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# Enhanced Laser Thrombolysis With Photomechanical Drug Delivery: An In Vitro Study

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***Background and Objective:*** **Current techniques for laser thrombolysis are limited because they can not completely clear thrombotic occlusions in arteries, typically leaving residual thrombus on the walls of the artery. The objective of this study was to investigate the possibility of using photomechanical drug delivery to enhance laser thrombolysis by delivering drugs into mural thrombus during laser thrombolysis.**
***Study Design/Materials and Methods:*** **Three experimental protocols were performed in vitro to quantitatively compare the effectiveness of thrombolysis by 1) constant infusion of drug, 2) laser thrombolysis, and 3) photomechanical drug delivery. A fiber-optic flushing catheter delivered drug (a solution of 1 μm fluorescent microspheres) and light ( a 1 μs pulsed dye laser) into a gelatin-based thrombus model. The process of laser-thrombus interaction was visualized using flash photography and the laser-induced pressure waves were measured using an acoustic transducer.**
***Results:*** **Lumen sizes generated by mechanically manipulating the catheter through the thrombus were smaller than those generated by laser ablation. The microspheres could be driven several hundred microns into the mural thrombus.**
***Conclusion:*** **Photomechanical drug delivery has potential for enhancement of laser thrombolysis. Two mechanisms seem to be involved in photomechanical drug delivery: 1) mural deposition of the drug at the ablation site and 2) increased exposure of the thrombus surface area to the drug. Lasers Surg. Med. 23: 151–160, 1998.** **© 1998 Wiley-Liss, Inc.**

**Key words: localized drug delivery; high-speed photography; hydrodynamic flow**

## INTRODUCTION

Laser thrombolysis is a promising method of clearing arteries that are obstructed by thrombi [1]. It has potential advantages over surgery, balloon angioplasty, and other forms of vascular intervention. Laser pulses can be delivered into arteries through fiber-optic catheters, thereby avoiding major surgery. The thrombus is removed by the laser pulses rather than by mechanically overstretching the arterial wall, potentially reducing the high rate of restenosis that occurs with balloon angioplasty. Ablation can be achieved by using nearly any laser source, e.g., a holmium:YAG laser [2–4], but wavelengths that are strongly absorbed by thrombus and poorly absorbed by vascular tissue allow safe, selective targeting of thrombus. Use of small fiber-optic catheters offers the possibility of removing thrombus in small vessels (e.g., cerebral vessels) or in larger

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vessels (e.g., by-pass grafts) [5]. for laser thrombolysis is the incomplete removal of the thrombus after the laser thrombolysis procedure. We propose that localized mural delivery of clot-dissolving drugs during laser thrombolysis may mitigate this problem, i.e., the majority of the clot can be removed by laser pulses and the mural clot is dissolved by the drugs. The present study was motivated by this concept.

Current techniques for localized drug delivery use catheters to infuse thrombolytic agents into thrombus at an angioplasty site. The local deposition of therapeutic agents may provide prolonged thrombolytic action at the infusion site [6]. Two mechanisms may be involved in these procedures: displacement of thrombus due to the balloon dilation and thrombolytic action by therapeutic agents. However, the primary problems with the modified balloon catheter designs are their cumbersome size and long inflation times, as well as the risk of medial injury occurring during the balloon inflation process, thus potentially limiting the benefits of local drug delivery.

We have recently demonstrated that drug could be delivered into thrombus by use of hydrodynamic pressures following the laser-induced bubble expansion and collapse [7]. The bubbles were formed at the fiber tip due to the absorption of laser energy by the surrounding absorbing liquids. The spatial distribution of photomechanically delivered drug depended on parameters such as laser energy, absorption coefficient, fiber size, and material strength. The bubble formation on the thrombus surface due to the absorption of laser energy by the thrombus could also cause flow motion near the cavitation bubble at speeds of up to 12 m/s [8]. We hypothesize that hydrodynamic flow resulting from the bubble formation during laser thrombolysis can be used as a driving force to facilitate drug delivery. This form of localized drug delivery has been termed "photomechanical drug delivery" [9] to distinguish it from "photoacoustic drug delivery" [10], which relies on large pressure gradients gradients to cause cell membranes to temporarily become permeable. Photoacoustic drug delivery requires nanosecond or shorter laser pulses; this work used microsecond laser pulses.

Our objective in this in vitro study was twofold. First, we wished to quantitatively compare the effectiveness of laser thrombolysis alone, laser thrombolysis accompanied by photomechanical drug delivery, and constant infusion of a drug. Such a comparison is important to establish any benefit that may be associated with photomechanical drug delivery. Second, we wished to identify the mechanism of photomechanical drug delivery during laser thrombolysis through visualization of bubble formation with flash photography and measurement of laser-induced pressure waves by using a piezoelectric polyvinylidenefluoride (PVDF) transducer. Solutions of fluorescent microspheres were used as a drug model that allowed us to easily visualize the sphere distribution in thrombus under fluorescence microscopy. Gelatin-based thrombus phantoms were used to avoid the complicated biological variations of real thrombus.

