Imaging of vascular malformations with a high-intensity focused ultrasound probe for treatment planning

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ABSTRACT

Objective: We aimed to investigate whether a current commercially available high-intensity focused ultrasound (HIFU) probe can adequately image targeted vascular malformations (VMs) in anticipation of HIFU treatment planning and delivery.

Methods: We enrolled 10 consecutive patients who were scheduled to undergo treatment of symptomatic peripheral VMs confirmed by routine preoperative contrast-enhanced magnetic resonance imaging and soft tissue duplex ultrasound. The lesions were situated no more than 6 cm from the skin. After induction of general anesthesia and before surgical intervention, we prepared and positioned the Sonablate HIFU probe (SonaCare Medical, LLC, Charlotte, NC) to obtain multiple B-mode images of the targeted VM in the transverse and longitudinal dimensions. We then rated the quality of the images and the feasibility of the imaging process itself using a previously devised questionnaire aimed at evaluating the adequacy of the images for potential HIFU treatment planning and delivery. The patients subsequently underwent surgical intervention and clinical follow-up for their VM per the standard protocol.

Results: The study included 10 participants aged 21 to 67 years (mean ± standard deviation, 36.5 ± 16.5 years). Six patients (60%) identified as female. The VMs imaged consisted of eight venous (80%), one lymphatic (10%), and one combined lymphovenous (10%) malformation. The lesions were in the extremities only (50%), trunk only (20%), trunk and extremities (20%), or neck and extremities (10%). Pain related to the VM was present in all 10 patients (100%). In all 10 patients, the boundary and location of the VM could be visualized via the HIFU probe despite the diminished B-mode imaging resolution. The absence of Doppler functionality in the HIFU probe did not prevent the identification of the VMs in any patient up to a depth of 6 cm. The results from the postimaging survey showed that difficulty in preparing the study device for imaging was 1.1 ± 0.3 and difficulty in use was 1.1 ± 0.1, with a score of 1 equal to easy and 5 to difficult. The stability of the acoustic coupling to the patient was 1.3 ± 0.2, with a score of 1 representing very stable.

Conclusions: We were able to ultrasonically identify and outline all targeted peripheral VMs using a commercially available HIFU probe in anticipation of treatment planning and delivery. Baseline magnetic resonance imaging and soft tissue duplex ultrasound remain essential tools for guiding probe placement and HIFU imaging. (J Vasc Surg Venous Lymphat Disord 2021;9:1467-72.)

Keywords: High-intensity focused ultrasound; Lymphatic malformation; Minimally invasive treatment; Vascular malformation; Venous malformation

Vascular malformations (VMs) are congenital lesions that arise from abnormal vascular development due to somatic mosaic mutations within the affected endothelial cells.[1-3] No definitive cure or Food and Drug Administration (FDA)—approved treatment modality currently exists. The commonly used treatment techniques vary widely, depending on physician expertise, experience, and preference, and have had variable success, recurrence, and complication rates.[3-8] A need exists for a more definitive, durable, and safe therapeutic modality.

Recent insight into the pathogenesis of VMs has provided information regarding the prominent role endothelial cells play in the formation and propagation of VMs.[9,10] Existing clinical experience with potent, but toxic, embolic agents, such as absolute ethanol, which destroy endothelial cells via protein denaturing properties has rendered further support to this concept.[5,6] Therefore, destruction of endothelial cells within VMs represents a key therapeutic maneuver to achieve durable ablation and lesion regression. However, this process must be performed in a precise and localized fashion to avoid adjacent tissue injury and unwanted necrosis.

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High-intensity focused ultrasound (HIFU) is a minimally invasive technology that uses focused ultrasound (US) waves to ablate targeted tissue within the body without ionizing radiation.[11] Through the precise delivery of US waves, HIFU is able to rapidly elevate the temperature of the targeted tissue, leading to disruption of the lipid membranes, denaturation of proteins, destruction of vascular endothelial cells, and, ultimately, coagulative necrosis without damage to the surrounding tissue.[12-15] These physiologic processes are key elements in achieving durable ablation and regression of VMs.

