Applied Physics Letters

RESEARCH ARTICLE | AUGUST 16 2023

Vortex-ultrasound for microbubble-mediated thrombolysis of retracted clots

Howuk Kim ; Bohua Zhang ; Huaiyu Wu ; Junjie Yao ; Chengzhi Shi ; Xiaoning Jiang

Appl. Phys. Lett. 123, 073701 (2023)
https://doi.org/10.1063/5.0155223

AIP Publishing

Applied Physics Letters ARTICLE pubs.aip.org/aip/apl

Vortex-ultrasound for microbubble-mediated thrombolysis of retracted clots

Cite as: Appl. Phys. Lett. **123**, 073701 (2023); doi: 10.1063/5.0155223
Submitted: 18 April 2023 · Accepted: 2 August 2023 ·
Published Online: 16 August 2023

Howuk Kim,[1,2] Bohua Zhang,[1] Huaiyu Wu,[1] Junjie Yao,[3] Chengzhi Shi,[4,5,a)] and Xiaoning Jiang[1,a)]

AFFILIATIONS

[1]Department of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, North Carolina 27695, USA
[2]Department of Mechanical Engineering, Inha University, Incheon 22212, South Korea
[3]Department of Biomedical Engineering, Duke University, Durham, North Carolina 27708, USA
[4]George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
[5]Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, Georgia 30032, USA

[a)]**Authors to whom correspondence should be addressed:** xjiang5@ncsu.edu and chengzhi.shi@me.gatech.edu

ABSTRACT

Endovascular sonothrombolysis has gained significant attention due to its benefits, including direct targeting of the thrombus with sonication and reduced side effects. However, the small aperture of endovascular transducers restricts the improvement of their potential clinical efficiency due to inefficient acoustic radiation. Hence, in an earlier study, we used vortex ultrasound with an endovascular ultrasound transducer to induce shear stress and enhance the clot lysis. In this study, the vortex acoustic transduction mechanism was investigated using numerical simulations and hydrophone tests. Following this characterization, we demonstrated the performance of the vortex ultrasound transducer in thrombolysis of retracted clots in *in vitro* tests. The test results indicated that the maximum lysis rates were 79.0% and 32.2% with the vortex ultrasound for unretracted and retracted clots, respectively. The vortex ultrasound enhanced the efficiency of the thrombolysis by approximately 49%, both for retracted and unretracted clots, compared with the typical non-vortex ultrasound technique. Therefore, the use of endovascular vortex ultrasound holds promise as a potential clinical option for the thrombolysis of retracted clots.

Thrombosis refers to the formation of blood clots that block the blood flow in veins or arteries.[1] For example, deep vein thrombosis (DVT), a representative symptom of thrombosis, is found in the deep venous system of the legs. DVT can be caused by smoking, leg injury, cancer, or genetic factors.[2] Thrombus in the legs may result in leg pain, swelling, and even fatal reactions due to pulmonary embolism.[3,4]

Currently, the most prevalent modalities for thrombolysis are found in surgical methods, pharmacological approaches such as recombinant tissue plasminogen activator (rt-PA), and catheter thrombectomy.[5–7] However, some technical limitations still exist in the current methods in terms of low thrombolytic efficiency, risk of tissue damage, bleeding complications, and distal embolism due to relatively large clot fragments.[1,8,9] For example, thrombolytic medications, such as rt-PA, may exhibit low clinical efficiency owing to their relatively long treatment time.[10,11] The usage rate of catheter-directed thrombolysis is increasing (~0.7% per year) for DVT, though the risk of intracranial hemorrhage is still present.[12] Therefore, many researchers have studied alternative approaches to overcome the intrinsic constraints of the currently available modalities.

In recent decades, therapeutic ultrasound has been considered as an alternative methodology to overcome intrinsic clinical limitations and side effects in numerous therapeutic areas.[13] Sonothrombolysis is a therapeutic ultrasound technique for the dissolution of blood clots in the vascular system with the aid of ultrasound.[13,14] Endovascular sonothrombolysis, which normally refers to the catheter-directed ultrasound thrombolysis, directly delivers acoustic energy and drugs to the target area, minimizing the safety concern.[15,16] Therefore, endovascular sonothrombolysis has drawn more attention than noninvasive sonothrombolysis, and some catheter-directed devices are already commercially available.[17]

One of the most critical concerns in the catheterized ultrasound transducer is its insufficient degree of acoustic power. The relatively small (<2 mm) aperture size presents a challenge in achieving a high acoustic pressure output at a relatively low frequency (<2 MHz), owing to the short Fresnel focal distance.[15,18] The narrow therapeutic area and low mechanical index (<0.3) due to the design constraint have an impact on the thrombolysis performance.[18,19] Therefore, research efforts have been focusing on overcoming the technical

limitations of current endovascular sonothrombolysis in terms of innovations in transducer design[20,21] and the infusion of microbubbles (MBs) or nanoparticles.[15,22,23] Notably, sonothrombolysis of retracted clots is also a challenging research topic because of the structural robustness of clots. In general, retracted blood clots have a relatively stiff structure owing to the densification of the fibrin network and hardening caused by mechanical stress applied to the fibrin structures. According to a recent report, even when using microbubble (MB)-mediated therapeutic ultrasound, the thrombolytic rate was below 20% for 20 min.[24] Therefore, a breaking-through item needs to be investigated to improve the efficiency of endovascular sonothrombolysis.

