Thrombus Formation Using Endovenous Lasers

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Abstract:

Endovenous laser ablation is a commonly used, effective treatment of the incompetent great saphenous vein (GSV). Despite its efficacy, complications have been observed following the procedure, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Thermally induced thrombus formed during laser exposure in the vein lumen is a possible precursor to more serious side effects like DVT. Post-procedure thrombus extensions through the saphenofemoral junction (SFJ) have been observed. These experiments were performed to simulate thrombus formation during endovenous laser closure by measuring coagulum formation in in-vitro laser exposures in porcine blood and consequently investigate the role of procedure equipment in thrombus formation. Continuous wave (CW) 810, 940, 980, 1310 and 1470 nm lasers were tested along with microsecond pulsed wave 1064 nm Nd:YAG, 1320 nm Nd:YAG, and 2100 nm THC:YAG lasers. Standard fibers with diameters of 365, 550 and 600 µm as well as two prototype modified tip fibers were tested. The results of this study show that pulsed lasers with high peak power densities form less coagulum. Fiber specifications were found not to influence coagulum formation, and prototype modified tip fibers designed to prevent contact between the fiber tip and the vein wall did not eliminate coagulum formation.

Keywords:

endovenous laser closure, varicose vein, thrombus, pulsed laser

1 Introduction:

Along with other methods such as surgical ligation/stripping, sclerotherapy, and radio frequency ablation, pulsed and continuous wave mid-infrared lasers are effectively used to treat incompetent great saphenous veins via thermal coagulation of the vein lumen (often referred to as endovenous laser ablation or ELA). Formation of thermally induced soft thrombus occurs during ELA, and the presence of thrombus in the occluded vein is often observed following endovenous closure procedures. It is hypothesized that this soft thrombus can be detrimental in a number of ways. Thrombosis of the GSV can theoretically progress to pulmonary embolism or deep vein thrombosis of the common femoral vein (CFV) by propagation through the saphenofemoral junction. Thrombus extension through the SFJ has been observed following thermal vein closure, along with DVT due to thrombus extension from the occluded GSV into the deep venous system or other causes. DVT or thrombus extension through the SFJ into the CFV has been observed at a frequency of 0.3% after ELA and 2.1% after radiofrequency ablation.

Soft thrombus formed on the fiber optic tip can also become carbonized upon further heating. Carbonized blood has been observed on fiber tips at temperatures in excess of 1,000°C, with a variety of laser wavelengths. Increased pain and
Ecchymosis can result from vein-wall perforations,\textsuperscript{5,8} which can be caused by contact between the heated fiber tip and the vein wall.\textsuperscript{8,12} This carbonized blood has been found to reduce the transmission of light to the laser target, thus reducing procedure efficacy.\textsuperscript{7,12}

Due to its role as a precursor to various complications of ELA, minimizing soft thrombus formation during ELA may help reduce complication rates. Pulsed mid-infrared lasers similar to those used in endovenous laser closure have been used since at least the 1980s for laser thrombolysis in the treatment of strokes.\textsuperscript{13} Considering this established use in thrombus destruction, it is likely that pulsed lasers equivalent to those used in laser thrombolysis would also generate less soft thrombus in the presence of blood during ELA. The purpose of this study was to identify factors influencing thrombus formation during ELA, such as laser wavelength, peak power density of pulsed laser/fiber combination, blood sample temperature, and fiber optic specifications by manipulating these factors in-vitro and observing the resulting effect on coagulum formation.

