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Investigations of Basic Ablation Phenomena During Laser Thrombolysis

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ABSTRACT

This paper presents studies of microsecond ablation phenomena that take place during during laser thrombolysis. The main goals were to optimize laser parameters for efficient ablation, and to investigate the ablation mechanism. Gelatin containing an absorbing dye was used as the clot model. A parametric study was performed to identify the optimal wavelength, spot size, pulse energies, and repetition rate for maximum material removal. The minimum radiant exposures to achieve ablation at any wavelength were measured. The results suggest that most visible wavelengths were equally efficient at removing material at radiant exposures above threshold. Ablation was initiated at surface temperatures just above 100°C. A vapor bubble was formed during ablation. Less than 5% of the total pulse energy is coupled into the bubble energy. A large part of the delivered energy is unaccounted for and is likely released partly as acoustic transients from the vapor expansion and partly wasted as heat. The current laser and delivery systems may not be able to completely remove large clot burden that is sometimes encountered in heart attacks. However, laser thrombolysis may emerge as a favored treatment for strokes where the occlusion is generally smaller and rapid recanalization is of paramount importance. A final hypothesis is that laser thrombolysis should be done at radiant exposures close to threshold to minimize any damaging effects of the bubble dynamics on the vessel wall.

Keywords: Heart attack, Stroke, Cavitation

1. INTRODUCTION

Laser thrombolysis seeks to treat cardiovascular disease by removing clot blocking vital vessels using microsecond pulses delivered via a fluid optical guide. The removal of the clot results in a restoration of blood flow while maintaining vascular integrity. Some of the main advantages of laser thrombolysis over conventional treatment of cardiovascular disease are higher efficacy rates and potential safety. Recently, there has been considerable interest in using this technique to remove cerebral clots in the arteries of the brain. This can be an important step towards the treatment of stroke that can be caused by occlusions in the brain arteries.

Both basic research into the physical ablation phenomena and clinical trials are required to make laser thrombolysis a safe and rapid procedure, so that it may be accepted as a standard treatment modality for vascular disease. This paper addresses some of the questions regarding the basic physical processes during laser thrombolysis. The ablation process is initiated by a light pulse delivered through the fluid catheter. The temperature of the thrombus increases as it absorbs the light reaching levels sufficient for vaporization. Vapor bubbles expand and collapse and disrupt the thrombus. The relationship between these phenomena and their contribution to thrombus removal is not clear. With a better understanding of the ablation process, it may be possible to specify optimal parameters for the design of the laser and delivery systems. The areas studied in this paper are: (*i*) Optimal laser parameters for efficient ablation, (*ii*) Ablation threshold exposures for thrombus and artery, and (*iii*) Vapor bubble formation during the ablation process.

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To elucidate the physical aspects of laser ablation, most experimental work reported here is done on gelatin tissue phantoms containing an absorbing dye. The gel models are reproducible and allow comparative experiments using various optical properties and laser and delivery parameters. The ablation thresholds for gel are roughly equivalent with those of clot at similar absorptions as reported by other investigators. This comparison is a rather limited validation of gel as optical model for clot. Also, the mechanical properties of the two materials differ. Nevertheless the processes that take place in these controlled models should provide insight into the phenomena that take place during ablation of clot. Gel has been used to model soft tissues by numerous researchers.[1–5]

2. FACTORS AFFECTING ABLATION EFFICIENCY

This section describes experiments carried out to determine the optimal wavelength, spot size, pulse energy, and repetition rate for laser thrombolysis. Laser parameters were deemed optimal when the maximum amount of gelatin was removed per pulse per unit energy (ablation efficiency). A unique spectrophotometric method was developed to measure the mass removed.[6] Ablation efficiency was defined as mass of gelatin removed per unit energy per pulse. Wavelength studies were conducted by varying the absorption of gelatin between 10–2000 cm^{-1} corresponding to clot absorption in the 400–600 nm range. Laser energy at 506 nm was delivered via optical fibers of 300–1000 μm core diameter to investigate the effect of spot size. The pulse energies ranged from 25–100 mJ, and the repetition rate was varied from 1–10 Hz. Arteries were simulated by 3 mm inner diameter plastic tubes, and the gel was ablated under water.

