. Tissue glue was placed over the sutures to prevent possible leakage. Several sizes of connectors were

available to attach arteries of different diameters. One of the tubing connectors attached to the artery was inserted into a section of the plastic tubing that was glued to the side of the bottom stage of the gel box. The other tubing connector, attached to the artery, was inserted into a section of the plastic tubing that was glued into an acrylic slider. This allowed the phantom to accommodate vessels of different lengths.

The bottom stage of the gel box was filled with 600 ml of 0.75% agarose gel, made by mixing agarose (UltraPure™ Agarose, Catalog Number 15510-027, Invitrogen, Carlsbad, California, USA) with hot water and then cooling the mixture down. The agarose gel completely surrounded the arterial wall, and stabilized the artery preventing its movement during the experiments, thus modeling the structural configuration of in-vivo tissues surrounding the vessels. Without the gel, the artery tended to move up and down with each fluid pulse. In addition, the gel prevented the movement of the artery due to exposure to the HIFU field. The agarose gel allowed simultaneous optical and ultrasonic visualization of the imbedded vessels. The top stage of the gel box was filled with water to provide coupling of HIFU and imaging transducers to the gel.

The imbedded artery was punctured with a hypodermic 18 Gauge needle (bevel size of 5 mm, diameter of 1.25 mm) to simulate penetrating vascular injury. During puncturing, the beveled edge of the needle was placed completely inside the artery lumen (without damaging the posterior wall of the artery). The injury site was localized using B-mode and Power Doppler ultrasound. Ultrasound imaging was also used to guide and monitor the HIFU treatment. The injury was treated until hemostasis was achieved, as confirmed by Power Doppler imaging and visual observation (as the lack of blood flow at the injury site). The ultrasound imaging transducer (C15, frequency 4–2 MHz, Sonosite, Bothell, WA, USA) was attached to the HIFU transducer (Sonic Concepts, Woodinville, WA, USA) (Fig. 2a) by a custom-made housing which aligned the two transducers such that the HIFU focus was in the ultrasound imaging plane (Fig. 2b). The single-element HIFU transducer had a focal length of 6.3 cm, diameter of 7 cm and frequency of 3.4 MHz. A custom-built driving unit, consisting of a frequency generator and an amplifier, was used to drive the HIFU transducer and control HIFU pulse repetition frequency and duty cycle to provide an interference-free window in B-mode ultrasound images (Vaezy et al. 2001a). The width and length of the focus, obtained from –6 dB field map contour plots, were 0.6 mm and 4 mm, respectively. The free-field HIFU intensity, calculated as acoustic power divided by the –6 dB focal area, was 16,000 W/cm².

Selected areas of injured vessels were excised from the artery after the treatment and placed in 10% formalin, for standard histology preparation. Histology slides, stained with Mason's trichrome, were observed under a light microscope.

Results

The phantom was able to mimic physiological conditions of a variety of human arteries, providing flow rates of 50–500 ml/min, pulse rates of 62–138 beats/min, and peak pressures of 100–250 mmHg. The pressure and velocity profiles could be adjusted by controlling the resistance of the flow system and the volume of air in the plenum. With the plenum completely filled with water, the Doppler velocity waveforms showed a series of very short periodic spikes that had a high peak velocity (Fig. 3a). When a small volume of air (6 ml) was present at the top of the plenum (Fig. 3b), the Doppler waveforms represented an under-damped system in which the velocity decreased sharply from the first positive peak followed by oscillations of declining amplitudes until the next pulse began. By increasing the volume of air in the plenum (volume of 20 ml, Fig. 3c), the Doppler waveform started to resemble the arterial signal. Figure 4 gives a comparison between a signal from the in-vivo human carotid artery (Fig. 4a) and the signals obtained in the flow phantom (Fig. 4b&4c).

The artery imbedded in the agarose gel was visible both optically and under ultrasound imaging (Fig. 5a and 5b). Before puncturing, the flow through the artery was seen as a single colored line in Power Doppler ultrasound images (Fig. 5b). After the puncture was made, bleeding was observed (in a channel made by the needle) both optically (by eye) as a jet of blood (arrow, Fig. 5c), and as a colored line in Power Doppler ultrasound images (arrow, Fig. 5d). A hyperechoic spot which appears at the location of HIFU focus in B-mode ultrasound images (Vaezy et al. 2001a) was used to target the HIFU treatment (circle, Fig. 5f). The bleeding from the puncture site was reduced during the HIFU treatment (arrow, Fig. 5e) until it stopped completely. In nine trials, HIFU application resulted in a complete arrest of bleeding in 55 ± 31 s (mean $\pm$ standard deviation). A successful treatment of the injured vessel wall, resulting in hemostasis, was confirmed both optically (Fig. 5g) and using Power Doppler ultrasound imaging (Fig. 5h). Using Power Doppler, the flow was observed through the artery (Fig. 5h), indicating that the vessel was not occluded during the treatment.

Sealing of puncture wounds in blood vessels appeared to be achieved by coagulation of extravasated blood and coagulation and shrinking of the vessel wall surrounding the puncture site. Under the light microscopy, clotted blood could be observed in the arterial puncture sealed with HIFU (arrow, Fig. 6a). The puncture site was covered with a fibrin cap (arrowhead, Fig. 6a), which likely facilitated hemostasis. A control (untreated) blood vessel wall is shown in Fig. 6b for comparison.