2 Materials and Methods:

2.1 Experimental Equipment

Numerous continuous and pulsed wave lasers were tested in this study in conjunction with several fiber types. Experiment details can be seen in Figures 1 and 2. Continuous wave 810, 940, 980, 1310 and 1470 nm lasers along with microsecond pulsed 1320 nm Nd:YAG (neodymium:yttrium-aluminum-garnet), 1064 nm Nd:YAG, and 2100 nm THC:YAG (thulium-holmium-chromium:yttrium-aluminum-garnet) lasers were used. Pulsed lasers were operated with pulse lengths of 100, 300, 350, 500 or 1000 µsec at repetition rates of 12, 20 or 50 Hz. Multiple fibers were used: a 600 µm core hard plastic clad silica core (HCS) fiber with a numerical aperture (NA) of 0.37 and low water content (OH); a 550 µm core silica clad silica core (all silica) fiber with NA = 0.21 and low OH; a 365 µm all silica fiber with NA = 0.21 and low OH; a prototype forward emitting 550 µm all silica fiber with the tip encapsulated in a 1.74 mm outside diameter quartz sleeve sealed to prevent contact between fiber tip and surrounding medium; and a prototype 365 µm all silica fiber with a slightly recessed tip within a distally clad 2.5 mm long stainless steel sleeve to prevent back-burning of the fiber cladding. Prototype modified tip fibers were included in this study to model commercially available fibers with fiber-centering devices that have been shown to reduce vein perforations by minimizing contact with the vein wall during treatment.\textsuperscript{7,8} In-vivo procedures utilized a constant fiber withdrawal velocity to evenly distribute laser energy\textsuperscript{3} using a pullback mechanism (cardiovascular device used to withdraw a catheter from the vessel lumen at constant, precise rates). Blood sample temperatures were measured with an Omega HH509 digital thermometer. An Ophir Laserstar power meter with an L40 detector head was used to measure laser power.
2.2 Experimental Methods

In this study 33 experiments were conducted with various combinations of lasers, laser settings, and fibers. All experiments utilized a power setting of 7.0 W. Laser powers were verified at 7.0 W before experiments using a laser power meter. Fibers were introduced approximately 10 cm into 15 mL of porcine blood in sodium EDTA in a 10 mL graduated cylinder and activated for 30 seconds with a pullback velocity of 0.5 mm/sec. Porcine blood was used because of its similarity to human blood. Because of the extreme fragility of the coagulum, larger blood samples (30 mL) were used if coagulum loss to contact with the cylinder wall was expected. A single blood sample was used for each experiment lasting 10 trials. Samples were inverted and mixed after trials to produce a uniform sample temperature. After mixing, sample temperatures were taken using the thermometer probe at the depth of fiber introduction (approximately 10 cm). Upon trial completion, approximately 25 mm of the distal fiber with attached coagulum was cut off (not possible for permanent tip fibers), and the difference between fiber mass with attached coagulum and cleaned fiber mass was used to measure coagulum formation. Coagulum removal was ensured by cleaning the fiber with a 3% hydrogen peroxide solution. After coagulum measurement, fibers were stripped and cleaved to restore optical transmission, which was verified by the circular tail-free appearance of the aiming beam. If the tip was found to produce an irregular aiming beam it was cut off, stripped and cleaved once more. For fibers with permanent tips (protected, encapsulated) coagulum was collected with a pre-measured KimWipe. The difference between the mass of the wipe with and without coagulum was considered the coagulum mass. Laser power was recorded after trials for permanent tip fibers to verify optical transmission. Upon exhaustion of the initial porcine blood supply, another sample was obtained. These samples were designated as Source 1 or Source 2, respectively.

2.3 Statistical analyses

General linear model analysis of variance (ANOVA) was used through the statistical program Minitab® to analyze the relationships between coagulum mass formed and blood sample used, laser wavelength, laser wave type, and fiber optic type. Significance was assumed if p<0.05

3 Results:

ANOVA produced a coefficient of determination (R²) of 88.44%. Source 2 blood was found to generate significantly less coagulum than Source 1 blood (p<0.05). Several experiments initially carried out with Source 1 blood were repeated under identical conditions with Source 2 blood. Significantly less coagulum was generated with Source 2 blood in each of these experiments (p<0.05). Coagulum masses from experiments conducted with Source 1 and Source 2 blood can be seen in figures 1 and 2, respectively. Source 2 blood was obtained at a later date than Source 1 blood, most likely from a different specimen. The purpose of this study was to investigate the
influence of laser specifications on coagulum formation, not to determine the differences in blood content influencing coagulum formation; therefore the cause of the observed difference in coagulum formation between Source 1 blood and Source 2 blood was not investigated. However, due to their differing coagulation tendencies, comparisons between experiments using blood from different sources were impossible.

