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A theoretical study of the thermal response of skin to cryogen spray cooling and pulsed laser irradiation: implications for treatment of port wine stain birthmarks

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Abstract. The successful treatment of port wine stain (PWS) patients undergoing laser therapy is based on selective thermal coagulation of blood vessels without damaging the normal overlying epidermis. Cryogen spray cooling of skin may offer an effective method for minimizing epidermal thermal injury. Inasmuch as the density of melanosomes and depth of PWS blood vessels can vary considerably, an optimum cooling strategy is required on an individual patient basis. We present a theoretical study of the thermal response of various pigmented PWS lesions to spray cooling in conjunction with flashlamp-pumped pulsed dye laser irradiation (585 nm). Results of our model indicate that precooling of skin using tetrafluoroethane as the cryogen spray is sufficient to eliminate epidermal thermal injury when using incident fluences less than 10 J cm^{-2} and 8 J cm^{-2} on patients with intermediate and high epidermal melanin content, respectively. Cryogens that have lower boiling points than tetrafluoroethane may allow successful treatment when using fluences equal to or greater than those indicated.

1. Introduction

Successful laser treatment of port wine stain (PWS) birthmarks is based on selective photothermolysis whereby absorption of the laser light by haemoglobin in PWS blood vessels results in irreversible thermal injury (Anderson and Parrish 1983). The ideal laser treatment should cause irreversible laser injury to the PWS blood vessels without damaging the overlying epidermis. Unfortunately, the native epidermal melanin acts as an 'optical shield' that absorbs the laser light and reduces the heat generated in PWS blood vessels.

In recent years, cooling of skin has been used as a technique for preventing thermal injury to epidermis. One method has involved use of ice or chilled water prior to or during laser irradiation (Gilchrest *et al* 1982, Dreno *et al* 1985). Although epidermal thermal injury has been reported to be prevented with use of these cooling methods, deeper layers of skin including PWS blood vessels may also be cooled and as a result remain resistant to photothermolysis (Nelson *et al* 1995a). Therefore, an appropriate cooling and irradiation method should cool selectively the epidermal layer but allow photocoagulation of deeper PWS blood vessels.

Evaporation of a cryogen sprayed on skin has been shown to provide a mechanism for selectively cooling the skin, whereby the degree and spatial distribution of cooling

within skin can be achieved in a controlled manner by adjusting the cryogen spurt duration (Anvari *et al* 1995). Transient temperature reductions of the order of 30–40 °C have been achieved on the skin surface in 5–80 ms using tetrafluoroethane ($C_2H_2F_4$; b.p. = -25 °C, an environmentally compatible, non-toxic, and non-flammable freon substitute) as a cryogenic spray.

Encouraging preliminary clinical results in PWS patients have been reported by spraying the skin with millisecond spurts of tetrafluoroethane in conjunction with pulsed dye laser irradiation (Nelson *et al* 1995a, b). Nevertheless, the optimum cooling strategy needs to be determined on individual patient basis as density of melanosomes as well as depth of the PWS blood vessels vary considerably. We present a theoretical study of the thermal response of skin resulting from spray cooling in conjunction with temperature increases due to pulsed laser irradiation for various pigmented PWS lesions. In particular, we calculate temperature distributions within skin when precooling the skin with a cryogen spray prior to laser irradiation as well as cooling it during and after laser irradiation, and compare the results with the temperature distribution obtained in the absence of cooling. Results of this study can be used as a guide to select the optimum cooling strategy in clinical studies of treatment of PWS birthmarks on an individual patient basis.

2. Theory

2.1. Assumptions

(i) We classify PWSs into three categories based on the epidermal melanin content and on the depth of the PWS (Barsky *et al* 1980). Category I is defined as a thin PWS (200 μm thickness) below an epidermis with low melanin content. Category II is a thick PWS (700–850 μm thickness) below an epidermis with intermediate melanin content (corresponding to an olive complexion). Category III is a thick PWS below an epidermis with high melanin content (corresponding to a black complexion). Each category of PWS is divided into two subclasses: (A) superficial, where the depth of the most superficial dermis–PWS interface is 150 μm below the surface of skin, and (B) deep, where the depth of the most superficial dermis–PWS interface is at 300 μm .