Discussion and Summary

Flow phantom provided a controlled, repeatable and convenient environment with known flow parameters for preliminary testing and optimization of ultrasound image-guided HIFU hemostasis of vascular injuries. In our phantom, flow rates of 50–500 ml/min were achieved, with pulse rates between 62 and 138 beats/min, and peak pressures between 100 and 250 mmHg. In comparison, an average human pulse is 70 beats/min (Mohrman et al. 2003), and an average flow rate in a human carotid artery is 415 ml/min (Weskott and Holsing 1997) with peak blood pressure of approximately 140 mmHg (Spencer et al. 2001). The velocity and pressure profiles in the phantom could be adjusted as needed to mimic a variety of human physiological states (both normal and traumatic).

Our study showed the feasibility of using an in-vitro phantom in ultrasound image-guided acoustic hemostasis research. In previous in-vivo studies, it was shown that visually-guided HIFU hemostasis of punctured, surgically exposed porcine carotid arteries could be achieved in 128 ± 45 s (Vaezy et al. 1998). When the in-vivo treatment was guided by audio Doppler, the treatment time was reduced to 8.4 ± 6.4 s (Martin et al. 1999). The treatment times required in our phantom studies (55 ± 31 s) were in the range of previously reported in-vivo times. The coagulated blood inside the puncture site and the fibrin cap over the puncture site in our phantom experiments were similar in appearance to the previously observed in-vivo arterial punctures treated with HIFU (Vaezy et al. 1998). The arteries remained patent after the HIFU treatment. Preserving vessel patency was expected, since blood flow inside the artery causes significant cooling effect in the HIFU treatment region (Chen et al. 1993), thus preventing coagulation of blood inside the vessel. This result was in agreement with our previous in-vivo studies (Martin et al. 1999; Zderic et al. 2006). The vessel patency and lack of thrombus formation inside the vessel lumen after HIFU treatment were also observed in our survival studies (in a rabbit model) in which we monitored the animals for up to 60 days after visually-guided HIFU sealing of punctures in femoral arteries (Zderic et al. 2006).

The bleeding from the puncture sites was visible in ultrasound images allowing guidance of the HIFU treatment in our experiments. The bleeding signal was clearly seen as a colored line in Power Doppler mode extending from the puncture site through the needle track in the agarose

gel. In an in-vivo situation involving similar puncture wounds, the track of the semi-rigid needle is rarely present because the muscle and surrounding tissues tend to close around the puncture as the needle is removed, which can make the observation of bleeding more difficult. This lack of a needle track in the in-vivo situations could potentially complicate ultrasound targeting and transcutaneous HIFU treatment of arterial punctures in patients.

The tissue mimicking material which surrounds the channel should ideally have the same physical and acoustic properties as the human tissues that surround the blood vessels. Previous studies usually used tissue mimicking material based on agar, with added compounds to change gel properties (Frayne et al. 1993). For example, propanol and glycerol were used to increase the acoustic velocity, and cellulose particles and graphite were used to increase the attenuation (Frayne et al. 1993; Peopping et al. 2002; Rickey et al. 1995). In addition, formaldehyde was added to decrease compliance, increase melting point, and make the tissue mimicking material resistant to bacterial degradation (Peopping et al. 2002). In our studies, a 0.75% agarose gel was used as a tissue mimic that allowed good optical and ultrasound observation of the imbedded blood vessel. However, the attenuation of this gel was similar to water and thus it did not provide good mimicking of tissue attenuation properties (Greaby 2005). Developing a tissue mimicking gel that will have the acoustic and physical properties of human soft tissues while keeping the transparency would be very beneficial in the image-guided hemostasis studies (Lafon et al. 2005), allowing both good mimicking of transcutaneous HIFU treatment and easy visual observation of the injury site.

The phantom experiments can reduce the number of animals used in HIFU research and facilitate controlled and reproducible studies. The flow phantom described in this manuscript can be utilized in a variety of therapeutic and diagnostic ultrasound studies. In particular, our phantom studies provided preliminary results on the efficiency of Doppler-guided HIFU as a method for transcutaneous localization and sealing of peripheral vascular injuries, while preserving the vessel patency. We believe that our flow phantom can be a useful tool for development and optimization of ultrasound-guided HIFU hemostasis devices.

Acknowledgments

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Figure 1.
Schematic diagram of the flow phantom. ID-inner diameter.

Figure 2. Experimental setup for the image-guided HIFU treatment of arterial punctures, observed optically (a) and using ultrasound imaging (b).

Figure 3. Pulsed Doppler signal obtained in the flow phantom: a) with the plenum completely filled with water, b) with 6 ml of air in the plenum, and c) with 20 ml of air in the plenum. The horizontal axis represents time in s and the vertical axis represents flow velocity in cm/s. The pulse rate was 96 beats/min.

Figure 4.

Comparison of blood flow signal shapes obtained in the in-vivo artery and in the flow phantom. a) Pulsed Doppler velocity signal from the in-vivo human carotid artery. b) Pulsed Doppler velocity signal obtained in the flow phantom. The systolic velocity in the flow phantom could be adjusted in the 10–240 cm/s range. c) The pressure signal obtained during Pulsed Doppler velocity measurements shown in b).

Figure 5.

The artery (circled) was observed both optically through the agarose gel (a) and using Power Doppler ultrasound (b). When the vessel was punctured, a jet of blood (arrow) was observed optically (c) and also detected as a colored line in Power Doppler ultrasound images (d). When HIFU was applied to the puncture site, the bleeding visibly declined (e, arrow) and a hyperechoic spot (circle) appeared in the B-mode ultrasound image (f) at the location of HIFU focus. Hemostasis was confirmed visually (g) and using Power Doppler ultrasound (h). After the treatment, the vessel remained patent with no visible narrowing.

Figure 6.

a) Punctured porcine carotid artery sealed with HIFU. The puncture (arrow) is filled with clotted blood, and covered with a fibrin cap (arrowhead). b) An untreated vessel wall of the control artery.