## MATERIALS AND METHODS

### Sample Preparation

The thrombus phantoms used in the drug delivery experiments used a uniformly absorbing gelatin made by adding 0.07 g of Blue 15 dyes (Sigma Chemical Co., St. Louis, MO) into 40 ml of 3.5% 175 Bloom liquid gelatin (Sigma Chemical Co., St. Louis, MO) and curing in the 1 cm cuvettes. The gelatin-water mixture was heated to 60°C with stirring until it became clear before adding the dye. The percentage was determined by the weight ratio of gelatin to water. The Bloom number is the standard method for indicating the toughness of gelatins and is a measure of surface tension. Higher Bloom numbers indicate stronger gelatins. The blue gelatin samples had an absorption coefficient of 100 $cm^{-1}$ at 577 nm. This absorption coefficient was comparable to the bulk absorption (97 $cm^{-1}$ of fully-oxygenated blood (hematocrit of 30) at 480 nm, the laser wavelength used in the initial clincial trials of laser thrombolysis [11]. Previous work has shown that the ablation efficiency was relatively insensitive to the absorption coefficient between 100–1,000 $cm^{-1}$ [12]. The cured gelatin samples were carefully removed from the cuvette and cut into ~5 mm thick sections before the experiments.

We did not try to measure the Bloom number of the clots used in this study [13,14] but instead observed that the gel phantoms had grossly similar physical properties. These gelatin samples tended to be tougher than clot samples because the ablation efficiency of gelatin was roughly 2–3 times less than for clot [15]. This discrepancy was compensated by the fact the gelatin phantoms were very reproducible. The formation of blood clots is subject to the presence or absence of hun-

dreds of chemical factors, as well as physical factors like pressure, flow, and temperature [16]. We found that blood collected from different pigs and cured for equal times at equal temperatures did not always yield similar strength clots [17]. Finally, some investigators are actively working on creating physical models of clot that more accurately resemble clot [18].

The samples for flash photography were made by pouring clear gelatin into 1 cm cuvettes to form 2–3 cm thick samples with cylindrical geometries. The channels were constructed about 2 mm in diameter to simulate blood vessels; the normal adult human coronary artery is 2–4 mm in diameter. A piece of porcine clot was inserted into the channel and then was covered with distilled water at room temperture. The porcine clot was obtained by allowing fresh non-heparinized blood of domestic swine stored in a cylindrical glass tube to clot at room temperature for 5 hours, and then this clotted blood was stored at 8°C overnight before the experiments.

A solution seeded with fluorescent latex microspheres (Molecular Probes, Inc., Eugene, OR) was used as a drug model. The microspheres had the important advantage that they did not diffuse into the gelatin phantoms as molecular dyes did. The microspheres consisted primarily of polystyrene chains and were supplied as suspensions (2% solids with 1 μm diameter) in water plus 2 mM sodium azide. They were non-porous, hydrophobic, and photostable. The excitation and emission maxima were at 488 nm and 515 nm, respectively. The concentration of the solution was about $7.5 \times 10^7$ spheres/ml made by adding 0.5 ml of the suspensions with a concentration of $3 \times 10^{10}$ spheres/ml into 200 ml of distilled water. The solution was clear and did not absorb the laser light at 577 nm. No attempt was made to correlate the solution of microspheres with any specific drugs; the microspheres were used for visualization of fluid flow in the medium.

### Experiments

The effectiveness of thrombolysis was evaluated by comparing the sizes of lumen created by mechanical action due to manual manipulation of a fiber-optic flushing catheter or by laser ablation, and the areas stained by the fluorescent microspheres. A basic assumption of this study was that the stained areas could potentially be dissolved by a delivered thrombolytic drug. Three experimental protocols were employed. First, the solution was infused into the thrombus through a fiber-optic flushing catheter that was manually manipulated inside the thrombus during the constant infusion procedure. Second, the solution was infused into the laser-created channel after laser thrombolysis. Finally, the solution was delivered into the thrombus in coincidence with the laser pulses, i.e., laser ablation and drug delivery were occurring simultaneously. The solution was injected at a rate of 4 ml/min through the catheter for a similar time (~30 seconds) in the three experiments. These parameters were characteristic of the clinical laser thrombolysis experiments [19]. All samples were carefully washed with clear water before being frozen and sectioned. Frozen sections were examined under optical transmittance and fluorescence microscopy. The areas and penetration of the microspheres in the gelatins were measured. The penetration depth was measured from the edge of the lumen to the fluorescent microspheres inside the gelatin sample.

