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A Comparison of Microvascular Responses to Visible and Near-Infrared Lasers

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Abstract

Background and Objective—Pulsed dye laser (PDL) is a commonly used treatment for Port Wine Stain birthmarks (PWS). However, deeper components of PWS are often resistant to PDL. Deeper penetrating lasers, including the long pulsed Neodymium:Yttrium Aluminum Garnet (Nd:YAG) laser have been used, but carry greater risk. This study evaluates the distinct blood vessel thermal responses to visible (595 nm) and near infrared (1,064 nm) lasers using animal and numerical models.

Study Design/Materials and Methods—Blood vessels in the rodent dorsal skin chamber (DSC) were irradiated by a 595 nm PDL and a long-pulsed 1,064 nm Nd:YAG laser. Laser-induced immediate and 1-hour post-structural and functional changes in the vessels were documented. Numerical simulations were conducted using a 1,000 μm depth SD mouse skin fold to simulate experimental conditions.

Results—PDL irradiation produced immediate blood vessel hemorrhage. Modeling indicated this occurs due to preferential heating of the superior parts of large blood vessels. Nd:YAG irradiation resulted in blood vessel constriction; modeling indicated more uniform heating of vessel walls.

Conclusion—PDL and Nd:YAG lasers result in distinct tissue responses. This supports different observable clinical treatment end points when using these devices. Vessel constriction associated with the Nd:YAG may be more difficult to observe and is one reason this device may carry greater risk. *Lasers Surg. Med.* 46:479–487, 2014.

Keywords

dorsal skin chamber; laser irradiation; Nd: YAG laser; pulsed dye laser

INTRODUCTION

Port Wine Stain birthmarks (PWS) are congenital vascular birthmarks that occur in approximately 0.3% of children [1]. Histopathological analysis of PWS reveals a normal epidermis overlying an abnormal plexus of benign vascular malformations consisting of ectatic capillaries of diameters varying from 10 to 300 μm [2]. Most PWS are pale pink patches at birth that progressively darken and thicken with age. This often results in increased cosmetic disfigurement and psychological distress, prompting many patients and their families to seek treatment.

Laser therapy is the most commonly utilized treatment for PWS [2]. Based on the selective photothermolysis theory of Anderson and Parrish [3], the ideal wavelengths for laser treatment of PWS are the peak absorptions of hemoglobin (418, 542, or 577 nm). In practice, however, the pulsed dye laser (PDL), with a longer wavelength (585 or 595 nm) is most often used and provides increased penetration and decreased epidermal melanin light absorption [4]. Following multiple sessions, most patients show significant lightening of their PWS, however less than 20% of patients exhibit complete clearing [2].

Deeper components of PWS are often resistant to PDL, but can be treated with deeper penetrating devices [5]. The long pulsed Neodymium:Yttrium Aluminum Garnet (Nd:YAG) laser has a wavelength of 1,064 nm which falls in the broad absorption band of hemoglobin (800–1,100 nm) and allows for tissue penetration of up to 5–6 mm [6]. Groot et al. [7] found that 80% of deep vascular lesions, including vascular tumors (e.g., hemangiomas), vascular malformations (e.g., port-wine stains), small-caliber ectasias (e.g., telangiectasias), and large-caliber ectasias (e.g., dilated leg and facial veins), treated with a long pulsed Nd:YAG demonstrated 50% or greater resolution following one treatment session. Similarly, Yang et al. [5] found that patients with hypertrophic PWS demonstrated better lightening scores following Nd:YAG laser therapy as compared to PDL. Moreover, some patients prefer Nd:YAG to PDL because it is associated with less purpura [5]. Similarly, dual-wavelength lasers with combined wavelengths of 532/1,064 nm [8–10] and 595/1,064 nm [11,12] have also been shown to be effective in treating some vascular lesions resistant to PDL. However, despite these promising results, the Nd:YAG and dual-wavelength lasers are associated with an increased risk of scarring with treatment above the minimal purpura dose.

For optimal clinical results to prevent the scarring and other side effects, the treatment endpoint (TEP), which is based on blood vessel thermal response to irradiation, should be carefully selected [5]. The TEP for PDL is instant purpura [2], whereas the TEP for Nd:YAG is immediate blood vessel clearing [7]. Grey discoloration can also be a TEP for the Nd:YAG, but this generally represents overtreatment and is not the desired endpoint. The TEP distinction suggests that lasers with wavelengths in the visible and the near infrared bands, damage blood vessels differently.