At present, it is unclear whether the US functionality of current commercially available HIFU probes can provide the necessary imaging quality required to identify and map in multiple dimensions the extent of the targeted malformation as an essential first step for HIFU treatment planning and delivery.

The Sonablate system (SonaCare Medical LLC, Charlotte, NC) was designed specifically for US-guided ablation of prostatic tissue using a transrectal probe, capable of both ultrasonically imaging the tissue and ablating the tissue using HIFU. The Sonablate system received FDA approval for the indication of prostatic tissue ablation in December 2016 [FDA, 510(k) premarket notification no., K160942] and is being used worldwide for this purpose.[16-18]

The purpose of the present study was to investigate whether the US imaging capability of the Sonablate HIFU probe would be sufficient for imaging peripheral VMs in anticipation of future HIFU treatment planning and delivery.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, prospective, phase 0 pilot study
- **Key Findings:** The boundary and location of the vascular malformation were visualized in all 10 study patients via a high-intensity focused ultrasound probe despite diminished B-mode imaging resolution. Preparation and use of the device occurred with minimal difficulty and stable acoustic coupling.
- **Take Home Message:** It is possible to ultrasonically identify and outline peripheral vascular malformations using a commercially available high-intensity focused ultrasound probe in anticipation of treatment planning and delivery.

METHODS

The Sonablate system consists of a console, a transrectal probe, an articulated positioning arm, and a water management/chilling unit (Fig 1, *A*). The console is used to control the US imaging and HIFU ablation functions of the system. The articulated arm is used to precisely position and orient the probe such that the region being imaged and/or ablated is positioned in front of the probe tip, which houses the combined US imaging and HIFU transducer. The probe also houses two motors that control the linear position and sector orientation of the transducer.

The transducer consists of an outer element and an inner piezoelectric element. The outer element is used to generate the HIFU required for tissue ablation. Its spherical and concave shape focuses the US wave emanating from its surface, creating the transducer's focal zone. Tissue located within the focal zone can be ablated with HIFU owing to the rapidly induced temperature elevation to >55°C as the US energy is absorbed. The tissue located outside the focal zone will be spared, enabling a targeted and noninvasive therapy. The size of the focal zone is fixed such that each HIFU sonication ablates a typical 3 × 3 × 12-mm tissue volume within 3 seconds. The inner element is used to generate the US signals required to implement the pulse-echo US imaging functionality of the system. Translating and rotating the transducer using the motors in the probe enables the system to ablate tissue via the superposition of individual focal lesions.

US images are generated by the Sonablate device by mechanically translating or rotating the single-element US imaging transducer, which is integrated in the transducer assembly of the probe tip. Linearly translating the transducer within the probe tip creates a two-dimensional linear (sagittal) image. Rotating the transducer within the probe tip generates a two-dimensional sector (transverse) image. These images are used to align and position the probe such that the region targeted for ablation will be located within the focal zone of the HIFU transducer. The imaging transducer has a center frequency of 6.5 MHz and a mechanical index of <1 (FDA mandate: mechanical index of ≤1.9).

Finally, the water management/chiller unit circulates chilled and degassed water around the transducer in the probe tip, which is covered by a distensible and acoustically transparent sheath that creates a closed water volume around the probe tip. The water and sheath provide a path for the US energy to couple into the patient for imaging and ablation and cools the HIFU transducer during operation. Furthermore, by adjusting the water volume within this closed system, the distance between the probe tip and the tissue can be adjusted to allow positioning of the target region within the HIFU transducer's focal zone in preparation for ablation.

Because the ideal scenario for HIFU treatment entails focal ablation of targeted lesions without non–target ablation of the intervening skin and soft tissue structures, the Sonablate probe was specifically chosen for its on-label designation as an intervention tissue-sparing HIFU device.