The fiber-optic flushing catheter consisted of a 1 mm Teflon tube containing a 300 μm optical fiber. The fiber tip was terminated 1 mm from the distal tip of the catheter. The drug was infused into the thrombus through the tube connected with a syringe. The flow rate was controlled by a syringe pump (Harvard Apparatus, Dover, MA). Laser radiation was provided by a 1 μs pulsed dye laser (Palomar Medical Technologies) emitting 577 nm light at 3 Hz. Ninety laser pulses of 30–70 mJ were delivered via the flushing catheter onto the thrombus phantoms under clear liquids. The spot size on the target surface was 450 μm obtained by measuring the burn pattern on a deep-dyed polyester film.

To visualize the laser interaction with porcine clot, time-resolved flash photography was used as previously described [17]. Each photograph recorded a single event and was taken three times at various moments after the laser pulse. The bubble size was fairly reproducible during the bubble expansion, whereas the appearance of the cavitation bubbles varied widely during the bubble collapse. Single pulses of 50 mJ were delivered onto porcine clot through a 300 μm fiber with its tip about 1 mm from the clot surface.

The laser-induced pressure waves were measured using a PVDF transducer (KP 117, Ktech). The active square area of the transducer was 1 $mm^2$. The sensitivity was ~32 mV/bar and the rise time was ~400 ns. The transducer was directly connected to a digital storage oscilloscope (DSA 602A, Tektronix, Inc., Beavevton, OR) with a high impedence input (1 MΩ) by means of a 1 m long

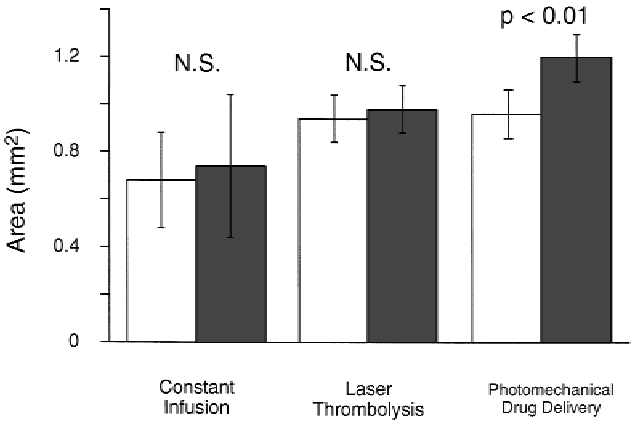


Fig. 1. Comparison of lumen areas generated by three different methods: constant infusion, laser thrombolysis, and photomechanical drug delivery. Ninety laser pulses of 50 mJ were delivered into gelatin samples with an absorption coefficient of 100 $cm^{-1}$ for both laser thrombolysis and photomechanical drug delivery experiments. A flushing catheter with a 300 μm fiber was used for the light delivery. The open bars represent the lumen area and the filled bars indicate the areas including the lumen area and the stained area. Error bars present the standard deviation of four samples.

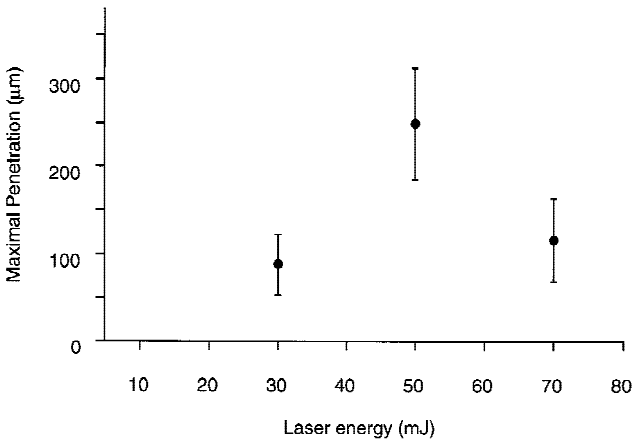


Fig. 2. Maximal penetration of fluorescent microspheres inside gelatin samples as a function of laser energy. The laser pulses were delivered via a flushing catheter with a 300 μm fiber. Error bars denote the standard deviation of four samples.

coaxial cable. The transducer was positioned 16 mm away from the ablation site. The experiments were performed on thrombus phantoms with an absorption coefficient of 100 $cm^{-1}$ at 577 nm. The samples were immersed in a container filled with distilled water at room temperature. Pulse energies of 30–75 mJ were delivered via the flushing catheter placed 1 mm above the gelatin surface. The flow rate was 4 ml/min.

