

Research Article

Development of Piezoelectric Ultrasonic Thrombolysis Device for Blood Clot Emulsification

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Ultrasonic thrombolysis is an effective method to treat blood clot thrombus in a blood vessel. This paper reports an OD 5 mm and an OD 10 mm piezoelectric thrombolysis transducers that vibrate longitudinally and generate a pressure field at the distal vibration tip. Studies of vibration mode, pressure field pattern, and cavitation effect were carried out. The transducers were also tested for blood clot emulsification. The results indicate both transducers are effective. The OD 10 mm transducer with a long transmission wire has shown to provide a strong cavitation effect and work effectively at low frequency, high amplitude, and high power conditions. The OD 5 mm transducer was found to operate effectively under higher frequency, low amplitude, and lower power conditions. The cavitation effect is moderate, which facilitates precision and controls over obtaining a more uniform emulsification result.

1. Introduction

Vascular thrombotic occlusive disease is a major cause of morbidity and mortality in the developed world. The development of blood clot or thrombus in a blood vessel compromises distal blood flow and is the usual cause of a heart attack or stroke. Established treatment is the urgent removal or dissipation of the occluding thrombus. This is achieved with the use of a simple aspiration catheter, mechanical thrombectomy, or pharmacological agents such as thrombolytic drugs [1–5]. Ultrasonic emulsification of the blood clot is another technique for thrombolysis. This is achieved by acoustic cavitation and mechanical fragmentation [6, 7]. Compared with conventional mechanical thrombectomy techniques, ultrasonic thrombolysis exhibits the advantage of inherent tissue selectivity [8, 9]. This is because thrombus is highly susceptible to ultrasonic cavitation emulsification, while the arterial walls, which are lined with cavitation-resistant matrix of collagen and elastin, are not. Ultrasound energy has also been shown to improve

myocardial reperfusion in the presence of coronary occlusion [10].

The ultrasonic thrombolysis device generally comprises an external power generator, a piezoelectric transducer, and an ultrasonic catheter. The power generator supplies the system with electrical energy that is required to produce ultrasonic energy. The transducer, which is made up of PZT crystals, converts the electrical energy into high-power ultrasonic energy. The ultrasonic catheter is connected at the proximal end of the transducer. The ultrasonic energy is transmitted through the catheter to the target thrombus [1, 2, 11–17].

The effect of ultrasonic thrombolysis is dependent on the following parameters: power level, vibration tip size, frequency, and length of the transmission wire. This paper compares two designs of an ultrasonic thrombolysis transducer, one with a 10 mm outer diameter (PZT) and a second smaller transducer with a 5 mm outer diameter (PZT). Compared to the OD 5 mm transducer, the OD 10 mm transducer is working at a higher power level and

it supports a longer transmission wire. The tip of the wire is directed to the clot via a standard catheter. Because the OD 5 mm transducer has a much smaller dimension, it facilitates operation at finer and more sensitive locations where precision and control are essential. The performance of the two transducers are compared and discussed in this paper. These results have implications in the subsequent development of ultrasonic transducers for their applications in the clinical setting.

2. Structure and Prototype of the Transducer

Figure 1 shows the structure of the piezoelectric thrombolysis transducer designed in the present work [3]. The transducer consists of five parts. The first part is the end cap. It serves to prestress the adjacent PZT stack and also adjusts the mechanical impedance applied to the stack. The second part is the PZT stack, which is clamped between the end cap and horn. It is the most crucial part of the transducer, where vibration is generated. The third part of the transducer is the horn, which functions to magnify the displacement produced by the PZT stack. The fourth part is a long and thin transmission wire, which should be flexible but sufficiently stiff for energy transmission. The last part is a distal vibration tip that consists of a ball or a short cylinder with an enlarged diameter ($OD \sim 1.5$ mm) compared to the connecting transmission wire ($OD \sim 0.5$ mm). The enlarged diameter increases acoustic power emission to the surrounding liquid and blood clot [11]. In practical operation, the transmission wire will go through a catheter lumen and the vibration tip exits the catheter and reaches the blood clot in the culprit blood vessel. The vibration produced by the PZT stack is transmitted through the horn to the transmission wire and finally the distal vibration tip. The acoustic energy emitted from the tip is then used to emulsify the clot.