Participants were recruited from December 1, 2019 to October 31, 2020 through a single clinical site. All the patients scheduled for treatment of VMs that lacked central

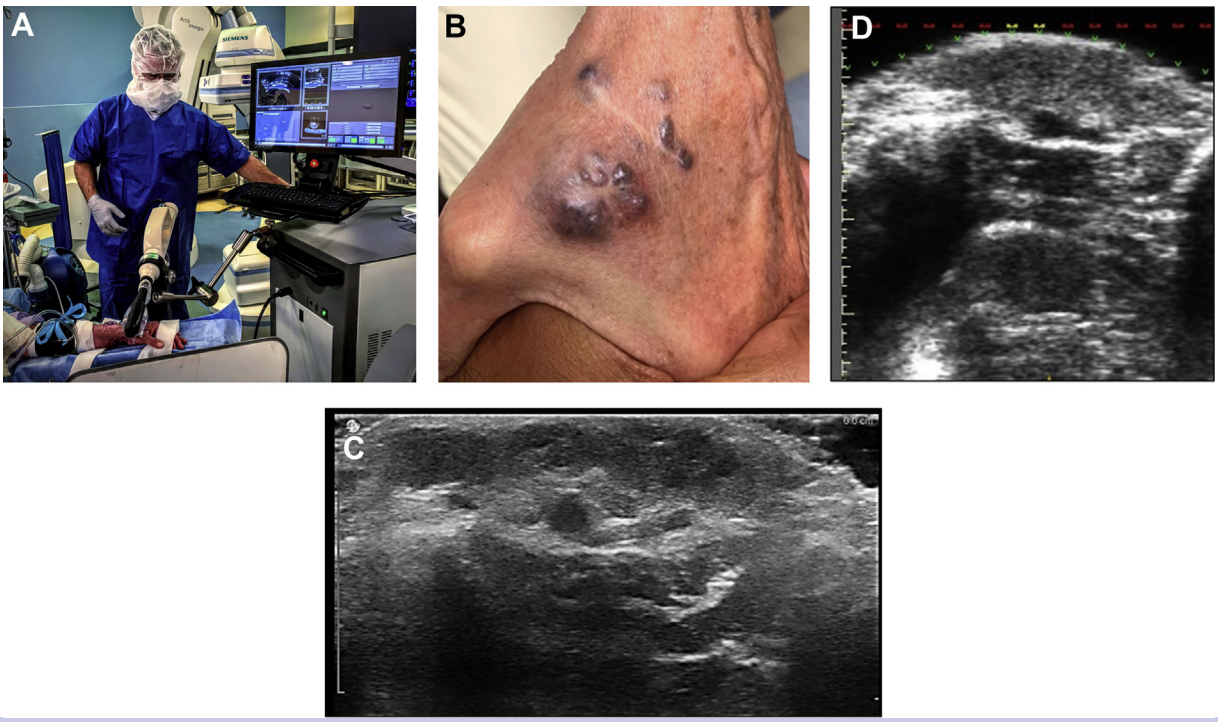

Fig 1. A, Demonstration of Sonablate high-intensity focused ultrasound (HIFU) probe placement using the adjustable probe arm and associated software and the program used for scanning and imaging the targeted region of the body. This is the platform via which HIFU treatment planning and, ultimately, treatment delivery would be performed. **B,** Venous malformation (VM) on the dorsum of the left hand first web space in a patient with blue-rubber bleb nevus syndrome. Note the healed surgical incision from a previous failed attempt at excision. **C,** Preoperative diagnostic ultrasound (US) B-mode imaging of the same lesion. **D,** Sonablate probe B-mode US image demonstrating the outline, contour, borders, depth, and traversing anomalous vasculature of the same lesion.