Using blood from both sources, microsecond pulsed wave lasers generated significantly less coagulum on the fiber tip than CW lasers (p<0.05). Comparing experiments conducted with Source 1 blood, the 1470 nm CW laser formed more coagulum than the 810 nm CW laser, which generated more than the 1320 nm pulsed wave laser (p<0.05). The same trend occurred in experiments with Source 2 blood (p<0.05). Significant differences between other laser wavelengths with Source 2 blood were not evident. The pulsed 1320 nm laser generated significantly less coagulum in experiments with Source 2 blood than all of the other CW lasers (810 nm, 940 nm, 980 nm, 1470 nm; p<0.05) except the 1310 nm laser (p>0.05). A typical coagulum formed after 1320 nm pulsed laser exposure, visible in figure 3, is much smaller than the coagulum formed after 980 nm CW laser exposure, visible in figure 4. Both lasers were operating with a 600 µm HCS fiber at identical wattage. When compared with other experiments using the same blood source and laser wavelength type, no significant difference in coagulum mass was found between fibers of varying diameter (p>0.05). Modified tip fibers did not eliminate coagulum formation and were found to lose power with repeated use (Figure 5). Experiments conducted with the prototype protected tip fiber did not generate more or less coagulum than other fibers (p>0.05), although the prototype encapsulated tip fiber did generate significantly less (p<0.05).

Sample temperature rose at a similar rate during every experiment, although temperature did not appear to be correlated to coagulation mass. Higher linear endovenous energy density (LEED) delivered through laser exposure has been shown to be associated with a greater prevalence of vein wall perforations. Similar to LEED, the peak power density (PPD) of the experimental setup appeared to be inversely proportional to the average amount of coagulum generated (Figure 6). Peak power density was calculated (for pulsed lasers only) by dividing laser energy per pulse by the product of pulse length and fiber cross-sectional area. Shorter pulse lengths and lower repetition rates corresponded to less coagulum formation on the fiber tip. Pulsed 1320 nm laser specifications can be seen in Figure 7 in order of decreasing coagulum formation.

4 Discussion:

Thermally induced soft-thrombus formation appears to be influenced by a variety of factors. In-vitro thermally induced blood coagulation, a process comparable to thrombus formation during endovenous thermal vein closure, has been shown to be a complex phenomenon involving numerous cell-modifying processes. Furthermore, cutaneous laser treatment, a procedure performed with lasers very similar to those used in endovenous laser treatment, has been shown to cause intravascular consumption of fibrin-promoting factors. It is feasible that endovenous laser treatment could have similar effects on blood chemistry as well. It is well established that individual variance
in blood content can affect blood coagulation; it would follow that these variances would influence thrombus formation during ELA as well. This is a possible explanation for the differing coagulation tendencies of Source 1 and 2 blood, although further investigations are necessary. All relevant factors influencing thrombus formation should be acknowledged when considering thermal endovenous closure procedures.

While in-vitro procedures can measure coagulum formation in simulated conditions, soft thrombus formed during closure of the GSV can break off from the fiber during treatment or be stripped off as the fiber is being withdrawn from the point of access, making the post-treatment appearance of the fiber unrepresentative of the amount of thrombus formed in the coagulated vein. Higher energy (LEED) has been proposed to avoid the creation of thrombus, which can recanalize and cause treatment failure. Results of these experiments provide support for the theory that pulsed lasers generate less coagulum when compared with continuous wave lasers implying that pulsed lasers also create less thrombus during ELA. Of these pulsed lasers, only the 1320 nm Nd:YAG is commercially available, and for this reason its settings were investigated more extensively than the other pulsed lasers (Nd:YAG 1064 nm and THC:YAG 2100 nm). Shorter pulse lengths and higher peak power densities appear to result in less coagulum formation. In addition, the use of lower repetition rates (20 Hz) may be superior to current protocols using 50Hz with regards to coagulum formation.

Fiber diameter did not appear to strongly influence coagulum formation. Prototype modified tip fibers did not eliminate coagulum formation. Although the encapsulated tip fiber did generate significantly less coagulum than the other fibers tested in similar conditions (CW lasers in Source 1 blood), it is likely due to the loss in laser transmission throughout the experiment. Therefore, no conclusion can be drawn regarding the effect of encapsulated tip fibers on coagulum formation, other than they appear to generate coagulum in a similar manner to other fibers.

