### **BASIC RESEARCH STUDIES**

# A portable high-intensity focused ultrasound device for noninvasive venous ablation

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*Background:* Varicose veins and other vascular abnormalities are common clinical entities. Treatment options include vein stripping, sclerotherapy, and endovenous laser treatment, but all involve some degree of invasive intervention. The purpose of this study was to determine ex vivo the effectiveness of a novel hand-held, battery-operated, high-intensity focused ultrasound (HIFU) device for transcutaneous venous ablation.

*Methods:* The ultrasound device is  $14 \times 9 \times 4$  cm, weighs 650 g, and is powered by 4 lithium ion battery packs. An ex vivo testing platform consisting of two different models comprised of sequentially layered skin-muscle-vein or skin-fat-vein was developed, and specimens were treated with HIFU. The tissues were then disassembled, imaged, and processed for histology. The luminal cross-sectional area of vein that had been treated with HIFU and nontreated controls were measured, and the values presented as median and interquartile range (IQR). The values were compared using a Wilcoxon rank-sum test, and statistical significance was set at P < .05.

*Results:* On gross and histologic examination, veins that had been treated with HIFU showed evidence of coagulation necrosis. The surface of the muscle in direct contact with the vein had a pinpoint area of coagulation, whereas the adjacent fat appeared undisturbed; the skin, fat, and the surface of the muscle in contact with the transducer remained completely unaffected. The cross-sectional area was 3.79 mm<sup>2</sup> (IQR, 3.38-4.22) of the control vein lumen and 0.16 mm<sup>2</sup> (IQR, 0.04-0.39) in those that had been treated with HIFU (P = .0304).

*Conclusion:* This inexpensive, portable HIFU device has the potential to allow clinicians to easily perform venous ablation in a manner that is entirely noninvasive and without the expense or inconvenience of large, complicated devices. This device represents a significant step forward in the development of new applications for HIFU technology. (J Vasc Surg 2009;=:===.)

*Clinical Relevance*: Although sclerotherapy, radiofrequency ablation, and endovenous laser treatment are less invasive than previous surgical treatments for varicose veins, they are still invasive procedures and have concomitant risks, complications, and expenses. The development of a transcutaneous, noninvasive treatment modality holds significant promise for the treatment of varicose veins and venous malformations.

Varicose veins affect approximately 30 million Americans.<sup>1</sup> The underlying etiology of this condition invariably involves venous valvular incompetence, and if untreated, varicosities and the concomitant venous hypertension can lead to significant morbidity in addition to an unpleasant cosmetic appearance. If lifestyle modification and other conservative treatments are not successful, a number of surgical options may be offered. Vein stripping and vein

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ligation had been commonly performed procedures but have been largely supplanted by less invasive methods, including sclerotherapy, radiofrequency ablation, and endovenous thermal ablation (EVLT).<sup>2,3</sup> Even these minimally invasive methods, however, require a surgical procedure and carry the risk of complications such as phlebitis, bruising, blood clots, skin ulceration, and infection.<sup>4</sup> Although much less common, venous malformations may also cause significant morbidity and are currently treated primarily by the same minimally invasive techniques.<sup>5</sup>

Ultrasound (US) imaging has been available for many decades as a diagnostic modality that allows for visualization of tissues by penetrating a medium and measuring the reflection.<sup>6</sup> In addition to the commonly used diagnostic applications, this technology has many potential therapeutic applications. Because the transducer of this high-intensity ultrasound (HIFU) device is concave, the beam of acoustic waves is conical and thereby focuses the energy onto a single focal point, inducing precise tissue necrosis without

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Fig 1. The ultrasound device is  $14 \times 9 \times 4$  cm, and weighs 650 g. The diameter of the transducer is 3 cm.

any untoward effect on surrounding and intervening tissue. If it is necessary to thermally ablate a larger volume of tissue, the beam is focused at multiple locations. HIFU is currently being used in conjunction with magnetic resonance imaging and US imaging in select clinical situations for the treatment of uterine fibroids and lipomas, the delivery of drugs to the brain, and the sealing of blood vessels.<sup>7-11</sup>

The technology and means of application are highly variable, with intensity ranging from 0.5 to 9000 W/cm<sup>2</sup>, and with most requiring some degree of invasiveness to apply the US beam to the tissue of interest. However, all HIFU generators currently in clinical use are bulky (frequently >20 ft<sup>3</sup> in total), cumbersome, and expensive, thereby hindering the broad application of this promising technology.<sup>12</sup>

In contrast, we have developed a novel, hand-held, battery-operated HIFU device. To our knowledge, no peer-reviewed articles have reported the use of US in a completely noninvasive transcutaneous fashion for the ablation of pathologic veins. The purpose of this study was to determine the efficacy of our HIFU device for completely noninvasive venous ablation. To do so, an ex vivo testing platform was developed to determine the ability of the device to ablate the venous lumen without affecting surrounding and intervening tissues.