To date, most research has focused on blood vessel thermal response to lasers with visible band wavelengths [13,14] or combined dual-wavelengths [8,15]. However, Suthamjariya et al. [16] compared the thermal response of blood vessels irradiated with a 1,064 nm laser versus a 532 nm laser and found that at high fluences (e.g., 60–500 J/cm²), the 1,064 nm, and 532 nm lasers produced similar thermal effects, including but not limited to vasoconstriction, vessel disappearance, vessel wall rupture, vessel hemorrhage, and perivascular tissue shrinkage. We conducted a similar animal model study but extended the observation period to 1-hour post-treatment and conducted model simulations to compare blood vessel thermal responses to irradiation with a more commonly utilized visible wavelength of 595 nm and the near infrared wavelength of 1,064 nm.

MATERIALS AND METHODS

Laser System

A 595 nm PDL (Vbeam, Candela Corp., Wayland, MA) and a long-pulsed 1,064 nm Nd:YAG laser (Star TR, Won Technology Corp., Seoul, Korea) were used with hand pieces that projected uniform circular beams with 5 and 2 mm diameters, respectively. Although the circular beam sizes were different and smaller than those used clinically, sizes greater than or equal to 2 mm have little effect on energy deposition and are sufficient for individual vessel irradiation [17]. Furthermore, we considered any difference in laser penetration to be negligible for a given blood vessel's temperature distribution. Pulse widths of 6, 20, and 40 ms were used for the 595 nm laser and 5, 10, 20, 30, and 40 ms for the 1,064 nm laser. Fluences were varied systematically from 8 to 15 J/cm² with 2 J/cm² increments for the 595 nm laser and from 100 to 1,000 J/cm² with 50 J/cm² increments for the 1,064 nm laser. Both lasers were used without activation of the cooling device, since laser irradiation was conducted from the dermal side of the dorsal skin chamber (DSC).

In Vivo Animal Model

DSC is a commonly used animal model that provides a relevant range (30–300 μ m) of blood vessel lumen size [13].

The dorsal blood vessels of the Danforth's short tail (SD) mouse were the designated targets. Eighty-four male SD mice with body weights of 100–120 g from Xi'an Jiaotong University Medical School Animal Center were housed in a single cage with free access to food and water. The mice were fitted with titanium DSC. Detailed surgical procedure can be found in a previous publication [18].

All procedures involving the animal experiments were approved by the Institutional Animal Care and Use Committees of the Xi'an Jiaotong University.

Irradiation Procedure

The basic experimental set-up consisted of a SD mouse fitted with a DSC, a microscopy camera with 10 times magnification (Wild, model BX41, Olympus, Hatagaya, Japan), and the laser system.

The mouse was placed on the microscope platform and its microcirculation was examined through the central viewing hole of the chamber. The microscope was used to determine the blood vessel diameter using software (Olympus U-TVO.63XC). A total of 106 blood vessels were selected and treated. Their diameters ranged from less than 30 to up to 300 μm and were representative of human PWS blood vessels.

For laser irradiation, the central viewing hole of the chamber glass was removed to provide direct exposure to target blood vessels from the dermal side of the DSC. The laser was triggered with the aiming beam directly overlying the target blood vessels.

Laser settings were based on values used clinically in China. Irradiation was terminated for any evidence of severe collagen damage. After each irradiation, the immediate blood vessel effects were qualitatively examined using the microscopy camera. Examination and documentation was again performed 1 hour after irradiation.

Statistical Analysis

The thermal responses of the blood vessels after 595 and 1,064 nm laser irradiation were separated into two groups. Group differences in thermal responses after the laser to the two wavelengths were then compared. The statistical significances of these differences were determined by Chi-Squared Tests using SPSS Statistics (SPSS 19.0, IBM, Corp., Armonk, New York).

Numerical Models

To evaluate blood vessel photocoagulation patterns, numerical simulations were conducted. To represent a 1,000 μm depth SD mouse skin, we created a vascular model consisting of six blood vessels, with diameters ranging from 10 to 120 μm , arranged as parallel cylindrical tubes within the dermis (Fig. 1). To represent the blood vessels evaluated in the experimental DSC and PWS blood vessels found in human skin, three larger target blood vessels with diameters of 120 μm were considered 650 μm from the skin surface. Similarly, three smaller blood vessels with diameters of 10, 30, and 50 μm were considered 250 μm from the skin surface to represent normal capillaries, small PWS blood vessels and medium PWS blood vessels, respectively. Other anatomic structures in skin, such as nerve endings, sweat and sebaceous glands, and hair follicles were not considered.

