血管内レーザー焼灼術におけるレーザー一生存体熱的相互作用の計算機シミュレーションモデルの開発

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Development of a Computer Simulation Model of Intravascular Laser-Tissue Thermal Interaction for Endovenous Laser Ablation

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Abstract

Endovenous laser ablation (EVLA) is popular as a less invasive treatment for varicose veins. To reduce undesired side effects, such as postoperative pain and subcutaneous hemorrhage, a semiconductor laser device with a wavelength of 1,470 nm and the ELVeS Radial 2ring™ fiber (CeramOptec, Germany) have been developed. To obtain regulatory approval for such new medical devices in a short period of time and with minimal clinical trials, it is necessary to establish an objective technique for evaluating efficacy and safety in a manner that is not influenced by the operator’s skill. The purpose of this study was to develop a computer simulation model for estimating the intravascular temperature during EVLA and to evaluate the efficacy and safety of the new devices. The simulation was performed under the same irradiation conditions as an ex vivo experiment of EVLA, and validated by comparing the measured and calculated temperatures. When the output power was 7.0 W, the measured peak temperatures were about 90°C and coincided well with the calculated temperatures. On the other hand, when the output power was 10.0 W, the calculated temperatures exceeded 100°C and were higher than the experimental values by 13°C or more. We speculate that the overestimation of the temperature was caused by the latent heat, because vacuolation was observed in the histological images of
the venous walls after laser irradiation. Therefore, the results of this simulation are comparable to the measured values. This simulation model should be useful for determining the optimal irradiation condition, and the method of quantitative analysis developed in this study will play a key role in theoretical interpretation of thermal effects during EVLA.

**Key words:** varicose veins, endovenous laser ablation, computer simulation, Monte Carlo method, heat conduction equation

1. Introduction

Endovenous laser ablation (EVLA) is popular as a less invasive treatment for varicose veins. In this treatment, the optical fiber guiding the laser light is inserted into the vein, and the venous wall is irradiated from the inside, thereby occluding the vein. This treatment is aimed at achieving shrinkage via thermal denaturation of the venous wall. When the vein tissue is irradiated, some of the laser light is reflected onto the tissue surface, whereas the rest is absorbed/scattered and transmitted throughout the tissue. The energy of the laser infiltrating the tissue is absorbed and converted into heat.

It is important to choose the appropriate medical device. Initially, EVLA was performed using a bare fiber with a flat output end. However, in this approach, the power density at the tip becomes very high, and a carbonized film called ‘hot tip’ derived from the carbonization of the blood is formed. This hot tip efficiently absorbs laser light, causing perforation of the venous wall. More recently, a radial fiber (ELVeS Radial™ fiber, CeramOptec, Germany) that emits light in the entire circumferential direction (i.e., 360°) was proposed. Because the surface of the venous wall is directly irradiated by laser light from the radial fiber, the power density is greatly reduced relative to the bare fiber, preventing excessive irradiation and perforation. Indeed, in a comparative study using a 1,470-nm laser delivered by a bare or radial fiber, the incidences of postoperative pain and subcutaneous hemorrhage were much lower when using radial fibers.

However, operability became a problem because the radial fiber sometimes stuck to the venous wall. To solve this problem, a radial two-ring fiber (ELVeS Radial 2ring™, CeramOptec) with two irradiation sites was developed. As just described, several optical fiber types have been proposed, and their qualitative effects have been disclosed, but their quantitative effects are not disclosed to surgeons. Electrical and mechanical safety can be evaluated by applying the standards established by IEC regulation. However, to determine efficacy and safety of new medical devices, developers must establish their own evaluation methods. Furthermore, in clinical trials of medical devices, it is possible that results may differ depending on the skill of the operator.

One effective way to address these concerns would be to develop a computer simulation model of EVLA. Such a model could then be used to evaluate an optical fiber at the design phase. Moreover, the establishment of objective evaluation techniques for efficacy and the safety facilitates faster approval of new medical devices. The model could also be used to conduct exhaustive examinations of laser irradiation conditions, which are difficult to perform in clinical trials.