#### MATERIALS AND METHODS

**HIFU device.** The HIFU device used in this study (Fig 1) was developed in the Department of Biomedical Engineering at Cornell University.<sup>13,14</sup> It weighs 650 g and is housed in a 14-  $\times$  9-  $\times$  4-cm watertight plastic enclosure (No. 073; Serpac, Fareham, United Kingdom) that contains an ultra efficient low-power US-generating circuit and four 7.4-volt, 2200 milliampere/h lithium ion rechargeable battery packs (No. 18650 Battery Space, Richmond, Calif) connected in series through a dual-draw rotary switch.<sup>15</sup> The user can adjust power delivery to the



**Fig 2.** Diagrammatic representation of ultrasound system and transducer probe shows the three ultrasound energy standoffs. The shorter the transducer standoff, the deeper the ultrasonic energy penetration and focal ablation region; the longer the standoff, the less penetration of energy.

transducer probe to one of three settings through the rotary switch interface in 7.4-volt increments over the range of  $\pm$  14.8 volts. A battery recharge adapter at the back of the system is wired to charge the complete system in less than 30 minutes.

The US probe is constructed from lead zirconate titanate (PZT-4), 1.54-MHz, and 3-cm-diameter piezoelectric ceramic with a radius of curvature of 3.81 cm (EBL Products, East Hartford, Conn). The air-backed ceramic is housed in a polyvinyl chloride ergonomic plastic assembly that was built on a lathe and milling system in the Department of Biomedical Engineering. The transducer was constructed with multiple interchangeable clear acrylic fronts to act as protective covers to the ceramic and focal standoffs to allow the user to select the appropriate plane and depth of focused US energy (Fig 2).

The portable HIFU device was calibrated with a force balance and electroacoustic conversion factors with electrical impedance spectroscopy. The device supplies continuous US power and at the three different power settings, delivers the following intensities to the focal point: low power, 3.5 to  $4 \text{ W} (230-350 \text{ W/cm}^2)$ , medium power, 7.8



**Fig 3.** The skin-muscle-vein model is shown (left) before ultrasound treatment and (right) after ultrasound treatment. Note the lack of coagulation necrosis of the skin, the minimal area of coagulation necrosis on the surface of the muscle that had been in direct contact with the vein (*arrow*), and the distinct contraction of the vein.



Fig 4. Skin-fat-vein model is shown (left) before ultrasound treatment and (right) after ultrasound treatment. Note the lack of coagulation necrosis of the skin (*left*) and fat (*middle*), and the distinct contraction of the vein (*right*).

to 8.5 W (520-790 W/cm<sup>2</sup>), and high power, 14 to 15 W (930-1400 W/cm<sup>2</sup>).  $^{13}$ 

Testing platform. Because our current device has not vet incorporated a visualization mode, an ex vivo testing platform was developed that involved the sequential layering of combinations of skin, muscle, fat, and vein, which allows for direct side-view real-time visualization. The first model was a combination of skin, muscle, and vein (Fig 3). The skin segment  $(3 \times 3 \text{ cm})$  was harvested from a Sprague-Dawley rat. The rat was anesthetized, shaved, depilated, skin was removed from the ventral surface, after which the animal was euthanized. This protocol was approved by the Weill Cornell Medical College Institutional Animal Care and Use Committee (#0704-607A), and all work was performed in compliance with the Guide for the Care and Use of Laboratory Animals.<sup>16</sup> The muscle and vein were harvested from a lamb hind limb that was obtained from a local butcher shop. A segment of muscle  $(3 \times$  $3 \times 3$  cm) that had been cleaned to remove all traces of fascia or fat was placed on top of the skin, and a 3-cm segment of femoral vein was pinned in place on top of the muscle.

The second model involved a combination of skin, fat, and vein (Fig 4). The skin and vein were obtained in the same fashion. Fat from a freshly slaughtered pig was obtained from the same butcher shop. The third model involved the same combination as in the second, except



**Fig 5.** A segment of vein in skin-fat-vein model filled with heparinized rat blood is shown (**left**) before and (**right**) after treatment with the high-intensity focused ultrasound device.

that the vein was filled with rat blood that had been collected after systemic anticoagulation with heparin (200 U/kg; Fig 5).

