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NOTE

Modelling multiple laser pulses for port wine stain treatment

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Abstract. Many port wine stains (PWS) are still resistant to pulsed dye laser treatment. However, anecdotal information suggests that multiple-pulse laser irradiation improves patient outcome. Our aims in this note are to explain the underlying mechanism and estimate the possible thermal effects of multiple pulses in vascular structures typical of PWS. Based on linear response theory, the linear combination of two thermal contributions is responsible for the total increase in temperature in laser irradiated blood vessels: direct light absorption by blood and direct bilateral thermal heat conduction from adjacent blood vessels. The latter contribution to the increase in temperature in the targeted vessel can be significant, particularly if some adjacent vessels are in close proximity, such as in cases of optical shielding of the targeted vessel, or if the vessels are relatively distant but many in number. We present evidence that multiple-pulse laser irradiation targets blood vessels that are optically shielded by other vessels. Therefore, it may be a means of enhancing PWS therapy for lesions that fail to respond to single-pulse dye laser treatment.

1. Introduction

We have previously described a three-dimensional reconstruction of a port wine stain (PWS) which consisted of clusters of small (10 to 50 μm) blood vessels within 0.5 mm of the epidermal–dermal junction (Smithies *et al* 1997). This particular area of the (large) PWS was resistant to single-pulse dye laser treatment, possibly as a consequence of two synergistic factors: reduced light fluence available for the deeper dermal vessels and, hence, reduced absorption of light due to optical shielding from the more superficial vessels; and strong thermal cooling of the vessels in the clusters because of their small size.

Dierickx *et al* (1995a) reported in 12 PWS patients that up to 81 consecutive laser pulses delivered to exactly the same spot with a 10 s time interval between pulses improved therapeutic outcome (i.e. increased blanching). In particular, they reported a lower radiant exposure threshold for blanching and PWS clearing as compared with a single laser pulse. Our aims were to explain the underlying mechanism and estimate the possible thermal effects of multiple pulses on vascular structures representing the PWS, including clusters of vessels.

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2. Model

Consider a blood vessel represented as an infinitely long cylinder of diameter d in an infinite medium, which is homogeneous and isotropic. Using the approach of Anderson and Parrish (1981), and following the notation of Dierickx *et al* (1995b), we assume that a pulsed dye laser with an exposure duration of 0.5 ms, incident over the full length of the vessel, creates a Gaussian shaped radial temperature distribution immediately after exposure:

$$\Delta T(r, t) = \frac{\Delta}{1 + t/\tau} \exp\left(-\frac{2(r/d)^2}{1 + t/\tau}\right) \quad \tau = d^2/8\alpha. \quad (1)$$

Here, $\Delta T(r, t)$ denotes the temperature increase at coordinate r from the vessel centre at time t after the end of the laser pulse, Δ is the maximum temperature increase in the centre of the vessel immediately after the laser pulse, τ the thermal relaxation time of a blood vessel of diameter d (Anderson and Parrish 1981) and α is the thermal diffusivity of the medium. Equation (1) is the Green's function solution of one-dimensional radial temperature diffusion in response to a line source of infinite temperature, here applied at $t = -\tau$ s. We emphasize that equation (1) is not the true temperature distribution immediately after the laser pulse, because the blood vessel is usually irradiated from one side, so the fluence is not exactly radially symmetric. However, at longer times or larger radial distances, it is likely to be an excellent approximation. We neglected cooling due to blood flow because perfusion ceases following laser coagulation of targeted blood vessels.

2.1. Two parallel blood vessels at distance D

We assume that the two parallel blood vessels, labelled as 'zero' and 'one', are identical in size but have different maximal increases in temperature Δ_0 and Δ_1 immediately after the laser pulse due to different local fluences, for example because of optical shielding due to other, more superficial, blood vessels. The total temperature distribution in each blood vessel then consists of a linear combination of two terms: (a) its own increase in temperature due to the laser pulse and (b) the increase in temperature due to thermal heat conduction from the adjacent vessel. For the 'zeroth' vessel the two contributions are respectively given by equation (1) at $r = 0$, and by equation (1) at $r = D$. Using $\Delta T_{\text{tot}}(0, t)$ to denote the total increase in temperature at the centre of the 'zeroth' vessel, the result is

$$\Delta T_{\text{tot}}(0, t) = \frac{\Delta_0}{1 + t/\tau} + \frac{\Delta_1}{1 + t/\tau} \exp\left(-\frac{2(r/d)^2}{1 + t/\tau}\right) \equiv \Delta T(0, t) + \Delta T(D, t). \quad (2)$$

