Shock-Wave Thrombus Ablation, a New Method for Noninvasive Mechanical Thrombolysis

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Successful experimental and clinical experience with thrombus ablation has been attained with high-power acoustic energy delivered in a catheter. The goal of this study was to investigate the feasibility of noninvasive thrombus ablation by focused high-power acoustic energy. The source for high-power acoustic energy was a shock-wave generator in a water tank equipped with an acoustic lens with a fixed focal point at 22.5 cm. Thrombus was prepared in vitro, weighed (0.24 ± 0.08 g), and inserted in excised human femoral artery segments. The arterial segments were ligated, positioned at the focal point and then randomized into either test (n = 8) or control (n = 7). An x-ray system verified the 3-dimensional positioning of the arterial segment at the focal point. A 5 MHz ultrasound imaging system continuously visualized the arterial segment at the focal point before, during and after each experiment. The test segments were exposed to shock waves (1,000 shocks/24 kv). The arterial segment content was then flushed and the residual thrombus weighed. The arterial segment and thrombus were fixed and submitted to histologic examination. The test group achieved a significant ablation of thrombus mass (0.25 ± 0.15 vs 0.07 ± 0.003 g; p = 0.0001) after application of shock waves. Arterial segments showed no gross or microscopic damage. Ultrasound imaging revealed a localized (1.9 ± 0.5 cm^2), transient (744 ± 733 ms), cavitation field at the focal point at the time of application of focused shock waves. Thus, focused high-power acoustic energy can effect noninvasive thrombus ablation without apparent damage to the arterial wall. The mechanism underlying shock-wave thrombus ablation may be associated with the cavitation effect.

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Acute thrombosis of the coronary and peripheral arteries is the major cause of morbidity and mortality. Despite major advances in thrombolytic therapy for acute myocardial infarction, it still has considerable shortcomings. Approximately 30% of patients with acute myocardial infarction are eligible for thrombolytic therapy, and early reperfusion rates are approximately 70%.[1] Because of these limitations, more efficient and applicable therapies are being vigorously investigated. Rosenschein et al[2,3] have reported the development of high-power, low-frequency, ultrasound catheter for arterial recanalization. This method was investigated both in experimental and clinical settings. These studies suggest that high-power, acoustic energy selectively ablates thrombi with a wide margin of safety. We hypothesized that high-power acoustic energy from an external acoustic generator can be focused and converged into the body to induce selective ablation of a target thrombus. The goal of this study was to test the feasibility of noninvasive acoustic thrombus ablation in a thrombotic artery model in vitro.

METHODS

Thrombotic artery model preparation: Human femoral and iliac arteries were obtained during postmortem examinations. The arterial segments were fixed in 10% neutral formalin for 24 hours, and then transferred to a saline solution and kept at 4°C for <7 days. Every 48 hours, the saline solution was changed. Fresh thrombus was prepared by filling a 3 mm diameter plastic tube with fresh, human blood mixed with thrombin (1 ml blood/20 NIH unit bovine thrombin, T4648, Sigma, St. Louis, Missouri). After 30 minutes, the thrombus was removed from the plastic tube and dissected to a length approximately one third that of each arterial segment. The thrombus was weighed (Model AB-4, Christian Becker, Germany) and inserted in the artery. The artery was filled with saline solution to preclude an artificial acoustic interface between air and fluid (i.e., air bubbles), and ligated at both ends.

Shock-wave ablation protocol: A shock-wave lithotripter (HM3, Dornier Medical Systems, Marietta, Georgia) was used as a source for focused, high-power, acoustic energy. Underwater, high-current, electrical spark-gap discharges (pulse duration approximately 1 ms) generated underwater explosive vaporization of water between the spark-gap electrodes. This generated shock waves in the surrounding fluid, which propagated spherically from the site of origin. Positioning the spark-gap electrode in a symmetric, hemi-ellipsoid, metal reflector focused the shock waves. The reflector reflects and converges the shock waves at a focal point where 90% of the energy is concentrated on a spherical area

approximately 2 cm in diameter. The distance between the spark-gap and focal point is 22.5 cm.