2. Purpose

The purpose of this study was to develop a computer simulation model that takes into account light and heat propagation to estimate the intravascular temperature during EVLA and to evaluate the efficacy and safety of the devices. The results of the computer simulation and an ex vivo experiment were compared for a combination of a 1,470-nm laser diode and a radial two-ring fiber.

3. Materials and Methods

3.1 Sample

In this study, porcine jugular vein and venous blood were used. Venous blood was centrifuged to remove supernatant containing heparin, plasma, platelets, and white blood cells. The pelleted erythrocytes were resuspended in physiological saline and centrifuged; the supernatant was removed; and phosphate-buffered saline (PBS) was added to adjust hematocrit to 42%.

3.2 Laser diode and optical fiber

A semiconductor laser device with a wavelength of 1,470 ± 30 nm (LEONARDO™ 1,470, CeramOptec, Germany) was used and operated in continuous wave mode. The radial two-ring fiber used was the ELVeS Radial 2ring™ fiber (CeramOptec) with a diameter of 1.85 mm and two light-emitting portions as shown in Fig.1. The emitting portions of the fiber have a conical shape. Consequently, the laser light is emitted perpendicular to the fiber axis around the entire circumference (i.e., 360°). In this paper, Cone 1 and Cone 2 indicate the conical portions, and Edge indicates the tip of the fiber, as also shown in Fig.1.

3.3 Light distribution and output power ratio

Estimation of the temperature distribution in the vein requires simulation parameters such as the beam radius of the laser and the energy of irradiation at each position. An optical system was constructed to measure the intensity distributions along the fiber and in a direction perpendicular to the fiber. The optical fiber was fixed using a clamp and connected to the laser device operated with a setting power of 6.0 W. For measurement along the fiber axis, a slit was set along the fiber axis, and its width was set to 0.34 mm so that light emitted within an angle of ±5 from Cone 1 or Cone 2 was detected. For measurement along the direction perpendicular to the fiber axis, the slit was set perpendicular to the Edge of the fiber, and its width was set to 0.51 mm, so that light emitted within an angle of ±5 from the Edge was detected. A knife edge was set in a direction perpendicular to the slit and moved...
in each direction at a speed of 10 μm/s using a motorized linear translation stage (SGSP 26-85 (X), SIGMAKOKI, Japan). Laser power passing through the slit and knife edge was detected with an integrating sphere–type photodiode detector (S146C, Thorlabs, USA) and recorded using a personal computer through an interface (PM100USB, Thorlabs). The laser intensity profile of the outgoing beam at each position of the optical fiber was calculated from the time change of the total quantity of transmitted light.

Another optical system was constructed to measure the output power ratio from Cone 1, Cone 2, and Edge. The radial two-ring fiber was fixed using a clamp and connected to the laser device, and the output power was set to 6.0 W. The radial two-ring fiber was inserted in the integrating sphere–type detector, and output power from each portion was measured as described above.

3.4 Temperature measurement on the outer surface of venous wall

A K–type sheathed thermocouple (T35LC-200L2K9B, Okazaki Manufacturing, Japan) was used as the temperature measurement sensor. The sheath is constructed by inserting a thermocouple element wire into an Inconel® tube and filling with insulating magnesium oxide. The temperature-measuring part is located at the tip. The temperature was measured with a high-precision temperature/voltage unit (NR-TH08, KEYENCE, Japan) connected to the temperature sensor, and the data measured using a multi-data acquisition system (NR-500, KEYENCE, Japan) were recorded at a sampling frequency of 10 Hz.

3.5 Light propagation and heat conduction simulation

In this section, we describe the principles of simulation, combining thermal conduction calculation and the calculation of light propagation in blood and vein tissue using a Monte Carlo simulation.