Linearity of thermal heat conduction forces the overall thermal response in the centre of the zeroth vessel, at $r = 0$, to be a linear combination of the individual Green's functions of each vessel at $r = 0$. This implies, for example, that the component of increase in temperature rise in the first vessel, which results from heat diffusion from the zeroth vessel, does *not* contribute to heat diffusion in the opposite direction, from the first to the zeroth vessel and, consequently, does *not* contribute to $\Delta T_{\text{tot}}(0, t)$. This principle is based on the simple concept that heat conduction cannot alter its direction of propagation.

2.2. N parallel blood vessels at distance D_i ($i = 1$ to N) from the central vessel at $r = 0$

Similar to equation (2), the total increase in temperature in the centre ($r = 0$) of the central, zeroth, vessel is

$$\Delta T_{\text{tot}}(0, t) = \Delta T(0, t) + \sum_{i=1}^N \Delta T(D_i, t) \quad (3a)$$

Figure 1. Increase in temperature (arbitrary units) in the centre of the central blood vessel as a function of time. Thick curve: according to equation (1), for a single central blood vessel of diameter $d = 0.05$ mm located parallel to the air–skin interface, using $\Delta = 1^\circ\text{C}$, labelled by $\Delta T(0, t)$. Dashed curve: the effect of thermal heat propagation from $N = 6$ identical blood vessels located parallel to the air–skin interface, $d = 0.05$ mm, at equal distance ($D_i = 0.1$ mm) from the central vessel, according to equation (3a) with $\Delta_i = 1^\circ\text{C}$, or $\sum_{i=1}^6 \Delta T(D_i, t) = 6\Delta T(0.1 \text{ mm}, t)$, labelled by $6\Delta T(0.1 \text{ mm}, t)$. Dotted curve: similarly, for 12 such vessels surrounding the central vessel at equal distance ($D_i = 0.2$ mm), or $\sum_{i=1}^{12} \Delta T(D_i, t) = 12\Delta T(0.2 \text{ mm}, t)$, labelled by $12\Delta T(0.2 \text{ mm}, t)$. Medium thick curve: the total increase in temperature in the central vessel, $\Delta T_{\text{tot}}(0, t)$, equation (3a). Here, $\tau = 2.84$ ms for all vessels.

where $\Delta T(0, t)$ is defined as in equation (2) and $\Delta T(D_i, t)$ is the component of increase in temperature in the central vessel which results from heat diffusion from the i th vessel, at distance D_i , defined as

$$\Delta T(D_i, t) = \frac{\Delta_i}{1 + t/\tau_i} \exp\left(-\frac{2(D_i/d_i)^2}{1 + t/\tau_i}\right). \quad (3b)$$

Figure 1 shows the temperature behaviour at $r = 0$ after a single pulse, equation (1), as well as the sum of the contributions to $\Delta T_{\text{tot}}(0, t)$ from six vessels at equal distance from the central vessel of $D_i = 0.1$ mm, $i = 1$ to 6, and 12 vessels at equal distance $D_i = 0.2$ mm, $i = 7$ to 18. All vessels have a diameter $d_i = 0.05$ mm and $\Delta_i = 1^\circ\text{C}$. From equation (1), the thermal relaxation time is $\tau = 2.84$ ms for all vessels, using $\alpha = 1.1 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$. We emphasize that the results for smaller or larger values of d are very similar to those of figure 1 (results not shown).

Obviously, heat exchange also occurs between the other laser heated vessels. According to equation (3a), the total increase in temperature $\Delta T_{\text{tot}}(r_k, t)$, in the k th vessel, at arbitrary position $r = r_k$, within a distribution of N other parallel vessels, follows from

$$\Delta T_{\text{tot}}(r_k, t) = \frac{\Delta_k}{1 + t/\tau_k} + \sum_{i=1}^N \frac{\Delta_i}{1 + t/\tau_i} \exp\left(-\frac{2(D_{ik}/d_i)^2}{1 + t/\tau_i}\right) \quad i \neq k. \quad (3c)$$

The first term on the right-hand side (RHS) represents the increase in temperature in the targeted k th vessel due to direct laser light absorption; the second terms on the RHS are the components of increase in temperature in the k th vessel which result from heat conduction from all other vessels, at distances D_{ik} .