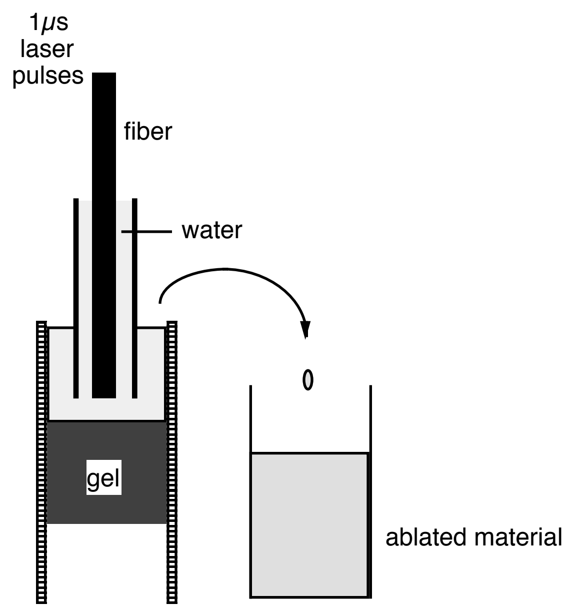

Figure 1. Gelatin containing an absorbing dye is confined in a 3 mm diameter tube. Laser energy is delivered in 1 μs pulses via a solid glass fiber at a distance of 1 mm to the gelatin. The ablated material is collected in water and the mass is measured using a spectrophotometric method.

Ablation of gelatin was characterized by a snapping sound and visible removal of material. The spectrophotometric method of measuring the ablation mass proved accurate and reproducible with an error estimate of less than 5%. The diameter of the crater was roughly equal to the laser spot size. An increase in crater depth with multiple pulses was observed. At pulse energies of 25, 50, and 100 mJ, no material was removed at an absorption coefficient of 10 cm^{-1} (figure 2). Pulse energies of 50–100 mJ resulted in ablation efficiencies of less than 1μg/mJ at 30 cm^{-1}. At higher absorption coefficients the ablation efficiency increased and remained roughly constant between 2–3μg/mJ from 100–1000 cm^{-1} for all three pulse energies. More gelatin was removed with larger fibers at the same energy. The 1000 μm fibers ablated about twice as efficiently as 300 μm fibers (figure 3). The ablation efficiency was roughly constant at all pulse energies for a *single* spot size. Ablation efficiency was slightly lower at higher repetition rates (not shown).

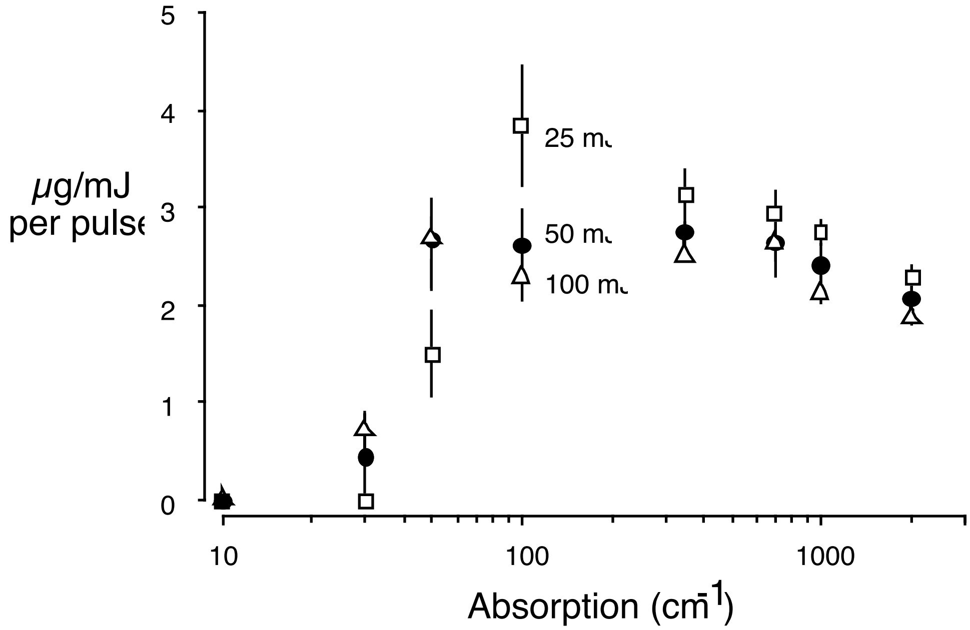

Figure 2. Ablation efficiency as a function of absorption at different pulse energies. The squares, circles, and triangles represent pulse energies of 25, 50, and 100 mJ respectively. A 1000 μm core diameter glass fiber was used for laser delivery. Values are averages of 10 pulses. Error bars denote standard deviation of 10 samples.

