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Laser Pulse Duration Must Match the Estimated Thermal Relaxation Time for Successful Photothermolysis of Blood Vessels

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Abstract. The relationship between photothermal damage to blood vessels of diameter, d , and laser pulse duration, t_p , was verified in a series of studies using the chick chorioallantoic membrane (CAM). A total of 879 individual CAM blood vessels ($d=50\text{--}130\text{ }\mu\text{m}$) was irradiated, using a laser pulse duration of 0.45 or 10 ms. Laser-induced vascular damage was observed in real time, recorded on videotape, and evaluated in a double-blind fashion. Permanent damage was confirmed by inspection 24 h after laser exposure. Under the conditions of this experiment, only when laser pulse durations are approximately equal to the estimated thermal relaxation times (τ) of the CAM microvessels can the critical core intravascular temperature, necessary to destroy vessels irreversibly, be achieved and sustained for sufficient time. Shorter pulse durations are more effective for damaging smaller blood vessels; conversely, longer pulse durations are more effective for damaging larger diameter vessels.

INTRODUCTION

The pulse duration of laser exposure (t_p) governs the spatial confinement of heat and should, in principle, match the thermal relaxation time (τ) for the targeted port-wine stain (PWS) blood vessels. τ is defined as the time required for the core temperature, produced by the absorbed light energy within the target blood vessel, to cool to one-half of the original value immediately after the laser pulse (1). The value for τ is directly proportional to the squared diameter (d) of the targeted PWS blood vessel and inversely proportional to the thermal diffusivity [$\tau=d^2/16\chi$, where χ is the thermal diffusivity (taken here to be that of water, $1.4 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$)]. PWS blood vessel diameters vary on an individual patient basis and even from site to site on the same patient, over a range of 10–200 μm (2). For blood vessels

with diameters of 50, 90 and 130 μm , τ has calculated values of 1.1, 3.6 and 7.6 ms, respectively.

Only when laser pulse durations are approximately equal to τ can the critical core intravascular temperature, necessary to destroy large PWS blood vessels irreversibly, be achieved and sustained for sufficient time. If longer pulse durations are employed ($t_p \gg \tau$), heat diffuses outside the vessel during exposure. The target specificity is reduced, resulting in thermal damage to skin structures adjacent to the heated vessels. Conversely, if too short a laser pulse is used ($t_p \ll \tau$), peak intravascular temperatures produce explosive vaporization of tissue water, or photoacoustic transients, which can result in vessel rupture. In such cases, repair mechanisms may revascularize the PWS (1).

MATERIALS AND METHODS

The relationship between photothermal damage to blood vessels of diameter, d , and laser pulse duration, t_p , was verified in a series of studies conducted in our laboratory using the chick chorioallantoic membrane (CAM) (3). The CAM vasculature is located in a transparent matrix (4); this allows direct measurement of individual blood vessel diameter, visualization of blood flow, and real-time observation of photothermal effects on blood vessels, such as vessel dilation, constriction, haemostasis and rupture, using light microscopy ($30\times$). Thus, the influence of the pulse duration of laser exposure in relationship to individual CAM blood vessel diameter can be studied conveniently without having to perform light microscopic histopathology.

The protocol for CAM preparation was a modification of a previously described technique (5). Sterile Teflon O-rings were placed on the surface of the CAM, each demarcating a location where individual blood vessels were clearly visible and to which the laser beam was directed (3, 6).

A flashlamp-pumped pulsed dye laser (Candela, Wayland, MA) was used for whole field multiple-vessel irradiation and delivered pulses of duration $t_p=0.45$ ms (wavelength, $\lambda=585$ nm). The beam was focused to a 5-mm-diameter circular spot of uniform light intensity. The optical energy density incident on the CAM was varied between $F=3$ and 6 J cm^{-2} per pulse.

A continuous wave (CW) argon-ion pumped dye laser (Coherent, Palo Alto, CA) was used for single-vessel irradiation and delivered a maximum power of 1.4 W focused to a 0.5-mm-diameter circular spot of uniform light intensity. The CW laser was pulsed with a mechanical shutter and delivered pulses of duration $t_p=10$ ms ($\lambda=585$ nm), yielding an energy density of 7 J cm^{-2} per pulse.