nervous system involvement and were <6 cm from the skin were invited to participate. The study population included 10 adults with symptomatic, peripheral (no central nervous system involvement and excluding the head) VMs <6 cm from the skin surface who had undergone additional intraprocedural imaging of their VM with the Sonablate probe immediately before treatment with direct-stick embolization and/or surgical excision. All 10 patients provided written informed consent, and all the patients were under the care of the same treating physician, who also served as the operator of the study device. The patients had previously undergone preoperative soft tissue duplex US and contrast-enhanced magnetic resonance imaging (MRI) in accordance with the routine preoperative protocol. To assess whether the US imaging function of the Sonablate probe was adequate for identifying and outlining VMs, a set of ~10 to 20 US images that included the VM in the field of view were collected for each patient (Fig 1, *B-D*).

Before Sonablate imaging, the skin surface overlying the targeted VM was shaved and marked in accordance with the usual standard protocol for embolization. After the induction of general anesthesia, an US coupling gel was applied to the skin surface overlying the VM, the articulated probe arm was mounted to the operating room table's side rail in close proximity to the VM, and the probe was positioned within and held in place by the probe arm, ensuring that its orientation and position were suitable for imaging the desired region located in front of its probe tip and that adequate acoustic coupling existed between the sheath and the probe tip. The tourniquet (Fig 1, *A*) was not used during the imaging portion of the procedure. The tourniquet was used selectively at the discretion of the treating surgeon away from the sterile field during the embolization portion of the procedure. When used, it was insufflated to just above the diastolic pressure with various durations of insufflation, depending on the length and extent of the embolization procedure. This technique has been expounded extensively in previous reports.[3,19] The position of the probe, articulated arm, and probe tip water volume were adjusted until good coupling had been achieved and the targeted VM was centrally located within the probe's imaging planes. Next, the Sonablate probe was used to collect images at various angles, probe orientations, and probe positions to replicate the image orientation and probe placement that had been used with the diagnostic US scanner.

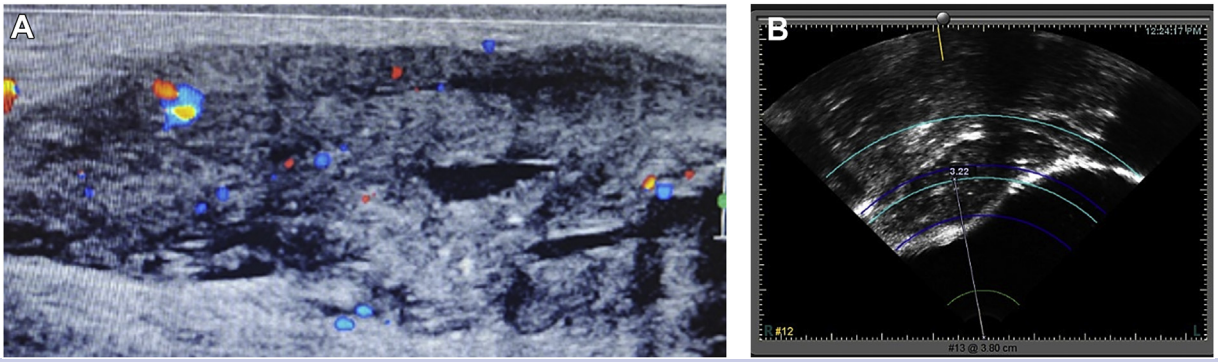

Fig 2. A, Duplex ultrasound B-mode image with color-flow Doppler revealing a venous malformation (VM) of the left neck and shoulder with interspersed macrocytic lymphatic channels. **B,** high-intensity focused ultrasound (HIFU) B-mode imaging of one portion of this large VM in a transverse window demonstrating the extent and contour of the lesion at a depth of 3.22 cm from the skin.