Recently, we reported an intravascular sonothrombolysis modality, in which we utilized a vortex flow induced by a small-aperture (<1.8 mm) ultrasound transducer.[25] Technically, the in-plane pressure gradient generated by the transducer produces a spiral stream during the fluid motion. As such, the vortex sonothrombolysis device showed an unprecedented thrombolysis rate in an *in vitro* demonstration of cerebral venous sinus thrombosis CVST with a 1-h fresh clot. However, the efficacy of vortex sonothrombolysis has not yet been addressed in relatively old blood clots (i.e., retracted blood clots).

This study aimed to further investigate the clinical potential of endovascular vortex sonothrombolysis with both unretracted and retracted blood clots. Although sonothrombolysis has been limited by its technical ability to dissolve retracted blood clots due to the relatively robust fibrin structures, we hypothesized that introducing shear stress through vortex ultrasound (VUS) could effectively break the structure of blood clots [Fig. 1(a)]. This study investigated vortex ultrasound produced by an in-house miniaturized transducer, followed by *in vitro* thrombolysis tests.

The operating mechanism of the transducer can be categorized into normal acoustic pressure and induced shear stress effects. First, the transducer vibrates along the thickness direction, producing an acoustic pressure output from the aperture of the transducer in the normal direction. In addition, the device generates an in-plane pressure gradient by applying a phase difference (φ) at multiple apertures in the transducer to induce a shear effect. The harmonic pressure outputs generated by each transducer aperture exhibits a constant phase difference, which produces a sequential maximum variation in the radiated acoustic pressure. The sequential change in the maxima over the phase results in an in-plane pressure gradient and a particle velocity field along the circumferential direction, causing a shear force. In this study, phase variation was implemented by adopting a transducer design with a differential aperture height h at a specific frequency f as follows:

$$h = \frac{\lambda}{N} = \frac{c}{fN}, \tag{1}$$

where λ is the wavelength, c is the speed of sound, and N is the number of sub-apertures. The main advantage of such a design is that a single co-axial cable can operate the device without an electrical phase delay, which is advantageous for fabrication simplicity and cost-effectiveness. Based on the mechanical phase-delaying method, we designed and made a miniaturized ultrasound transducer to implement the vortex acoustic phenomenon using a small aperture (<3 mm). A high number of sub-apertures is advantageous to achieve a smooth transition of the vortex flow; however, the corresponding acoustic radiation efficiency decreases as the surface area of a sub-aperture becomes small at a given frequency. Therefore, we employed 2-by-2 sub-apertures with the phase difference of $\pi/2$ between each transducer, so that a helical wave front can be generated while the acoustic pressure output is still reasonably high. The fabrication method used in this study is similar to that used in our previous report[25] (see the supplementary material for details). A photograph of the prototype device is presented in Fig. 1(b).

We conducted numerical simulations to demonstrate the feasibility of the transducer design in terms of the transition of acoustic pressure in the axial direction during the operation. The boundary conditions and material properties for the simulation are described in the supplementary material. The numerical simulation predicted the acoustic pressure output of the vortex ultrasound transducer. In addition, the simulation explains the acoustic phenomenon caused by the phase delay to multiple apertures. Figure 2(a) shows the acoustic pressure field of the cross-sectional plane (x–y plane) at 2λ-distance away from the transducer. In the animation results (i.e., pressure transition over phase variation), we observed the swirling movement of the acoustic pressure field. Figure 2(b) shows the acoustic pressure field along the vertical plane. The simulated results verified that a height adjustment with a quarter wavelength for each aperture could result in sequential phase variation in the target space. Figure 2(c) is the corresponding velocity distribution with respect to phase in the cross section of the acoustic media at 2λ-distance away from the transducer. The circumferential velocity in the vortex ultrasound (VUS) was significantly larger in magnitude than that in the non-vortex ultrasound (NVUS) case. The circumferential component of the velocity can produce vortex movement in the acoustic media during operation of the

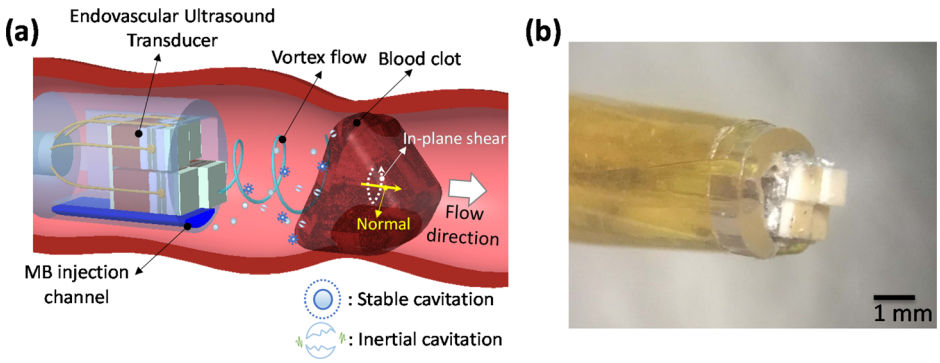

FIG. 1. Schematic representation of the clinical concept of the microbubble-mediated vortex-ultrasound thrombolysis (a) and the prototyped vortex ultrasound transducer (b).

