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Therapeutic Response During Pulsed Laser Treatment of Port-wine Stains: Dependence on Vessel Diameter and Depth in Dermis

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Abstract. Selective photothermolysis with pulsed lasers is presumably the most successful therapy for port-wine stain birthmarks (flammeus nevi). Selectivity is obtained by using an optical wavelength corresponding to high absorption in blood, together with small absorption in tissues. Further on, the pulse length is selected to be long enough to allow heat to diffuse into the vessel wall, but simultaneously short enough to prevent thermal damage to perivascular tissues. The optical wavelength and pulse length are therefore dependent on vessel diameter, vessel wall thickness and depth in dermis. The present work demonstrates that in the case of a 0.45 ms long pulse at 585 nm wavelength, vessels of 40–60 μm require minimum optical fluence. Smaller vessels require higher fluence because the amount of heat needed to heat the wall becomes a substantial fraction of the absorbed optical energy. Larger vessels also require a higher dose because the attenuation of light in blood prevents the blood in the centre of the lumen from participating in the heating process. It is shown that the commonly used optical dose in the range of 6–7 J cm^{-2} is expected to inflict vessel rupture rather than thermolysis in superficially located vessels. The present analysis might serve to draw guidelines for a protocol where the optical energy, wavelength and pulse length are optimized with respect to vessel diameter and depth in dermis.

INTRODUCTION

The principle of laser-induced photothermolysis is to inflict damage on microvessels of the skin in such a manner that the temperature of the surrounding normal dermis is maintained below the threshold for damage (1). Selectivity is obtained by using a wavelength corresponding to high absorption in blood, together with a pulse duration that allows heat to diffuse across the target structures. The selected wavelengths are usually 577 nm, which corresponds to an absorption peak in oxyhaemoglobin, or 585 nm, which is close to an isosbestic point in the absorption spectrum of haemoglobin and oxyhaemoglobin. The penetration depth in whole blood at these wavelengths is in the range of 30–50 μm (2,3).

The dimensions of the vessels vary over a range of 10–200 μm in diameter, but ectatic venules up to 300 μm are also found. The vessels are typically located at a depth from the skin surface of 200–300 μm and deeper. One study reports a mean vessel area of $2\text{--}4 \times 10^{-9} \text{ m}^2$ corresponding to a mean vessel diameter of 50–70 μm , and a wall thickness in the range of 4–6 μm (4).

The optimal response mechanism is assumed to be that heat deposited in the blood diffuses into the vessel wall inducing irreversible thermal damage. To minimize angiogenesis and regeneration, it is assumed optimal to induce thermal necrosis to the full thickness of the vessel wall rather than initiating vessel rupture.

In a study of 30 patients with a 0.45 ms long laser pulse at 585 nm wavelength, three groups

of responders have been identified: good responders (16 patients), with shallowly located medium-sized ectatic venules; moderate responders (eight patients), with medium-sized, but more deeply located, ectatic vessels; and poor responders (six patients), with an increased density of more normal-size vessels. The mean vessel diameter of the good and poor responders were, respectively, $36\ \mu\text{m}$ and $41\ \mu\text{m}$, whereas the size of their normal vessels were $14\ \mu\text{m}$ and $16\ \mu\text{m}$, respectively. The average size of the vessels in the port-wine stain lesion of the poor responders was $19\ \mu\text{m}$, ie only slightly larger than the value of $12\ \mu\text{m}$ for the neighbouring normal skin. The depth of the lesions from the epidermal/dermal junction for the good, moderate and poor responders were, respectively, $200\ \mu\text{m}$, $306\ \mu\text{m}$ and $263\ \mu\text{m}$. The vessel number density of the good and moderate responders were 25% and 9.5% higher than the corresponding values for normal skin, whereas the poor responders had 53% higher density (5).

The present work elucidates the observations in terms of mathematical modelling. The detailed structures of the port-wine stain vessels and the overlying dermis and epidermis vary, however, with different locations and patients. Further on, since the properties are not known, a priori, it is impossible to make an exact mathematical model. The aim of the present study, that is based on analytical solutions of the thermal and optical diffusion equations for a simplified and idealized geometry, is to obtain a qualitative understanding of the relative importance of the various parameters.