### Statistical Analysis

All data were reported as mean ± standard deviation. The lumen size, stained area, and penetration depth of the microspheres in the gelatin samples were compared. The statistical significance of differences was determined using a two-tailed Student's *t*-test. An unpaired *t*-test was used to analyze the data for constant infusion, laser thrombolysis, and photomechanical drug delivery. A value of $P < 0.05$ was considered to be significant.

## RESULTS

Figure 1 shows the measured lumen sizes generated by manually manipulating the catheter or by laser ablation, and areas stained by the fluorescent microspheres. The lumen sizes generated by manipulating the catheter were smaller than those generated by laser ablation. The lumen sizes were not significantly increased through drug delivery (i.e., by adding the stained area) in both constant infusion and laser thrombolysis. However, the lumen size was increased up to 25% after the photomechanical drug delivery procedure.

The distribution of the microspheres in the gelatin samples was not uniform around the laser-created channels. The penetration measurements revealed that the maximal penetration was not simply correlated with the laser energy (Fig. 2). When the laser energy exceeded somewhere between 50–70 mJ, the penetration depth decreased. However, the lumen sizes increased significantly with increasing laser energy (Fig. 3).

Visualization of the interaction of a laser pulse with clot showed the formation of a bubble in the clot (Fig. 4). The bubble dynamics on clots was similar to the dynamics on gelatin targets. Figure 5 shows the cavitation bubble growth and collapse produced by a 50 mJ laser pulse. The bright spot in the sixth frame was the reflected flash of light from the strobe. The bubble expansion caused the slight dilation of the channel. The maximal dilation was reached after about 60 μs and amounted to 130% of the initial channel diameter. The subsequent bubble collapse induced an invagination of the channel wall. The minimal diameter was ~88% of the initial value. No oscillation of the cavitation bubble was observed. The mass ejection followed the bubble collapse.

Figure 6 shows a representative pressure trace for a laser pulse of 30 mJ delivered onto gelatin under water. The initial pressure peak

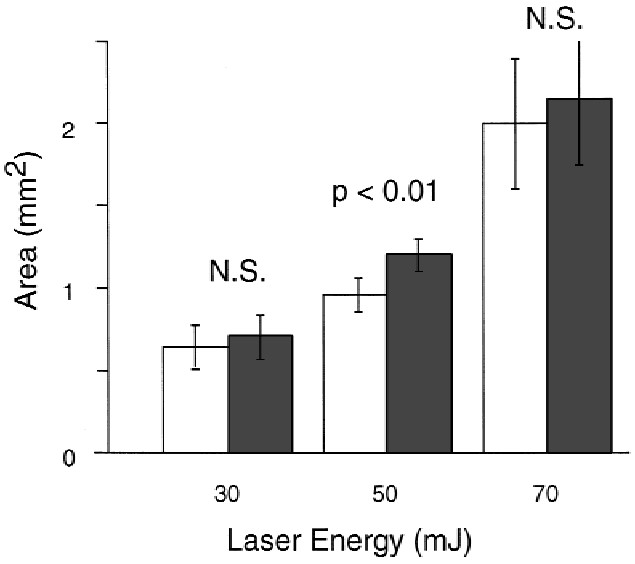


Fig. 3. Lumen size created by laser ablation and increased area (the sum of the lumen and stained area due to the drug delivery) as a function of laser energy. Ninety pulses were delivered via a flushing catheter with a 300 μm fiber onto the gelatin samples with an absorption coefficient of 100 $cm^{-1}$. The open bars represent the lumen size and the filled bars indicate the increased area. Error bars represent the standard deviation of four samples.

was due to a thermo-elastic expansion wave. The second peak at 300 μs was generated by the collapse of the cavitation bubble. The times were corrected to account for the time delay associated with the time it takes the acoustic signal to propagate from the ablation site to the transducer. The velocity of the sound wave was assumed to be 1,500 μm/μs. The measured acoustic pressure transients (expansion and collapse) as a function of laser pulse energy are shown in Figure 7. The lumen size generated by laser ablation alone and the increased lumen size (the sume of the lumen size and the stained area) enhanced by photomechanical drug delivery are plotted as a function of bubble expansion pressure on gelatin (Fig. 8).

## DISCUSSION

This study investigated the potential of using the microsecond laser-induced mechanical effects to drive drug locally into thrombus to enhance laser thrombolysis using three different methods: 1) constant infusion of drug, 2) laser thrombolysis, and 3) photomechanical drug delivery. Unlike previous studies [6,20,21], we used a solution of 1 μm fluorescent microspheres as a drug model rather than thrombolytic agents such as streptokinase and urokinase. Thus, thrombolysis due to thrombolytic action was determined by measuring the areas stained by the microspheres. The stained areas were assumed to be potentially dissolvable by delivered drugs. The larger the stained areas were, the more effective the thrombolytic action would be. A gelatin-based thrombus model was used for both photomechanical drug delivery and acoustic pressure measurements. The interaction of porcine clot and microsecond laser pulses was also visualized using time-resolved flash photography.