3.5.1 Simulation of light propagation

To calculate the light propagation in blood and vein tissue, we used simulation codes MCML (Monte Carlo modeling of light transport in multi-layered tissues) and CONV (Convolution for responses to a finite-diameter photon beam incident on multi-layered tissues) developed by Wang et al.8-10. MCML and CONV can be used to calculate light propagation in a flat multilayered substance. Assuming that blood and vein tissue have a flat and uniform structure, we set the thickness of the blood (the distance from the side surface of the optical fiber to the vein surface) and the vein. The measured values shown in Table 1 are the absorption coefficient and the scattering coefficient of venous blood and vein at 1,470 nm. The refractive index and scattering anisotropy factor are 1.38 and 0.911,12, respectively. The refractive index of the optical fiber is the value of fused silica at 1,500 nm13. The simulation assumes that laser light with a Gaussian intensity distribution is perpendicularly incident on the blood from the optical fiber, at each coordinate in the cylindrical coordinate system, with the center of the laser beam as the axis, the energy density absorbed by the tissue is calculated. The number of trials (number of incident photons) in the Monte Carlo simulation was set to 10⁶, and the grid size was set to 10 μm in both the depth and radial directions.

3.5.2 Simulation of heat conduction

In the calculation of heat conduction, the process of temperature rise and thermal diffusion process over time was numerically calculated based on the energy density distribution in tissue, calculated by Monte Carlo simulation. In the simulation of light propagation, the energy density distribution was calculated in a cylindrical coordinate system, with the center of the laser beam as the axis, whereas in the heat conduction calculation, a two-dimensional unsteady state heat conduction equation is employed for the sake of simplicity, as follows:

\[ \rho \ C_p \ \frac{\partial T}{\partial t} = \lambda \left( \frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} \right) + S. \]

The energy density calculated by the Monte Carlo simulation is input as the energy density \( S [\text{W/m}^3] \) of the heat source. The heat source moves at a constant speed. The thermodynamic temperature \( T [\text{K}] \) at the time \( t [\text{s}] \) is calculated. Here, it is assumed that the density \( \rho [ \text{kg/m}^3] \), specific heat \( C_p [\text{J/(kg K)}] \), and thermal conductivity \( \lambda [\text{W/(m K)}] \) of the blood and venous wall are constant regardless of the temperature change, as shown in Table 114. In the actual simulation, the formula above is discretized by the finite volumetric method using integers \( i, j \), and \( k \) for \( x, y \), and \( t \), respectively, as follows:
where $V_{ij}$ is the volume, $A_i$ and $A_j$ are the cross-sectional areas for $x$ and $y$ directions, respectively, and $q$ indicates the heat flux. For example, the heat fluxes for positions $(i+1/2,j)$ and $(i,j+1/2)$ are expressed as follows:

$$q_{i+1/2,j} = -\frac{\lambda}{\Delta x}(T_{i+1,j} - T_{i,j}),$$

$$q_{i,j+1/2} = -\frac{\lambda}{\Delta y}(T_{i,j+1} - T_{i,j}).$$

Iterative calculation was performed from the initial temperature and converged using the sequential relaxation method according to $S$ [W/m3] at each position. The temperature at each coordinate was sequentially calculated at a time step of 0.1 s, and the temperature distribution at each time was calculated. In this simulation, complicated processes such as bubble generation, deformation of vein tissue, and degeneration due to tissue coagulation were ignored.

### 3.5.3 Calculation of the temperature distribution

Based on the distribution in the axial direction of the laser light intensity of the optical fiber obtained from evaluation of the light emission profile (see Section 4.1), the length at which the incident light intensity was $1/e^2$ of the maximum value was set as the beam diameter. Based on the light emission ratio measurement result (see Section 4.1), the power emitted from Cone 1, Cone 2, and Edge were determined from the total output power. Because the laser beam incident on the tissue from each cone is irradiated onto the entire circumference perpendicular to the optical fiber, the total power was converted to the power densities from each cone by the method shown in Fig.2. A simulation model was constructed to compare the ex vivo experiment with the simulation is shown in Fig.3. The initial temperature of optical fiber, blood, and venous tissue was set to 20°C according to the conditions of the ex vivo experiment. The boundary condition at the center of the vein was set to thermal insulation, and those of other boundaries were fixed at 20°C. On the assumption that the optical fiber remains in contact with the inner wall of the vein, the size of the tissue model was set to 20 mm in the axial direction and 5.0 mm in the radial direction. From the measurement result of the light
intensity profile (see Section 4), the diameters of the laser beams emitted from the optical fiber were set to 0.45, 0.54, and 0.81 mm for Cone 1, Cone 2, and Edge, respectively. The output power of the laser was set to 7.0 or 10.0 W. The power ratio of Cone 1, Cone 2, and Edge was allocated to the value based on the light emission ratio measurement (see Section 4). The temperature at each coordinate was sequentially calculated at time step 0.1 s, and the temperature distribution at each time was calculated. The time change of temperature at each measurement point was calculated by setting the venous wall thickness to $\mu \pm \sigma$, where $\mu$ and $\sigma$ are the mean and standard deviation of the measured venous wall thickness, respectively.