OPTICAL ABSORPTION IN BLOOD VESSELS

Scattering of light in blood is insignificant compared to absorption at wavelengths shorter than about 600 nm, where the reduced scattering coefficient is in the order of 1% of the absorption coefficient. The optical penetration depth, δ , ie the distance corresponding to a decrease in power by a factor of $1/e=0.37$, is therefore approximately equal to the inverse absorption coefficient. The absorption coefficients of whole blood of 80% oxygenation and 0.41 haematocrit, are $\mu_{a,b}=33\ \text{mm}^{-1}$ and $\mu_{a,b}=23\ \text{mm}^{-1}$ for, respectively, 577 nm and 585 nm wavelength. Corresponding optical penetration depths are $30\ \mu\text{m}$ and $43\ \mu\text{m}$ (6).

The absorbed optical power density, ie the power per unit volume, can, provided that the radial dimensions of the vessel are much less than the optical penetration depth, be expressed:

$$q=\mu_{a,b}\phi \quad (1)$$

where $\mu_{a,b}$ is the blood absorption coefficient and ϕ is the optical fluence rate at the site of the vessel.

The light distribution in vessels with comparable or larger diameters than the optical penetration depth will decay with distance from the irradiated perimeter. This phenomenon that gives the light distribution along a diameter of the vessel is shown in Fig. 1.

The asymmetric curves correspond to irradiation by a collimated beam (incident on the left hand side). The absorbed power density is normalized to unity at the surface and the density decays with distance in accordance with Beer's law (see equation A1). The symmetric curves give the distribution in the case of an isotropic light field of the same fluence rate as in the collimated case. The absorbed power density at the perimeter is always below unity because the part of the light that is transmitted through the blood is depleted. This phenomenon is insignificant in the case of smaller vessels as shown in Fig. 1(a), whereas the density drops by almost 50% in the case of vessels with a diameter larger than the optical penetration depth [see Fig. 1(c, d)]. The average absorbed power density, q_{av} , can then be expressed (see equation A4):

$$q_{av}=\mu_{a,b,eff}\phi_{per} \quad (2)$$

where $\mu_{a,b,eff}$ is an effective absorption coefficient and ϕ_{per} is the optical fluence rate at the perimeter. This effective absorption coefficient is dependent on vessel diameter as well as on wavelength and symmetry of the light field. However, the effect of symmetry is rather small as demonstrated in Fig. 2 (see equations A2 and A5).

The effect on wavelength is given in Fig. 3. The effective absorption coefficient is about the same as the ordinary absorption coefficient when the penetration depth is larger than the vessel diameter, ie for wavelengths in the 600–900 nm region (red/near-infra-red). However, in the 500–600 nm region (green/yellow), the difference is quite significant for a typical port-wine stain lesion with 20–100 μm vessels. The visual redness of a lesion is therefore not only dependent on the dermal volume blood

Fig. 1. Absorbed power density across the lumen of vessel of diameter (a) 10 μm , (b) 20 μm , (c) 40 μm and (d) 100 μm . Optical penetration depth of blood 40 μm .

Fig. 2. Effective absorption coefficient vs vessel diameter. ---, isotropic case; —, collimated case. Absorption coefficient $\mu_{a,b}=25\text{ mm}^{-1}$, ie penetration depth 40 μm .

Fig. 3. Effective absorption coefficient vs wavelength. —, capillaries; ---, 20 μm diameter vessels; ···, 50 μm diameter vessels; —·—, 100 μm diameter vessels. Haematocrit 0.41 and 80% oxygenation.

fraction and depth of the vessels, but also strongly dependent on the vessel size (see equation A5). The redness introduced if the blood is distributed in smaller vessels is significantly larger than if the same amount of blood had been distributed in larger vessels, eg in a 50 μm vessel, the effective absorption coefficient is only about 50% of the value when the erythrocytes are contained within capillaries.

