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Targeted Long-Term Venous Occlusion Using Pulsed High-Intensity Focused Ultrasound Combined with a Pro-Inflammatory Agent

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Abstract

Esophageal and gastric varices are associated with significant morbidity and mortality for cirrhotic patients. The current modalities available for treating bleeding esophageal and gastric varices, namely endoscopic band ligation and sclerotherapy, require frequent sessions to obtain effective thrombosis and are associated with significant adverse effects. A more effective therapy that results in long-term vascular occlusion has the potential to improve patient outcomes. In this study, we investigated a new potential method for inducing long-term vascular occlusion by targeting segments of a rabbit's auricular vein *in vivo* with low duty cycle, high peak rarefaction pressure (9 MPa) pulsed high-intensity focused ultrasound in the presence of intravenously administered ultrasound microbubbles followed by local injection of fibrinogen and a pro-inflammatory agent (ethanol, cyanoacrylate or morrhuate sodium). The novel method introduced in this study resulted in acute and long-term complete vascular occlusions when injecting a pro-inflammatory agent with fibrinogen. Future investigation and translational studies are needed to assess its clinical applicability.

Index Terms

high-intensity focused ultrasound (HIFU); vessel occlusion; fibrinogen; pro-inflammatory agent; bubble cavitation; endothelial damage

Introduction

The development of a method that could safely induce rapid and durable vascular occlusion would result in a wide variety of clinical applications, from inducing hemostasis due to

bleeding from major trauma, tumors and rectal hemorrhoids to the treatment of varicose veins. One clinical situation that would especially benefit from occluding a vessel for therapeutic purposes is the treatment of esophageal and gastric varices. Esophageal and gastric varices develop as a consequence of portal hypertension in cirrhotic patients to create a collateral circuit to “bypass” the fibrosed portal venous system and return blood to the systemic circulation. In cirrhotic patients, 60–90% will develop esophageal and/or gastric varices in their lifetime and 30–40% of these varices will result in an upper gastrointestinal bleed. In patients who develop bleeding varices, 20–30% will die as a result of their initial variceal bleed and of the surviving patients, 70% will develop a recurrent variceal bleed within one year (Jensen 2002, Graham and Smith 1981). Esophageal and/or gastric varices are associated with significant morbidity and mortality in this growing patient population.

The first line of therapy for acute variceal bleeding is endoscopic band ligation or injection sclerotherapy. In addition to the risks of inducing further bleeding, mucosal ulceration and perforation, current endoscopic therapies have the inconvenience of requiring multiple endoscopic sessions for the treatment of esophageal and/or gastric varices due to the recurrence of varices and the inability to reliably occlude the entire varix during a single endoscopic session. Sclerotherapy has also been associated with serious, life-threatening complications such as acute respiratory distress syndrome (ARDS) and thromboembolic events (Chen *et al.* 2001; Cheng *et al.* 1998; Cohen *et al.* 1985; Schuman 1985; Schuman *et al.* 1987; Turler *et al.* 2001). A more effective and safer therapy to eradicate targeted varices is therefore needed to treat patients with bleeding varices.

The application of high-intensity focused ultrasound (HIFU) for inducing vascular occlusion by thermal coagulation has previously been reported (Delon-Martin *et al.* 1995; Hwang *et al.* 2003; Vaczy *et al.* 1998). Due to the observed collateral tissue damage caused by the thermal effects of HIFU, recent studies have begun to investigate cavitation-induced effects of pulsed high-intensity focused ultrasound (pHIFU) for vascular occlusion (Hwang *et al.* 2010). A recent study demonstrated the ability to induce vascular occlusion using low duty factor, high peak rarefaction pressure pHIFU without inducing any thermal tissue injury to the exposed tissue (Hwang *et al.* 2010). Inertial cavitation (IC) refers to the forceful oscillations of a bubble when exposed to an acoustic field, resulting in rapid expansion and subsequent collapse of a bubble. The violent collapse of a bubble can exert strong mechanical forces to nearby structures resulting in irreversible cell membrane damage and possibly cell death. Cavitation-induced vascular endothelial surface damage by pHIFU has been demonstrated in previous studies where the area of vascular injury served as a nidus for thrombus formation (Deng *et al.* 1996). This effect has been augmented in the presence of circulating ultrasound agents (UCA), which provide a nucleus for cavitation and also allow for significant reductions of the acoustic pressure threshold (Hwang *et al.* 2005; Hwang *et al.* 2006). Clot propagation was enhanced by injecting fibrinogen into the vessel following cavitation-induced damage to the endothelial surface (Hwang *et al.* 2010). Fibrinogen is a serum protein that is converted to fibrin by thrombin that will then polymerize within an existing fibrin clot, the final sequence in the coagulation cascade (Cotran *et al.* 1989). Injection alone of fibrinogen did not lead to vessel occlusion or to the development of distant thromboemboli (Hwang *et al.* 2010).