Again, equations (3a) and (3c) constitute the sum of individual Green's functions of each vessel at positions $r = 0$ and $r = r_k$, respectively. We recall that the temperature contribution

of all other vessels to the total increase in temperature in the targeted vessel is through direct bilateral heat conduction only, and not through heat conduction via other vessels, because heat conduction in a homogeneous medium cannot change its direction of propagation.

2.3. Multiple pulses on N parallel blood vessels at distance D_i ($i = 1$ to N) from a central vessel

Equations (3a) and (3b) represent the total increase in temperature in the central, zeroth, vessel in response to the first laser pulse. Assuming that the pulses are separated by a time interval t_p (s), two laser pulses give a total increase in temperature of

$$\Delta T_{\text{tot}}(0, t) = \left(\Delta T(0, t) + \sum_{i=1}^N \Delta T(D_i, t) \right) + \left(\Delta T(0, t - t_p) + \sum_{i=1}^N \Delta T(D_i, t - t_p) \right). \quad (4)$$

The two expressions within large brackets denote the individual Green's function thermal response of each vessel to the first and second pulses respectively. Similarly, for M pulses, we have

$$\begin{aligned} \Delta T_{\text{tot}}(0, t) = & \left(\Delta T(0, t) + \sum_{i=1}^N \Delta T(D_i, t) \right) + \left(\Delta T(0, t - t_p) + \sum_{i=1}^N \Delta T(D_i, t - t_p) \right) \\ & + \left(\Delta T(0, t - 2t_p) + \sum_{i=1}^N \Delta T(D_i, t - 2t_p) \right) + \dots \\ & + \left(\Delta T(0, t - (M-1)t_p) + \sum_{i=1}^N \Delta T(D_i, t - (M-1)t_p) \right). \end{aligned} \quad (5)$$

From equation (3c) it is straightforward to derive the temperature response to multiple pulses in the k th vessel, replacing $r = 0$ in equation (5) by $r = r_k$, and D_i by D_{ik} , where $i \neq k$.

We emphasize that equation (5) is the exact expression for temperature response, subject to the validity of our assumptions and linear response theory. We also performed numerical finite difference simulations, and found no differences between the numerical and analytical results.

3. Results

Figure 2 shows schematically the anatomy of a cluster of parallel blood vessels, consisting of six vessels surrounding a central vessel. We chose identical vessels of diameter $d = 0.05$ mm, representative of typical PWS vessels (Barsky *et al* 1980, Dierickx *et al* 1995b), at distance $D_i = 0.1$ mm horizontally below the air-skin interface. We assume an unequal light fluence distribution, resulting in different values for Δ_i of each vessel, chosen as indicated in figure 2. Our choice mimics optical shielding of the central vessel by all surrounding vessels, hence, laser irradiation produces the smallest increase in temperature in the central vessel. Figure 2 shows the predicted increase in temperature for a series of consecutive pulses at time intervals of $t_p = 7$ ms. Although the central vessel has the lowest (chosen) increase in temperature of 18°C immediately after a laser pulse, versus 25°C in two of the peripheral vessels, its rate of temperature decay following each pulse is slower, as a result of cumulative thermal heat propagation from all other vessels. Hence, the temperature just before each laser pulse increases more rapidly in the central vessel as opposed to the outer vessels, achieving equal maximal temperatures at the seventh pulse.

Figure 3 shows results in a PWS model consisting of a network of 'vertical' blood vessels, of $d = 0.05$ mm, perpendicular to the air-skin interface. For convenience, although not

Figure 2. Increases in temperature in the central (C) and one peripheral (P) vessel of a cluster of six parallel vessels surrounding the central vessel, all located horizontally below the air–skin interface as indicated in the pictogram. Equation (5) was used for the results of the central vessel, whereas the predictions of the peripheral vessel were based on equation (3c). All peripheral vessels have equal distance $D_i = 0.1$ mm from the central vessel. Vessel diameters are $d_i = 0.05$ mm, so $\tau = 2.84$ ms for all vessels. Values chosen for Δ_0 (central vessel) and the Δ_i s (peripheral vessels) are indicated in the pictogram, mimicking different fluence distributions due to optical shielding from all other vessels. The time interval between consecutive pulses is $t_p = 7$ ms.