The heat transferred through pulsed laser irradiation to the skin model described above was

determined by the heat transfer equation, $\rho_i c_i \frac{\partial T(x, z, t)}{\partial t} = k_i \nabla^2 T(x, z, t) + Q_i(x, z)$, where i represents either the dermis or blood vessels ρ represents the density, c_p represents the specific heat, k represents the thermal conductivity, T represents the temperature, and t represents the time. $Q_i(x, z)$ represents the heat generated laser energy through absorption and can be determined by the Monte Carlo method [4,19]. Blood perfusion and metabolic heat generation were neglected as short pulses were used.

The corresponding thermal damage was simulated by the Arrhenius rate process integral,

$$\Omega(\tau) = \int_0^{\tau} A \exp\left(\frac{-\Delta E}{RT(\tau)}\right) dt, \text{ where } A \text{ represents the frequency factor (1/s), } E$$

represents the activation energy (J/mol), and R represents the universal gas constant (8.314 J/mol K). We assumed $A = 1.8 \times 10^{51}$ L/s and $E = 327,000$ J/mol for skin and $A = 7.6 \times 10^{66}$ L/s and $E = 327,000$ J/mol for blood [4]. Ω was calculated for a period of time until thermal damage ceased.

In the simulation, a spot size and pulse duration of 5 mm and 6 ms were used for the 595 nm laser and 2 mm and 5 ms for 1,064 nm laser. Fluences of 13 and 80 J/cm² were mathematically determined to meet the threshold energy required to produce thermal damage to a 120 μ m vessel for the 595 and 1,064 nm lasers, respectively. The initial temperature of the skin was assumed to be 30°C as supported by the literature [19]. The thermo-physical properties of blood and skin are provided in Table 1 [19,20].

RESULTS

Blood Vessel Thermal Response Immediately After Laser Irradiation

As shown in Table 2, 32 blood vessels, with diameters ranging from 40 μ m to more than 160 μ m, and an average diameter of 120 μ m, were irradiated by the 595 nm laser. Notably, 15 blood vessels immediately hemorrhaged, and five blood vessels demonstrated surrounding collagen damage. Of the remaining blood vessels, four blood vessels temporarily coagulated, seven blood vessels demonstrated mild constriction or decrease in diameter, and one blood vessel fully constricted. Figure 2 depicts an example of blood vessel hemorrhage due to PDL irradiation.

As shown in Table 3, 72 blood vessels, with diameters ranging from 30 μ m to more than 300 μ m, and an average diameter of 120 μ m, were irradiated by the 1,064 nm laser and demonstrated effects that were greatly dependent on fluence and pulse duration. In general, irradiation with longer pulse durations required higher incident fluences to produce blood vessel constriction. The majority of blood vessels constricted completely following irradiation with fluences between 250 and 800 J/cm². Fluences less than 250 J/cm² produced blood vessel constriction or temporary coagulation, and fluences greater than 400 J/cm² often resulted in target blood vessel hemorrhage and surrounding collagen thermal damage. Figure 3 depicts an example of complete blood vessel constriction due to Nd:YAG irradiation.

Blood Vessel Thermal Response One Hour After Laser Irradiation

The thermal response 1 hour after 595 nm laser irradiation is summarized in Table 4. Of note, only the 21 vessels with perfusion elimination immediately post-treatment were evaluated (the 11 additional vessels with perfusion immediately post- were excluded). No additional vessels achieved perfusion reduction at 1 hour. Slightly more hemorrhage was seen 1 hour following irradiation as compared to immediately after irradiation, but no recanalization was observed.

The thermal response 1 hour after 1,064 nm laser irradiation is summarized in Table 5. Again, ten vessels that had temporarily coagulated (3 blood vessels) or experienced a decrease in diameter (7 blood vessels) following irradiation, and two vessels from an SD mouse that unexpectedly died shortly after irradiation, were excluded from the table. The

vessels that temporarily coagulated were excluded because the thrombi that appeared shortly after irradiation disappeared within 10 seconds and did not result in any morphological changes to the blood vessels. Similarly, the vessels that decreased in diameter still contained blood flow, so there was no need to monitor these vessels for recanalization. Fifty-three blood vessels did not show significant change 1 hour after irradiation compared to immediately after irradiation and seven blood vessels recanalized.

Of note, vessels irradiated by the 1,064 nm laser and short pulse durations of 5 ms that hemorrhaged immediately after the laser irradiation (Table 3), demonstrated more hemorrhage 1 hour after irradiation. In addition, hemorrhage of the surrounding capillaries was seen 1 hour after irradiation with incident fluences greater than 450 J/cm² for 20 ms pulse duration and 550 J/cm² for 40 ms pulse duration, where complete constriction, and occasional collagen damage, had been observed immediately after irradiation (Table 3).