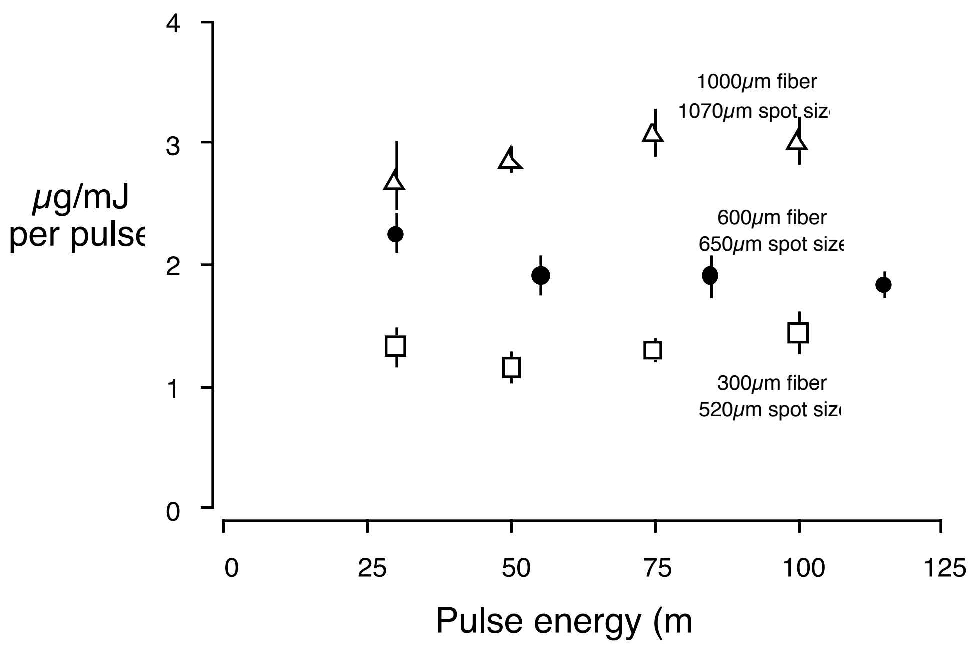

Figure 3. Ablation efficiencies at various pulse energies and spot sizes. The squares, circles, and triangles represent 300, 600, and 1000 μm fibers respectively. Absorption coefficient of the gelatin was 300 cm^{-1}. Values are averages of 10 pulses. Error bars denote standard deviation of 10 samples.

It has now been shown that absorption has little effect on the mass removal in the absorption region of 100–1000 cm^{-1} at pulse energies of 25–100 mJ. This has a direct implication for the choice of wavelength for laser thrombolysis as seen in figure (4), with the caveat that a change in ablation efficiency can be expected due to the different mechanical strengths of thrombus and gelatin. Thrombus has an absorption range of 100–1000 cm^{-1} in the waveband between 410–590 nm, and therefore any wavelength in this range can be chosen without significantly compromising the efficiency. Selectivity would still be retained since vessel wall absorption is less than 10 cm^{-1} in this waveband. The peak temperatures reached and the amount of material vaporized during laser irradiation of an absorbing body is directly dependent upon the absorption. Since this experiment has shown that absorption does not strongly influence material removal above threshold, vaporization is not likely to be dominant in the removal process. The dominant factor in mass removal under a liquid is some mechanical action which is most likely the result of expansion and/or collapse phases of the vapor bubble.

