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Laser thrombolysis using a millisecond frequency-doubled Nd-YAG laser

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ABSTRACT

A frequency-doubled Nd:YAG laser at 532 nm with pulse durations of 2, 5, and 10 ms was used to ablate blood clot phantoms. The clot phantoms were prepared with 3.5% (175 Bloom) gel and Direct Red 81 dye to have an absorption coefficient of 150 cm^{-1}. Ablation thresholds were determined by a fluorescent technique using flash photography to detect the gel surface. The threshold was 15±2 mJ/mm^2 and corresponded to calculated temperatures of 80±10°C. Ablation efficiency experiments were conducted at 20 mJ. Ablation efficiencies were approximately 1.7±0.1 μg/mJ for the millisecond pulses and were comparable to previously published efficiencies for ablation of clot with a 1 μs pulsed dye laser.

Keywords: ablation, threshold, ablation efficiency, clot, stroke

1. INTRODUCTION AND BACKGROUND

Laser thrombolysis is the selective removal of clot from an occluded artery by directed laser energy. Laser thrombolysis was originally performed in coronary arteries with a 1 μs pulsed dye laser to clear thrombosed arteries, but conventional therapies (e.g., balloon angioplasty) are very successful. Current work centers around proving the safety and efficacy of laser thrombolysis as a treatment for stroke. A large number of stroke cases are ischemic, caused by a clot occluding a cerebral artery. Laser thrombolysis has been used clinically for coronary arteries, but deploying a catheter into the cerebral arteries requires the use of a small, flexible optical fibers. The laser pulse energy required to ablate clot depends on the spot size, but is roughly 10 mJ. The irradiances reached when coupling 10 mJ into a 100 μm fiber in 1 μs approach the optical breakdown threshold for quartz. Reducing the irradiance by using a longer laser pulse would mitigate this problem. If ablation threshold and efficiencies for longer pulses are comparable to the microsecond pulses, then the long pulse laser would be a more suitable device for laser thrombolysis. Additionally, the compact, efficient, self-contained solid state millisecond lasers currently available would be more manageable in a clinically setting than the microsecond pulsed dye laser.

With a pulse duration in the millisecond realm, thermal confinement becomes a concern. Thermal confinement is determined by the thermal diffusivity of the material and the initial distribution of the laser energy. It can be described as

$$\tau_{th} = \frac{\delta^2}{\kappa}$$

where τ_{th} is the time of thermal confinement, δ is the absorption depth, and κ is the thermal diffusivity of the material. For the gel used in these experiments, κ=0.0014 cm^2/s and $\delta = 0.007$ cm. This gives a thermal confinement time of about 30 ms, which, though longer than the pulses used in these experiments, it is close enough that thermal confinement must be considered.

These experiments use a frequency-doubled Nd-YAG laser at 532 nm, to ablate a clot phantom. The ablation threshold and ablation efficiency are compared to those for the 1 μs pulses published previously.[1] Clot phantoms are confined in 3 mm diameter tubes and a 300 μm fiber is positioned above the phantom for the ablation experiments.

The results show that ablation threshold and efficiency for the 2, 5, and 10 ms pulses are comparable to the 1 μs pulses.

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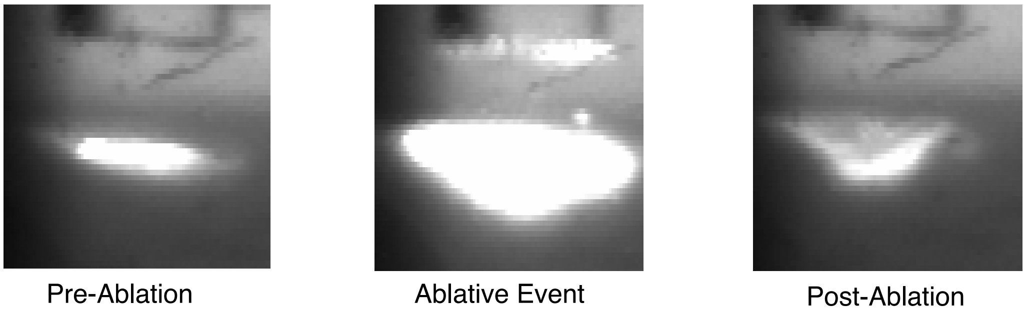

Figure 1. The subthreshold pulse has fluorescence indicating the undisturbed gel surface (left). The ablative pulse (middle). A subsequent subthreshold pulse indicates a lower surface due to ablation (right).

2. MATERIALS AND METHODS

2.1. Laser Parameters

The laser used for these experiments was a frequency-doubled Nd-YAG laser (Coherent VersaPulse) operating at 532 nm. The laser energy was delivered from the laser cavity through an optical fiber delivery system with focusing optics that produced a spot of 2–10 mm at the focal point. The 2 mm setting was used in all experiments. This spot was launched into a 300 μm fiber through additional focusing optics.