Statistical Significance of Blood Vessel Thermal Responses

There was a greater incidence of immediate blood vessel hemorrhage with 595 nm laser irradiation (46.9%, Table 2) compared to 1,064 nm laser irradiation (4.2%, Table 3), whereas there was a greater incidence of blood vessel constriction with 1,064 nm irradiation (73.6%, Table 3) compared to 595 nm laser irradiation (3.1%, Table 2). These differences are statistically significant (Chi-Squared tests, $P < 0.01$).

Blood Vessel Energy Deposition and Temperature Distribution After Laser Irradiation

The Monte Carlo method calculates the distribution of energy deposition (Q) within the skin following laser irradiation (Fig. 4). The incident laser fluence used in the calculation was 13 J/cm² for the 595 nm laser and 80 J/cm² for the 1,064 nm laser. Due to selective photothermolysis, the laser light energy deposition in vessels was higher than that of the surrounding dermis for both wavelengths. Moreover, energy deposition within small blood vessels with diameters of 10, 30, and 50 μm was nearly uniform for both lasers. Similarly, the energy deposition within larger blood vessels with diameters of 120 μm was uniform for the 1,064 nm laser (Fig. 4b), but it was strongly attenuated for the 595 nm laser due to strong light absorption of hemoglobin in the visible band (Fig. 4a).

Figure 5 depicts the temperature distribution in the simulated skin model following 595 nm and 1,064 nm irradiation with pulse durations of 6 ms and 5 ms and incident fluences of 13 and 80 J/cm², respectively. For vessels irradiated by the 595 nm laser, the blood vessel temperature was considerably higher in superior portions of the vessel and the time required to reach the coagulation temperature of 70°C was shorter for the superior as compared to inferior portions of the vessel (Fig. 5a). Conversely, the 1,064 nm laser demonstrated relatively uniform heating of the vessel lumen (Fig. 5b).

The distinct heating pattern is further illustrated by a second stimulation (Fig. 6), which shows relatively uniform heating of luminal blood immediately following 1,064 nm laser irradiation and higher temperatures in the superior component of luminal blood vessels compared to the inferior components of luminal blood vessels treated with the 595 nm laser.

DISCUSSION

Our study confirmed statistically significant (Chi-Squared tests, $P < 0.01$), distinct blood vessel thermal responses to visible and near infrared light and supports the TEPs of purpura for 595 nm irradiation and vessel clearing for 1,064 nm irradiation (Tables 2 and 3).

PDL irradiation produced immediate blood vessel hemorrhage while Nd:YAG irradiation generally resulted in blood vessel constriction. Of interest, contrary to our general findings, two blood vessels paradoxically dilated following irradiation with the 1,064 laser (Table 3). This is thought to have been due to endothelial damage or suppression of neurohumoral control [18].

We also saw that immediate blood vessel response is certainly dependent on blood vessel size. Larger blood vessels experienced a more dramatic response of either hemorrhage (Fig. 2b) or complete blood vessel constriction (Fig. 3b) immediately following PDL or Nd:YAG laser irradiation. However, smaller vessels allowed for greater dissipation of energy to the surrounding dermis, resulting in a muted blood vessel response.

Similarly, based on the model prediction in our previous study [21], the blood vessel thermal response is also influenced by pulse duration. Higher pulse durations would result in lower blood vessel temperature but higher surrounding dermal tissue temperature due to heat conduction. Fixed pulse durations were used in this study to support the experimental observations and further studies are required to demonstrate this phenomenon.

One hour following irradiation, only seven blood vessels treated with the 1,064 nm lasers recanalized (Tables 4 and 5). These vessels are thought to have recanalized because of insufficient energy absorption to achieve permanent damage. Four blood vessels were irradiated with 5 and 30 ms pulse durations and relatively low incident fluences. One vessel, irradiated with a 10 ms pulse duration and was located parallel to other smaller blood vessels, which resulted in competition for light absorption. Two additional vessels, irradiated with 20 ms pulse durations, had small diameters of approximately 30 μm , which allowed for dissipation of absorbed energy.

We further supported the distinct blood vessel thermal responses via numerical simulations. While both lasers were capable of inducing thermal damage to the 120 μm lumen (Figs. 5 and 6), the 595 nm heated the superior portions of large blood vessels more than the inferior portions, presumably due to limited light penetration (Figs. 5a and 6a). Hence, the hemorrhage seen after irradiation (Table 2) may be caused by the constriction of vessel walls superiorly, resulting in compression of blood toward the bottom of the vessel, increased pressure and leakage of blood. Conversely, the 1,064 nm laser produced uniform heating (Figs. 5b and 6b) and proportional constriction of blood vessel walls due to its deeper penetration. Thus, most blood vessels irradiated with 1,064 nm laser constricted and seemingly disappeared, as the blood was moved along the axis of the vessel.