(ii) We represent skin by a one dimensional, semi-infinite medium and model the effect of laser irradiation by assuming an instantaneous deposition of energy that induces temperature increases at skin locations where light is absorbed by (a) melanin within epidermis and (b) blood within PWS vessels. This simplified representation of conversion of laser energy into heat generation within the skin does not explicitly take into account the laser light distribution within the tissue (van Gemert *et al* 1986, Jacques and Prahl 1987, Keijzer *et al* 1989, Miller and Veitch 1993). However, we assume laser-induced initial temperature distributions that are consistent with predicted temperature rises based on pulsed photothermal radiometry (PPTR) of PWS lesions (Milner *et al* 1995).

We assume that at $t = t_{\text{laser}}$, the time when laser energy is deposited, the instantaneous temperature rise due to light absorption by melanin is constant over the epidermis. This assumption is based on the belief that in the region near the surface where melanin absorption takes place, optical backscatter of laser light induces a nearly uniform temperature rise (van Gemert *et al* 1991, Verkruijsse *et al* 1993). We assume that at $t = t_{\text{laser}}$, the temperature distribution within the PWS layer decreases exponentially with depth with an effective blood absorption coefficient μ_a^{blood} (m^{-1}) for a dermis composed of $p\%$ blood by volume (Milner *et al* 1995). The reduced scattering coefficient within the PWS layer can be neglected since it is much smaller than the absorption coefficient at 585 nm (Verkruijsse *et al* 1993).

Laser-induced temperature rises in one dimension are given by

$$\Delta T(z, t_{\text{laser}}) = \begin{cases} \Delta T_{0,\text{epidermal}} & \text{for } z_1 \leq z \leq z_2 \\ (\Delta T_{0,\text{PWS}}/f_{\text{area}})e^{[-\mu(z-z_3)]} & \text{for } z_3 \leq z \leq z_4 \\ 0 & \text{for all other } z \end{cases} \quad (1)$$

where positions z_1 and z_2 define the interval over which epidermal melanin absorption takes place, z_3 and z_4 define the interval where blood absorption takes place (i.e., the region within the skin where the PWS is located) (figure 1), $\Delta T_{0,\text{epidermal}}$ ($^{\circ}\text{C}$) is the epidermal temperature rise due to melanin absorption, $\Delta T_{0,\text{PWS}}$ is the average temperature rise at the most superficial dermis-PWS interface (z_3), and f_{area} is the fractional vascular area in a plane parallel to the skin-air interface. It is related to the fractional vascular volume, f_{vol} , (dermis volume fraction composed of PWS), as $f_{\text{area}} \approx (f_{\text{vol}})^{2/3}$ and is assumed to be independent of depth.

Figure 1. A schematic diagram of skin structure in the model and assumed laser-induced temperature distributions in PWS skin (figure not drawn to scale).

Assuming that the laser pulse is sufficiently short (e.g., $\approx 450 \mu\text{s}$) that there is no significant heat diffusion during the irradiation time, the epidermal temperature rise at the

end of the laser pulse is computed as (Anderson *et al* 1989)

$$\Delta T_{0,epidermal} = \frac{E_0 \mu_a^{epidermal}}{\rho c} \left[1 + 2 \frac{1 + r_i}{1 - r_i} R_d \right] \quad (2)$$