The thrombotic arterial segments were randomized into test (n = 8) and control groups (n = 7). Transillumination confirmed the position of the thrombus in the artery. Radiopaque markers on both sides of the thrombus identified and defined the thrombotic section during application of shock waves. Each segment was suspended from a metal frame and immersed in a water bath. The water was kept at constant temperature (35 ± 1°C). The metal frame with the suspended thrombotic artery could be moved along 3 spatial axes by means of a motor-driven, positioning device. An x-ray location system, using 2 independent, image conversion systems arranged along nonparallel axes, verified the 3-dimensional positioning of the thrombotic segment at the intersection of the 2 nonparallel axes (i.e., focal point) (Figure 1). The test arteries were exposed to 1,000 shocks at 24 kv. This dosage was chosen with regard to the 500 to 1,500 discharges to which patients are typically exposed, and based on experience derived from animal studies of shock-wave–induced tissue damage.[4] The control arteries underwent identical treatment, but without exposure to shock waves.

After the application of shock waves, the arterial ligatures were removed, and the arterial content was flushed with 10 ml of saline solution. The residual solid thrombus was separated from the fluid portion and reweighed. The extent of thrombus ablation was evaluated from the change in solid thrombus weight.

Histopathologic analysis: The arterial segments and thrombi were fixed in 10% neutral formalin. From each segment, 4 rings were excised and processed routinely. Sections were mounted on glass slides and stained with hematoxylin-eosin and Movat-pentachrome stains. An experienced cardiovascular pathologist (GDA) unaware of the experimental details and results performed the pathologic evaluations. The overall integrity of the vessel, continuity of the elastic structures, and cellular damage were assessed in the arterial segments. The composition and architecture were studied in the thrombi.

Cavitation analysis: An ultrasound imaging system was used to study the production of cavitation by the shock waves to elucidate the mechanism of shock-wave thrombus ablation.[3] A 5 MHz multi-element linear-phase array ultrasound imaging transducer, with an axial resolution of 0.3 mm and a lateral resolution of 1.2 mm, at a depth of 4 cm (Ultramark 9, Advanced Technology Laboratories, Inc., Bothell, Washington), imaged the arterial segment in the water bath before, during and after each experiment. The ultrasound image on display was continuously recorded on a videotape with 240 videolines of resolution (AG 6300 Panasonics). Cavitations were defined as highly echogenic, transient microbubbles on the ultrasound image display.[3] Quadruplicates of the maximal area of each cavitation field were measured and averaged (Freeland Systems, Prism Imaging, Chicago, Illinois). The times from the spark-gap discharge to the earliest production of cavitation, to