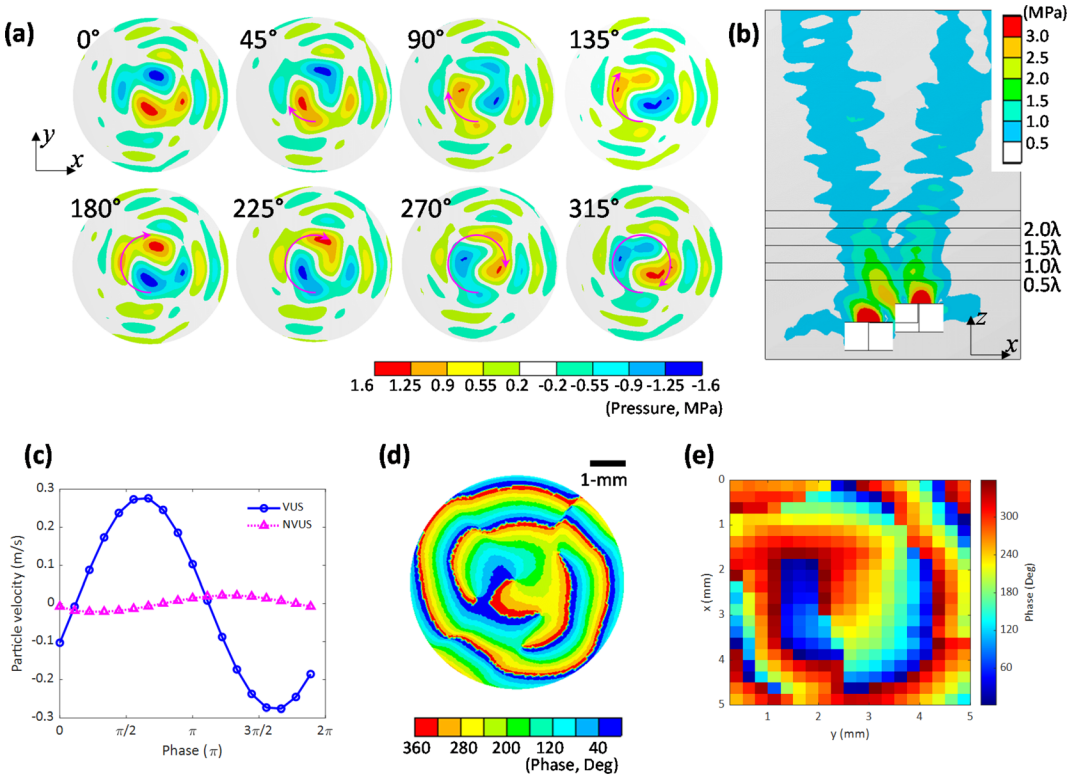

FIG. 2. Simulation results for the generation of the vortex ultrasound: (a) pressure field at 2λ-distance away from the transducer in the x–y plane, (b) the maximum pressure level in the x–z plane, (c) particle velocity in the circumferential direction captured on a point ($x = 0$, $y = 0.5$ mm), and the phase diagrams obtained from (d) the simulation model and (e) the hydrophone test result at 2λ away from the transducer.

transducer. The phase diagram of the acoustic field also demonstrates the pressure distribution of the spiral pattern, which results in vortex flow in the axial direction (i.e., z-axis). Figures 2(d) and 2(e) compare the phase diagrams obtained from the simulation model and prototype device, respectively. Both results indicate that the design adopting the mechanical phase-delaying method can produce a vortex flow in the acoustic media. Details of the characterization of the prototype device are provided in the supplementary material. Table I summarizes the performance of the devices.

Following the characterization of the transducer, we built a blood flow-mimicking system for *in vitro* demonstration of thrombolysis using a miniaturized vortex ultrasound transducer. The test setup is illustrated in Fig. 3. The internal pressure of the flow was controlled to be approximately 0.5 kPa by adjusting the flow level coming from a water tank (37 °C). The pressure during the test was monitored using a pressure gauge. Blood clot samples were placed inside a transparent plastic pipe, where a mesh-like structure prevented the clot from flowing away owing to the dynamic flow. The position of the ultrasound transducer was manually controlled using a 3D motion stage vertically in the flow channel. As in our previous study, we utilized MB contrast agents to stimulate the cavitation of bubbles and to break down the fibrin structure in blood clots.[15,18,23] A microbubble solution (VesselVue®, SonoVol, Inc., Durham, NC, USA) was infused in the forward direction of the transducer through the microflow channel and combined as a part of the endovascular transducer (Fig. 1). A syringe pump (NE 1010, New Era Pump Systems Inc., Farmingdale, NY, USA) was used to infuse the MB solution via a flow channel at a rate of 0.1 ml/min. MB was premixed with saline water to obtain a

TABLE I. Performance of the vortex and the non-vortex ultrasound transducers.