The device works in the longitudinal mode. Figure 2 shows the mode shape of the device, that is, amplitude distribution along the length. It can be seen that the vibration tip has much larger displacement than the PZT stack. This is due to the amplification of the horn and the transmission wire. The capability that the transmission wire is able to amplify the displacement is because the wire has a smaller cross section than the horn. As the vibration tip has a larger vibration amplitude and a smaller area compared to the diameter of the PZT stack, the energy produced by the PZT stack will be focused at the tip [11–13].

For practical testing, an OD 10 mm transducer and an OD 5 mm transducer were fabricated. The OD 10 mm transducer operates at ~ 26.7 kHz. This frequency is located in the low ultrasonic frequency range. It was chosen because it produces less tissue heating, and the increased penetration results in a larger acoustic field with more uniformity [18, 19]. The length of transmission wire is 1 m. Maximum input power is 20 W. The OD 5 mm transducer operates at a higher frequency of ~ 66.8 kHz. The diameter of the PZT stack is 5 mm, and the transmission wire is shortened to 20 cm. Maximum input power applied is 2 W. In both cases, the transmission wire is made of a high-strength material, Ti-6Al-4V, to achieve a high vibration velocity [20]. The

vibration tip is made of epoxy, and the size of the tip has a diameter of 1.5 mm and length of 3 mm. Figure 3 shows the electrical conductance spectrum of the two transducers measured using the HP4194A impedance analyzer. The position of the conductance peak indicates the resonant frequency of the transducer. It can be seen for both cases that there are multiple peaks in the spectrum. This is because when the transmission wire becomes longer, different orders of vibration modes could be excited. The transducer could hence be working at different orders. Nevertheless, only the one with maximum longitudinal vibration amplitude is the most efficient for blood clot emulsification.

3. Acoustic Field at the Vibration Tip

During practical operation, the vibration tip will be surrounded by liquid and produces an acoustic field. Figure 4 shows the simulation of acoustic field generated by an OD 1.5 mm and length 3 mm vibration tip. The tip is connected to an OD 0.5 mm transmission wire, and the vibration frequency of the tip is 30 kHz. The simulation was carried out using ANSYS finite element acoustic analysis [21, 22]. Figure 4 demonstrates that the maximum ultrasonic pressure is located at the top and bottom surfaces of the vibration tip, which is normal to the displacement direction. The ultrasonic pressure magnitude is highest at the tip; hence, emulsification is most effective at the tip. The radiating area multiplied by the normal surface velocity of the tip is known as the source strength [23]. Because the ultrasonic pressure amplitude is proportional to the source strength [21, 23], horn is applied to amplify the vibration velocity from the PZT crystal, and a ball or short cylinder tip is attached at the distal end of transmission wire to enhance the radiating area.

As the acoustic pressure becomes larger and larger, a phenomenon, called cavitation, could be observed at the tip of the transducer. Cavitation is the generation and bursting of bubbles within a liquid medium due to the high amplitude of the acoustic pressure applied. Along with the bursting of the bubbles is the high intensity shock wave and impinging of the liquid, which is sufficient to disrupt an adjacent object [24]. Figure 5 shows the cavitation bubble clusters generated at the vibration tip in silicon oil. The cluster is usually generated at the center of the surface and then flows away along the acoustic axis. As it moves away from the tip, the bubbles generated might agglomerate and float upwards due to the buoyancy force. The cavitation threshold of the water is larger than silicon oil, and it is also a function of frequency, temperature, and static pressure [25]. Generally, in water, visible bubble clusters can only be observed when the acoustic field is very strong. The generation of the bubble clusters at the tip surface is suggestive of the high-intensity acoustic energy at this location.

Traditionally, there exist two mechanisms for the emulsification of the clot, namely, cavitation and mechanical defragmentation. Defragmentation is attributed to a punching effect from mechanical displacement [6, 7]. This effect is however less likely than cavitation in our case because of the use of a blunt tip. Cavitation refers to the direct energy that induces blood clot emulsification. Figure 6 shows the

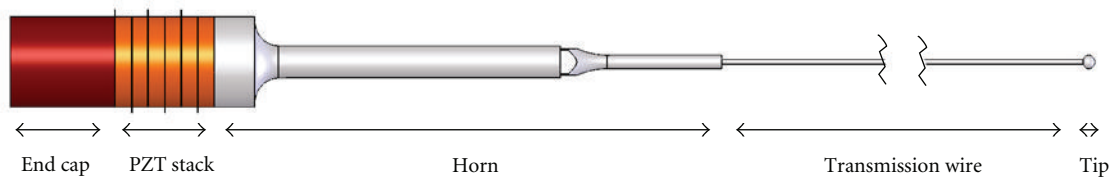


FIGURE 1: Schematic illustration of the piezoelectric thrombolysis device.