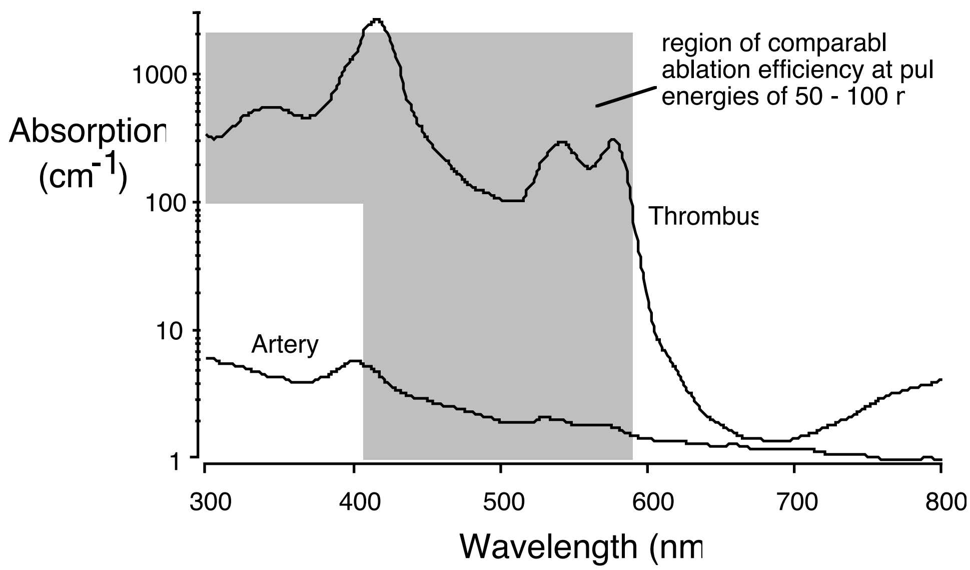

Figure 4. Wavelengths for laser thrombolysis: An absorption range of 100–1000 cm^{-1} corresponds to the waveband between 410–590 nm for thrombus absorption. Ablation efficiency is independent of wavelength in this range at pulse energies above threshold. Selectivity is still maintained due to low absorption by artery.

The higher ablation efficiencies with larger fibers at similar energies suggest that larger diameter catheters would be better at creating wider lumen during laser thrombolysis. Clearly, the size of the catheter constrained by flexibility requirements and the size of the vessel. The repetition rate currently in clinical use is 3 Hz. The results of this study imply that laser thrombolysis can be done at about 10 Hz without seriously compromising the efficiency.

3. ABLATION THRESHOLDS

The results of the experiments described in the previous section suggested that almost all visible wavelengths were suitable for efficient ablation. They also showed that increasing the pulse energy resulted in more mass removal. However, the energy cannot be increased indiscriminately since that will lead to ablation of the arterial wall. The radiant exposure therefore has to be maintained at a level that is both efficient and safe: above the ablation threshold for thrombus and below that for arterial wall. Threshold values for atherosclerotic plaque, thrombus, vessel wall, and blood are available in literature only at selected wavelengths.[7,8] Since the choice of wavelength is largely flexible, threshold information for the entire visible region is crucial. Determination of thresholds will also help understand the basic ablation process.

Microsecond pulses were delivered to gel targets under water, and the pulse energy was increased until ablation was detected. The onset of ablation was detected by mass removal measurements, direct visualization, and detection of an acoustic emission. The absorption of the gel target was varied from 10–2000 cm^{-1} to cover clot absorption in the waveband of 400–600 nm (figure 4).