HEATING OF BLOOD VESSELS

The heat absorbed in the blood will diffuse out of the lumen during and after the pulse. An estimate of the maximum heat flow to the wall can be found by assuming that the blood is heated instantaneously to about 100 $^{\circ}\text{C}$ when the laser pulse is applied, and that the blood is kept at this temperature during the rest of the pulse. The temperature distributions in the

Fig. 4. Temperature distribution in vessel wall (diameter $20\ \mu\text{m}$). —, continuous wave; ---, 1.5 ms pulse length; ···, 0.45 ms pulse length; —·—, 0.1 ms pulse length.

vessel wall at the end of 0.1, 0.45 and 1.5 ms long pulses are shown in Fig. 4, together with the steady-state distribution from a continuous wave laser. The blood perfusion is assumed to be about 10 times larger than the normal value of $\tau_{bl}=2 \times 10^3\ \text{s}$ (corresponding to $3\ \text{ml}\ 100\ \text{g}^{-1}\ \text{min}^{-1}$) (7) (see equations A7 and A8).

These results indicate that in the case of a 0.45 ms pulse, only the inner $5\text{--}7\ \mu\text{m}$ of the vessel wall is heated above the temperature required for thermal denaturation, i.e. $60\text{--}70^\circ\text{C}$, even when the blood is heated to the boiling point at the beginning of the pulse. Therefore, a complete thermal necrosis to the entire wall will only be obtained for a thickness less than about $5\ \mu\text{m}$. A complete thermal necrosis to a vessel wall thickness in the range of $10\text{--}20\ \mu\text{m}$ will require an exposure time longer than about $2\text{--}3\ \text{ms}$. The depth of necrosis represents, however, no limitation for the continuous laser case where the depth is determined by the thermal penetration depth of about $5\ \text{mm}$, but the selectivity of damaging the vessels is lost.

The lumen diameter and wall thickness of a typical arteriole are, respectively, $30\ \mu\text{m}$ and $20\ \mu\text{m}$, and the corresponding dimensions for a metarteriole are $35\ \mu\text{m}$ and $10\ \mu\text{m}$ (8). The perivascular temperature for an arteriole is thus expected to be significantly below the threshold for thermal necrosis, whereas the major part of the wall of a metarteriole will be damaged. Thus problems are anticipated of damaging ordinary arterioles. It will, on the other hand, be much easier to inflict damage to the venules; ordinary venules have a diameter and wall thickness of, respectively, $20\ \mu\text{m}$ and $2\ \mu\text{m}$, and the corresponding dimensions for

Fig. 5. Required in situ dose for heating the blood to the boiling point and to compensate for heat loss during the pulse. —, 585 nm and 0.45 ms; ---, 577 nm and 0.45 ms; ···, 585 nm and 0.1 ms; —·—, 577 nm and 0.1 ms.

collecting venules are $50\ \mu\text{m}$ and $5\ \mu\text{m}$. The port-wine stain vessels with an average vessel diameter and wall thickness of, respectively, $50\text{--}70\ \mu\text{m}$ and $4\text{--}6\ \mu\text{m}$ are expected to undergo thermal necrosis for a 0.45 ms long pulse, whereas a 0.1 ms long pulse should be adequate for thin-walled vessels with wall thickness less than $3\ \mu\text{m}$.

The optical fluence, Ψ , required to heat the blood to 100°C during the early part of the pulse and then compensate for the conduction loss during the entire pulse duration is illustrated in Fig. 5. Smaller vessels require higher fluence because the amount of heat needed to heat the wall then becomes a substantial fraction of the absorbed optical energy. Larger vessels also require a higher dose because the attenuation of light in blood prevents blood in the centre of the lumen from participating in the heating process. The curves are based on the mathematical model presented in equation A11. This model assumes that heat convection in blood equalizes thermal gradients across the lumen very efficiently; a thermal-diffusion-limited heat transport in the blood will result in a lower increase in the required fluence with increasing vessel diameter.

The required irradiant optical for heating of the vessels is not only dependent on the dimensions and depth of the vessels, but also on the optical properties of the skin. The calculated distribution of optical fluence vs distance from the skin surface is shown in Fig. 6 (6). These results are based on an analytical diffusion model of light distribution. The scattering coefficient and average cosine of the scattering

Fig. 6. Ratio between in situ fluence and irradiant fluence vs distance from skin surface (fair Caucasian skin). (a) 577 nm; (b) 585 nm. —, 1%; ---, 1%+4% (50 μm); ..., 1%+4% (20 μm).