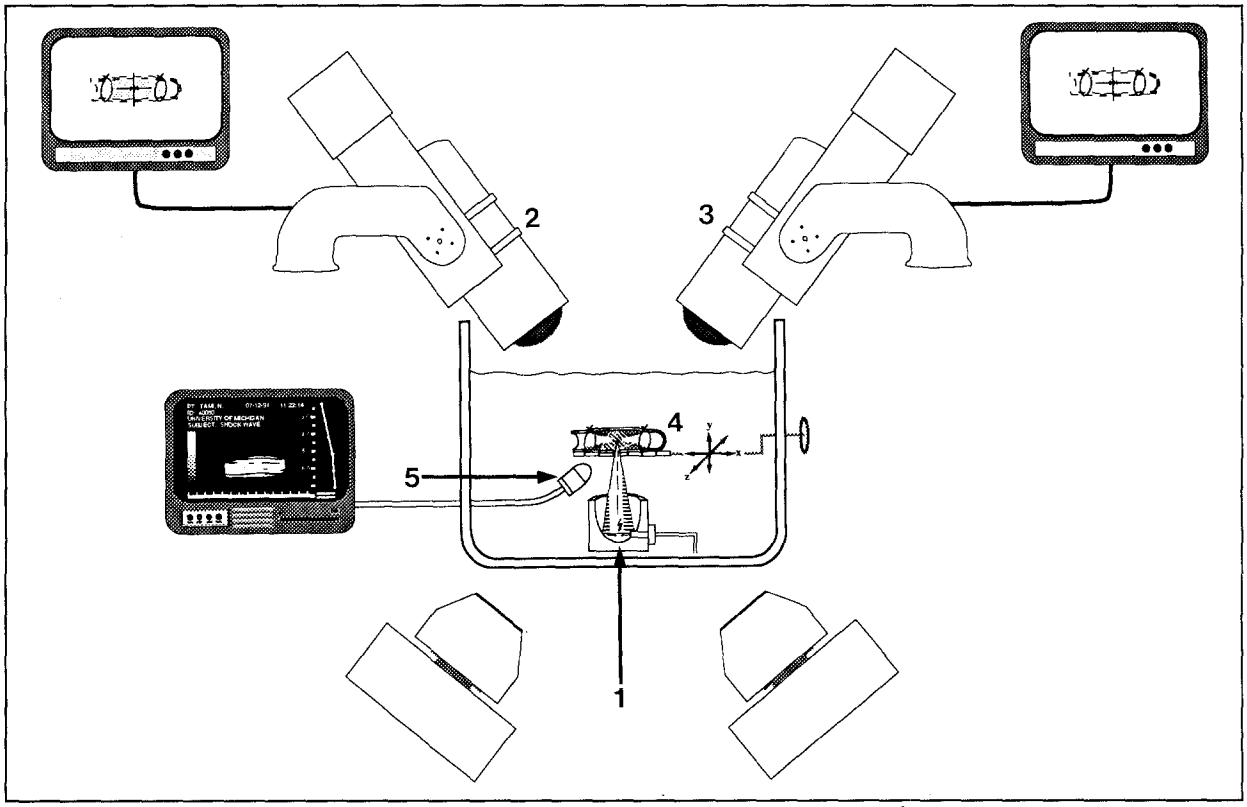

FIGURE 1. Experimental setup. Underwater spark-gap electrode *(1)* generates shock waves. Semi-ellipsoid metal reflector converges energy to focal point where thrombotic arterial segment is positioned. Two independent x-ray image conversion systems *(2 and 3)* are arranged along nonparallel axes and verify 3-dimensional positioning of thrombotic arterial segment. Thrombotic arterial segment *(4)* is suspended from metal frame that can be moved along 3 spatial axes to position thrombotic segment at focal point. Ultrasound imaging system *(5)* visualizes arterial segment at focal point.

attainment of maximal area of the cavitation field and to final clearance of the cavitation were measured in 10 cycles of application of shock waves and averaged. Time was measured by counting the number of videoframes from the spark-gap discharge (recorded as electrical interference on the ultrasound image) to the event and multiplying by 33 ms (at frame rate of 30 frames/s; each frame represents 33 ms). Echocardiographic studies were performed with and without the presence of an arterial segment at focal point to determine the contribution of acoustic impedance mismatch between the arterial segment and water to the production of cavitation.

Statistical analysis: Data were summarized as mean ± SD. Differences between groups were analyzed using the unpaired, 2-tailed Student's *t* test. A p value <0.05 was considered significant.