The pulse duration of the laser was set to 2, 5, and 10 ms. The pulse shapes were observed with a photodiode (Thorlabs DET-200) with a rise time of 1 ns. The pulse shapes were true square waves with no spikes or unusual features. The repetition rate was 1 Hz. The energy through the fiber was 20 mJ and all ablation efficiency experiments were performed at this clinically appropriate energy. A series of absorbing neutral density filters were used to reduce the laser pulse energy in the threshold level studies.

2.2. Target Preparation

A gel preparation was used to model thrombus that consisted of 3.5% 175 Bloom gelatin (Sigma Chemical) in water, 0.18% Direct Red 81 (Sigma Chemical) was added to produce a thrombus phantom with an absorption coefficient of 150 cm^{-1} at 532 nm (comparable to bulk whole blood absorption at this wavelength). The gel was drawn into 3 mm diameter silicone tubes (Patter Products) and set overnight. The tubes were approximately 6 cm in length with the center occupied by 2 cm of gel.

2.3. Threshold Detection

The pulses were monitored with a flash photography set up. A CCD camera (Motion Analysis, CV-251) was coupled to a video monitor (Panasonic PVM-1271Q). The laser pulse was detected by a photodiode (Thorlabs, DET-200) which triggered a flashlamp (EG&G, MVS-2601) and the CCD. The moment of image capture was set by a delay generator (Stanford Research Instruments, DG 535). A filter for the 532 nm light was used to prevent the CCD from being blinded by the laser pulse.

The ablation threshold for the microsecond pulses was determined by visual detection of bubble formation in the gel within the 3 mm tubes. A 100 μm fiber was positioned 500 μm above the gel surface to produce a spot size of 190 μm. Spot size was determined by irradiating black ablation paper under water. Four gel ablation threshold trials were conducted.

The ablation threshold for the millisecond pulses was detected by using the fluorescence of the thrombus phantom (Figure 1) The initial gel surface was visualized using a subthreshold pulse that caused the surface to fluoresce during the time of the laser pulse. A subsequent pulse of higher energy was emitted as an ablative attempt. The subthreshold pulse was again used to examine the gel surface. This process was repeated at successively higher energies until ablation was detected. The spot size was measured directly by evaluation of the subthreshold fluorescent spot.

The radiant exposure of the 1 μs pulsed dye laser was continuously varied, but the experimental apparatus used with the millisecond laser required using neutral density filters to change the radiant exposure from the nominal

20 mJ. The smallest increment of absorbance was 0.1, resulting in a change in energy by a factor of 1.25. This is a small loss in precision of measurement, although the loss is not so great when considering that the pulsed dye laser energy varied on the order of 5–10% between pulses.

2.4. Ablation Efficiency

Ablation efficiency experiments were conducted at four laser pulse durations, 1 μs, 2 ms, 5 ms, and 10 ms. The tubes containing the thrombus phantoms were set in a rigid frame which allowed insertion of a flushing catheter containing a 300 μm fiber for delivery of laser energy. The catheter was connected to a syringe pump (Syringe Infusion Pump 22, Harvard Apparatus) which flushed 2 ml/min of deionized water around the fiber to clear and collect ablated material. The fiber was positioned 500 μm above the gel surface. The ablated mass was collected in a standard spectroscopy cuvette for later measurement. The flow was continued for about 90 seconds after the last pulse to ensure that all ablated mass was collected. This procedure was repeated without firing the laser to provide control samples to determine the amount of mass removed from the target by the flow of water alone. The mass was determined by a spectrophotometric means.[2] Five samples and controls were used for each data point.

The microsecond ablation efficiencies were determined at 1.5, 5.0 and 7.5 mJ. One hundred pulses at 1 Hz were used for each sample. The pulse energies were measured with a Joule meter (Molectron). The millisecond ablation efficiencies used 30 pulses at 1 Hz and 20 mJ. The pulse energies were measured with a calorimeter (Scientech).

3. RESULTS

3.1. Ablation Threshold

All four microsecond ablation thresholds resulting in threshold detection at 0.6 mJ. This translates to a threshold radiant exposure of 21 mJ/mm^2.

Ablation threshold for the 1 μs pulse from the pulsed dye laser is compared to the thresholds for the 2, 5, and 10 ms pulses in the top graph in Figure 2. The ablation threshold for the 1 μs pulse is 21 mJ/mm^2 which agrees with the calculated threshold to bring the gel temperature to 100°C. The threshold for the 2 ms pulse is 15±2 mJ/mm^2 which indicates ΔT of 52±15°C. The initial temperature was 25°C. The threshold for the 5 ms pulse was 16±2 mJ/mm^2 which indicates ΔT of 56±6°C. The threshold for the 10 ms pulse was 12±1 mJ/mm^2 which indicates a ΔT of 43±5°C.