angle of epidermis are $\mu_s = 25 \text{ mm}^{-1}$ and $g = 0.8$, respectively. The melanin absorption coefficient is averaged over the full thickness of the epidermis, and the values for fair Caucasian skin are $\mu_{a,m} = 1.05 \text{ mm}^{-1}$ and $\mu_{a,m} = 0.99 \text{ mm}^{-1}$ for, respectively, 577 nm and 585 nm wavelengths (6, 9, 10). The dermal scattering parameters are taken to be equal to those of the epidermis, whereas the absorption coefficient is assumed to be determined by the blood content. It is assumed that the absorption coefficient of the normal dermis corresponds to a blood fraction of 1%, ie $\mu_{a,d} = 0.01 \mu_{a,b}$. The simplified model used for Fig. 6 assumes that the port-wine stain region extends up to the dermal-epidermal junction. The additional absorption coefficient due to the ectatic venules is calculated for two cases; an additional blood fraction of 4% distributed in, respectively, vessels of 20 μm and 50 μm average diameter (see equation A5). The epidermal thickness was set at 100 μm and the index of refraction of skin was

Fig. 7. Required irradiant fluence (in J cm^{-2}) for heating of blood to 100 °C. Dermal blood fraction: 5% (1% distributed as in normal skin plus 4% in ectatic vessels of average diameter 50 μm). Pulse length: 0.45 ms. (a) 577 nm; (b) 585 nm.

set at $n = 1.4$. The upper curves in Fig. 6(a, b) correspond to normal skin, and the middle and lower curves correspond, respectively, to the 50 μm and the 20 μm cases.

On the basis of the light distribution model used in Fig. 6, the energy required to heat the blood can be expressed in terms of the irradiant dose. The required irradiant doses for heating the blood to 100 °C (see equation A11) are shown in Figs 7–9. All figures give the doses vs vessel diameter and vessel depth, and the horizontal planes correspond to the irradiant fluence required to heat the epidermis to the threshold damage temperature of 70 °C.

DISCUSSION

The results shown in Fig. 7 indicate that vessels of 40–60 μm diameter require minimum optical fluence in the case of a 0.45 ms long pulse. When the irradiant dose is limited to the epidermal damage threshold limit of 6 J cm^{-2} , the blood in these vessels will be heated to boiling point down to about 400 μm and 500 μm for, respectively, 577 nm and 585 nm wavelength. However, smaller vessels require a higher optical fluence because the energy

Fig. 8. Required irradiant fluence (in J cm^{-2}) for heating of blood to 100°C . Dermal blood fraction: 2% (1% distributed as in normal skin plus 1% in ectatic vessels of average diameter $50\ \mu\text{m}$). Pulse length: 0.45 ms. (a) 577 nm; (b) 585 nm.

needed to heat the vessel wall to a depth equal to the thermal diffusion length then becomes of the same magnitude as the energy required to heat the blood itself. A dose of $6\ \text{J cm}^{-2}$ will only destroy $10\ \mu\text{m}$ diameter vessels down to about $300\ \mu\text{m}$, and this depth is slightly smaller in the case of 585 nm than 577 nm. Larger vessels also require a higher dose because the energy absorbed in the centre of the vessels is reduced when the optical penetration depth becomes equal to or larger than the diameter. The discussed dose will destroy $150\ \mu\text{m}$ diameter vessels down to about $350\ \mu\text{m}$ and $450\ \mu\text{m}$ at, respectively, 577 nm and 585 nm.

The corresponding values in the case of a port-wine stain with a smaller blood fraction (2%) are shown in Fig. 8. The general tendency is the same as discussed in connection with Fig. 7, but the $6\ \text{J cm}^{-2}$ dose can now destroy $40\text{--}60\ \mu\text{m}$ diameter vessels down to about $700\ \mu\text{m}$ and $800\ \mu\text{m}$ depths for, respectively, 577 nm and 585 nm wavelength. However, small vessels still represent a problem, and $10\ \mu\text{m}$ vessels will only be destroyed down to about 50% of these depths. In fact, the capillaries that have diameters of about $4\ \mu\text{m}$ will hardly be damaged at all.

Fig. 9. Required irradiant fluence (in J cm^{-2}) for heating of blood to 100°C . Dermal blood fraction: 2% (1% distributed as in normal skin plus 1% in ectatic vessels of average diameter $50\ \mu\text{m}$). Pulse length: 0.1 ms. (a) 577 nm; (b) 585 nm.