3.6 Ex vivo irradiation system

To simulate the clinical environment of EVLA and measure the temporal change in the temperature of the outer surface of the venous wall, the ex vivo irradiation system shown in Fig.4 was constructed. Both ends of the porcine jugular vein were connected with threads, and tension was applied and fixed in a box. Porcine venous blood prepared at a hematocrit of 42% was injected intravenously. A radial two-ring fiber was inserted intravenously from the outside of the box through the connector. At that time, the venous wall and the optical fiber were brought into close contact by applying negative pressure with a syringe. A thermocouple was installed so that the distance from the surface of the radial two-ring fiber was equal to the vein thickness. The fiber connected to the laser device was pulled with a motorized linear translation stage (SGSP 26-85 (X), SIGMAKOKI, Japan) at a speed of 1.0 mm/s, and laser irradiation was performed. A stage controller (SHOT-602, SIGMAKOKI) and SGTERM software (SG Commander, SIGMAKOKI) were used to control the motorized linear translation stage. The time change of temperature on the outer surface of the venous wall during laser irradiation was measured using the temperature measurement system.

3.7 Measurement of vein thickness before and after laser irradiation and histological evaluation

Before or after laser irradiation, the vein was cut with medical scissors. The irradiated and non-irradiated portions were cut in the minor axis direction, embedded in Tissue-Tek O.C.T. Compound (Sakura Finetechnical, Japan), frozen, and fixed. The portion that was over-irradiated due to sticking at an output power of 10 W was excluded. After freezing, the tissue was cut into a thickness of 10 µm with a cryostat microtome (CM1850, Leica Microsystems, Germany). The sliced sample was mounted on slide glass and stained with hematoxylin–eosin (HE). After HE staining, a stained image was acquired with a digital slide scanner (NanoZoomer 2.0-RS, Hamamatsu Photonics, Japan). Using the image, venous wall thicknesses before and after cauterization were measured.
4. Results

4.1 Measured output power ratio

Fig. 5 shows the relationship between the laser beam intensity output from the optical fiber and the measurement position in the long axis direction. The laser light output from Cone 1 had two peaks at 11.9 ± 0.1 mm (mean ± standard deviation) and 12.1 ± 0.1 mm. The laser light output from Cone 2 had one peak at 17.6 ± 0.2 mm. The maximum peak ratio of Cone 1 to Cone 2 was 3.87.

Fig. 6 shows the relationship between the intensity of the laser beam output from the optical fiber and the measurement position in the short axis direction. The laser light output from the tip of the optical fiber had a peak at 2.3 ± 0.2 mm.

Based on the distribution of laser light intensity obtained from this experiment, we calculated the beam width at which the incident light intensity was $1/e^2$ (~13.5%) of the maximum value. The beam diameters of Cone 1, Cone 2, and Edge were 0.45, 0.54, and 0.81 mm, respectively.

The output power ratios of Cone 1, Cone 2, and Edge were 52%, 46%, and 2%, respectively. The difference in power ratio between the cones was as little as 5.9 %, and the output powers were similar for Cones 1 and 2. The power ratio output from the Edge direction was very small relative to the Cones. In the simulation, all power was divided among Cone 1, Cone 2, and Edge based on the power ratio measurement.

4.2 Measurement of vein thickness before and after laser irradiation and histological evaluation

The thickness of the venous wall was measured at 15 positions in each sample. In addition, the presence or absence of three heat-affected layers (carbonized layer, vacuolar stratified layer, and solidified layer generated inside the vein after laser irradiation) was confirmed. We defined the carbonization layer as the range of black discoloration; the vacuolar stratified layer as the range in which moisture vaporizes and the vacuoles generated in the tissue are spherical and continuously distributed; and the solidification layer as continuous hyaline degeneration(17).