As shown in Figure 1, the lumen areas generated by manually manipulating the catheter after the constant infusion procedure were smaller than those created by laser ablation, and the thrombolysis process may not be enhanced effectively by thrombolytic action using either the constant infusion of drugs or drug infusion after laser thrombolysis procedure. The results also show that there are no significant differences in the lumen areas generated by constant infusion and laser thrombolysis. However, previous studies demonstrated that the thrombolysis rate using constant infusion is much slower than using laser thrombolysis. For example, it would take 30 minutes to lyse 32% of porcine thrombus (i.e., thrombus that weighed 133 ± 31 mg before treatment would weigh 90 ± 26 mg after treatment) by using a constant infusion of urokinase [6], whereas only about 3 minutes would be needed to lyse a similar amount of the thrombus using laser thrombolysis (i.e., less than 400 laser pulses of 60 mJ operating at 577 nm and 3 Hz via a 300 μm fiber) [17]. It is evident that the lumen areas increase with increasing laser energy (Fig. 3).

Laser thrombolysis can be enhanced by use of photomechanical drug delivery. For example, the mechanical effects of the bubbles resulted in deeper penetration: 250 ± 60 μm for photomechanical drug delivery vs. 50 ± 20 μm ($P < 0.01$) for drug infusion after laser thrombolysis. The stained area generated by photomechanical drug delivery was about four times larger than that obtained infusing the drug after laser ablation: 0.24 ± .05 $mm^2$ vs. 0.06 ± 0.01 $mm^2$ ($P < 0.01$). A similar result was reported by Girsky et al. [22] for photomechanical drug delivery to porcine clot confined in carotid arteries. Similar parameters such as laser energy, fiber size, and fluorescent microsphere solution were used for their experiments. Their results (photomechanical drug delivery vs. drug infusion after laser thrombolysis) were that the penetration was 330 ± 40 μm vs.

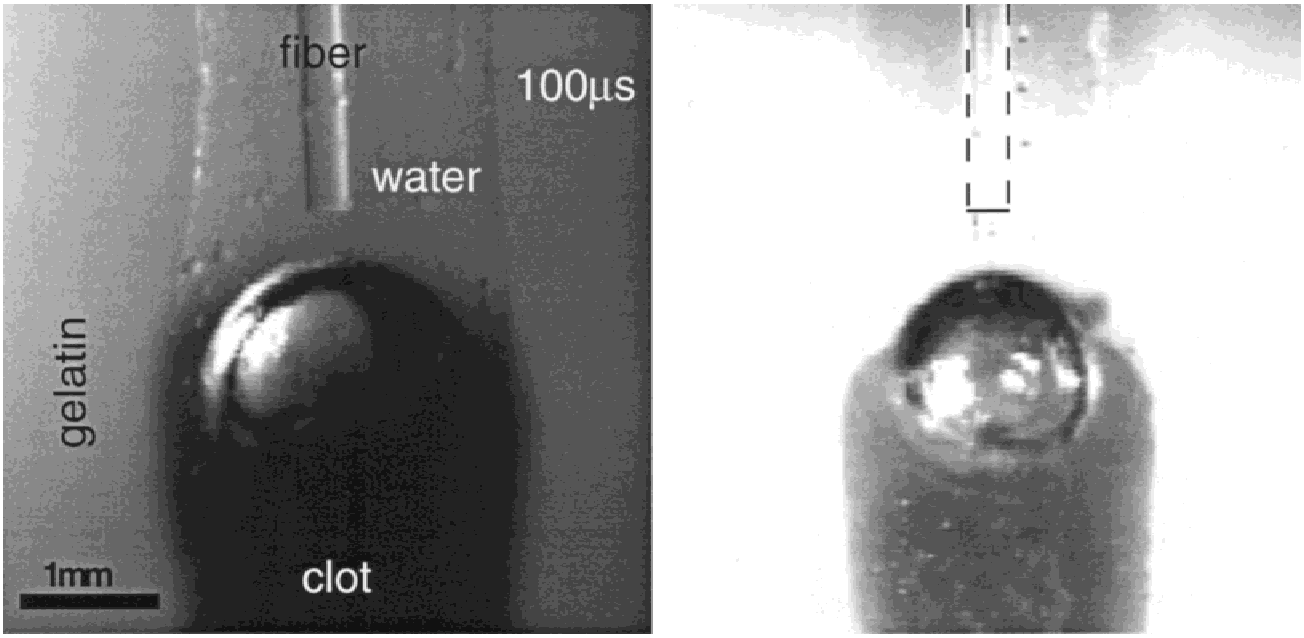


Fig. 4. A laser-induced cavitation bubble formed in the clot. The right photo was taken to show the spherical shape of the bubble on the left.