The primary end point of the present study was to investigate whether the imaging quality of the Sonablate device was adequate for identifying and outlining the targeted VMs. Assessment of the imaging quality of the Sonablate probe was conducted using a set of questions that were answered by the probe operator. The secondary end point of the study evaluated the ease of use of the Sonablate device for VM imaging, because the steps in setting the Sonablate probe for imaging are exactly the same as setting the probe for HIFU therapy. This was assessed in the form of a survey that was completed by the probe operator immediately after imaging. The full versions of both sets of questions were developed jointly by us based on previous experience in the prostatic realm and are included in the Appendix (online only).

The Yale University institutional review board approved the present study on April 29, 2019 (approval no. HRP-503 B).

RESULTS

The present study included 10 participants, with an age range of 21 to 67 years (mean ± standard deviation, 36.5 ± 16.5), 6 (60%) of whom had identified as female (Supplementary Table I, online only). The types of VMs imaged included eight VMs (80%), one lymphatic malformation (10%), and one combined lymphovenous malformation (10%). The VMs were categorized by location: extremities only (50%), trunk only (20%), trunk and extremities (20%), and neck and extremities (10%). Pain related to the VM was present in all 10 patients (100%). Other presenting symptoms included functional impairment (80%), cosmetic disfigurement (30%), and swelling (30%).

In all 10 patients, the boundary and location of the VM could be visualized using the Sonablate probe, and the shape and size of the visualized lesion were sufficiently similar to the diagnostic scanner's image (Fig 2, *A* and *B*; Supplementary Fig, online only; Supplementary Table II, online only). Although the overall boundaries and contours of the malformations were appreciated using the Sonablate probe, the diagnostic probe showed better imaging resolution that provided a clearer delineation in all patients. The absence of Doppler functionality in the Sonablate images did not prevent the identification of VMs in any of the patients, and the Sonablate's signal/noise ratio was sufficient for imaging lesions up to a depth of 6 cm. The detail provided by the Sonablate images was not sufficient in any of the cases for VM subtype stratification.

The ease of use of the Sonablate probe for VM imaging was assessed using a postimaging survey that focused on the difficulty in preparing and using the probe and the probe's stability during imaging. The difficulty in preparing the probe was gauged with multiple questions using a scale of 1 to 5, with 1 equal to easy and 5 equal to difficult. The average score for all questions related to the difficulty of preparing the probe for imaging was 1.1 ± 0.3. The difficulty of use during imaging was assessed in a similar fashion, and the average score for all pertinent questions was 1.1 ± 0.1. The stability of the probe was evaluated using two parameters: the stability of the acoustic coupling of the probe to the patient and the effects of patient motion on the stability of the coupling, with a score of 1 representing very stable and no effects, respectively. The average score for those questions was 1.3 ± 0.2.

DISCUSSION

In the present phase 0 pilot study, we have demonstrated the US imaging feasibility of the Sonablate HIFU probe as an essential preliminary step for HIFU treatment planning of peripheral VMs using current commercially available technology. New treatment opportunities for HIFU are constantly evolving,[20-23] and the feasibility of HIFU for the treatment of VMs has been investigated by other groups, with encouraging initial results.[24-26] Most of these studies used MRI guidance to direct and deliver HIFU. Although MRI-guided HIFU offers exquisite tissue contrast and accurate quantitative feedback from the targeted region, it has significant difficulties in widespread clinical adoption, including the high cost and technical equipment requirements.[27] US-guided HIFU procedures

have the potential to address both limitations by providing a treatment alternative that is significantly less costly and simpler to perform.

Given the inherent complexities of developing dedicated HIFU technology for the specific indication of VM ablation and the inevitable delay associated therein, identifying alternative indications for commercially available technology is a viable option that could expedite treatment access for patients in need. Additionally, success with an existing device might encourage technical developments in this area, facilitating the development of a specialized HIFU device.

Concern existed that the challenges related to using an extracorporeal US imaging modality would significantly affect the signal/noise ratio and diminish the quality of the resulting image. This was averted through thorough skin preparations, including shaving and marking the target area. For superficial malformations, skin marking might not be necessary. However, we found that skin marking, used in conjunction with the diagnostic US images, expedited the interrogation of the malformation. Additionally, probe placement, coupling, and orientation played a significant role in VM visualization.