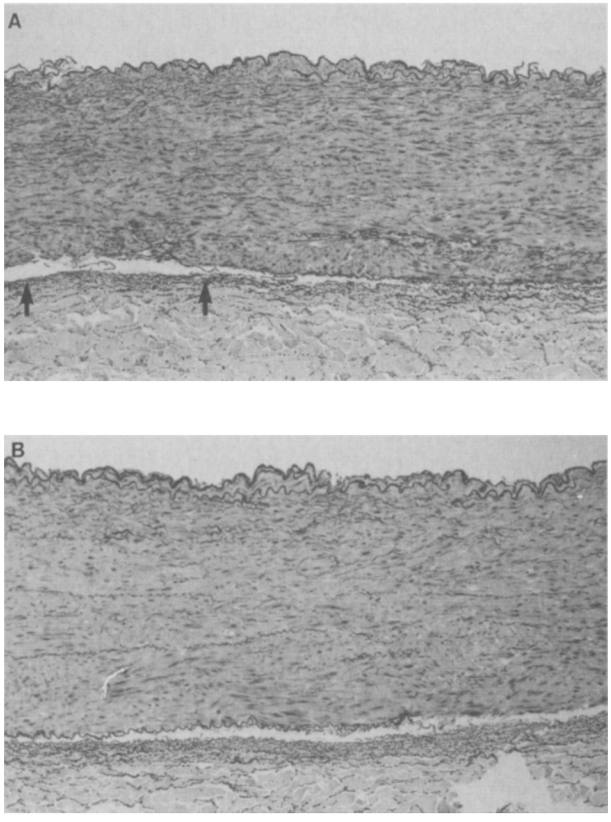

FIGURE 2. ***A,*** **representative histologic section of arterial segment exposed to high-power, acoustic energy. Arterial wall is structurally intact. Elastic fiber variability in internal elastic lamina, which reflects state of vessel at autopsy, is in similar proportions in control segment. Cleavage plane at outer edge of media** ***(arrows),*** **similar to that in control, is artifact of handling.** ***B,*** **representative histologic section of control arterial segment not exposed to high-power, acoustic energy. Structural features of this vessel are virtually identical to those of vessel after exposure. (Movat pentachrome stain; ×120, reduced by 30%.)**

RESULTS

Thrombus ablation: The thrombus generated in vitro had a diameter of 3 mm, length of 3.2 ± 0.4 cm, and weight of 0.24 ± 0.08 g. In the test group, application of shock waves dramatically reduced the weight of solid thrombus (0.25 ± 0.16 vs 0.07 ± 0.003 g; p = 0.0001).

Histopathologic analysis: After application of shock waves, there were no perforations or other gross signs of damage to the arterial segments. Histologic examination revealed occasional cleavage planes between the intima and media along the internal elastic membrane, and between the media and adventitia along the external elastic membrane. These cleavage planes were similar in magnitude in both groups. Accordingly, these breaks were attributed to handling and processing, rather than to acoustic trauma.[5] The variability of the elastic fibers in the internal elastic lamina, which is associated with the existence of arteriosclerotic changes, was in similar proportions in both groups. Otherwise, no change in the architecture of the arterial wall was observed (Figure 2). No cellular damage was noted in the intima, media or adventitia. The residual thrombi in both groups were identical in composition and structure.

Cavitation analysis: Immediately after the application of shock waves (≤33 ms), a localized, transient, dense field of cavitation was formed at the focal point, the site of maximal energy density, encompassing the thrombotic arterial segment. The field of cavitation at-