Threshold radiant exposures ranged from $160\pm10\,\mathrm{mJ/mm^2}$ at $10\,\mathrm{cm^{-1}}$ to $8.5\pm0.5\,\mathrm{mJ/mm^2}$ at $1000\,\mathrm{cm^{-1}}$. A vapor bubble was formed at pulse energies close to those designated as threshold in the previous experiments (figure 5). The thresholds agree with those found by Prince *et al.* for microsecond ablation of atheroma and normal aorta at similar absorption coefficients ($68\,\mathrm{mJ/mm^2}$ at $54\,\mathrm{cm^{-1}}$ and $160\,\mathrm{mJ/mm^2}$ at $26\,\mathrm{cm^{-1}}$ respectively).[7] LaMuraglia *et al.* reported a threshold radiant exposure of $11\,\mathrm{mJ/mm^2}$ for the ablation of fresh thrombus at a wavelength of 482 nm. The absorption of thrombus at this wavelength is $\sim$100–200 $\mathrm{cm^{-1}}$, and according to the measurements on gel the threshold radiant exposure for this range lies between 15–20 $\mathrm{mJ/mm^2}$ (figure 6). The experimental values reported here also agree with thresholds measured by de la Torre *et al.* for bubble formation in lysed blood at various hematocrits within 10%.[9] This close correlation goes towards the validity of gelatin as an optical model for soft tissue. A calculation of threshold temperatures shows that the surface needs to be heated to about 100°C for ablation to be initiated. Apparently the latent heat to completely vaporize the irradiated disk is not needed. Instead, any extra energy above that required to raise the surface temperature to 100°C is probably used to initiate vaporization at a few discrete spots over the irradiated area.

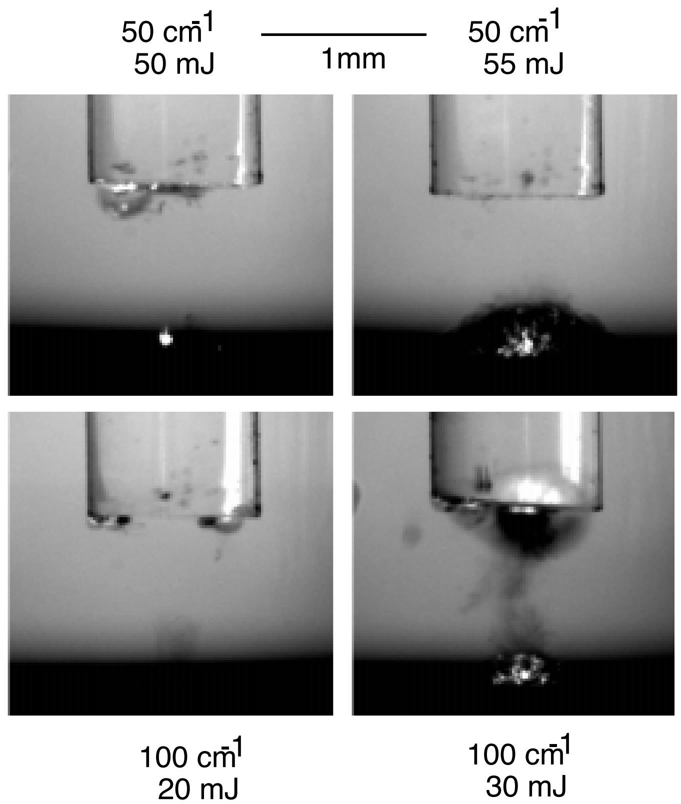

Figure 5. Ablation under water was visualized with flash photography. At threshold a vapor bubble is formed and material is removed. Pictures were taken 5 μs after the laser pulse.

In conclusion, microsecond ablation thresholds have been measured as a function of the absorption coefficient μ_a. Since the choice of laser wavelength determines the absorption coefficients of thrombus and vessel wall, ablation thresholds for thrombus and vessel wall at any wavelength in the visible region can now be predicted. The radiant exposure for laser thrombolysis can then be chosen such that it is above the threshold for thrombus, but below that of artery. However, it is important to note that the threshold values reported in this thesis were measured *in vitro*. The situation *in vivo* may be very different. For example, there may be a thin layer of blood on the inside of the vessel wall. A radiant exposure lower than the artery threshold may then result in ablation of the blood layer and lead to adjacent damage to the vessel below. Another factor to be considered is that the intravascular bubble formed during ablation of thrombus may be large enough to dilate the artery and cause dissections. The energy required to form such a large bubble may be less than that required to ablate artery directly thereby imposing a tighter restraint