where E_0 (J m^{-2}) is the incident laser fluence, $\mu_a^{epidermal}$ (m^{-1}) is the epidermal absorption coefficient (e.g., 500, 1800, and 2700 m^{-1} at 585 nm corresponding to types I, II, and III, respectively) (Svaasand *et al* 1995), ρ is the density (kg m^{-3}), c is the specific heat capacity ($\text{J kg}^{-1} \text{ }^\circ\text{C}^{-1}$), r_i is the averaged internal reflectance at the air-tissue interface, and R_d is the diffuse reflectance resulting from light that enters the tissue, is scattered, and subsequently reemerges from the tissue, and can be approximated as (Jacques *et al* 1993)

$$R_d = e^{-78 \mu_a^{epidermal}} \quad (3)$$

From diffusion theory, the optical penetration depth, δ , is calculated as

$$\delta = 1 / \sqrt{3 \mu_a [\mu_a + \mu_s (1 - g)]} \quad (4)$$

where μ_s is the scattering coefficient (e.g., $47\,000 \text{ m}^{-1}$ for epidermis at 585 nm), and g is the anisotropy factor (e.g., 0.79 for epidermis at 585 nm) (Verkruijsse *et al* 1993). For example, with an incident fluence of 7 J cm^{-2} and assuming minimal loss of optical fluence within a thin $10 \text{ }\mu\text{m}$ stratum corneum, the term $2(1 + r_i)/(1 - r_i) = 7.1$ (Jacques *et al* 1993), and the term $\rho c = 3.76 \times 10^6 \text{ J m}^{-3} \text{ }^\circ\text{C}^{-1}$ for tissue with 75% water content by weight (Jacques *et al* 1993), $\Delta T_{0,epidermal}$ is $82 \text{ }^\circ\text{C}$ for a category II PWS.

We calculate $\Delta T_{0,PWS}$ in a similar manner as calculating $\Delta T_{0,epidermal}$ except that we assume matched refractive indices at dermis-PWS interface so that

$$\Delta T_{0,PWS} = E(z = z_3) \mu_a^{blood} / \rho c. \quad (5)$$

We estimate the value of fluence at the most superficial dermis-PWS interface (i.e., $E(z = z_3)$) by assuming that incident fluence, E_0 , attenuates exponentially ($e^{-z/\delta}$) within the epidermis and dermis before reaching the dermis-PWS interface. For example, for an incident fluence of 7 J cm^{-2} on a category IIA PWS, values of E at epidermis-dermis interface, ($E(z = z_2)$), and at dermis-PWS interface, ($E(z = z_3)$) are 5.1 and 4.3 J cm^{-2} , respectively. With an effective blood absorption coefficient of 1900 m^{-1} at 585 nm, corresponding to fractional vascular volume, $f_{vol} = 0.1$ (Verkruijsse *et al* 1993) reported optical properties for dermis ($\mu_a = 220 \text{ m}^{-1}$, $\mu_s = 20\,500 \text{ m}^{-1}$, and $g = 0.79$ at 585 nm) (Verkruijsse *et al* 1993), $f_{area} = (0.1)^{2/3} \approx 0.21$, and the previously given laser parameter, $\Delta T_{0,PWS}/f_{area} = 103 \text{ }^\circ\text{C}$ for a category IIA PWS.

(iii) We assume cooling starts at $t = 0$ and represent the thermal boundary condition at the skin surface as

$$\kappa \frac{\partial T(z, t)}{\partial z} \Big|_{z=0} = \begin{cases} h[T_\infty - T(0, t)] & \text{for } t \leq \tau \\ 0 & \text{for } t > \tau \end{cases} \quad (6)$$

where κ ($\text{W m}^{-1} \text{ K}^{-1}$) is the thermal conductivity of skin ($0.45 \text{ W m}^{-1} \text{ K}^{-1}$) (Duck 1990), T ($^\circ\text{C}$) is the temperature within the skin, z (m) is the distance into the skin (with the origin at the skin surface), t (s) is the time, h ($\text{W m}^{-2} \text{ K}^{-1}$) is the heat transfer coefficient, and T_∞ ($^\circ\text{C}$) is the temperature of the resulting cryogen-ice film (formed as a result of water condensation) at the skin surface during the cryogen spurt, τ . The value of h has been determined experimentally to be about $40\,000 \text{ W m}^{-2} \text{ K}^{-1}$ (Anvari *et al* 1995), and is assumed here to be constant during the cryogen spurt. With tetrafluoroethane as the cryogen spray, T_∞ ($^\circ\text{C}$) is measured to be about $-10 \text{ }^\circ\text{C}$, and is assumed to be constant.