A significant improvement can be achieved for the smaller vessels if the pulse length is reduced to 0.1 ms. This is illustrated in Fig. 9 which shows the same case as in Fig. 8 with the exception of the reduced pulse length. The vessel diameter that requires the minimum dose is now shifted to a smaller value, and $10\ \mu\text{m}$ diameter vessels can be destroyed down to about $700\ \mu\text{m}$ depth.

Reduction of the pulse length thus reduces the required optical dose for heating the blood. However, a proper thermolysis of the entire thickness of the wall requires that the diffusion length is equal to or larger than the wall thickness. The lumen diameter and wall thickness of typical arterioles are, as discussed previously, $30\ \mu\text{m}$ and $20\ \mu\text{m}$, respectively, and the corresponding dimensions for metarterioles are $35\ \mu\text{m}$ and $10\ \mu\text{m}$. The diffusion length for a 0.45 ms long pulse is thus smaller than the thickness of the arteriole wall. Therefore, only the inner part of the wall is expected to undergo thermolysis; the optimal pulse lengths for these vessels are in the range of 1–3 ms.

The situation is, however, quite different for the venules. Ordinary venules have a typical diameter and wall thickness of, respectively, $20\ \mu\text{m}$, and $2\ \mu\text{m}$, and the corresponding

dimensions of collecting venules are $50\text{ }\mu\text{m}$ and $5\text{ }\mu\text{m}$. The diffusion length of a 45 ms long pulse is therefore near optimal for the collecting venules. The required dose for thermolysis of smaller, thin-walled venules will, as discussed above, be reduced if the pulse is shortened. The required dose for a $15\text{ }\mu\text{m}$ diameter venule and a 0.1 ms long pulse at 585 nm is two-thirds of that for a 0.45 ms pulse. The reduced diffusion length for the 0.1 ms pulse, ie $4\text{ }\mu\text{m}$, is, however, still large enough to inflict thermolysis of the entire $2\text{ }\mu\text{m}$ thick wall. The dose can be reduced further to about 50% if the wavelength is also changed to 577 nm.

However, the depth of damage should not be the only criterion used for the dosimetry. The 6 J cm^{-2} , 0.45 ms, 585 nm dose that can damage 30–60 μm diameter vessels down to 400–500 μm depth in a typical port-wine stain, is about three times larger than the threshold value for the superficial vessels. The excess heat will initiate evaporation of the blood, and resulting vapour pressure might easily introduce rupture to thin-walled venules. Therefore, the dose can be too small to destroy deeply located small vessels, but, simultaneously, can be too high to ensure proper heating of the entire wall of superficial larger vessels.

In order to optimize thermolysis and minimize rupture, the optical dose should initially be reduced to a level that eliminates vapour pressure build-up in the most superficial ectatic venules. In the case of 30–100 μm diameter venules at a depth of 200 μm , this corresponds to an incident dose of about $2\text{--}3\text{ J cm}^{-2}$ at 585 nm wavelength and 0.45 ms pulse length. Deeper located vessels in the same lesion can be treated with subsequent treatments with increased optical dose; a dose of $5\text{--}6\text{ J cm}^{-2}$ is sufficient to treat vessels at 800 μm depth provided that regeneration of vessels in the previously treated upper regions are avoided. It is possible to increase the optical dose above the threshold damage level if the epidermis and the previously treated upper dermis is protected from thermal damage by selective cooling. Selectivity is obtained by taking advantage of the dynamics of the cooling process. A sudden cooling of the skin surface will create a cold region that expands into deeper dermal layers with time. The cold region propagates into the skin as a dispersive wave, and the time required to reach a certain depth is proportional to the square of the distance from the surface. The time delay before the

cold front propagates through the epidermis is about 50–100 ms, and the time required to reach a port-wine stain layer at, eg 2–300 μm depth, is in the order of 300–800 ms. Therefore, if the skin is appropriately cooled immediately prior to laser exposure, it is possible to protect the epidermis and upper dermis without affecting the temperature of the port-wine stain. This cooling can be done with a cryogen spray, eg with Freon 12, 134a or 22 (11).

Lesions with an abnormal density of small, deeply located thin-walled vessels can be treated more optimally with shorter pulses, eg a pulse of 0.1 ms length and 6 J cm^{-2} can destroy 5–15 μm diameter vessels down to 800 μm depth in a lesion with about 1% blood content.