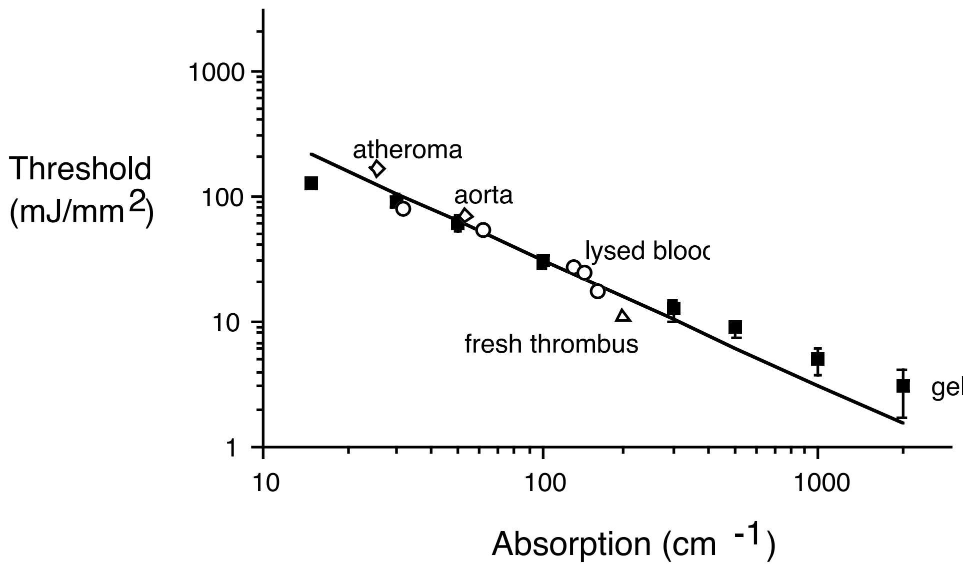

Figure 6. Threshold radiant exposures measured on gel are compared with those for tissue from literature. Thresholds for atheroma and aorta were measured by Prince *et al.* at 482 nm. LaMuraglia *et al.* measured the ablation threshold for fresh thrombus at 482 nm. Thresholds for lysed blood were measured by de la Torre *et al.* . at 577 nm for various hematocrits. A calculation of threshold surface temperatures yields 100°C.

on the maximum energy used.

4. VAPOR BUBBLE FORMATION

The results of the parametric ablation study suggest that mechanical effects dominate over thermal effects for three reasons. The mechanical effects were suspected to be caused by the dynamics of a vapor bubble formed when some of the material was vaporized. Indeed, the visualization experiments in the third chapter show vapor bubble formation at ablation threshold and none below threshold.

A study of the bubble dynamics during laser ablation may provide insight into the ablation process. Of more practical interest would be correlating the ablation mass with bubble sizes and energies. Are bigger and more energetic bubbles needed to remove more material? To answer this question, bubble energies have to be calculated. An estimate of the total energy going into the bubble action will also be helpful in reaching an energy balance for the ablation process.

Flash photography was used to record bubble dynamics on gel targets of various absorption coefficients. A photograph of the bubble action is taken at various moments after the laser pulse. Pulse energies of 25–100 mJ were delivered via glass fibers of 300–1000 μm core diameter. The gelatin was ablated in 1 cm cuvettes. Ablation efficiency was measured by the spectrophotometric method.[6]

Bubbles up to 5 mm in diameter were formed. The lifetimes of the bubbles formed were of the order of 400–600 μs. Higher pulse energies produced bigger bubbles with longer lifetimes. The size and shape of the bubbles were very reproducible except at times close to collapse. Bubble expansion and collapse occurred at roughly similar rates. Figure (7) is a montage of individual pictures showing the bubble history.

A simple model proposed by Lord Rayleigh was used to estimate bubble energies based on the maximum size and lifetime of the bubble.[10] Such a calculation shows that a very small fraction ($< 10\%$) of the total laser pulse energy is converted into the pressure-volume work done by the bubble. It is not clear what happens to the bulk of the energy. Obviously, the initial coupling of the pulse energy into the target is thermal due to absorption. The heated material expands and some energy is released into pressure transients. Part of the material is vaporized and forms the bubble. The bubble dissipates this energy in its expansion and collapse phases in the form of acoustic transients.[11] It is yet to be determined how much of the total laser energy goes into the initial pressure transients,