The boundary condition during the spurt represents the presence of the evaporating cryogen on skin surface. Once the cryogen is turned off, we assume an insulated boundary (i.e., $h = 0$) as most of the cryogen has evaporated shortly after the spurt.

2.2. Cooling modalities

We consider two distinct cooling modalities and compare the resulting temperature distributions with those in the absence of cooling. In the first modality, cooling is restricted to the time prior to laser energy deposition, whereas in the second modality, cooling continues for a limited time following laser irradiation. In both modalities, temperatures within skin at any time are calculated by solving the heat conduction equation. With uniform thermal properties and effects of blood perfusion neglected, the heat conduction equation becomes

$$\partial^2 T(z, t) / \partial z^2 = (1/\alpha) \partial T(z, t) / \partial t \quad (7)$$

where α is the thermal diffusivity of skin ($1.1 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$) (Duck 1990). Solutions to equation (7) for both cooling modalities against no cooling are analysed.

2.2.1. The thermal response with no cooling. The solution of equation (7) with the initial temperature distributions (1) is the sum of the responses to epidermal and PWS temperature rises:

$$\Delta T(z, t > t_{\text{laser}}) = \Delta T_{\text{epidermal}}(z, t > t_{\text{laser}}) + \Delta T_{\text{PWS}}(z, t > t_{\text{laser}}) \quad (8)$$

where $\Delta T_{\text{epidermal}}(z, t > t_{\text{laser}})$ and $\Delta T_{\text{PWS}}(z, t > t_{\text{laser}})$ are the respective thermal responses due to absorption of laser light in epidermis and PWS blood vessels. For an insulated boundary, (i.e., $h = 0$), they are given as (see appendix A)

$$\Delta T_{\text{epidermal}}(z, t > t_{\text{laser}}) = (\Delta T_{0, \text{epidermal}}/2) \{ \text{erf}(\tilde{Z}_i - \tilde{Z}) + \text{erf}(\tilde{Z}_i + \tilde{Z}) \}_{\tilde{Z}_i = \tilde{Z}_1}^{\tilde{Z}_i = \tilde{Z}_2} \quad (9a)$$

and

$$\begin{aligned} \Delta T_{\text{PWS}}(z, t > t_{\text{laser}}) = & (\Delta T_{0, \text{PWS}}/2f_{\text{area}}) e^{2\tilde{M}\tilde{Z}_3 + \tilde{M}^2} \{ e^{-2\tilde{M}\tilde{Z}} \text{erf}(\tilde{Z}_i - \tilde{Z} + \tilde{M}) \\ & + e^{2\tilde{M}\tilde{Z}} \text{erf}(\tilde{Z}_i + \tilde{Z} + \tilde{M}) \}_{\tilde{Z}_i = \tilde{Z}_3}^{\tilde{Z}_i = \tilde{Z}_4} \end{aligned} \quad (9b)$$

where

$$\tilde{Z} = z/2\sqrt{\alpha(t - t_{\text{laser}})} \quad \tilde{M} = \mu_a^{\text{blood}} \sqrt{\alpha(t - t_{\text{laser}})}. \quad (10)$$