Individual CAM blood vessels [$d=50$ (small), 90 (medium), 130 (large) $\pm 10\text{ }\mu\text{m}$] were irradiated, using a laser pulse duration of 0.45 or 10 ms. Each vessel was exposed three times at the same site, keeping the time interval between sequential exposures at 30 s, so that the subsequent radiation interacted with a vessel that had cooled down to ambient temperature. Laser-induced vascular damage was observed in real time, recorded on videotape, and evaluated in a double-blind fashion. The damage listed in Fig. 1 is composed of vessels

Fig. 1. Cumulative probability of individual CAM blood vessel damage following laser irradiation with $t_p=0.45$ ms (■), $F=3-6\text{ J cm}^{-2}$ (688 vessels); or $t_p=10$ ms (□), $F=7\text{ J cm}^{-2}$ (191 vessels).

exhibiting: (i) slight damage (vasodilatation/vasoconstriction, temporary occlusion); (ii) moderate damage (haemostasis); and (iii) severe damage (haemorrhage). Permanent damage was confirmed by inspection 24 h after laser exposure. Chi-squared tests using stepwise logistic regression analysis were used to assess the statistical significance of laser pulse duration, vessel diameter, and, in the case of the 0.45 ms pulse duration, fluence.

RESULTS AND DISCUSSION

Figure 1 presents the measured probability of individual CAM blood vessel damage following laser irradiation with $t_p=0.45$ ms (688 vessels) or $t_p=10$ ms (191 vessels). Blood vessels with diameter $50 \pm 10\text{ }\mu\text{m}$ showed significantly more damage ($p<0.0001$) when exposed to the 0.45 ms pulse duration than to the 10 ms exposure. Conversely, blood vessels with diameter $130 \pm 10\text{ }\mu\text{m}$ showed significantly more damage ($p<0.0001$) when exposed to the 10 ms pulse duration than to the 0.45 ms exposure; 85% of blood vessels with diameter $130 \pm 10\text{ }\mu\text{m}$ were not damaged at all by the 0.45 ms exposure. Furthermore, fluence, in the case of the 0.45 ms laser, was not statistically correlated with blood vessel damage; for example, for $F=3, 4, 5$ and 6 J cm^{-2} per pulse, blood vessels with diameter $50 \pm 10\text{ }\mu\text{m}$ were damaged after a single 0.45 ms pulse in, respectively, 43%, 45%, 40% and 45% of examples.

Figure 2 shows the calculated intravascular temperature change, ΔT , of a blood vessel, as a function of d , when exposed to a pulse

Fig. 2. Calculated intravascular temperature change, ΔT , of a blood vessel, as a function of d , when exposed to a laser at 585 nm with a pulse duration of 0.45 ms (—), $F=3 \text{ J cm}^{-2}$; or 10 ms (---), $F=7 \text{ J cm}^{-2}$.

duration of 0.45 or 10 ms. The calculations take into account heating caused by absorption of the laser energy ($\lambda=585 \text{ nm}$) incident on a blood vessel. In a cylindrical vessel of lumen diameter d , lying along the y -direction and exposed over length l to a collimated light beam propagating in the z -direction, the net absorbed energy is

$$Q_A = \int_0^l dy \int_{-d/2}^{d/2} dx \int_0^{2\sqrt{(d/2)^2 - x^2}} F \mu_a e^{-\mu_a z} dz \quad (1)$$

$$= (\pi/2) F l d [I_1(\mu_a d) - L_1(\mu_a d)]$$

Here $F \text{ (J cm}^{-2}\text{)}$ is the incident energy fluence; ld is the target area intercepting the light beam; $\mu_a = \mu_a(\lambda)$ is the absorption coefficient of blood; I_1 and L_1 are, respectively, the first-order modified Bessel and Struve functions (7) which have been tabulated (8). This result represents the incident optical energy absorbed by a cylinder, situated perpendicular to the direction of light propagation. The cylinder volume contains a homogeneous absorber, e.g. blood characterized by an absorption coefficient $\mu_a(585 \text{ nm})=170 \text{ cm}^{-1}$ or $\mu_a(577 \text{ nm})=430 \text{ cm}^{-1}$ (9). Blood has a rather large absorbance at $\lambda=585 \text{ nm}$ and for $d>100 \mu\text{m}$ ($\mu_a d>1.7$), more than 70% of the light incident on the upper surface of the vessel is absorbed.