In the present study, the Sonablate device was able to properly visualize the VMs in all participants through the use of transverse and sagittal imaging fields. Although the imaging provided by the Sonablate device allowed for adequate visualization, as could be expected, the imaging function was not as sophisticated as the diagnostic scanner, which was evident in several respects. For the patient with a microcystic lymphatic malformation, the Sonablate device was unable to effectively visualize the small caliber channels seen on the images obtained with the diagnostic US. However, the overall boundaries and contours were adequately appreciated, and this lack would likely not hinder HIFU treatment when corroborated with the preprocedural imaging studies. Similarly, the Sonablate images did not provide sufficient detail to allow for VM subtype stratification. However, this was not an intended use of the modality and would have no effects on HIFU treatment. Additionally, lesions at a depth $>$5.5 cm could not be imaged properly, which was evident in one patient with lesions in the pelvis and buttock. Finally, it is essential to correlate the preprocedural MRI or US studies with the periprocedural US interrogation before Sonablate probe placement. This, in conjunction with the appropriate skin markings and anatomic landmark identification, allowed for rapid localization of the VM using the Sonablate probe.

It was important to assess the ease of use of the Sonablate device because the setup protocol for imaging effectively is the same as that for the setup for HIFU treatment. For lesions located in the extremities, we found that acoustic coupling could be maximized by orienting the probe parallel to the orientation of the target limb and that proximal placement of a tourniquet enhanced visualization of the malformation. All the patients were placed under general anesthesia in anticipation of direct-stick embolization and/or surgical excision, which provided the additional advantage of being able to alter the patient's position to facilitate optimal coupling and minimized the influence of patient movement on the stability of the acoustic coupling. For lesions affecting the torso and abdomen, we found excursions of $<$5 mm secondary to respiratory function, for which general anesthesia would be critical during treatment delivery for temporary cessation of ventilation to minimize motion and maximize focal point beam accuracy. However, for the purposes of HIFU image acquisition in the present study, no cessation of ventilation was performed.

Although other studies have used the Sonablate probe for extracorporeal US imaging of atherosclerotic extremity arteries,[28] to the best of our knowledge, no study to date has evaluated the US imaging function of the Sonablate device for identifying, outlining, and treatment planning of peripheral VMs.

The study's treating surgeon was trained in the setup and use of the Sonablate device by the manufacturer before the start of the present study. The instructions for use and a video preparatory course were available to the surgeon and operative nursing personnel. Additionally, support personnel from the device manufacturer were present during imaging of 9 of the 10 patients to help with device operation, as needed, allowing the treating surgeon to focus on the probe positioning and image acquisition aspects to collect the data required to adequately address the study's primary and secondary end points.

The treating surgeon was responsible for operation of the probe and completion of the postprocedural questionnaire. This was designed to evaluate the treating surgeon's confidence and comfort level in adequately identifying and outlining a given VM for potential future HIFU treatment delivery. It was, therefore, important to base this objective assessment on the treating surgeon's evaluation of the HIFU imagining capability, because the surgeons will ultimately be responsible for the future delivery of HIFU energy. We believe the intervening surgeon was best positioned to evaluate the captured HIFU images within the context of the patient's anatomy and preoperative imaging studies. This can be further verified in the future with larger scale clinical trials.

CONCLUSIONS

We have demonstrated the feasibility of US imaging of peripheral VMs using a current commercially available HIFU probe in anticipation of HIFU treatment planning and delivery with adequate identification and outline of peripheral VMs and lymphatic malformations in a pilot series of 10 patients. Preoperative MRI and soft tissue duplex US remain essential tools for guiding probe placement and HIFU imaging.