**Experimental design.** To minimize resistance in both models, the skin was thoroughly moistened with

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phosphate-buffered saline (PBS), and the muscle was injected with PBS (1.75 mL). The transducer was filled with US transmission gel (National Medical Alliance; Carmel, Ind) placed directly beneath the skin and activated for 20 seconds, deactivated for 10 seconds, and reactivated for 20 seconds. The tissue was disassembled after each experiment was completed, and photographs were taken to record the gross appearance. The experiment was repeated in triplicate in each model.

**Tissue processing and histology.** Samples of vein that were treated with HIFU were processed for histology by first being fixed in 10% buffered formalin for 24 hours, then dehydrated and embedded in paraffin. Non-HIFU-exposed controls were processed for frozen sectioning in the same manner. Ten-micrometer sections were stained with hematoxylin and eosin, and bright field photomicrographs were taken with an upright microscope (Nikon, Tokyo, Japan). The slides were reviewed by a blinded pathologist from the Department of Pathology.

Luminal area measurement and statistical analysis. The luminal cross-sectional area of vein that had been treated with HIFU (n = 6) and nontreated controls (n = 6) were measured, and values were presented as median mm<sup>2</sup> and interquartile range (IQR). The values were compared using a Wilcoxon rank-sum test, and statistical significance was set at P < .05.

#### RESULTS

On gross examination, coagulation of the vein was observed in the region that had been treated with HIFU (Figs 3 and 4). The surface of the muscle in direct contact with the vein had a pinpoint area of coagulation, whereas the skin, fat, and the surface of the muscle in contact with the transducer remained completely unaffected. Similar findings were observed in the blood-filled vein, with significant contraction of the vein at the region treated with HIFU (Fig 5).

On histologic examination, a marked narrowing of the venous lumen was observed in the veins that had been treated with HIFU (Fig 6). This was due to coagulative-type necrosis and loss of elastic fibers in the adventitia, and marked edema and constriction of the media. The skin was completely undamaged. The luminal cross-sectional area of veins treated with HIFU was 0.16 mm<sup>2</sup> (IQR, 0.04-0.39), which was significantly different than the 3.79 (IQR, 3.38-4.22) for untreated veins (P = .0304).

#### DISCUSSION

The significant disadvantage common to all currently available minimally invasive surgical techniques for venous ablation is that they are all, to some degree, invasive. In response to the desire for a completely noninvasive method for the venous ablation, we have developed a novel therapeutic US device, which was tested in this ex vivo study. The results clearly indicate the effectiveness of our device in producing a 96% reduction in venous luminal area without affecting the intervening tissue. With a mean luminal cross-sectional area of 0.16 mm<sup>2</sup>, we suspect that thrombosis and



**Fig 6.** A section of vein is shown that **(left)** had not been treated with the high-intensity focused ultrasound (HIFU) device and **(right)** which had been treated with HIFU. Treatment resulted in a 96% reduction in luminal area. Hematoxylin and eosin staining at original magnification ×40.

complete occlusion of the vein will occur in vivo. The qualitative gross and histologic results are impressive, and importantly, are strengthened by the statistically significant decrease in luminal diameter observed in veins that had been treated with HIFU.

Furthermore, the therapeutic effect of the US energy is not affected by the presence of blood or the proteins or fluid content contained therein, indicating that this technology is likely to be effective in the setting of dilated, blood-filled vessels. Because of limitations in visualization, we were not able to test an in vivo model with flowing blood. Such flow within the vessel may possibly change the application parameters, and this will be a focus of our next round of studies that incorporate a visualization mode.

The development of a transcutaneous, noninvasive method for the treatment of varicose veins has a number of significant challenges.<sup>17-19</sup> The primary difficulty results from the variable resistance of different tissues between the transducer and the target tissue, in this case, skin, muscle, fat, and vein, with skin having the highest resistance. The conical pattern of the US waves is helpful in solving this problem by having lower energy density at points closer to the transducer. Furthermore, by incorporating PBS into the skin and fat (by applying it to the external surface) and muscle, the resistance of the intervening tissues was decreased enough to nearly eliminate any undesired collateral thermal damage. The injection of this physiologic electrolyte solution is analogous to the use of tumescent solution in liposuction and EVLT procedures, which induces both analgesia and provides thermal insulation to the adjacent tissues.<sup>20</sup>

The ex vivo model used in this study provides important preliminary data to validate the use of our novel underlying technology for the completely noninvasive ablation of veins. It was designed because our current devices lack the ability to directly visualize the target vein during

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treatment. Although this represents a major limitation to clinical application, our next-generation devices will be capable of rapidly alternating between therapeutic and diagnostic (M-mode) US power levels, thereby "splicing" together the modes and avoiding the distortion of the visual image that results from high power levels. We believe that accurate real-time visualization will allow the user to safely focus the HIFU on the target vein thus avoiding adjacent structures, including arteries and nerves.