Device type	Frequency (MHz)	Impedance at the resonance (Ω)	Acoustic intensity, I_{spta}[a] (W/cm^2)	Mechanical index	Electromechanical conversion efficiency[b]
Non-vortex ultrasound	1.7	96	6.53	1.23	0.54
Vortex ultrasound	↑	↑	5.65	1.14	↑

[a]spta: spatial-peak temporal-average.
[b]Refers to the acoustic power obtained by the simulation model.

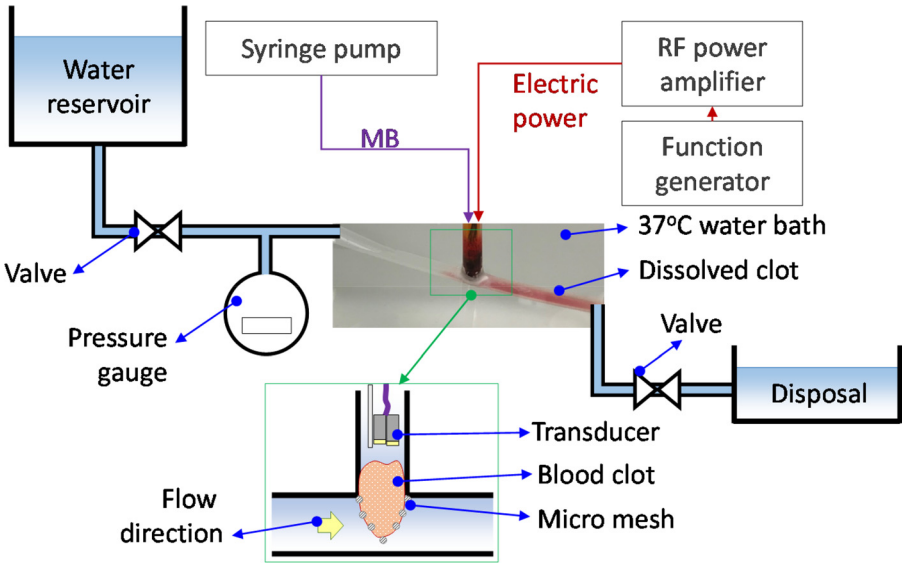

FIG. 3. *In vitro* test setup for the assessment of vortex ultrasound-assisted thrombolysis.

dose of 10^8 numbers/ml. The contrast agent was infused in the forward direction of the transducer for 30 s, followed by sonication for 2 min. The total treatment time was 30 min for each test case. We assessed the benefit of vortex ultrasound combined with microbubbles in thrombolysis by comparing the mass reduction rates of clots under the following test conditions: (1) controlled, (2) MB + NVUS, (3) VUS only, and (4) MB + VUS. Each test was repeated three times. As for the test specimens, 50 ml of fresh bovine blood (Lampire Biological Laboratories, Pipersville, PA) was mixed with 5 ml of 2.75% (w/v) $CaCl_2$ solution (Fisher Scientific, Fair Lawn, NJ) to obtain a volume ratio of 10:1. The solution mixture was loaded into flint glass pipettes (6.35 mm in diameter) and placed in a 37 °C water bath for three hours to allow the blood to coagulate. Meanwhile, for the cultivation of retracted blood clots, the blood mixture was transferred to borosilicate glass pipettes (Fisher Scientific, Fair Lawn, NJ, 6.95 mm in diameter) with a hydrophilic inner surface,[24–26] followed by the incubation at 37 °C in a water bath. The coagulated blood samples were stored at 4 °C for 3 days. Finally, the clot samples were cut into a cylindrical shape to weigh 180 mg ± 10%.

We first tested the performance of the vortex ultrasound transducer in thrombolysis of unretracted blood clots. Figure 4(a) shows the thrombolysis results of the mass reduction rates in each test condition. The first comparison group (i.e., MB + NVUS) utilized a plane wave transducer combined with MB infusion, which has been used previously.[15,27] In the conventional method, there was a statistically significant ($p < 0.05$) mass reduction rate of approximately 42.8%. Meanwhile, the case of the VUS only exhibited an impressive lysis rate of over 43.9% without the aid of the MB, which was also statistically significant in comparison with the control group. In the last case, we combined VUS with MB infusion. The lysis rate under the previous test condition was approximately 65.8%. The test results have shown the vortex ultrasound to have a significant impact on thrombolysis with a low p-value ($p < 0.005$), confirming its effectiveness in breaking down blood clots. Figure 4(b) compares the influence of duty cycle on thrombolysis. A longer duty cycle is beneficial for enhancing the thrombolytic rate. The lysis rates were approximately 73.5% and 79.1% on the average and at the maximum, respectively. Figure 4(d) shows a photograph of blood clots before and after NVUS treatment, and Fig. 4(e) shows a photograph of the VUS treatment. We observed a significant reduction in the mass and volume of the clot when applying VUS with the MB, as shown in Fig. 4(e).