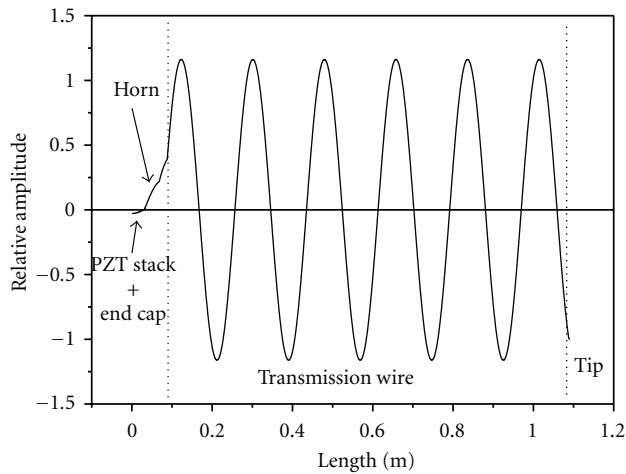


FIGURE 2: Vibration amplitude distribution along the length of the transducer.

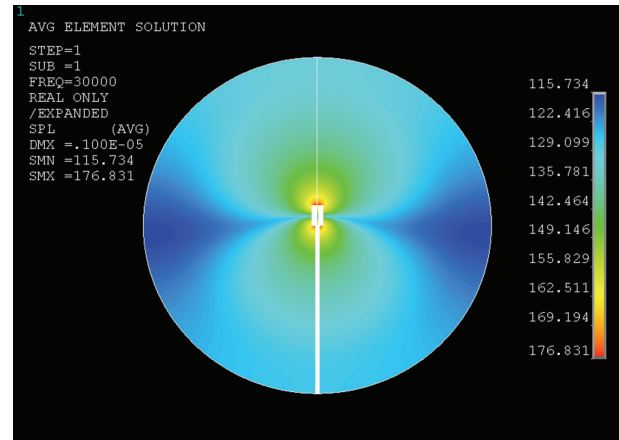


FIGURE 4: Ultrasonic pressure pattern around the vibration tip of the transducer.

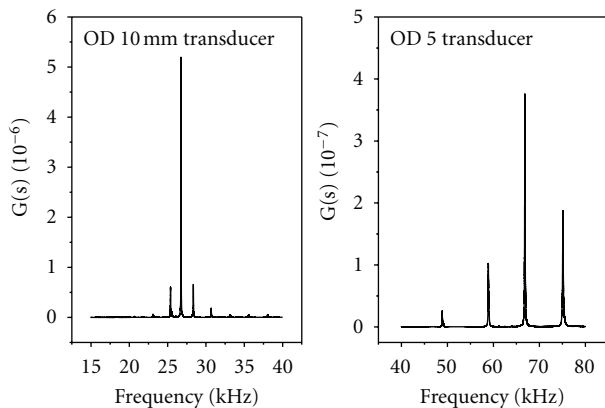


FIGURE 3: Electrical conductance of the piezoelectric transducer.

breaking of blood clot in an ultrasonic cleaning bath (MRS ultrasonic cleaner DC150H). The bath generates 40 kHz acoustic wave, which is used to clean the glassware and disperse chemicals based on the principle of cavitation [26]. No visible cavitation bubbles are observed because the bubbles are too small and the energy is not focused. When the clot is moved to the location with maximum cavitation, the clot was immediately broken into pieces. There is no mechanical punching effect in this example. It hence demonstrates that cavitation alone without mechanical defragmentation is sufficient for clot emulsification.

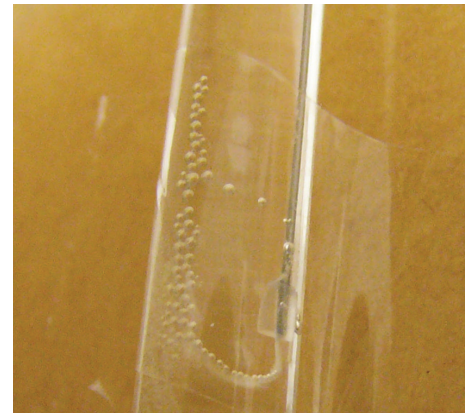


FIGURE 5: Acoustic cavitation and streaming generated at the tip of the transducer.