Figure 3. Increase in temperature in the central vessel of a PWS model (thin lines), consisting of a central vessel, $d = 0.05$ mm, surrounded by 18 concentric rings of blood vessels, all located vertically with respect to the air–skin interface. The k th ring has radius kD , where $D = 0.2$ mm, and contains $6k$ vessels regularly distributed along the circumference. Thick lines: temperatures from multiple pulses of one single vessel not surrounded by other vessels. (A) Time interval $t_p = 10$ s. (B) Time interval $t_p = 1$ s.

required in our formulation, we distributed the vessels in concentric rings around the central vessel, to simplify the computations. The rings are separated by 0.2 mm from each other, mimicking the basal layer's reticular periodic pattern. Each ring contains a multiple of six vertical blood vessels, i.e. the first ring has six vessels, the second has 12, the third 18, and the

k th ring has $6k$ vessels. We assumed that 18 of those rings were homogeneously laser irradiated, hence we used a laser spot size of $18 \times 0.2 \times 2 = 7.2$ mm diameter. The temperature predictions for two different pulse sequences are shown in figures 3A and B, where figure 3A replicates a condition used by Dierickx *et al* (1995a), i.e. 16 pulses at $t_p = 10$ s time interval.

4. Discussion

We have shown that in response to pulsed laser irradiation the temperature of a targeted blood vessel can be significantly increased if adjacent blood vessels are heated simultaneously. This linear response mechanism of propagation of thermal heat conduction from the concentric rings of blood vessels to the central vessel predicts a continuous increase of (a) the maximum temperature at the end of a laser pulse and (b) the same increase in temperature of the dermal volume. The latter dermal heating implies that the concept of selective photothermolysis becomes at risk at the dermal level. These predictions may therefore explain Dierickx *et al*'s observations that ulceration could occur at the site of irradiation if epidermal cooling was not applied, and good PWS blanching with multiple pulses at lower radiant exposures than with single pulses if conductive cooling was applied (Dierickx *et al* 1995a). Our predictions also suggest that shorter times between pulses, for example of 1 s (figure 3B), cause a more rapid increase in temperature.

An obvious question to be addressed is whether one higher-energy single pulse and multiple pulses of lower energy will produce identical thermal effects. Here, we propose that differences exist, with favourable effects produced by multiple pulses. First, multiple pulses at proper repetition rates particularly favour the increase in temperature of vessels that are optically shielded by adjacent surrounding vessels (figure 2). Obviously, blood vessels which can influence each other optically, producing shading effects, will influence each other thermally, because the multiple thermal heating propagating from the neighbouring vessels is likely to be significant (figure 1). Second, in a PWS the heat propagating from the concentric rings of heated blood vessels is likely to increase the dermal temperature more homogeneously than would be possible by the light distribution from a single laser pulse, which decreases exponentially with skin depth during the pulse. Therefore, multiple pulses will favour damage to PWS blood vessels where the fluence rate is reduced because of optical shielding from other vessels, i.e. those in a cluster and deeper dermal vessels. We hypothesize that if inadequate heating of shielded and deeper vessels is the primary cause of failure of PWS treatment with single-pulse laser therapy, multiple pulses may achieve a favourable outcome because of the higher temperatures attained in such vessels. However, multiple pulses and preheating of the dermis, for example by infrared laser irradiation from an Nd-YAG laser at 1064 nm wavelength as modelled by Stureson and Andersson-Engels (1996), will produce identical effects, except when clusters of vessels are present instead of single vertical vessels, and repetition rates similar to those simulated in figure 2 are technically possible. Furthermore, the lower radiant exposure threshold for clinical response and clearing by multiple-pulse therapy may allow either a larger spot size or, using current radiant exposure values, deeper therapeutic effects.

In conclusion, we have presented evidence that multiple-pulse laser irradiation favours blood vessels that are optically shielded by other vessels. Therefore, it may be an alternative therapy for PWS that fail to respond to single-pulse dye laser treatment.

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