The sequence of intravenous injection of UCAs followed by pHIFU exposure then local injection of fibrinogen to targeted auricular veins in rabbits resulted in the formation of acute vascular occlusion (Hwang *et al.* 2010). However, these vascular occlusions were not durable over a 14 day period likely due to the inherent fibrinolytic system. Fibrinolysis is inhibited by plasminogen activator inhibitor-1, which in turn is upregulated in the setting of local inflammation due to the effects of interleukin-1 (Bevilacqua *et al.* 1986; Schleef *et al.* 1988). By eliciting a local inflammatory response with a pro-inflammatory agent, clot stability may be promoted by a down regulation or suppression of the fibrinolytic system. The hypothesis of this study is that long-term selective vascular occlusion is possible by damaging the endothelial surface of a targeted vein segment by applying low duty factor focused ultrasound pulses in the presence of circulating UCA followed by a local injection of fibrinogen and a pro-inflammatory agent.

Methods and Materials

Materials

Definity™ (Lantheus Medical Imaging, N. Billerica, MA, USA) was used for the ultrasound contrast agent, activated by shaking the vial for 45 seconds using a Vialmix™ (Lantheus Medical Imaging, N. Billerica, MA, USA). For all treatment arms 1.5 ml of Definity™ was diluted with 22.5 ml normal saline prior to use.

Fibrinogen was dissolved in a solution of a fibrinolysis inhibitor, aprotinin prior to injection (Tisseel VH fibrin sealant, Baxter Healthcare Corp., Westlake Village, CA, USA). The pro-inflammatory agents used in this study were 95% ethanol, cyanoacrylate (Indermil, Covidien, Mansfield, MA, USA) and sodium morrhuate (American Regent, Shirley, NY, USA), sodium salts of the fatty acids of cod-liver oil currently being used as a sclerosing agent for sclerotherapy of vessels.

Ultrasound Exposure

A clinical extracorporeal HIFU system (FEP-BY02, Beijing Yuande Bio-Engineering Ltd., Beijing, China) was used for this study, consisting of 251 individual PZT elements (center frequency of 1 MHz and diameter of 16 mm) arranged on a concave spherical surface and driven all in phase. The HIFU transducer had an outer diameter of 33.5 cm and an inner diameter of 12 cm with an integrated ultrasound imaging probe (S3, Logiq 5, GE, Korea) mounted in a central hole. The -6 dB beam size in the focal region was approximately 1.6 mm × 10 mm (lateral × axial) as measure with a hydrophone (HGL-0085, Onda, Sunnyvale, CA). Pressure measurements were performed using a fiber optic hydrophone (FOPH 2000, RP Acoustics, Leutenbach, Germany). Acoustic power measurements of the HIFU transducer was performed using a radiation force balance system. Ultrasound exposure conditions for all treatments were as follows: 9 MPa peak rarefaction pressure, 10 ms pulse, 1 Hz pulse repetition frequency (PRF), and 45 pulses per site. The time-averaged acoustic power was 0.19 W.

Experimental Protocol

New Zealand white rabbits weighing 4–5 kg each were used for these experiments, which were carried out according to National Institute of Health guidelines under a protocol approved by the Institutional Animal Care and Use Committee at the University of Washington. Rabbits were sedated with a subcutaneous injection of acetylpromazine (1.0 mg/kg)/ketamine (22 mg/kg) and then anesthetized with inhaled 1.5–2.5% isoflurane. The auricular surfaces were shaved and depilated to facilitate ultrasound coupling. To obtain intravenous (IV) access, a 21-gauge catheter was inserted into the proximal auricular vein of one ear. After achieving adequate anesthesia, the rabbit was placed on a platform connected with a 3-D motion stage with its ear mounted to a custom-built holder such that the targeted region of the auricular vein could be reliably positioned at the focus of the HIFU transducer. The ear within its custom-built holder was immersed into water tank filled with degassed water maintained at 36 to 37°C using a circulating water heater (VWR International, West Chester, PA). To minimize reflection from the water surface and standing wave formation, a phantom tissue, constructed of 6.5% Alginate impression material (Jeltrate, Dentsply International, York, PA) and acoustic absorber were stacked on top of the ear, distal from the HIFU transducer beam pathway. The orientation of the vessel was perpendicular to the HIFU axis. The targeted auricular vein was aligned to the HIFU focus under the guidance of B-mode or Color Doppler imaging. Targeted vessels were exposed at three sites 3 mm apart for 45 s each.

All animals were administered 2 ml of diluted Definity™ (UCA) IV followed by pulsed HIFU exposure, then injected with 0.1 ml of fibrinogen into the lumen of the targeted vessel. There were 3 treatment arms that were administered local injections (0.1 ml) of one of the following pro-inflammatory agents: ethanol, cyanoacrylate or morrhuate sodium into the thrombosed vessel. The control arm received an injection of saline (0.1 ml).