4. In Vitro and In Vivo Test

The OD 10 mm transducer was tested both in vitro and in vivo. The in vitro test of the transducer was carried out in an anechoic tank filled with water and lined with sound absorption materials both at the walls and the bottom. The dimensions of the tank are $0.6 \times 0.6 \times 1.3 \text{ m}^3$. A holder made of natural latex of $30 \mu\text{m}$ thick was used to contain the blood clot. The clot was prepared by naturally coagulating fresh rabbit blood overnight at 6°C . During operation, the tip of the transducer was pointed at the clot surface. Figure 7 shows the stages that the blood clot was

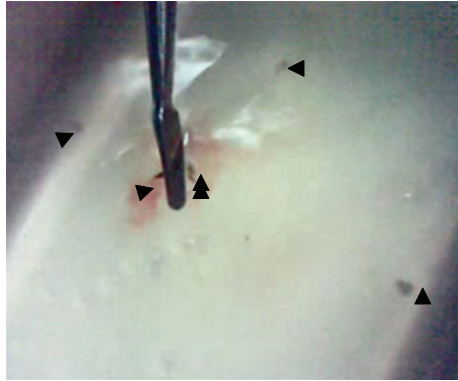


FIGURE 6: Cavitation energy breaks the blood clot into small pieces in an ultrasonic cleaning bath (arrows indicate the clot debris).

emulsified by the transducer. This series of 9 frames occurred over 4 seconds. The whole procedure documented rapid clot lysis (~ 750 mg/min) and confirmed its effectiveness in thrombolysis.

For the *in vivo* test, a rabbit inferior vena cava was used. The blood clot of 1 mL volume was injected into the vein through a catheter. One end of the vein was tied up using a string to avoid movement of the clot due to blood flow. The transmission wire was delivered to the clot area via the catheter. Figure 8 is an angiogram that shows the status of the blood clot before and after the application of ultrasound. Total procedure time was less than 1 minute, during which the transducer tip was advanced and retracted a short distance. The coagulated clot was found to disintegrate and emulsify effectively.

Although the OD 10 mm transducer was shown to be able to effectively emulsify the blood clot, we also evaluated the efficacy of a smaller device with a shorter transmission wire where more precise control is required. This was the OD 5 mm transducer which was proposed and studied. The transducer has a lower power consumption and shorter transmission wire. It generates ultrasound with moderate pressure level and is also more efficient for acoustic energy transmission. Figure 9 demonstrates the performance of the transducer. In Figure 9(a), the transducer was working at its maximum power level of ~ 2 W. We observed similar effect as the OD 10 mm transducer. An emulsification rate of 750 mg/min could also be achieved. Not only consuming lower power, the shorter transmission wire also allowed for effective transmission of energy to the clot. Figure 9(b) documents the transducer working at a power level of 1 W. The blood clot was contained in a plastic tubing and effectively emulsified into fine parties. The emulsification rate was 9 mg/min. These experiments document fine tuning of the OD 5 mm transducer from 9 mg/min up to 750 mg/min.

5. Discussions

The OD 10 mm transducer is effective for blood clot emulsification. However, the long transmission wire reduces energy transfer efficiency. Due to the length and flexibility

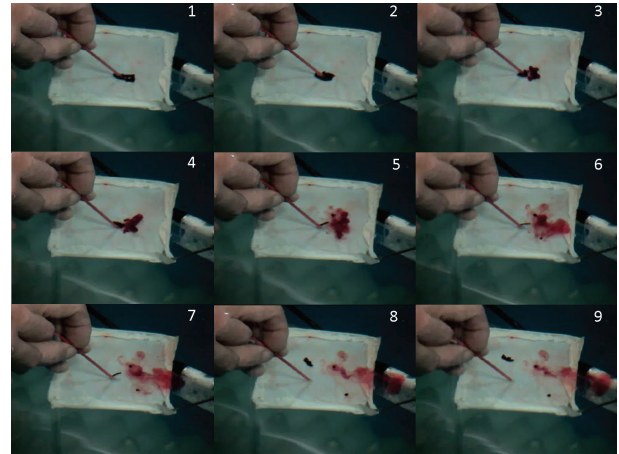


FIGURE 7: Demonstration of blood clot disintegrated by the OD 10 mm piezoelectric transducer.

of the transmission wire, the longitudinal vibration is always combined with unwanted bending motion. This not only reduces energy efficiency but also increases fabrication and control difficulties. From the aspect of fabrication, the transmission wire and PZT stack must attain a perfect coaxial configuration to minimize bending motion during excitation. On the other hand, the power required is usually at a higher level (10 to 20 W in the current case). Another potential side effect of the OD 10 mm transducer is strong acoustic streaming, which is the flow of liquid induced by a nonlinear acoustic field [27]. The streaming effect tends to repulse the blood clot and hence increases control difficulties. This could be seen from Figure 7, where the emulsified debris was blown away by the streaming effect.