Fig. 5 Profiles of the laser power density on the surface of the fiber along the central axis, measured by scanning the slit in front of the power meter.

Fig. 6 Profiles of the laser power density on the surface of the fiber along the minor axis, measured by scanning the slit in front of the power meter.
4.3 Temperature of the outside surface on the venous wall in the ex vivo irradiation system

Fig.7 shows the temperature of the thermocouple on the outside surface of the vein at each output power. The positions of the first peaks were aligned at the same time. The temperature change, with two peaks, was measured in the thermocouples. At the output power of 7 W, the first peak temperature was 91 ± 5°C and the second peak temperature was 95 ± 4°C. At the output power of 10 W, the first peak temperature was 94 ± 3°C, and the second peak temperature was 100 ± 9°C. As the output power increased, the temperature of both peak points rose.

4.4 Histological analysis of venous walls after irradiation

The venous wall thickness before irradiation was 390 ± 90 μm, and the thicknesses after irradiation were 340 ± 80 and 340 ± 70 μm at output powers of 7 and 10 W, respectively. Thus, laser irradiation decreased not only the diameter, but also the average value of the thickness. However, this difference in thickness was not statistically significant (t test, p > 0.05) at any output power. Sectional stained images of the venous wall under each irradiation condition are shown in Fig.8. There was no carbonized layer in any venous walls after laser irradiation, although the vacuole formation and coagulation layer were observed. At an output power of 7.0 W, vacuole formation was observed up to the tunica media, and the layer was observed throughout the tunica externa. At an output power of 10.0 W, vacuole formation was observed in all layers up to the tunica externa.

4.5 Simulation results

Fig.9 show the time course of temperature on the outer surface of the venous wall. The laser output power was set to 7.0 or 10.0 W, and the retraction speed of the optical fiber was set to 1.0 mm/s. Only when the output power was 7.0 W and the thickness was μ − σ did the temperature exceed 100°C at both peak points. At an output power of 10 W, the temperature exceeded 100°C at both peak points in all thickness conditions.

5. Discussion
5.1 Manufacturing error of optical fiber

An optical fiber has two cone-shaped prisms in its core. A part of the laser light is irradiated via the first cone, and all the remaining laser light is irradiated via the second cone. This setup is designed to divide the laser light into two parts, thereby irradiating the entire circumference. Therefore, laser light is output only from the side face. In the measurement result of the long axis profile, as shown in Fig.5, the peak position has a maximum difference of several hundred micrometers. The profile with two peaks near one cone position was measured. The emission ratios between the cones differed by 5.9%. The beam width on the surface of the optical fiber also differed, as shown in Section 4.1. Comparison between all samples revealed a difference of several hundred micrometers in the physical arrangement of the cones. Based on these results, it seems that a production error in the cone was largely responsible for the difference in peak positions between the samples. Assuming that the light traveled in a parallel trajectory within the core, the output ratio should depend on the sectional area ratio of the cone, and the cross-sectional area ratio of the optical fiber and the emission ratio should be similar.

From the measured profiles of laser intensity in the short-axis direction, we confirmed that the laser beam was also...
5.2 Validation of the simulation

The light and heat propagation simulation developed in this study consists of calculations of light propagation and heat conduction in tissue using a Monte Carlo simulation. In actual EVLA, it might be necessary to consider not only light propagation and simple heat conduction, but also latent heat due to phase transformation of water in blood and venous tissue, as well as heat transfer phenomena due to blood flow accompanying the pulling back of the optical fiber. Therefore, there may be an error between the intravascular temperature distribution in the actual EVLA and the simulation. To address this issue, it is necessary to understand the error range in temperature in the real environment due to phenomena not considered in the simulation. Therefore, for this section, we constructed an ex vivo irradiation system simulating the clinical environment of EVLA using a 1,470-nm semiconductor laser and an optical fiber. We examined the temperature on the outer surface, histology, thickness of the venous wall, and the presence or absence of heat effects. On the other hand, the simulation was performed under the same irradiation conditions as the ex vivo experiment, and validated by comparing the calculated temperatures.