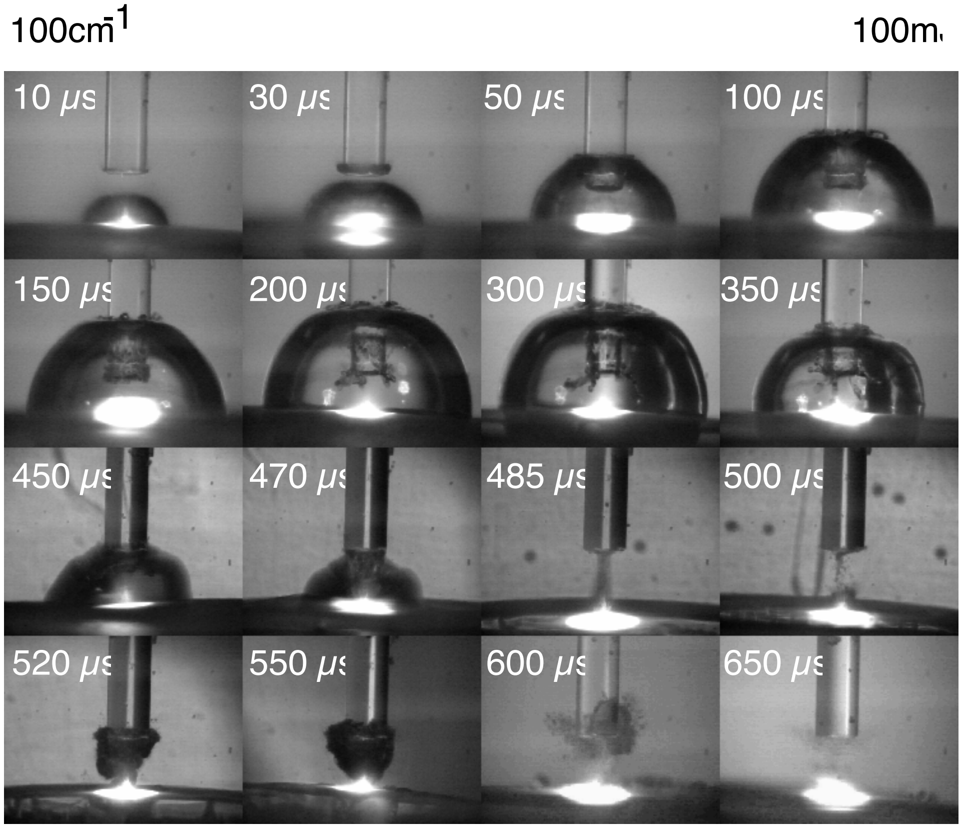

Figure 7. Montage of bubble pictures taken at different delays. Each bubble was an individual event and was formed by separate laser pulses.

and how much is wasted as heat. Numerical codes designed to model underwater explosions are now being used to clarify the energy balance issue.[12,11]

5. DISCUSSION

5.1. Can we work at threshold?

The total mass removed was linearly dependent on the energy of the bubble formed. This would suggest that the bubble was directly responsible for the ablation process. However, given the fact that the bubble energy accounts for very little of the total laser energy, it is also possible that the bubble is just a byproduct of some other mechanism at work. A big bubble can be dangerous since it can result in mechanical damage to the vessel wall (figure 8).

The question now arises: *how important is the bubble in the mass removal process?* Does it just happen to be formed, its size and energy being dependent on how much extra energy is left after the vaporization process? The actual work in the ablation process may be done by the unaccounted energy that manifests itself in an initial acoustic transient. It may then be possible to remove clot without creating a big bubble.

This question has implications important enough to warrant further studies of ablation efficiency near threshold. It is particularly critical for applications to stroke treatment where over-dilation of vessels must generally be avoided (vessel dilation may beneficial in the treatment of vasospasm). Threshold conditions can be achieved by choosing the appropriate combination of pulse energy, spot size, and absorption coefficient. The easiest way is to just reduce the pulse energy for a fixed spot size and absorption. If the bubble size can be drastically reduced by operating just above threshold, any compromise in total mass removal can be accommodated by firing more pulses, using a higher repetition rate, or both.