Although some patients may prefer the complete blood vessel constriction achieved by the 1,064 nm laser over the instant hemorrhage produced by the 595 nm laser due to shorter cosmetic recovery times [5], there are several caveats to the use of the 1,064 nm laser for the

treatment of PWS. First, while large blood vessels completely coagulate, capillaries and small blood vessels with diameters of less than 30 μm can persist due to heat conduction. Currently, it is clinically impossible to identify and selectively target larger vessels. Secondly, blood vessels that seemingly disappear immediately after irradiation, may recanalize due to insufficient energy absorption (Table 4). Thirdly, the TEP of gray color or immediate vessel clearing does not serve as an early enough or obvious marker for excessive energy deposition. With the 595 nm laser, we found that collagen damage occurred when incident energy surpassed the threshold incidence fluence for hemorrhage (Table 2). Thus, when using the 595 nm laser, clinicians can use the TEP of purpura, or instant hemorrhage, as a marker for vessel damage, and may avoid further increases in incident fluence that could potentially cause collagen damage. Unfortunately, the TEP of gray color, which is often used for the 1,064 nm laser, can also be a sign of overtreatment, and without a better marker, clinicians using the 1,064 nm laser are at increased risk of causing collagen damage and subsequent scarring—a well-known side effect of Nd:YAG laser therapy of PWS [22]. Though Yang et al. [5] reported the use of immediate subtle purpura or hemorrhage as a TEP for PWS treated with a 1,064 nm laser and indicated that such a TEP could be used to prevent scarring, our experiment failed to show any evidence of instant hemorrhage following 1,064 nm irradiation, except for vessels treated with the shortest pulse duration of 5 ms (Table 3).

One major limitation to our study is that the experiment was performed using an animal model. Although the findings contribute to our general understanding of the effects on human tissue, there may be differences, which would make our findings less applicable to clinical practice. Moreover, irradiation was performed from the dermal side of the DSC, which limits our understanding of epidermal effects. Another limitation to our study is that the observation time was limited to 1 hour, which does not allow for the assessment of long-term effects of irradiation. Future studies that include epidermal irradiation and longer evaluation periods may prove to be of value.

Furthermore, laser parameters were not necessarily reflective of those used outside of China. For example, significantly shorter pulse durations are typically used for PDL in the United States. In addition, studies are also necessary to define the optimal operational parameters for Nd:YAG laser. Our study showed that treatment using short pulse durations better coagulated small blood vessels. To better understand this finding and standardize the use of the Nd:YAG laser for treatment of vascular lesions, a thorough parameter study of the long pulsed Nd: YAG laser is necessary.

The numerical simulations were also limited by several factors. First, we assumed that principles based on human models were applicable to our SD mouse model, since hemoglobin is the main chromophore for both lasers. Secondly, our calculations may have over-estimated the vessel temperature, as we neglected the latent heat for water vaporization in our model. Finally, our model only provides qualitative observations on thermal damage. Future models that incorporate mechanical effects (including blood vessel shrinkage, constriction, and rupture) and bio-chemical reactions (such as met-hemoglobin formation and thrombus formation [8]), may add to the qualitative insight gained from this study.

CONCLUSION

This study demonstrates the distinct blood vessel thermal responses to both visible and near infrared laser irradiation. Generally, PDL irradiation was characterized by immediate blood vessel hemorrhage and Nd:YAG by complete blood vessel constriction. This supports different observable clinical TEPs when using these devices. Vessel constriction associated with the Nd:YAG may be more difficult to observe and is one reason this device may carry greater risk in clinical practice.

Acknowledgments

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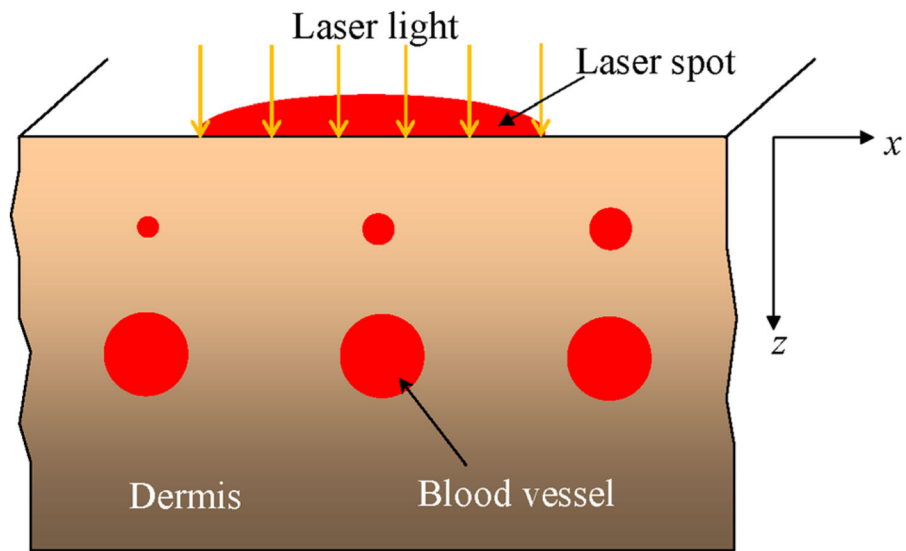


Fig. 1.
The schematic of the discrete blood vessels skin structure used in the simulation.