Based on the cross-sectional image of the vein, the thickness of the venous wall before laser irradiation varied depending on sample or position. The thickness of the venous wall decreased slightly after laser irradiation. Therefore, considering the variation in thickness before irradiation, the distance from the optical fiber surface to the thermocouple, i.e., the thickness of the venous wall, can be considered to be in one of two conditions: − and +. Then, the time courses of the two temperature distributions were calculated. The simulation was validated by comparing its predictions to the results of the experiment. The peak temperature at the second time was higher, and the interval between the peaks was about 6 s, exhibiting a shape very similar to that of the simulation. Fig.10 compares the peak temperatures obtained from the calculation and measurement. When the laser output was 7.0 W, the measured temperature was smaller than the calculated value of \( t = \mu - \sigma \) and larger than that of \( t = \mu + \sigma \). On the other hand, when the output power was 10 W, the simulation value was higher than the experimental value by 13°C or more. The rate of increase of the measured temperature relative to the rate of change in output power was low, and the temperature at which the rate of increase slowed was around 100°C. The overestimation of the temperature in this simulation might be due to the latent heat. We considered the possibility that the energy that should have been released was consumed to form vacuoles of moisture inside the venous wall; i.e., it was the latent heat required for vapor phase change. Therefore, at temperatures not exceeding 100°C, the temperature is overestimated due to the latent heat. However, the graphs of temperature change revealed similarities between the measured and calculated value, and light propagation and thermal conduction phenomenon of laser light in living tissue predominated other phenomena. For these reasons, the results of this simulation are considered to closely reproduce the actual measured values.

In addition, the cross section after the irradiation experiment revealed that the heat caused vacuolation and coagulation to occur inside the venous wall. Heat effects and temperature are correlated\(^{16-22}\). Human cells are irreversibly denatured at around 43°C, the cellular response to heating varies depending on the conditions. In addition, the time required for denaturation decreases exponentially as the heating temperature increases. For example, in an experiment using pig skin\(^{19}\), skin was irreversibly denatured after 6 h at...
44°C, 4 min at 50°C, 5 s at 60°C, and less than 1 s at 70°C. Carbonization occurs at 200–300°C, vacuolation at about 100°C (the boiling point of water), and coagulation at a temperature of 70°C or more. In this experiment, there was vacuolar stratification inside the tissue, so the inner temperature including that layer was 100°C or more. In the simulation of the temperature outside the venous wall in Fig.9, when the output is 7.0 W, it exceeds 100°C only when the thickness is \( \mu - \sigma \). When the output power is 10.0 W, it exceeds 100°C when the output power is 10.0 W. These results were strongly correlated with the experimental result regarding the heat-affected layer in Fig.8, and the simulation was validated by comparing the simulated temperature with the measured temperature, as well as by comparison between the simulation and the heat-affected layer.

6. Conclusion
In this study, we developed a computer simulation for estimating the intravascular temperature during EVLA and the efficacy and safety of devices. To estimate the temperature distribution in a vein by simulation, we measured the intensity of laser irradiation at each position and calculated the radius of the laser. The simulation was performed under the same irradiation conditions as in the ex vivo experiment, and validated by comparing the calculated temperatures. When the laser output was 7.0 W, the measured temperature was smaller than the calculated value of \( t = \mu - \sigma \) and larger than that of \( t = \mu + \sigma \). On the other hand, when the output power was 10 W, the simulation value was higher than the experimental value by 13°C or more. The cause of overestimation of the temperature in this simulation might be the latent heat. Indeed, it was revealed from the cross section after irradiation that vacuolation occurred inside the venous wall. Thus, at temperatures not exceeding 100°C, the simulation matches the real environment very well, whereas above 100°C, the temperature is overestimated due to the latent heat. For these reasons, the results of this simulation are considered to closely reproduce the actual measurements. Accordingly, the simulation could be used to determine the optimal irradiation condition. The quantitative analysis method developed in this study will play a key role in theoretical interpretations of thermal effects during EVLA, and the simulation results could be used to provide evidence for new device applications.

Acknowledgement
The authors would like to show the greatest appreciation to Masato Yoshimori for his assistance in the experiment.

Conflict of Interest
No conflict of interest.

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