AUTHOR CONTRIBUTIONS

Conception and design: RS, BL, NiN, AD, RG, NaN
Analysis and interpretation: JD, NaN
Data collection: JD, NaN
Writing the article: JD, RS, NaN
Critical revision of the article: JD, RS, BL, NiN, AD, RG, NaN
Final approval of the article: JD, RS, BL, NiN, AD, RG, NaN
Statistical analysis: JD
Obtained funding: Not applicable
Overall responsibility: NaN

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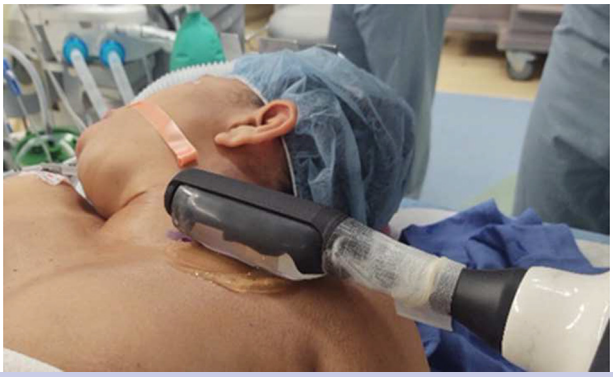

Supplementary Fig (online only). Sonablate high-intensity focused ultrasound (HIFU) probe placement for visualization of the targeted malformation.

Supplementary Table I (online only). Demographic data

Variable	No. (%) or Mean ± SD
Total participants	10 (100)
Age, years	36.5 ± 16.5
Sex	
Male	4 (40)
Female	6 (60)
VM type	
Venous	8 (80)
Lymphatic	1 (10)
Lymphovenous	1 (10)
VM malformation	
Extremities only	5 (50)
Trunk only	2 (20)
Trunk and extremities	2 (20)
Neck and extremities	1 (10)
Presenting symptoms	
Pain	10 (100)
Functional impairment	8 (80)
Cosmetic disfigurement	3 (30)
Swelling	3 (30)

SD, Standard deviation; *VM,* venous malformation.

Supplementary Table II (online only). End point analysis

Variable	Value
Adequacy of imaging (primary end point)	Response (yes; no), %
Boundary and location of VM readily visualized on Sonablate image	100; 0
Shape and size of VM on Sonablate image similar to shape of VM on diagnostic US image	100; 0
Absence of Doppler functionality on Sonablate images prevented identification of VMs	0; 100
Time-gain compensation controls of Sonablate US imaging offered sufficient signal/noise ratio to allow imaging of VMs at its furthest imaging depth (6 cm)	100; 0
Sonablate US images provided sufficient detail to allow for VM subtype stratification	0; 100
Ease of use (secondary end point)	Mean score ±SD
Difficulty in preparing Sonablate probe for VM imaging	1, easy; 5, difficult
Dressing probe	1 ± 0
Filling probe tip with degassed water	1 ± 0
Removing bubbles from probe tip	1 ± 0
Application of probe mullet	1 ± 0
Adjustment of water volume in probe tip	1.7 ± 0.5
Attaching Sonablate stepper to procedure table, probe arm to stepper, and Sonablate probe to probe arm	1 ± 0
Total	1.1 ± 0.3
Difficulty in using Sonablate probe for VM imaging	1, easy; 5, difficult
Manipulating probe	1 ± 0
Manipulating probe arm	1 ± 0
Manipulating stepper	1 ± 0
Manipulating patient for adequate imaging and comfort	1.2 ± 0.6
Ease of probe repositioning if US images show VM not properly visualized	1.1 ± 0.3
Total	1.1 ± 0.1
Evaluation of Sonablate probe stability for VM imaging	
Stability of acoustic coupling of probe to patient (1, very stable; 5, need to readjust constantly)	1.1 ± 0.3
Effect of patient motion on stability of acoustic coupling (1, no effects; 5, unacceptable effects)	1.5 ± 0.8
Total	1.3 ± 0.2

SD, Standard deviation; *US*, ultrasound; *VM*, venous malformation.