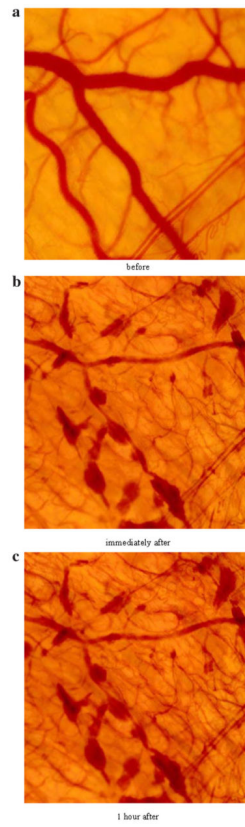


Fig. 2. Blood vessels (a) before, (b) immediately after, and (c) 1 hour after PDL irradiation with fluence of 12 J/cm^2 and pulse duration of 6 ms.

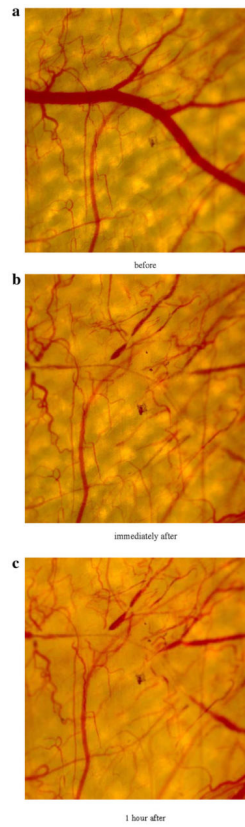


Fig. 3. Blood vessels (a) before, (b) immediately after, and (c) 1 hour after Nd:YAG laser irradiation with fluence of 350 J/cm^2 and pulse duration of 5 ms.

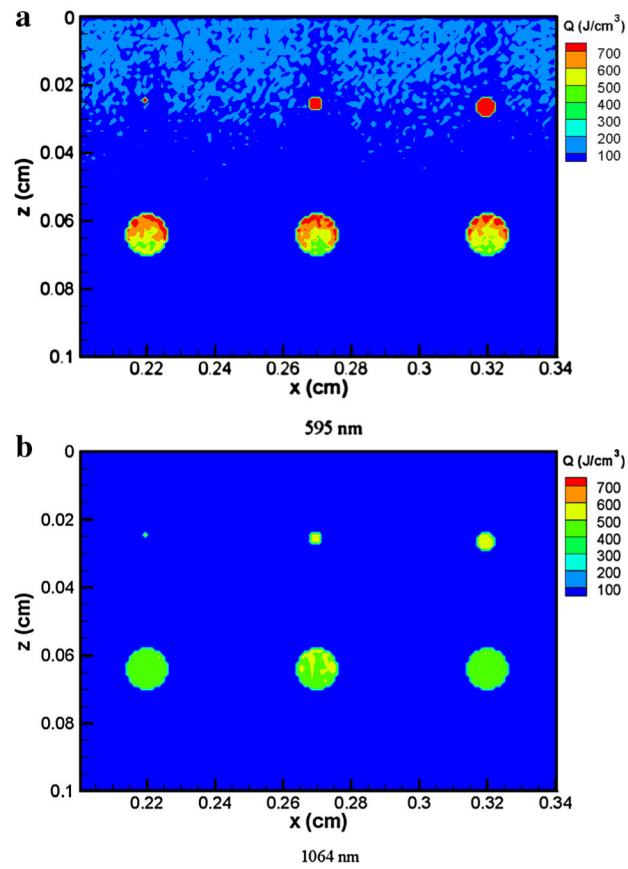


Fig. 4. The light energy deposition after (a) 595 ($13 \text{ J}/\text{cm}^2$) and (b) 1,064 nm ($80 \text{ J}/\text{cm}^2$) laser irradiation.