Next, we demonstrated the thrombolytic effects on retracted clots. Figure 4(c) shows that the NVUS produced a lysis rate of approximately 21.5%. On the other hand, the VUS treatment showed clear evidence of the improvement in sonothrombolysis; the lysis rate was approximately 32.2% (37.0%) at the average (maximum) level, which was a statistically significant enhancement compared with the control and the NVUS groups. The photographs in Figs. 4(f) and 4(g) show the reduction in the volume of the retracted clot before and after the NVUS and VUS treatments, respectively. We confirmed that VUS treatment was more effective in the lysis rate of a retracted blood clot than the control and standard (i.e., NVUS + MB) methods.

This study utilizes numerical simulation to demonstrate the mechanisms of a vortex ultrasound transducer. The FEA (Finite Element Analysis) simulation showed a spiral movement of the acoustic pressure [Fig. 2(a)] in the animation. In addition, the simulated phase diagram [Fig. 2(d)] exhibits a spiral pattern similar to the test results [Fig. 2(e)]. These results are in agreement with previous research results reported in Ref. 25. The spiral pattern in the phase distribution indicated a helical wavefront pattern, leading to an in-plane pressure gradient [Fig. 2(c)]. As such, the numerical simulation and hydrophone test verified that the transducer design with a height difference in the aperture could generate vortex movement in the fluid. Meanwhile, the amplitude in the acoustic pressure output (i.e., 0.96–1.49 MPa) showed that the corresponding mechanical index would be over 0.74, which is known to be sufficient to trigger active cavitation effects.[19] Therefore, the vortex ultrasound transducer can simultaneously induce the cavitation effect, generating spiral movement in the fluid. Regarding safety, the MI (Mechanical Index) level was well below the threshold recommended by the FDA (i.e., <1.9).[28] Temperature increase and vessel damage were also negligible at a duty cycle of 10%, according to a previous report.[25]

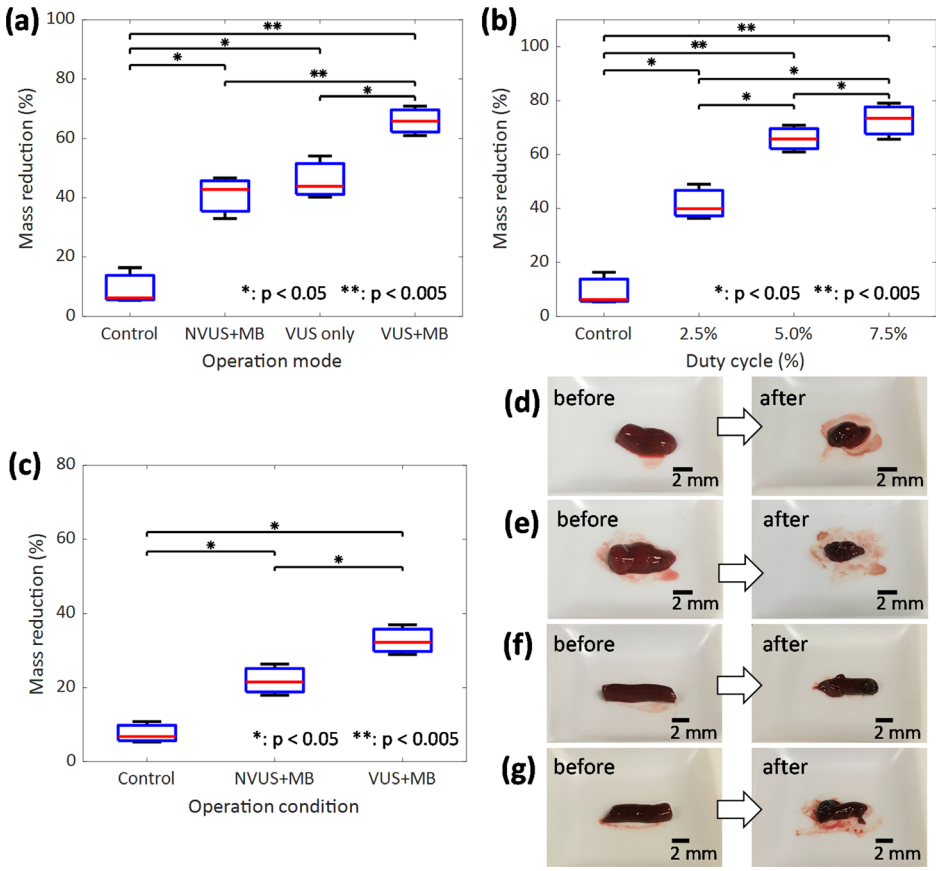

FIG. 4. Thrombolysis results in cases of unretracted and retracted blood clots: (a) mass reduction rate in unretracted clots for the control, the NVUS + MB, VUS only, and VUS + MB conditions; (b) mass reduction rate with respect to the duty cycle of the input pulse in VUS transducer; (c) mass reduction rate in retracted clots for the controlled, the NVUS + MB and VUS + MB conditions; unretracted blood clots before and after (d) NVUS + MB and (e) VUS + MB treatment; and retracted blood clots before and after (f) NVUS + MB and (g) VUS + MB treatment.