160 ± 20 μm ($P = 0.002$), and the stained areas were 0.13 ± .02 mm$^2$ vs. 0.020 ± 0.004 mm$^2$ ($P = 0.01$).

Flash photographs showed that cavitation bubbles were formed after the laser pulses interacted wit the clot (Fig. 5). Unlike our recent study [7], the laser energy was absorbed by the thrombus and vaporized a small amount of the thrombus, creating a very high-pressure gas, which rapidly expanded to generate a vapor bubble. The bubble growth and collapse caused dilation and subsequent invagination of the channel wall of the gelatin samples. The flow surrounding the bubble moved at speeds up to 12 m/s during the bubble expansion and collapse [8]. The transient displacement of thefluid may generate hydrodynamic pressures as driving forces pushing drug into the thrombus. This is a possible explanation of why the penetration of the microspheres was shallower using drug infusion after the laser thrombolysis procedure than that observed using photomechanical drug delivery. The thrombus ejection was observed following the collapse of the cavitation bubble. As a consequence, pressure impulses may also force fluid to move towards the gelatin surface due to momentum conservation. The thrombus surface would be exposed to the surrounding drugs periodically when a number of laser pulses were delivered.

Thus, two mechanisms seem to be involved in photomechanical drug delivery: 1) mural deposition of the drug at the ablation site due to the cavitation forces and 2) increased surface area of the thrombus available to interact with local drug concentrations. A study by Kandarpa et al. suggested that forecful local pulsatile infusion of fibrinolytic enzyme disrupts thrombi, increases clot surface area and hastens enzyme action compared with conventional constant infusion methods [20]. They used a reciprocating syringe pump to deliver small volumes of thrombolytic enzyme in short, rapid, frequent pulses at high exit-jet velocity (4.5 m/s) through a 4-F side-hole catheter. Pulsatile infusion lysed 61% of the thrombus by weight in an hour, whereas constant infusion lysed only 15%.

Laser-induced acoustic pressures have been demonstrated as the acoustic signatures measured during laser ablation of gelatin samples under water (Fig. 6). Unlike laser lithotripsy using a 2.5 μs flashlamp pumped dye laser [23], there is no significant difference between expansion and collapse pressures during laser thrombolysis (Fig. 7). This is presumably caused by the effects of material strength and pulse duration. Figure 8 indicates that the higher bubble expansion pressures result in larger lumen areas, which are in coincidence with our previous ablation study using porcine clot [17].