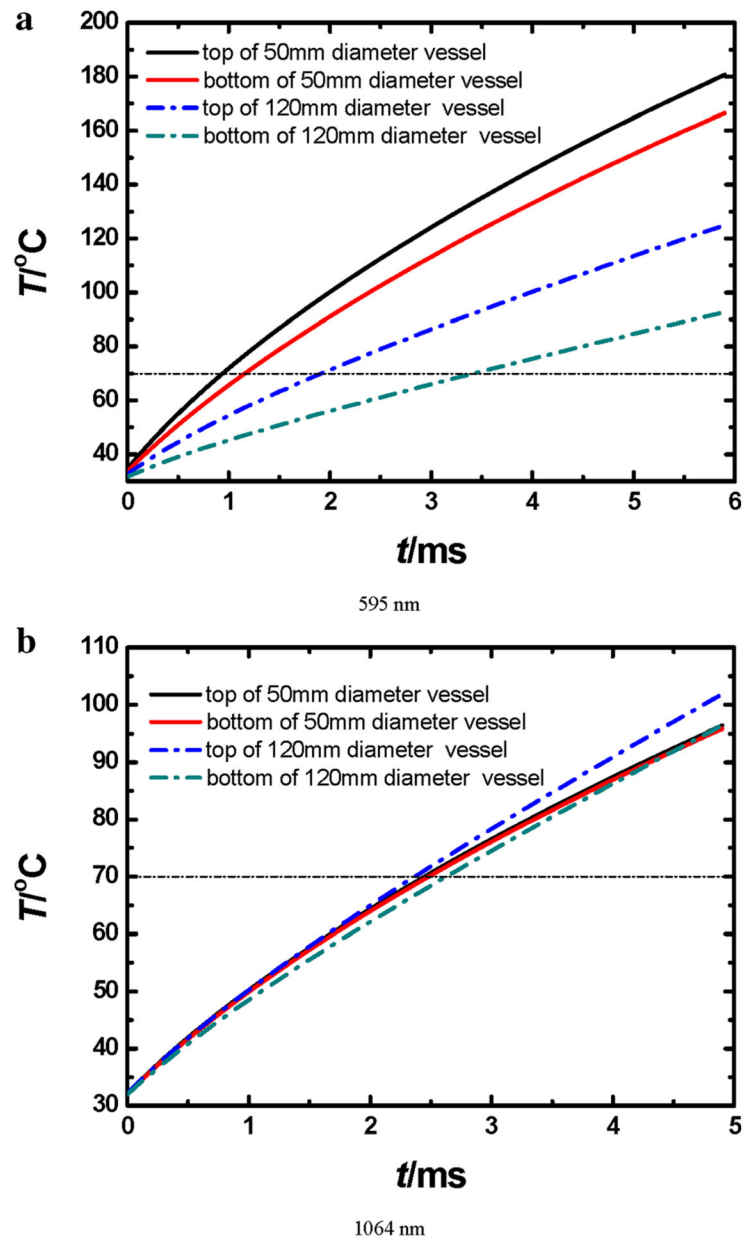


Fig. 5. The temperatures in superficial and deep portions of vessels measuring 50 and 120 μm in diameter following a single pulse of irradiation with the (a) 595 nm laser (6 ms; $13 \text{ J}/\text{cm}^2$) and (b) 1,064 nm laser (5 ms; $80 \text{ J}/\text{cm}^2$). The 50 μm blood vessel was located 250 μm below the skin surface, while the 120 μm blood vessel was located 650 μm below the skin surface. Both blood vessels located at the centerline of the laser spot center. The dotted line at 70°C indicates the coagulation temperature.

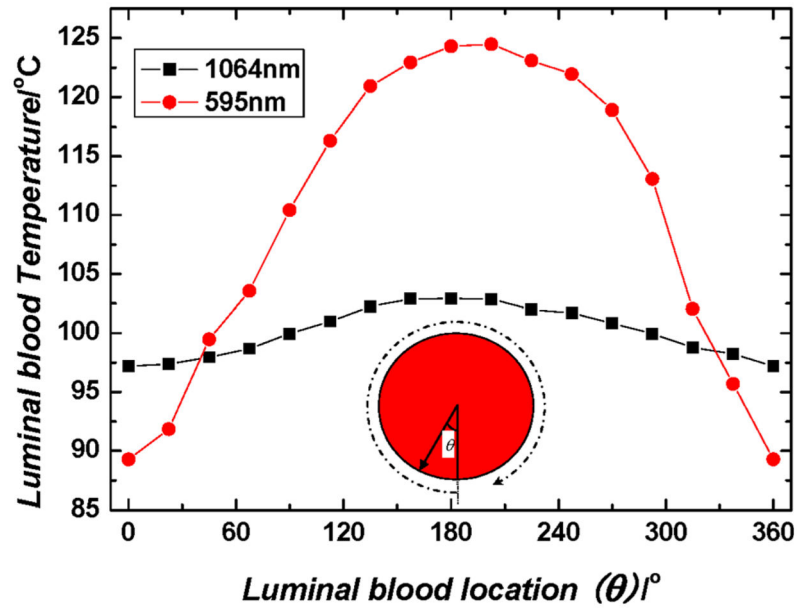


Fig. 6. Luminal blood temperature from a 120 μm vessel located 650 μm below the skin surface immediately following a single laser pulse with the 595 nm (6 ms; 13 J/cm²) versus 1,064 nm laser (5 ms; 80 J/cm²). The blood vessels located at the centerline of the laser spot center.