2.2.2. Thermal response with precooling and no postcooling. In this modality, spraying is restricted to the time prior to deposition of the laser energy and the laser pulse is applied immediately after the cryogen spurt. With a uniform initial temperature distribution, $T_0 = 30^\circ\text{C}$ (before cooling), the solution to equation (7) with boundary condition (6) is (Carslaw and Jaeger 1959)

$$\Delta T_{\text{cooling}}(z, t < t_{\text{laser}}) = (T_\infty - T_0) \{ \text{erfc}(\tilde{z}) - [e^{-\tilde{z}^2} \text{erfc} x(\tilde{h} + \tilde{z})] \} \quad (11)$$

where

$$\tilde{z} = z/2\sqrt{\alpha t} \quad \tilde{h} = (h/k)\sqrt{\alpha t} \quad (12)$$

and $\text{erfc} x(\tilde{x})$ is a short-hand notation for $e^{(\tilde{x})^2} \text{erfc}(\tilde{x})$ with $\text{erfc}(\tilde{x})$ being the complementary error function, $1 - \text{erf}(\tilde{x})$.

Equation (11) gives the temperature distribution within skin before the laser energy is deposited. Since an analytical solution to equation (7) with an initial temperature distribution given in (11) (before laser irradiation) is not readily obtainable, we approximate the initial temperature distribution (11) with an exponential function, $T_s e^{-kz}$, and choose k so that

$$\int_0^\infty |\Delta T_{cooling}^{exact}(z) - \Delta T_{cooling}^{approximate}(z)| dz \leq 0.01 \left| \int_0^\infty \Delta T_{cooling}^{exact}(z) dz \right|. \quad (13)$$

Temperature distributions following the laser energy deposition are then obtained by superposition of the thermal response due to cooling, and laser-induced epidermal and PWS temperature changes:

$$\Delta T(z, t > t_{laser}) = \Delta T_{cooling}(z, t > t_{laser}) + \Delta T_{epidermal}(z, t > t_{laser}) + \Delta T_{PWS}(z, t > t_{laser}) \quad (14)$$

where (see appendix A)

$$\Delta T_{cooling}(z, t > t_{laser}) = (\Delta T_s e^{-\tilde{z}^2/2}) [\operatorname{erfc} x(\tilde{K} + \tilde{z}) + \operatorname{erfc} x(\tilde{K} - \tilde{z})] \quad (15)$$

ΔT_s is the change in surface temperature at the end of the cryogen spurt and $\tilde{K} = k\sqrt{\alpha(t - t_{laser})}$. Expressions for $\Delta T_{epidermal}(z, t > t_{laser})$ and $\Delta T_{PWS}(z, t > t_{laser})$ are given in (9a) and (9b), respectively.

2.2.3. The thermal response with precooling and postcooling. In this modality, cryogen spraying continues after laser irradiation. The thermal response in skin after laser irradiation is obtained by superposition of responses due to spray cooling, epidermal heating, and PWS heating (equation (14)). The expression for $\Delta T_{cooling}(z, t)$ is given in equation (11); expressions for $\Delta T_{epidermal}(z, t > t_{laser})$ and $\Delta T_{PWS}(z, t > t_{laser})$ are now given as (see appendix B)

$$\Delta T_{epidermal}(z, t > t_{laser}) = \Delta T_{0,epidermal} \left\{ \frac{1}{2} [\operatorname{erf}(\tilde{Z}_i - \tilde{Z}) - \operatorname{erf}(\tilde{Z}_i - \tilde{Z})] - e^{-(\tilde{Z} + \tilde{Z}_i)^2} \operatorname{erfc} x(\tilde{H} + \tilde{Z} + \tilde{Z}_i) \right\}_{\tilde{Z}_i = \tilde{Z}_1}^{\tilde{Z}_i = \tilde{Z}_2} \quad (16a)$$