Evaluation of Vascular Occlusions

For the acute vascular occlusion studies, targeted vessels were evaluated one hour following treatment for evidence of vascular occlusion by the following three methods: 1) gross inspection of perfusion of infused normal saline via a catheter placed in the central auricular artery, 2) detection of flow with a Doppler ultrasound (72000, Escalon Vascular Access, New Berlin, WI) and 3) injection of Evan's blue dye upstream to the treated segment as a method of visual angiography where an occlusion had no flow of blue dye through the treated segment and no occlusion had blue dye visualized flowing through the treated segment.

The evaluation of vascular occlusions 14 days following treatment was determined by histologic examination only since Doppler and visual angiography with Evan's blue dye or normal saline could not distinguish between partially occlusive thrombi and no thrombi. Animals were either sacrificed one hour following treatment or recovered and monitored for an additional 14 days following treatment prior to euthanasia with an IV injection of sodium pentobarbital (120 mg/kg). Following euthanasia the auricular veins were dissected and fixed in a solution of 10% buffered formalin. Vessel segments were prepared for light microscopy by embedding the samples in paraffin. Embedded samples were sectioned and

stained with hematoxylin and eosin. The vessels were examined and graded as no thrombus, partial occlusive thrombus or complete occlusive thrombus by a single reviewer, experienced in histologic examination, blinded to the treatment protocol.

Statistical Analysis

The primary endpoints of both phases of the study were acute complete vascular occlusion and vascular occlusion 14 days following treatment. A Fischer's exact test was performed to compare the outcomes of the treatment arms to the control arm for both time points (acute and 14-day survival).

Results

Acute vascular occlusion

Acute vascular occlusion occurred in all treated vessels including control vessels. Figures 1A and 1B demonstrate a vessel prior to and immediately following pHIFU treatment. Mild erythema can be seen in the region of the treated vessel. There is no evidence of acute thermal injury.

Vascular Occlusion at Day 14

The results of vascular occlusion after 14 days following treatment for both the treatment arm with pro-inflammatory agents and the corresponding control arm are given in Table 1. All five rabbits treated with morrhuate sodium had complete vascular occlusion immediately and 14 days following treatment ($p = 0.002$). There was no evidence of significant local damage (e.g., ulceration) to the tissue surrounding the vessel treated with morrhuate sodium after 14 days (Figure 1C). In the group injected with cyanoacrylate, four of the five treated vessels demonstrated complete occlusion and one vessel had partial occlusion at day 14 ($p = 0.022$). A similar trend of vascular occlusion at day 14, although not statistically significant, was seen in vessels treated with ethanol where three out of five vessels treated with ethanol resulted in complete vascular occlusion ($p=0.099$). There was no statistically significant difference in complete vascular occlusion at day 14 between the three treatment groups.

Histological examination of vessels treated with all pro-inflammatory agents (ethanol, cyanoacrylate and morrhuate sodium) demonstrated a higher density of inflammatory cells, indicating an active inflammatory response, compared to control-treated vessels (pHIFU + UCA + fibrinogen). Figure 2A demonstrates a patent non-treated vessel. Figure 2B demonstrates a partially occluded vessel treated with pHIFU + UCA + ethanol. Figure 2C demonstrates a completely occluded vessel treated with pHIFU + UCA + fibrinogen + morrhuate sodium. No thermal or mechanical injury was observed by histology in all vessels treated with the pro-inflammatory agents used in this study.

Adverse Effects

There was no evidence of adverse systemic effects (acute or after 14 days) from local injection of fibrinogen or the pro-inflammatory agents with the exception of a mild local inflammatory response in the vessels treated with morrhuate sodium. All rabbits survived

until their planned date of sacrifice. There was no evidence of major ulceration, tissue damage or infection at the pHIFU-treated and injection sites 14 days post-treatment.

Discussion

This study confirms the ability to selectively and acutely occlude a targeted segment of a vein with pHIFU in the presence of circulating UCA followed by local injection of fibrinogen as previously reported (Hwang *et al.* 2010). More notably, this study demonstrates a novel method to induce *long-term* selective vascular occlusion of a targeted segment of a vein when a small volume (0.1 cc) local injection of the pro-inflammatory agent, morrhuate sodium, is added to the aforementioned sequence. These agents were chosen because of their current use as vessel sclerosants; however, the volumes used in this study are not sufficient to independently induce vascular occlusion. The proposed mechanism of achieving clot stability by locally injecting pro-inflammatory agents into clot is down-regulation or suppression of the fibrinolytic system via the up-regulation of plasminogen activator inhibitor-1 and interleukin-1, both of which are enhanced by local inflammation; however, we cannot conclusively confirm that this is the mechanism as the measurement of these cytokines and proteins were beyond the scope of this study. Histology in prior studies demonstrated that a significant inflammatory response does not occur as a result of pulsed HIFU treatment alone (Hwang *et al.* 2006; Tu *et al.* 2006). An elicited inflammatory response however was seen in this study in targeted vessels segments treated with morrhuate sodium where qualitatively a higher density of inflammatory cells was seen on histology compared to control. This gives evidence that a local intense inflammatory response does result in more durable vascular occlusions, which would be expected physiologically.