The fabrication tolerance could influence the performance of the vortex ultrasound since the phase variation between each sub-aperture is adjusted by the height change of each stack. In our fabrication, the thickness change of the backing layer was well controlled within $\pm 5\,\mu$m. The corresponding phase shift would be just around ± 0.036 rad in theory; that is, the maximum phase shift is estimated by $2\pi \cdot \Delta h/\lambda$, where Δh and λ indicate the height error in fabrication and the given wavelength, respectively. It was noticeable that the fabrication tolerance makes just 0.1% amplitude variation. Therefore, the effect of the fabrication error would be negligible with the current fabrication method.

In Fig. 4(a), the first test case (NVUS + MB), which was an established method in the past, could dissolve the blood clot within a reasonable lysis range, which is comparable to the results reported in a previous study.[18] Interestingly, the second case (VUS only) exhibited a similar lysis rate to the first test case (i.e., NVUS + MB). This indicated that the vortex ultrasound could dissolve blood clots without the aid of MB. The VUS only condition performed similarly in thrombolysis compared with the typical sonication method combined with MB infusion. However, the last test condition confirmed that the MB injection was more effective when combined with VUS treatment. Here, we achieved a lysis rate under a duty cycle of 5% condition. Therefore, we investigated the effects of pulse duration on thrombolysis. As shown in Fig. 4(b), it is evident that a longer period (e.g., 7.5%) of the pulse train was beneficial to expedite the thrombolysis rate. However, we did not attempt a longer duty cycle of over 7.5% to avoid any potential damage to the neighboring tissue (i.e., vessel wall).[29]

Figure 4(c) shows that the vortex ultrasound was more effective than NVUS in the thrombolysis of retracted clots. As hypothesized, the induced vortex flow can exert additional shear stress in the azimuthal direction over the clot, thus expediting the dissolution rate. Specifically, the lysis rate in VUS (32.2%) was improved by 49.8% compared with that in NVUS (21.5%). Moreover, the lysis rate was statistically different from that in the control group. According to Ref. 30, using rt-PA at a dose over 100 μg/ml could achieve a lysis rate of only about 15% in retracted porcine clots in a 30-min treatment. It was noticeable that they utilized a large (>6 cm) ultrasound transducer, while the initial weight of the clot was about 440 mg. In contrast, even if our test utilized a relatively lighter clot (i.e., ~180 mg), the lysis rate of about 30% was meaningful since we utilized a much smaller (~2.6 mm) transducer. The increase in the lysis rate was caused by adjunct fluid movement (i.e., vortex) generated by the vortex ultrasound transducer. Therefore, we confirmed that spiral fluid motion is beneficial for expediting the thrombolytic effect. However, we will need to further study the influence of stiffness in retracted clots on the lysis rate.[31] In addition, the lysis rates in the retracted clots may be further enhanced by improving the swirling rates and acoustic pressures of the transducer. For example, the swirling rate could be further increased by applying the electric phase-delaying method, where the phase change could be more smoothly controlled without

compromising the acoustic pressure output from the height adjustment. However, the complexity of fabrication can be increased by connecting more electric wires for the electric control of the phase.

This study considered only commercially available lipid-shelled microbubbles as the cavitation-inducing agents. However, some studies have reported that phase-changing nanoparticles can have more active cavitation effects upon sonification than MB.[24,26] Nanoparticles, being smaller and lighter than MB, have the ability to penetrate deep into blood clots and effectively break down the fibrin structures.[15,24,26] Therefore, in future studies, it would be interesting to investigate the clinical efficacy of vortex ultrasound combined with nanoparticles. Moreover, we could consider chemical agents, such as rt-PA, combined with ultrasound treatment.[27] Structure and frequency optimizations for a stronger shear force with the VUS transducer can also be included to improve the lysis rate with retracted clots.

In summary, this Letter reports the mechanism of an endovascular vortex ultrasound transducer and proves its thrombolytic efficacy in unretracted and retracted blood clots. Apertures with different heights could produce the maximum acoustic pressure output sequentially about the angle, which induced the spiral motion of the flow. Compared to the conventional NVUS method, vortex ultrasound effectively dissolved blood clots at a faster lysis rate. The lysis rate with the VUS was approximately 73.5% after 30 min. Moreover, VUS influenced thrombolysis of retracted blood clots. The lysis rate was 32.2% after 30 min, yet the typical NVUS remained at approximately 21.5%. To conclude, the endovascular VUS transducers offer an innovative clinical approach for thrombolysis. The clinical feasibility of this approach needs to be further established through its medical applications in DVT and CVST.

See the supplementary material for the complete description of the numerical simulation model and the details of the experiment method.

This research was supported in part by the National Institutes of Health (Grant Nos. R01HL141967, R41HL154735, and R21EB027304) and the National Science Foundation (Grant No. CMMI-2142555). The authors would like to thank SonoVol, Inc. for providing the microbubble contrast agent for the test.