The penetration depth of the microspheres in

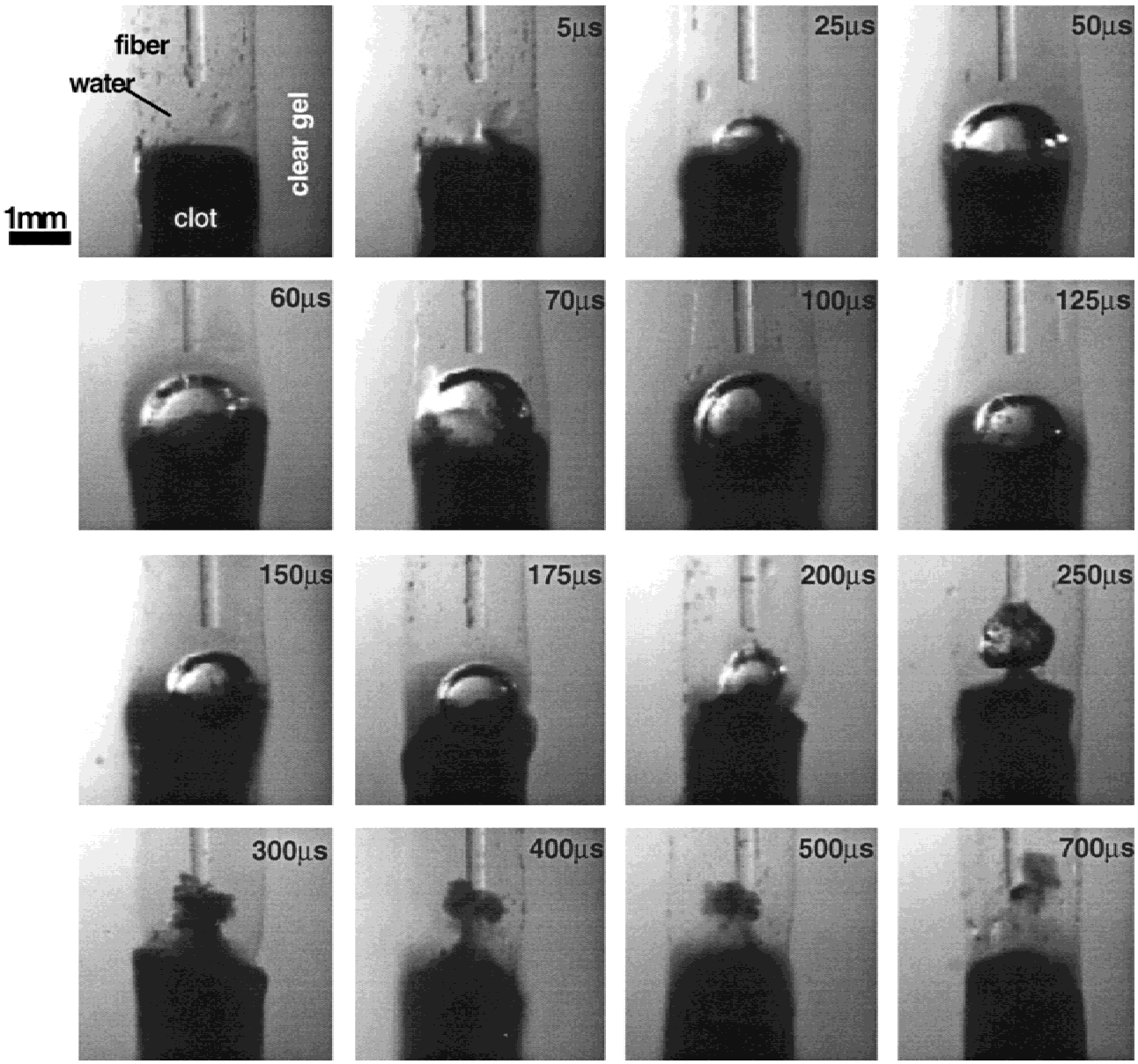


Fig. 5. A series of flash photographs of cavitation bubble growth and collapse after the laser pulse. Single pulses of 50 mJ were delivered onto the clot via a 300 μm fiber. The clot was confined in a gelatin sample with a cylindrical channel at center. The fiber was placed 1 mm above the clot under water.

gelatin samples was not simply correlated to the laser energy (Fig. 2). The penetration increased at least until the laser energy reached 50 mJ, and started decreasing somewhere between 50–70 mJ. One possible explanation is that two processes, mass removal and drug delivery, occur simultaneously during photomechanical drug delivery. A shallower penetration may be as a result of the fact that more mass surrounding the ablation site is removed although the drug can be driven into targets more deeply with higher pressures [7]. We postulate that there is a threshold effect. The maximum penetration is achieved at moderate pressures, since such a pressure can only remove a certain amount of the gelatin surrounding the ablation site, consequently a larger stained area remains after the ablation process. At high pressures, the ablation process becomes more explosive. Thus, more mass surrounding the ablation site is blown off, even though the microspheres are driven more deeply into the gelatin if we measure the penetration depth from the cen-

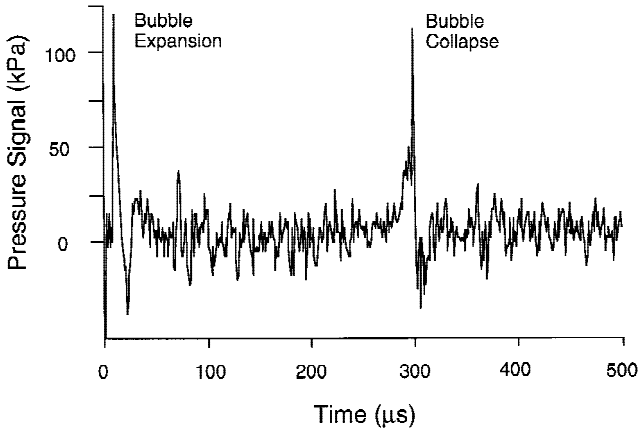


Fig. 6. The pressures induced by the cavitation bubble following laser irradiation. The times have been corrected for the propagation delay of the pressure signals from the ablation site to the pressure transducer.

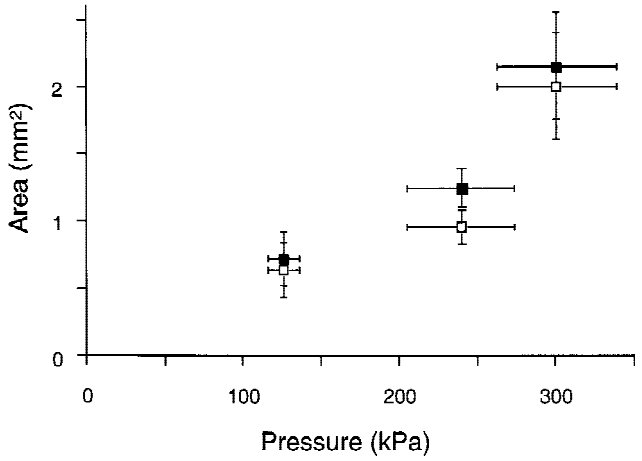


Fig. 8. The area produced by laser ablation (open squares) and photomechanical drug delivery (filled squares) as a function of bubble expansion pressure on gelatin samples (Fig. 3).