Cooling caused by thermal relaxation of the blood vessel is calculated as energy which diffuses out of a vessel exponentially as a function of time, so that for $t>t'$,

$$dQ(t,t') = dQ_A(t') e^{-(t-t')/\tau} \quad (2)$$

Here $dQ_A(t')$ denotes the incremental amount of optical energy absorbed in the exposed lumen during dt' at time t' ; $dQ(t,t')$ denotes the corresponding thermal energy after the time interval $(t-t')$. The thermal energy remaining in the vessel at time t is found by integrating equation (2) over the duration of the laser pulse, $0<t'<t_p$. The result is

$$Q_t = Q_A(\tau/t_p)[1 - e^{-t/\tau}], \quad t \leq t_p \quad (3)$$

To a first approximation, the energy q required to heat blood in a vessel of length l is given as

$$q = \rho c l \pi (d/2)^2 (T_f - T_i) \quad (4)$$

Here ρ is the mass density (1 g cm^{-3}) and c is the specific heat of blood (4.2 J g K^{-1}) taken to be equal to the corresponding values for water; T_i and T_f denote, respectively, the temperature before (30°C) and immediately after the laser pulse. Equating absorbed energy Q with coagulation energy q gives the desired relationship of $\Delta T = T_f - T_i$ versus the blood vessel diameter d for the two pulse durations t_p (Fig. 2). It should be noted that the fluences used in the model were practical values available from the two commercial devices used in these studies. The long-pulse exposure, $t_p=10 \text{ ms}$ ($F=7 \text{ J cm}^{-2}$ per pulse) causes a monotonic temperature rise, ΔT , with vessel diameter d , up until $d=130 \mu\text{m}$. For larger d , ΔT decreases as $1/d$. In contrast, for $t_p=0.45 \text{ ms}$ ($F=3 \text{ J cm}^{-2}$ per pulse), ΔT reaches its maximum at a smaller diameter, $d=50 \mu\text{m}$. We assume that $\Delta T \geq 50^\circ \text{C}$ is required to reach temperatures sufficient to produce coagulative necrosis of the blood vessel wall (10).

Figure 2 confirms the observations of Fig. 1 that shorter pulse durations are more effective for damaging smaller blood vessels; conversely, longer pulse durations are more effective for damaging larger diameter vessels. In conclusion, experiments in the CAM demonstrate that selection of the correct pulse duration of laser exposure is crucial to successful blood vessel destruction. Only when laser pulse durations are approximately equal to the thermal relaxation times of the targeted PWS blood vessels ($t_p \approx \tau$) can the critical core intravascular temperature, necessary to destroy vessels irreversibly, be achieved and sustained for sufficient time.

Currently, only a small proportion of PWS patients undergoing laser therapy obtain 100% fading, even after undergoing multiple

treatments (11). The principal reason for poor clinical results has been inadequate heat generation within large PWS blood vessels (9). The 0.45 ms pulse duration employed in state-of-the-art flashlamp-pumped pulsed dye lasers is too short to reach and sustain over sufficient time the critical core intravascular temperature necessary to destroy large PWS blood vessels irreversibly. Improved therapeutic outcome in many PWS patients is expected from the development of laser systems with pulse durations over a range of 0.25–15 ms (3, 9). Such a laser system, with a flexible user-specified pulse duration, is currently under development at the University of California. Furthermore, non-invasive optical and thermal sensing techniques are being developed in our laboratory which may be used as a means to determine directly the diameter of individual PSW blood vessels (12–14). This, in turn, will allow the attending physician to select the pulse duration of laser exposure to be delivered that matches the thermal relaxation times of the targeted vessels on an individual patient basis, appropriate over the time course of therapy.

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