AUTHOR DECLARATIONS

Conflict of Interest

Howuk Kim, Bohua Zhang, Huaiyu Wu, Chengzhi Shi, and Xiaoning Jiang are inventors of several intravascular sonothrombolysis technologies that were licensed to SonoVascular. Xiaoning Jiang has served as a consultant and a scientific advisor for SonoVascular, Inc.

Author Contributions

Howuk Kim and Bohua Zhang contributed equally to this article.

Howuk Kim: Data curation (equal); Methodology (equal); Software (equal); Validation (equal); Visualization (equal); Writing – original draft (equal). **Bohua Zhang:** Methodology (equal); Validation (equal); Writing – original draft (equal). **Huaiyu Wu:** Methodology (supporting); Validation (supporting); Writing – original draft (supporting). **Junjie Yao:** Methodology (supporting); Resources (supporting). **Chengzhi Shi:** Conceptualization (equal); Supervision (equal); Writing – review & editing (equal). **Xiaoning Jiang:** Conceptualization (equal); Funding acquisition (equal); Project administration (equal); Supervision (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

REFERENCES

[1]D. Fleck, H. Albadawi, F. Shamoun, G. Knuttinen, S. Naidu, and R. Oklu, "Catheter-directed thrombolysis of deep vein thrombosis: Literature review and practice considerations," Cardiovasc. Diagn. Ther. **7**, S228 (2017).
[2]E. Previtali, P. Bucciarelli, S. M. Passamonti, and I. Martinelli, "Risk factors for venous and arterial thrombosis," Blood Transfus. **9**, 120 (2011).
[3]S. R. Kahn, "The clinical diagnosis of deep venous thrombosis: Integrating incidence, risk factors, and symptoms and signs," Arch. Intern. Med. **158**, 2315 (1998).
[4]W. Huang, R. J. Goldberg, F. A. Anderson, A. T. Cohen, and F. A. Spencer, "Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: Population-based Worcester Venous Thromboembolism Study," J. Thromb. Thrombolysis **41**, 525 (2016).
[5]R. Chang, R. O. Cannon, III, C. C. Chen, J. L. Doppman, T. H. Shawker, D. J. Mayo, B. Wood, and M. K. Horne, III, "Daily catheter-directed single dosing of t-PA in treatment of acute deep venous thrombosis of the lower extremity," J. Vasc. Interventional Radiol. **12**, 247 (2001).
[6]W. T. Kuo, M. K. Gould, J. D. Louie, J. K. Rosenberg, D. Y. Sze, and L. V. Hofmann, "Catheter-directed therapy for the treatment of massive pulmonary embolism: Systematic review and meta-analysis of modern techniques," J. Vasc. Interventional Radiol. **20**, 1431 (2009).
[7]S. Z. Goldhaber, E. A. Magnuson, K. M. Chinnakondepalli, D. J. Cohen, and S. Vedantham, "Catheter-directed thrombolysis for deep vein thrombosis: 2021 update," Vasc. Med. **26**, 662 (2021).
[8]X. Xu, C. Li, T. Wan, X. Gu, W. Zhu, J. Hao, H. Bao, L. Zuo, H. Hu, and G. Li, "Risk factors for hemorrhagic transformation after intravenous thrombolysis in acute cerebral infarction: A retrospective single-center study," World Neurosurg. **101**, 155 (2017).
[9]A. Goyal, S. Saigal, Y. Niwariya, J. Sharma, and P. Singh, "Successful use of tPA for thrombolysis in COVID related ARDS: A case series," J. Thromb. Thrombolysis **51**, 293 (2021).
[10]A. S. Wolberg, F. R. Rosendaal, J. I. Weitz, I. H. Jaffer, G. Agnelli, T. Baglin, and N. Mackman, "Venous thrombosis," Nat. Rev. Dis. Primers **1**, 15006 (2015).
[11]A. J. Furlan, "Endovascular therapy for stroke—It's about time," N. Engl. J. Med. **372**, 2347 (2015).
[12]O. S. Akhtar, V. Lakhter, C. J. Zack, H. Hussain, V. Aggarwal, E. Oliveros, Y. Brailovsky, H. Zhao, R. Dhanisetty, R. A. Charalel, M. Zhao, and R. Bashir Zhao, "Contemporary trends and comparative outcomes with adjunctive inferior vena cava filter placement in patients undergoing catheter-directed thrombolysis for deep vein thrombosis in the United States: Insights from the National Inpatient Sample," JACC Cardiovasc. Interventions **11**, 1390 (2018).
[13]J. M. Escoffre and A. Bouakaz, *Therapeutic Ultrasound* (Springer, Switzerland, 2016).
[14]L. Goel and X. Jiang, "Advances in sonothrombolysis techniques using piezoelectric transducers," Sensors **20**, 1288 (2020).
[15]H. Kim, J. Kim, H. Wu, B. Zhang, P. A. Dayton, and X. Jiang, "A multi-pillar piezoelectric stack transducer for nanodroplet mediated intravascular sonothrombolysis," Ultrasonics **116**, 106520 (2021).
[16]H. Kim, H. Wu, M. Chen, X. Dai, R. Zhou, and X. Jiang, "Intravascular sonoablation for in-stent restenosis relief: Transducer development and the in-vitro demonstration," IEEE Trans. Biomed. Eng. **70**, 2172 (2023).