The use of the pro-inflammatory agent morrhuate sodium resulted in a local inflammation in the targeted vessel segment with no significant perivascular damage or systemic effects. This makes it an ideal method for vascular occlusion where no unintended injuries occurred. There were no adverse events observed in all the rabbits treated with our pro-inflammatory agents. All rabbits survived until their planned day of sacrifice. Despite initial local visible damage seen to the auricular vein after treatment with morrhuate sodium, histological examination revealed no thermal or mechanical damage at day 14 following treatment. On the contrary, other previous methods generating local inflammatory responses to obtain successful long-term occlusion of vessels have resulted in significant degrees of injury to the vessel and perivascular tissue (Schuman *et al.* 1985; Wahl *et al.* 2004).

Morrhuate sodium is presently used as a sclerosing agent for the treatment of varicose veins and gastrointestinal varices; however, our current approach differs from traditional endoscopic sclerotherapy for the treatment of bleeding varices. The sclerosing agent in our study is administered directly into the thrombus after a thrombus has already been formed, theoretically reducing any systemic administration and potential adverse effects associated with the drug (Schuman *et al.* 1985). The volume injected into the thrombus to illicit an inflammatory response is significantly less than what is needed to occlude a vessel with sclerotherapy, thereby minimizing local adverse effects such as ulceration and perforation.

Several improvements have been made to the HIFU experimental design since our last study. A clinical extracorporeal HIFU system was used instead of a custom-built transducer that required manual treatment of the auricular vessel (Hwang *et al.* 2005; Hwang *et al.* 2006). Pulses of HIFU were delivered instead of continuous exposure. Improved quality in auricular vein visualization resulted from the integration of a B-mode ultrasound imaging probe. This gave the advantage of more precise targeting of our focus. Continued redesign and developments to our HIFU set-up will better prepare our proposed protocol for future clinical use.

The novel method introduced in this study for inducing durable vessel occlusion has great potential for the clinical treatment of esophageal and/or gastric varices. Compared to the current available modalities available for bleeding varices, namely endoscopic band ligation and sclerotherapy, our proposed method would not require repeated procedures for effective vascular occlusion since long-term clot was observed. If effective variceal treatment could be administered in a single session, which would not only be more convenient to the patient but would also reduce the significant associated risks involved with endoscopy. The preliminary results of this study have also demonstrated a relatively safe modality to obtain effective vascular thrombosis. Sonication in the presence of circulating microbubbles may lead to local petechial hemorrhage and possible local hematoma formation; however, this is not likely to be of clinical significance. Only the targeted segment of vessel resulted in planned local intense inflammation with no significant collateral damage or systemic adverse effects seen. This was likely partly due to our enhanced HIFU design that allowed for direct visualization of the vessels being treated. Future translational studies will need to be investigated to determine its use for clinical application. An endoscopic HIFU device is currently in development to allow treatment of esophageal and gastric varices.

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Figure 1.

Treatment of a segment of the auricular vein (A) prior to treatment, (B) following treatment with US in the presence of circulating UCA, (C) following injection of fibrinogen and morrhuate sodium, and (D) 14 days post-treatment. Black bracket defines the segment of vessel treated.

Figure 2.

Representative cross-sectional H&E image of an auricular veins at 14 days post-treatment with pHIFU in presence of circulating UCA and following injection of (A) fibrinogen without presence of thrombus (B) ethanol with presence of a non-occlusive thrombus, and (C) morrhuate sodium a complete intravascular thrombus and inflammatory response.

Table 1

Observed frequencies of vascular occlusion 14 days following treatment by treatment group with pro-inflammatory agents

	pHIFU + UCA + Fibrinogen	pHIFU + UCA + Fibrinogen + EtOH	pHIFU + UCA + Fibrinogen + Cyanoacrylate	pHIFU + UCA + Fibrinogen + Morrhuate Sodium
Occlusion	2	3	4	5
Partial Occlusion	8	1	1	0
No occlusion	3	1	0	0
Totals	13	5	5	5
<i>p</i> -value	--	0.099	0.022	0.002

Abbreviations: pHIFU- pulsed high-intensity focused ultrasound; UCA – ultrasound contrast agent; EtOH – alcohol.