and

$$\Delta T_{PWS}(z, t > t_{laser}) = (\Delta T_{0,PWS}/f_{area}) e^{2\tilde{M}\tilde{Z}_3} \{ (e^{\tilde{M}^2/2}) [e^{-2\tilde{M}\tilde{Z}} \operatorname{erf}(\tilde{Z}_i - \tilde{Z} + \tilde{M}) + [(\tilde{M} + \tilde{H})/(\tilde{M} - \tilde{H})] e^{2\tilde{M}\tilde{Z}} \operatorname{erf}(\tilde{Z}_i - \tilde{Z} + \tilde{M})] + [\tilde{H}/(\tilde{M} - \tilde{H})] e^{-(\tilde{Z}_i + \tilde{Z}_i)^2 - 2\tilde{M}\tilde{Z}_i} \operatorname{erfc} x(\tilde{Z}_i + \tilde{Z} + \tilde{H}) \} \}_{\tilde{Z}_i = \tilde{Z}_3}^{\tilde{Z}_i = \tilde{Z}_4} \quad (16b)$$

where

$$\tilde{H} = (h/k)\sqrt{\alpha(t - t_{laser})}. \quad (17)$$

Evaluations of $\operatorname{erf}(x)$, $\operatorname{erfc}(x)$, and $\operatorname{erfc} x(x)$ were performed by an algorithm that uses Chebyshev polynomials to calculate values accurate to 18 or more digits (Cody 1969).

2.3. Epidermal thermal damage assessment

We use an index, Ω , to quantify the severity of epidermal thermal damage and assume that the rate of change of Ω follows an Arrhenius relationship (Glasstone *et al* 1941):

$$d\Omega/dt = A e^{-\Delta E/RT} \quad (18)$$

where A (s^{-1}) and ΔE ($J \text{ mol}^{-1}$) are constants, R is the universal gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$), and T (K) is the absolute temperature. Total damage accumulated

over a period t^* is obtained by integrating equation (18). We assume complete epidermal necrosis occurs when $\Omega = 1$ (Mckenzie 1990, van Gemert *et al* 1991) and use the empirical values of $A = 3.1 \times 10^{98} \text{ s}^{-1}$ and $\Delta E = 6.3 \times 10^5 \text{ J mol}^{-1}$ (Henriques 1947):

$$1 = Ate^{-\Delta E/RT}. \quad (19)$$

Threshold temperatures, $T_{\text{threshold}}$, for epidermal necrosis as a function of time are generated according to equation (19) (figure 2).

Figure 2. Threshold temperatures for epidermal thermal necrosis as a function of exposure time for $A = 3.1 \times 10^{98} \text{ s}^{-1}$ and $\Delta E = 6.3 \times 10^5 \text{ J mol}^{-1}$.

To specify an optimum cooling modality, we require that (i) the time-averaged temperature of the mean temperature between $z = 0$ and $z = z_2$ remain below $T_{\text{threshold}}$,

$$\left(\int_{t_{\text{laser}}}^{t^*} \int_0^{z_2} [\Delta T(z, t) + T_0] dz dt \right) / \int_{t_{\text{laser}}}^{t^*} \int_0^{z_2} dz dt < T_{\text{threshold}} \quad (20)$$

and (ii) in the PWS layer, areas of specified regions that remain above a coagulation threshold temperature (e.g. 60°C) for at least 10 ms after the laser pulse do not differ by more than 5% in the cases of cooling and no cooling,

$$\left\{ \int_{z_3}^{z_3+z^*} [\Delta T_{\text{no cooling}}(z, t = t_{\text{laser}} + 10 \text{ ms}) + T_0 - 60] dz \right. \\ \left. - \int_{z_3}^{z_3+z^*} [\Delta T_{\text{cooling}}(z, t = t_{\text{laser}} + 10 \text{ ms}) + T_0 - 60] dz \right\} \\ / \int_{z_3}^{z_3+z^*} [\Delta T_{\text{no cooling}}(z, t = t_{\text{laser}} + 10 \text{ ms}) + T_0 - 60] dz < 0.05 \quad (21)$$

where we have specified z^* to be the distance over which the temperature distribution within the PWS layer has decreased exponentially with depth by 22% ($e^{-0.25}$). The latter requirement is imposed to ensure that sufficient time exists for blood vessel photocoagulation and that cooling does not affect the PWS layer.