#### CONCLUSIONS

Although this novel device is still a prototype, we believe it represents a significant step forward in the development of new applications for high-intensity, therapeutic US technology. We believe that this relatively inexpensive, portable device may provide clinicians with the ability to perform venous ablation of venous varicosities and malformations in a manner that is entirely noninvasive, painless, and logistically easily performed without the expense or inconvenience of large, complicated devices.

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#### AUTHOR CONTRIBUTIONS

Conception and design: PH, GL, WO, JS Analysis and interpretation: PH, GL, NS, AL, AW, WO, JS Data collection: PH, NS, AS Writing the article: PH, NS Critical revision of the article: NS, GL, AL, AW, WO, JS Final approval of the article: PH, WO, JS Statistical analysis: PH, AW Obtained funding: WO, PH Overall responsibility: JS

#### REFERENCES

- Kouri B. Current evaluation and treatment of lower extremity varicose veins. Am J Med 2009;122:513-5.
- Gohel MS, Davies AH. Radiofrequency ablation for uncomplicated varicose veins. Phlebology 2009;24(suppl 1):42-9.

- Min RJ, Khilnni N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long-term results. J Vasc Interv Radiol 2004;15:203.
- Mundly L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. Br J Surg 2005;92:1189-94.
- Pappas DC, Persky MS, Berenstein A. Evaluation and treatment of head and neck venous vascular malformations. Ear Nose Throat J 1998;77: 914-22.
- Dalecki D. Mechanical bioeffects of ultrasound. Annu Rev Biomed Eng 2004;6:229-48.
- Funaki K, Fukunishi H, Funaki T, Kawakami C. Mid-term outcome of magnetic resonance-guided focused ultrasound surgery for uterine myomas: from six to twelve months after volume reduction. J Minim Invasive Gynecol 2007;14:616-21.
- Zderic V, O'Keefe GE, Foley JL, Vaezy S. Resection of abdominal solid organs using high-intensity focused ultrasound. Ultrasound in Med and Biol 2007;33:1251-8.
- Sung HY, Cho SH, Kim JI, Cheing DY, Han J-Y, Kim JK, et al. High intensity focused ultrasound therapy resulted in a complete response in a patient with advanced gastric cancer with liver metastases: a case report. Eur J Gastroent Hepatol 2008;20:707-9.
- White WM, Makin IRS, Slayton MH, Barthe PG, Glidich R. Selective transcutaneous delivery of energy to porcine soft tissues using intense ultrasound (IUS). Lasers Surg Med 2008;40:67-75.
- Damian DL, Yiasemides E, Gupta S, Armour K. Ultrasound therapy for lipodermatosclerosis. Arch Dermatol 2009;145:330-1.
- 12. Ishikawa T, Okai T, Sasaki K, Umemura S-I, Miyazaki N, Kushima M, et al. Sequential changes in rat femoral artery blood flow and tissue degeneration after exposure to high-intensity focused ultrasound. J Med Ultrasonics 2008;35:177-82.
- Lewis GK, Olbricht WL. Development of a portable therapeutic and high intensity ultrasound system for military, medical, and research use. Rev Sci Instrum 2008;79:1-7.
- Lewis GK, Wang P, Lewis GK Sr, Olbricht WL. Therapeutic ultrasound enhancement of drug delivery to soft tissue. 8th International Symposium On Therapeutic Ultrasound. AIP Conference Proc 2009;2113: 403-7.
- Lewis GK, Olbricht WL. Ultrasound wave generating apparatus. PCT Patent Application No. PCT/US2009/50297.
- Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Guide for the care and use of laboratory animals. Washington, DC: National Academy Press; 1996.
- Angel YC, Pichardo S, Salomir R, Petrusca L, Chapelon JY. Testing of a HIFU probe for the treatment of superficial venous insufficiency by using MRI. EMBS Annual International Conference 2006:3533-6.
- Pichardo S, Milleret R, Curiel L, Pichot O, Chapelon J-Y. In vitro experimental study on the treatment of superficial venous insufficiency with high-intensity focused ultrasound. Ultrasound Med Biol 2006;32: 883-91.
- Delon-Martin C, Vogt C, Chignier E, Guers C, Chapelon JY, Cathignol D. Venous thrombosis generation by means of high-intensity focused ultrasound. Ultrasound Med Biol 1995;21:113-9.
- Potter JK, Finn R, Cillo J. Modified tumescent technique for outpatient facial laser resurfacing. J Oral Maxillofac Surg 2004;62:829-33.

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