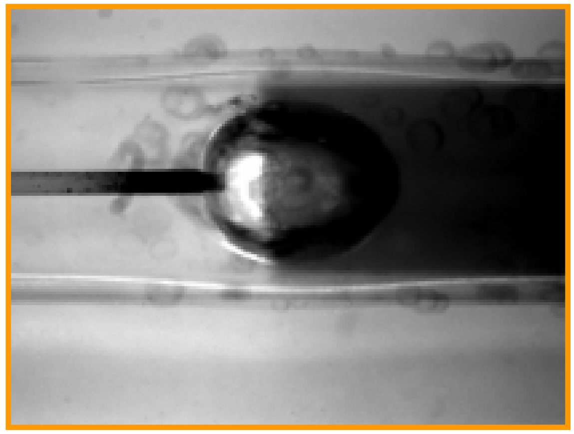

Figure 8. Vessel dilation due to bubble formation. The bubble was generated by ablating $100\,\mathrm{cm}^{-1}$ gel in a 3 mm tube. Pulse energy was 50 mJ and was delivered by a $300\,\mu$m fiber.

5.2. Where is laser thrombolysis now?

When this study was initiated, laser thrombolysis was seen as an alternate procedure to treat thrombosis of coronary arteries and bypass grafts that causes acute myocardial infarction. The thrombus burden encountered in bypass grafts can be quite large, maybe 3–5 mm in diameter and 10 mm in length. One of the disadvantages of current techniques of removing thrombotic occlusions had been the inability to completely remove a large thrombus burden.

Can laser thrombolysis remove large thrombus burden and clear completely thrombosed vessels? In this paper, it was reported that the channel drilled into the clot model had a diameter similar to the spot size, i.e., a 1 mm spot made a 1 mm wide hole. The mural gel was not removed. Most coronary arteries are about 3 mm in diameter. Complete vessel closure in coronary arteries is generally due to a large atherosclerotic occlusion and some thrombus, generally the size of a grain of rice. Complete removal of the thrombus in such cases may therefore be possible if the thrombus burden is small. However, complete closure of bypass grafts is mostly due to a large clot burden, and several passes of the catheter through the clot would be necessary to create a larger lumen. Once the catheter has been inserted and advanced to the clot, it is difficult to control its precise position within the vessel lumen, and the catheter tends to retrace the first path. It is unlikely that the presently configured delivery system can remove all the clot. Some of the newer animal results seem to confirm this hypothesis.[13] Any mural clot left behind would act as a substrate for further clot formation, and re-occlusion cannot be ruled out. However, clinical experience has suggested that re-occlusion was not a problem.[14]

Wider lumens could be formed by using a larger delivery catheter. The device will however then be less flexible making negotiating tortuous bends difficult and dangerous. Further, the threshold energy for ablation will be higher. Another way to remove more clot from the sides would be to use some kind of a side-firing device. This presents serious engineering challenges as it requires some reflective device to direct the laser beam sideways. There are some experimental prototypes that are currently being tested *in vitro*. Bubble dynamics will probably be different because the geometry has changed. A side-firing device will also encounter the situation where the vessel wall will lie directly under the targeted clot. If a sizable bubble is formed, the collapse may result in damage to the artery even if the vessel wall is not irradiated directly.

On the other hand, laser thrombolysis is regarded as an attractive treatment modality for strokes that are caused by thrombosis of cerebral arteries and sometimes by emboli originating elsewhere in the body. Part of the reason for this is that there is really no other viable treatment. Thrombolytics often take too long to take effect, and ballooning techniques are avoided. The critical part in treatment of cerebral occlusions is the rapid restoration of blood flow to prevent neurological deficit. Laser thrombolysis has already proven its ability to remove clot more rapidly than any other technique. Also, the clot burden in most stroke cases is very small. Presently, animal trials are planned using a canine model. Some of the main challenges lie in the engineering of a delivery device small enough to negotiate a cerebral vessel. Threshold energies for a small spot size ($\sim$100–200 μm) are low ($\sim$0.5 mJ), and any more energy delivered may cause a bubble big enough to burst the delicate vessel.

Laser thrombolysis is still in the developmental stage. This study has investigated and quantified some basic ablation phenomena taking place during laser thrombolysis. It has not addressed *in vivo* studies and biological effects of the laser radiation and therefore cannot claim to be a complete evaluation of laser thrombolysis. However, based on some of the observations, one can make intelligent guesses about what would happen *in vivo*.

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