In conclusion, proper treatment of port-wine stains requires a protocol where the optical energy, wavelength and pulse length are optimized with respect to vessel diameter and depth.

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Key words: Photothermolysis; Port-wine stains; Flashlamp-pumped dye laser; Mathematical modelling

APPENDIX

Vessel absorption

The spatial distribution of the absorbed power density is dependent on the light distribution. In the case of a collimated optical beam at normal incidence to the vessel wall, the distribution can be expressed:

$$q(x) = \mu_{a,b} \phi e^{-\mu_{a,b}x} \quad (\text{A1})$$

where x is the distance to the vessel surface along the direction of the beam, the blood absorption coefficient is $\mu_{a,b}$, and ϕ is the optical fluence rate. The fluence rate is defined as the total light flux falling on to an infinitesimally small sphere divided by the cross-sectional area of that sphere.

The corresponding average absorbed power density, q_{av} , can be found by integration of equation 1 over the cross-sectional area of the vessel. In the case of a collimated and uniform light distribution, this average density becomes:

$$\begin{aligned} q_{av} &= \phi \frac{\mu_{a,b}}{\pi a^2} \int_{y=-a}^a \int_{x=a-\sqrt{a^2-y^2}}^{x=a+\sqrt{a^2-y^2}} e^{-\mu_{a,b}x} dx dy \\ &= \frac{4\phi}{\pi a^2} e^{-\mu_{a,b}a} \int_0^a \sinh(\mu_{a,b}\sqrt{a^2-y^2}) dy \end{aligned} \quad (\text{A2})$$

where a is the vessel radius.

In an isotropic light field, the vessels will be irradiated from all directions. The net flux of diffuse optical photons propagating from the

highly scattering dermis into the highly absorbing blood can be expressed from a radiative type of boundary condition (6, 12, 13):

$$\begin{aligned} \frac{\phi}{4} - \frac{j}{2} &= 0 \\ \text{and} \\ \frac{\phi}{4} + \frac{j}{2} &= E \end{aligned} \quad (\text{A3})$$

The irradiation, E , at the surface of a vessel and the photon flux, j , into the blood-filled lumen are then given by $E=j=\phi/2$. The absorbed power density in the case of an isotropic and uniform light distribution on both sides of a parallel plane layer of blood of thickness $2a$ can be expressed:

$$q(x) = \mu_{a,b} \phi e^{-\mu_{a,b}a} \cosh(\mu_{a,b}x) \quad (\text{A4})$$

where x is the distance from the middle plane. This expression can also be used as an approximation in the case of cylindrical vessel where x is taken as the radial distance from the vessel axis.

The corresponding average density becomes:

$$q_{av} = \mu_{a,b} \frac{\phi}{2a} \int_0^{2a} e^{-\mu_{a,b}x} dx = \frac{\phi}{2a} (1 - e^{-\mu_{a,b}2a}) \quad (\text{A5})$$

This simple expression gives, as visualized in Fig. 2, a good approximation for the collimated case (see equation A2).

Thermal distribution

The bio-heat equation is given by (11):

$$\nabla^2 T - \frac{1}{\chi} \frac{\partial T}{\partial t} - \frac{1}{\chi} \frac{T}{\tau_{bl}} = -\frac{q}{\kappa} \quad (\text{A6})$$

where χ and κ are the thermal diffusivity and conductivity, respectively, τ_{bl} is the blood perfusion time, ie the time required to perfuse a volume of tissue with an equal amount of blood, and q is the power source density. The specific heat per unit volume is given by the ratio κ/χ .

The influence on thermal distribution by blood perfusion is, as follows from equation A6, only significant for time scales that are equal to or larger than the blood perfusion time. The perfusion time is in the order of several minutes. Therefore, the effect of contribution is insignificant for laser pulses of milliseconds duration.