[17]A. Mostafa, A. Briasoulis, M. Shokr, A. A. Briasouli, S. Panaich, and C. Grines, "Ultrasound accelerated thrombolysis in patients with acute pulmonary embolism: A systematic review and proportion meta-analysis," Int. J. Cardiol. **211**, 27 (2016).
[18]J. Kim, B. D. Lindsey, W. Y. Chang, X. Dai, J. M. Stavas, P. A. Dayton, and X. Jiang, "Intravascular forward-looking ultrasound transducers for microbubble-mediated sonothrombolysis," Sci. Rep. **7**, 3454 (2017).
[19]S. Datta, C. C. Coussios, L. E. McAdory, J. Tan, T. Porter, G. De Courten-Myers, and C. K. Holland, "Correlation of cavitation with ultrasound enhancement of thrombolysis," Ultrasound. Med. Biol. **32**, 1257 (2006).
[20]H. Wu, L. D. Goel, H. Kim, B. Zhang, J. Kim, P. A. Dayton, Z. Xu, and X. Jiang, "Dual-frequency intravascular sonothrombolysis: An *in vitro* study," IEEE Trans. Ultrason., Ferroelectr., Freq. Control **68**, 3599 (2021).
[21]H. Kim and X. Jiang, "Numerical study of a miniaturized, 1–3 piezoelectric composite focused ultrasound transducer," Appl. Sci. **13**, 615 (2023).
[22]B. Zhang, H. Kim, H. Wu, Y. Gao, and X. Jiang, "Sonothrombolysis with magnetic microbubbles under a rotational magnetic field," Ultrasonics **98**, 62 (2019).
[23]B. Zhang, H. Wu, L. Goel, H. Kim, C. Peng, J. Kim, P. A. Dayton, Y. Gao, and X. Jiang, "Magneto-sonothrombolysis with combination of magnetic microbubbles and nanodroplets," Ultrasonics **116**, 106487 (2021).
[24]J. Kim, K. J. B. Bautista, R. M. Deruiter, L. Goel, X. Jiang, Z. Xu, and P. A. Dayton, "An analysis of sonothrombolysis and cavitation for retracted and unretracted clots using microbubbles versus low-boiling-point nanodroplets," IEEE Trans. Ultrason., Ferroelectr., Freq. Control **69**, 711 (2022).
[25]B. Zhang, H. Wu, H. Kim, P. J. Welch, A. Cornett, G. Stocker, R. G. Nogueira, J. Kim, G. Owens, P. A. Dayton, Z. Xu, C. Shi, and X. Jiang, "A model of high-speed endovascular sonothrombolysis with vortex ultrasound-induced shear stress to treat cerebral venous sinus thrombosis," Research **6**, 0048 (2023).
[26]L. Goel, H. Wu, B. Zhang, J. Kim, P. A. Dayton, Z. Xu, and X. Jiang, "Nanodroplet-mediated catheter-directed sonothrombolysis of retracted blood clots," Microsyst. Nanoeng. **7**, 3 (2021).
[27]L. Goel, H. Wu, H. Kim, B. Zhang, J. Kim, P. A. Dayton, Z. Xu, and X. Jiang, "Examining the influence of low-dose tissue plasminogen activator on microbubble-mediated forward-viewing intravascular sonothrombolysis," Ultrasound Med. Biol. **46**, 1698 (2020).
[28]S. Chen, M. W. Urban, C. Pislaru, R. Kinnick, Y. Zheng, A. Yao, and J. F. Greenleaf, "Shearwave dispersion ultrasound vibrometry (SDUV) for measuring tissue elasticity and viscosity," IEEE Trans. Ultrason., Ferroelectr., Freq. Control **56**, 55 (2009).
[29]L. Goel, H. Wu, B. Zhang, J. Kim, P. A. Dayton, Z. Xu, and X. Jiang, "Safety evaluation of a forward-viewing intravascular transducer for sonothrombolysis: An *in vitro* and *ex vivo* study," Ultrasound. Med. Biol. **47**, 3231 (2021).
[30]C. K. Holland, S. S. Vaidya, S. Datta, C. C. Coussios, and G. J. Shaw, "Ultrasound-enhanced tissue plasminogen activator thrombolysis in an in vitro porcine clot model," Thromb. Res. **121**, 663 (2008).
[31]K. P. Mercado-Shekhar, R. T. Kleven, H. A. Rivera, R. Lewis, K. B. Karani, H. J. Vos, T. A. Abruzzo, K. J. Haworth, and C. K. Holland, "Effect of clot stiffness on recombinant tissue plasminogen activator lytic susceptibility *in vitro*," Ultrasound. Med. Biol. **44**, 2710 (2018).