Reducing the amount of blood present in the incompetent vein during treatment has been shown to improve light distribution and procedure efficacy; it can therefore be hypothesized that reducing blood present in the vein during thermal ablation may also reduce soft thrombus formation.

In summary, results of these experiments suggest that microsecond pulsed wave lasers with high peak power densities are the best choice to minimize soft thrombus formation during ELA treatments. Further studies are needed to investigate these factors in-vivo.

5. Acknowledgements:

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References:


Figure 1

Experiments completed using Source 1 blood, all at 7W. Error bars represent $\pm$ 1 standard deviation. Laser specifications: laser wavelength in nm, fiber diameter in $\mu$m, pulse length in usec and repetition rate in Hz, respectively. Pulselength and repetition rate not applicable for continuous wave (CW) lasers. Lasers used: CW 810 nm and 1470 nm lasers, and a pulsed 1320 nm Nd:YAG laser. Fibers used: a 365 $\mu$m all silica fiber (365 $\mu$m), a 365 $\mu$m all silica fiber with protective metal sleeve (365 $\mu$m prot.), a 550 $\mu$m all silica fiber (550 $\mu$m), a 550 $\mu$m all silica fiber with the tip encapsulated in a quartz sleeve (550 $\mu$m cap.), and a 600 $\mu$m HCS fiber (600 $\mu$m).
Figure 2

Experiments completed using Source 2 blood, all at 7W. Error bars represent ± 1 standard deviation. Laser specifications: laser wavelength in nm, fiber diameter in µm, pulse length in µsec and repetition rate in Hz, respectively. Pulselength and repetition rate not applicable for continuous wave (CW) lasers. Lasers used: CW 810, 940, 980, 1310, and 1470 nm lasers; pulsed Nd:YAG laser 1064 nm and 1320 nm lasers; and a pulsed THC:YAG 2100 nm laser. Fibers used: a 365 µm all silica fiber (365 µm), a 365 µm all silica fiber with protective metal sleeve (365 µm prot.), a 550 µm all silica fiber (550 µm), and a 600 µm HCS fiber (600 µm). *Denotes larger blood sample (30 mL).

<table>
<thead>
<tr>
<th>Laser Wavelength</th>
<th>Fiber Diameter</th>
<th>Pulse Length</th>
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<tr>
<td>810 nm</td>
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<tr>
<td>810 nm</td>
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<tr>
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<td>300 usec</td>
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<td>360 µm</td>
<td>300 usec</td>
<td>50 Hz</td>
</tr>
<tr>
<td>1470 nm</td>
<td>550 µm cap.</td>
<td>300 usec</td>
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Figure 3

Coagulum formed on a 600µm HCS fiber after 1320 nm pulsed wave laser exposure in porcine blood.
Figure 4

Coagulum formed on a 600 µm HCS fiber after 980 nm CW laser exposure in porcine blood.

Figure 5

Experiment trial number versus transmittance of prototype modified-tip fibers. The encapsulated-tip fiber was used with a 1470 nm CW laser, and the protected-tip fiber was used with an 810 nm CW laser. An Ophir Laserstar power meter with an L40 detector head was used to measure laser power before trials.
Figure 6

Peak power density of laser/fiber setup versus average coagulum mass formed for various experiments. Peak power density was calculated by dividing laser joules per pulse by the product of the fiber cross-sectional area and the pulsewidth. Error bars represent \( \pm \) 1 standard deviation. All experiments plotted used a pulsed Nd:YAG 1320 nm lasers in Source 1 blood with repetition rates of either 20 or 50 Hz, and pulselengths of 100, 300, 500, or 1000 \( \mu \)sec. 365 \( \mu \)m all silica, 550 \( \mu \)m all silica, and 600 \( \mu \)m HCS fibers were used. Smaller repetition rates, shorter pulse lengths, and smaller fibers will produce higher peak power densities.

Figure 7

Average mass of coagulum formed using the Nd:YAG 1320 nm pulsed laser in experiments using Source 1 blood. Error bars represent \( \pm \) 1 standard deviation. Laser settings: fiber diameter in \( \mu \)m, pulse length in \( \mu \)sec, and repetition in Hz, respectively.