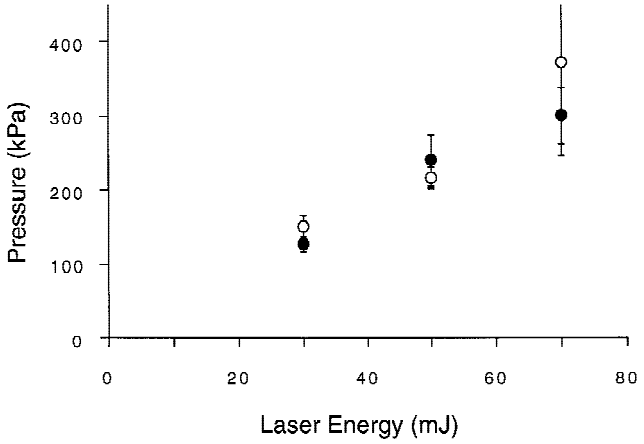


Fig. 7. Bubble expansion and collapse pressures as a function of laser energy. The pressure signals were detected with a PVDF transducer placed 16 mm away from the ablation site under water. The absorbing gelatin samples had an absorption coefficient of 100 $cm^{-1}$. The open circles represent the expansion pressure and the filled ones indicate the collapse pressure, respectively. Error bars represent the standard deviation of six samples.

ter of the lumen rather than from the channel wall to the microspheres. Thus, in general, the use of photomechanical drug delivery to enhance laser thrombolysis seems to be a trade-off between the mass removal by laser ablation and that by thrombolytic action.

## Implications

Intracoronary thrombus is an extremely common and difficult problem to treat in the cardiac catheterization laboratory. Laser thrombolysis has been successfully used in the treatment of coronary thrombus [11], but the current techniques of completely removing a large thrombus burden in arteries with a laser are limited. Any mural clot left behind will be a potential stimulus for reocclusion of the arteries. It is difficult to precisely control the catheter's position within a vessel once it is inserted into a clot, and the catheter most likely retraces its first path as multiple manipulations of the catheter are required, so some mural clot remains. Another potential disadvantage of laser thrombolysis using a pulsed-dye laser is the difficulty of removing clot that possesses high fibrin content. It is problematic whether clear fibrin can be removed along with the red blood. More laser energy is needed to ablate the clear fibrin after the red blood is removed since the absorption of red blood is much higher than that of the clear fibrin. It is possible that perforation and dissection of the artery could occur if laser energy above the ablation threshold of normal tissue is used to completely remove the clot. Thus, thrombolytic action to dissolve the fibrin would be beneficial for laser thrombolysis.

The results of this study demonstrate that laser thrombolysis could be enhanced by delivering drugs into mural thrombus during the laser thrombolysis procedure. Photomechanical drug delivery is adaptable to current laser thrombolysis using a fluid-core laser catheter [24] without any special requirements. One can perform photomechanical drug delivery by delivering the laser pulses with a constant injection of drug. Furthermore, the delivery system could be simple, since it consists of only two elements: an optical fiber or light guide for light-delivery and catheter tubing

for drug-infusion. The system can also be made small and flexible, which allows drugs to be delivered into a destination with small geometry (e.g., cerebral vessel). Previous studies have also demonstrated that effective thrombolysis could be achieved using either local infusion of urokinase [6,21] of ultrasound-mediated thrombolytic therapy [25–28]. A mechanical technique has been applied successfully in acute myocardial infarction and ischemic, thrombotic syndromes [29]. However, these techniques may not be feasible in many clinical situations where small vessels are involved, e.g., stroke treatment, due to the stiffness and relatively larger size of the catheters.

### Limitations of This Study

Although the potential of using photomechanical drug delivery for enhancement of laser thrombolysis has been demonstrated, it is not entirely clear how effective it would be in vivo using thrombolytic agents. The results will depend on the distribution and efficacy of the thrombolytic drug. Because we used laser parameters similar to those used in clinical trials, we have a general idea of how photomechanical drug delivery would work in that particular clinical scenario. However, we view these results as guidelines for photomechanical drug delivery, because our gelatin phantom will certainly differ from any thrombus found blocking a cerebral artery in vivo.

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