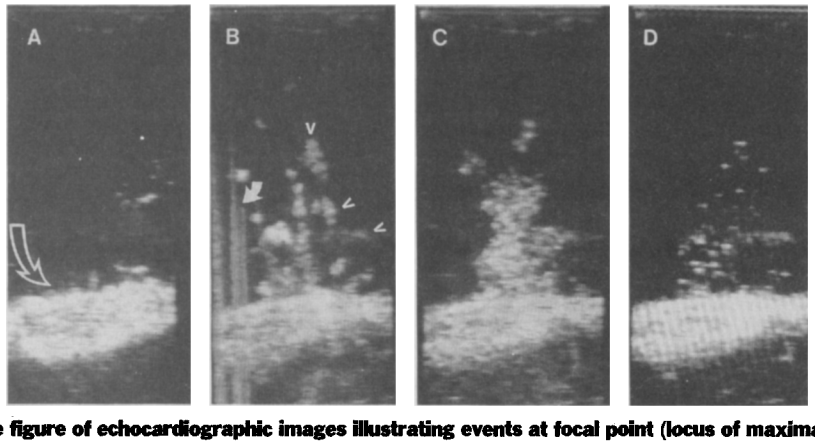

FIGURE 3. Composite figure of echocardiographic images illustrating events at focal point (locus of maximal, acoustic energy density) during experiment of shock-wave thrombus ablation. ***A,*** **at baseline, image shows arterial segment** ***(arrow)*** **immersed in water bath.** ***B,*** **generation of cavitation** ***(arrowheads)*** **at focal point immediately (≤33 ms) after application of shock waves. Time of shock-wave application is recorded as electrical interference** ***(arrow)*** **induced by spark-gap discharge.** ***C,*** **cavitation field, encompassing target thrombotic artery, reaches its maximal dimension (1.9 ± 0.5 cm^2) 129 ± 62 ms after application of shock waves.** ***D,*** **only few residual, stable cavitations remain in focal point 744 ± 233 ms after application of shock waves.**

tained its maximal dimension (1.9 ± 0.5 cm^2) within 129 ± 62 ms; thereafter, it gradually declined in size and density. After 744 ± 233 ms, only a few stable cavitations were apparent at the focal point (Figure 3). The production of cavitation after the application of shock waves was characteristic and independent of the presence of an arterial segment at the focal point.

DISCUSSION

The biological use of focused, high-intensity, acoustic energy was first studied by Lynn et al[6] in 1942. They demonstrated that focused, acoustic energy can produce deep, localized damage at the focal point in various biological tissues in vitro and in vivo, with minimal effect on the surface and no effect on the intervening tissue. Approximately 30 years later, the use of focused, acoustic energy reemerged in the biomedical field. Experimental investigation in the use of focused shock waves has led to nonsurgical treatment of upper urinary tract calculi.[7] Extensive experience with shock-wave lithotripsy has demonstrated the method to be safe and highly effective.[7,8]

This study is the first to show the feasibility of using focused, acoustic energy for noninvasive, targeted and selective thrombus ablation. When thrombotic human arterial segments were placed at the focal point of focused shock waves, a significant ablation of thrombus with no apparent damage to the arterial wall was observed. However, the absence of cellular damage in vitro is limited evidence for the safety of this method. Further in vivo experiments will be needed to confirm the safety of shock-wave thrombus ablation. The small reduction in thrombus weight observed in the control group is mainly attributable to clot retraction between the time of thrombus induction and the ablation experiment (12 ± 3 hours).

The data, documenting the effective and selective noninvasive thrombus ablation by high-power, acoustic energy, are consistent with those in studies of ultrasonic thrombus ablation by acoustic energy transmitted by a catheter.[2,3] Those studies also show that the level of acoustic energy necessary to ablate thrombus has a minimal effect on the arterial wall.

The mechanism of shock-wave lithotripsy is believed to be associated with the acoustic impedance mismatch between the target calculus and surrounding soft tissue. When the shock waves reach the target, the presence of the acoustic impedance mismatch produces pressure changes of magnitudes sufficient for shuttering the target calculus.[9] In this study, shock waves effected thrombus ablation despite the similarities in impedance properties between the fresh thrombus and the surrounding water, suggesting that a different mechanism may be operating here. During shock-wave thrombus ablation, a localized, transient field of cavitation is produced at the focal point encompassing the target thrombotic artery. Cavitations are believed to be responsible for the thrombus ablation in ultrasonic angioplasty.[3] These generate localized disruptive mechanical forces capable of degrading several polymers,[10,11] including fibrin polymer that forms the structural basis of solid thrombus. In ultrasonic thrombus ablation, the cavitation effect disrupts the fibrin polymer with the generation of an abundance of fibrin fragments.[2] Thus, the data suggest that the localized production of cavitation at the pont of maximal, acoustic energy density may be important in the mechanism for thrombus ablation.

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