3.2. Ablation Efficiency

Ablation efficiency for the 1 μs pulse from the pulsed dye laser is compared to the thresholds for the 2, 5, and 10 ms pulses in bottom graph in Figure 2. The ablation efficiencies are 1.5±0.1, 1.7±0.1, and 1.9±0.1 μg/mJ for the 2, 5, and 10 ms pulses, respectively.

4. DISCUSSION

Previous work by Sathyam *et al.* has investigated the effects of variations of energy, spot sizes, pulse repetition rate, and wavelength on ablation threshold and efficiency.[2] This work shows that changing the pulse duration by five orders of magnitude (from 1 μs to 10 ms) has very little effect upon the ablation of gelatin.

4.1. Ablation Threshold

The ablation threshold is slightly higher for the 1 μs pulse than for the millisecond pulses. The data agree with the radiant exposure (21 mJ/mm^2) necessary to raise the surface temperature of a 150 cm^{-1} gel at 25°C to 100°C. This is also consistent with previous ablation threshold studies.[4]

4.2. Ablation Efficiency

The ablation efficiency shows excellent agreement between the 1 μs data and the millisecond data. It agrees with previous work[2,4,5] indicating that the ablation mechanism for the millisecond pulse is also derived from mechanical action of the vapor bubbles.

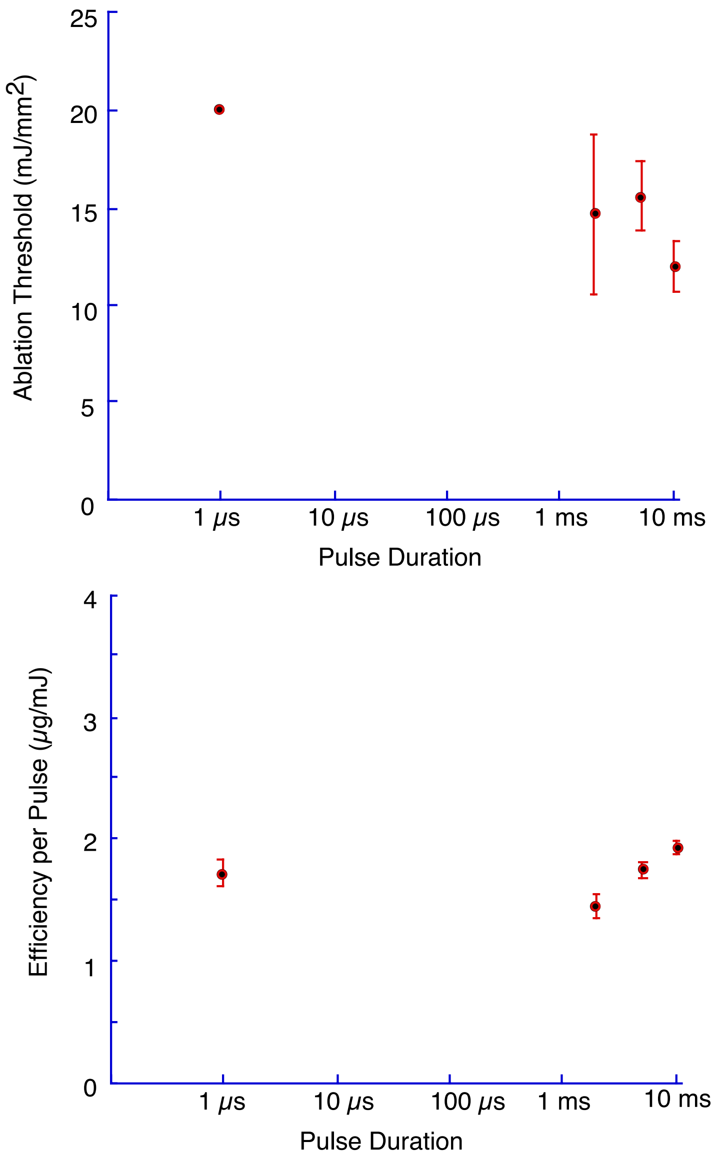

Figure 2. (Top) The ablation thresholds for microsecond and the millisecond pulses. (Bottom) The ablation efficiencies for the microsecond pulse and the millisecond pulses. The average and standard deviations of five samples at each millisecond pulse duration are shown.

5. CONCLUSION

The use of a solid state, millisecond pulse laser for stroke treatment can be a preferred alternative to the microsecond pulsed dye lasers. Reliable, clinically proven solid state lasers are currently available. These lasers are compact, portable, and are self-contained. Additionally, the efficacy of the laser as a treatment for ischemic stroke also lies in its suitability for launching into small fibers. The millisecond pulse avoids optical breakdown at the fiber face and has comparable clot phantom ablation properties. Since good correlation has been shown in the ability to ablate clot phantoms and clots,[2] the solid state, millisecond pulse laser is suitable as a clinical device for laser thrombolysis for stroke.

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