The OD 5 mm transducer has comparable performance with the OD 10 mm transducer. In contrast to the OD 10 mm transducer, it has a smaller dimension and works at a lower power condition, with a higher frequency and a shorter transmission wire. Because the magnitude of acoustic pressure is proportional to frequency and vibration velocity, the higher frequency means that we can achieve an equivalent pressure level using a lower amplitude of vibration velocity [23, 28]. Hence, the OD 5 mm transducer is less susceptible to unwanted bending motion and improved efficiency. The streaming effect is also less because of a lower vibration amplitude.

6. Conclusions

OD 10 mm and OD 5 mm transducers were fabricated for ultrasonic thrombolysis. The whole device consists of an end cap, a PZT stack, a horn, a transmission wire, and a vibration tip. The transducers vibrate longitudinally and generate maximum acoustic pressure at the tip. The OD 10 mm transducer works effectively at low frequency, high amplitude, and high power conditions. The OD 5 mm transducer on the other hand operates at high frequency, low amplitude, and low power conditions. Via cavitation, both transducers are able to effectively emulsify the blood

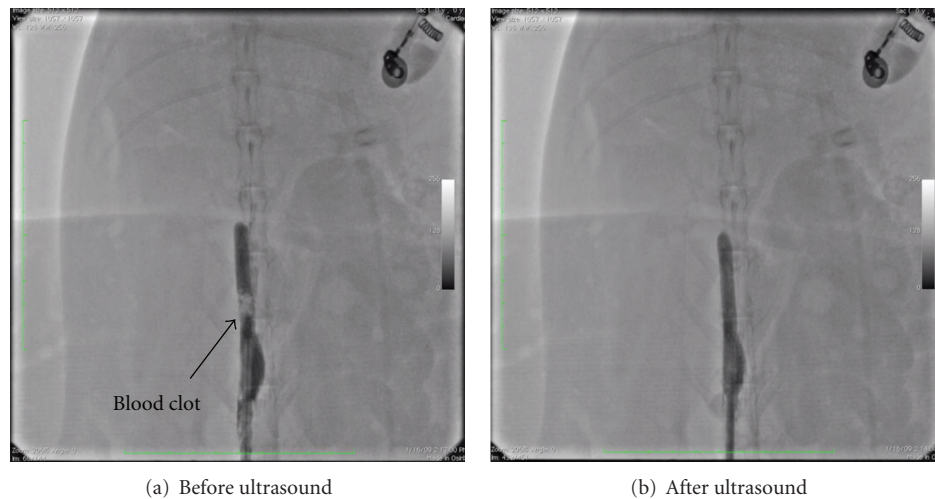


FIGURE 8: Angiogram shows that blood clot was disintegrated during the in vivo test.

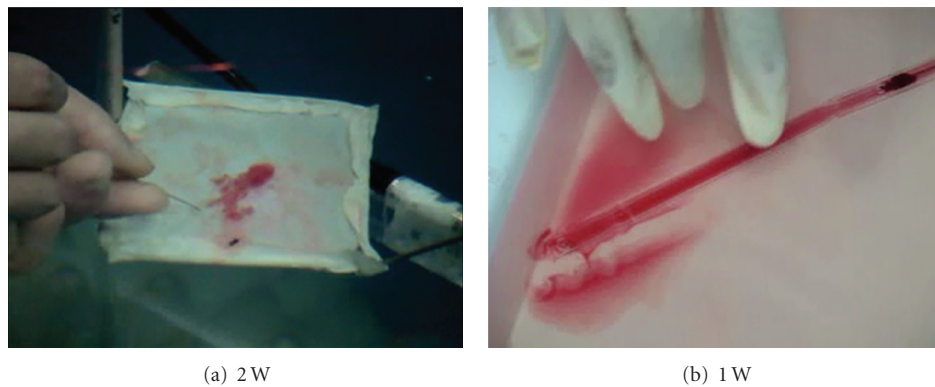


FIGURE 9: Blood clot emulsification by OD 5 mm transducer.

clot. The OD 5 mm transducer is reckoned to be superior as it is able to provide optimized energy transfer to perform emulsification with fewer side effects, such as streaming and bending motion. This results in a more energy efficient and precise solution.

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