The maximum heat delivered to the wall can be found by assuming that the blood is heated

instantaneously to about 100 °C when the laser pulse is applied, and that the blood is kept at this temperature during the rest of the

pulse. The temperature distribution at a time, t , after the initial heating can be expressed by equation A6 (13):

$$T = T_0 \left(1 + \frac{2}{\pi} \int_0^\infty \frac{J_0(\alpha r) Y_0(\alpha a) - J_0(\alpha a) Y_0(\alpha r)}{J_0^2(\alpha a) - Y_0^2(\alpha a)} \frac{e^{-\chi \alpha^2 t}}{\alpha} d\alpha \right) \quad (A7)$$

$$= T_0 \left(\sqrt{\frac{a}{r}} \operatorname{erfc} \left(\frac{r-a}{2\sqrt{\chi t}} \right) + \frac{(r-a)\sqrt{\chi t}}{4\sqrt{a r^3}} \left(\frac{1}{\sqrt{\pi}} e^{-\frac{(r-a)^2}{4\chi t}} - \frac{r-a}{2\sqrt{\chi t}} \operatorname{erfc} \left(\frac{r-a}{2\sqrt{\chi t}} \right) \right) + \dots \right)$$

where T_0 is the blood temperature rise and J_0 and Y_0 are the Bessel J and Y functions of zero order, respectively. The series expansion converges rapidly for short times, ie for $t < a^2/\chi$.

The validity of the result given in equation A7 is, however, limited to time scales that are much less than the blood perfusion time. In the case of very long time scales, ie for $t > \tau_{bb}$, the thermal distribution is determined by the blood perfusion. The corresponding steady-state value can be expressed from equation 6:

$$T = T_0 \frac{K_0 \left(\frac{r}{\delta_v} \right)}{K_0 \left(\frac{a}{\delta_v} \right)} \quad (A8)$$

where K_0 is the modified Bessel K -function of zero order and δ_v is the thermal penetration depth of skin. This parameter is defined by $\delta_v = \sqrt{\chi \tau_{bt}}$.

The thermal power transported out through the vessel wall for the case where the blood is instantaneously heated by an amount T_0 above normal tissue temperature, and then kept at this temperature can, for small values of the time, ie $t < a^2/\chi$, be expressed (equation A7):

$$P = -2\pi a \kappa \operatorname{grad} T|_{r=a}$$

$$= \frac{8\kappa T_0}{\pi} \int_0^\infty \frac{e^{-\chi \alpha^2 t}}{J_0^2(\alpha a) + Y_0^2(\alpha a)} \frac{d\alpha}{\alpha} \quad (A9)$$

$$= \kappa T_0 \left(\frac{2a\sqrt{\pi}}{\sqrt{\chi t}} + \pi - \frac{\sqrt{\pi \chi t}}{2a} + \frac{\pi \chi t}{4a^2} \dots \right)$$

where P is the power per unit length of the vessel.

The total energy transport out of the vessel energy for vessels satisfying $a > \sqrt{\chi t}$ is given by (equation A9):

$$W = \int_0^{\Delta t} P dt = \frac{\kappa}{\chi} 2\pi a T_0 \left(\frac{2}{\sqrt{\pi}} \sqrt{\chi t} + \frac{\chi t}{2a} - \frac{\sqrt{(\chi t)^3}}{6a^2 \sqrt{\pi}} + \frac{(\chi t)^2}{16a^3 \pi} + \dots \right) \quad (A10)$$

where W is the energy per unit length of the vessel that diffuses into the vessel wall.

The optical fluence, Ψ , required to heat the blood by an amount T_0 during the early part of the pulse and then compensate for the conduction loss during the entire pulse duration of Δt is (equations A5, A10):

$$\Psi = \frac{\frac{\kappa}{\chi} T_0 \pi a^2 + W}{\frac{1}{2a} (1 - e^{-\mu_a b^2 a}) \pi a^2} \quad (A11)$$

$$= \frac{\frac{\kappa}{\chi} T_0 2 \left(a + \frac{4}{\sqrt{\pi}} \sqrt{\chi \Delta t} + \frac{\chi \Delta t}{a} - \frac{\sqrt{(\chi \Delta t)^3}}{3a^2 \sqrt{\pi}} + \frac{(\chi \Delta t)^2}{8a^3 \pi} + \dots \right)}{(1 - e^{-\mu_a b^2 a})}$$

The expression in the nominator can, for cases where the vessel radius is much larger than $4/\pi \sqrt{\chi \Delta t}$, be approximated by the first two

terms, ie the thermal diffusion depth, d , into the vessel wall during the pulse is approximately given by $d \simeq 4/\pi \sqrt{\chi \Delta t} \simeq \sqrt{\chi \Delta t}$.