TABLE 1

Thermal and Optical Properties of Skin Components [19,20]

Physical properties	Dermis	Blood
Thermal conductivity, k (kW/(m K))	0.41	0.55
Specific heat, c (J/(kg K))	3.5	3.6
Density, ρ (kg/m ³)	1,090	1,060
Absorption coefficient, μ_a (cm ⁻¹)		
595 nm	2.4	49.3
1,064 nm	0.244	4
Scattering coefficient, μ_s (cm ⁻¹)		
595 nm	120	466
1,064 nm	105.57	458.58
Anisotropy index, g		
595 nm	0.8	0.995
1,064 nm	0.91	0.99

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TABLE 2

Immediate Blood Vessel Response to 595 nm Irradiation

Pulse duration (ms)	6 ms	20 ms	40 ms
Coagulation (12.5%)	3 ^a (8) ^b	1 (8)	
Diameter decrease (21.9 %)	1 (8)	1 (8)	1 (10)
	1 (10)	1 (12)	1 (12)
		1 (14)	
Complete constriction (3.1%)		1 (10)	
Hemorrhage (46.9%)	4 (10)	3 (12)	1 (12)
	3 (12)	1 (14)	3 (15)
Collagen damage (15.6 %)	4 (14)		1 (10)

^aThe numbers preceding the parentheses represent the number of blood vessels in particular events.

^bThe numbers within the parentheses represent the fluence.

TABLE 3

Immediate Blood Vessel Response to 1,064 nm Irradiation^a

Pulse duration (ms)	5 ms	10 ms	20 ms	30 ms	40 ms
Coagulation (4.2%)	1* (100)**	1 (250)	1 (250)		
Diameter decrease (9.7%)	1 (150)	1 (300)	1 (300)	2 (400)	
		1 (350)	1 (350)		
Complete constriction (73.6%)			1 (400)		
	1 (200)		4 (450)		2 (400)
	3 (250)	1 (350)	4 (500)	4 (400)	1 (450)
	2 (300)	2 (400)	3 (550)	2 (600)	2 (500)
	1 (350)	4 (450)	3 (600)	1 (700)	1 (550)
	3 (400)		2 (650)		3 (600)
			2 (700)		1 (800)
Hemorrhage (4.2%)	1 (400)				
	2 (450)				
Collagen damage (8.3%)	1 (450)	1 (500)	1 (700)		1 (850)
	1 (600)		1 (550)		

^aTwo blood vessels dilated after laser irradiation and were consequently excluded from the study.

* The numbers preceding the parentheses represent the number of blood vessels in particular events.

** The numbers within the parentheses represent the fluence.

TABLE 4**Blood Vessel Response 1 hour After 595 nm Laser Irradiation**

Pulse duration/ms	6 ms	20 ms	40 ms
No recanalization (100%)	4 ^a (10) ^b	1 (10)	1 (10)
	3 (12)	3 (12)	1 (12)
	4 (14)	1 (14)	3 (15)
Recanalization (0%)	0	0	0

^aThe numbers preceding the parentheses represent the number of blood vessels in particular events.

^bThe numbers within the parentheses represent the fluence.

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TABLE 5

Blood Vessel Response 1 hour After 1,064 nm Laser Irradiation

Pulse duration/ms	5 ms	10 ms	20 ms	30 ms	40 ms
No recanalization (88.3%)		1 (400)	4 (450)		2 (400)
	3 ^a (250) ^b				1 (450)
	1 (350)	2 (400)	4 (500)	3 (400)	1 (500)
	4 (400)	3 (450)	2 (550)	2 (600)	2 (550)
	3 (450)	1 (500)	2 (600)	1 (700)	3 (600)
	1 (600)		2 (650)		1 (800)
			3 (700)		1 (850)
Recanalization (11.7%)	1 (200)	1 (450)	1 (550)	1 (400)	
	2 (300)		1 (600)		

^aThe numbers preceding the parentheses represent the number of blood vessels in particular events.^bThe numbers within the parentheses represent the fluence.