3. Results

For a category IIB PWS (thick, deep, with intermediate epidermal melanin content) and an incident fluence of 6 J cm^{-2} , the centre of the epidermal layer (assumed to be located $10\text{--}50 \mu\text{m}$ below the surface of the skin) reaches a temperature of 100°C immediately after the laser pulse in absence of cooling (figure 3). Precooling the skin with a tetrafluoroethane spurt duration of 70 ms keeps the initial temperature jump due to laser irradiation below 80°C . Heat generated in the PWS diffuses to the skin surface as a delayed thermal wave and the temperature peaks to a local maximum value. Precooling the skin results in an overall temperature reduction within the epidermis.

Figure 3. The calculated temperature evolution in a category IIB PWS at the centre of the epidermal layer following deposition of the laser fluence (6 J cm^{-2}): - - -, no cooling and —, 70 ms precooling of skin with tetrafluoroethane. The epidermal layer is assumed to be located $10\text{--}50 \mu\text{m}$ below the surface of skin. Arrows indicate the instantaneous temperature jumps due to laser irradiation.

Optimum cooling parameters based on conditions (20) and (21) for different PWS categories are summarized in table 1. For category I PWS, our results indicate that cooling is not required. Calculated thermal responses indicate that precooling by tetrafluoroethane is sufficient to eliminate epidermal injury on category II PWS when the incident laser fluence is less than 10 J cm^{-2} . For a fluence of 10 J cm^{-2} , spraying with chlorodifluoromethane (CICHF_2 ; b.p. = -40°C) is indicated to allow successful treatment.

Maximum postcooling durations that would not result in considerable cooling of the PWS (in accordance with condition (21)) are in the range of 10–20 ms. For example,

Table 1. Optimum cooling parameters calculated for different categories of PWS.

Incident fluence (J cm^{-2})	PWS category			
	IIA	IIB	IIIA	IIB
5	n.c. ^a	n.c.	5-35 ms precooling or 5 ms precooling and 5-15 ms postcooling	5-80 ms precooling or 5 ms precooling and 5-15 ms postcooling
6	5-70 ms precooling or 5 ms precooling and 5-15 ms postcooling	5-100 ms precooling or 5 ms precooling and 5-15 ms postcooling	10-70 ms precooling or 10 ms precooling and 5-15 ms postcooling	10-90 ms precooling or 10 ms precooling and 5-15 ms postcooling
7	10-85 ms precooling or 10 ms precooling and 5-15 ms postcooling	10-145 ms precooling or 10 ms precooling and 5-20 ms postcooling	30-80 ms precooling or 30 ms precooling and 5-10 ms postcooling	30-130 ms precooling or 30 ms precooling and 5-20 ms postcooling
8	20-95 ms precooling or 20 ms precooling and 5-15 ms postcooling	20-150 ms precooling or 20 ms precooling and 5-15 ms postcooling	60-70 ms precooling ^b or 60 ms precooling and 5-10 ms postcooling ^b	60-120 ms precooling ^b or 60 ms precooling and 5-15 ms postcooling ^b
9	80-100 ms precooling or 80 ms precooling and 5-10 ms postcooling	80-150 ms precooling or 80 ms precooling and 5-15 ms postcooling	^c	^c
10	40-80 ms precooling ^b or 40 ms precooling and 5-10 ms postcooling ^b	40-130 ms precooling ^b or 40 ms precooling and 5-15 ms postcooling ^b	^c	^c

^a n.c., no cooling needed.^b Using chlorodifluoromethane as cryogen.^c Calculated spurt durations are so long that they cool the PWS blood vessels.

for an incident fluence of 7 J cm^{-2} on a category IIA PWS, precooling the skin with tetrafluoroethane for 70 ms reduces the peak epidermal temperature by almost 30°C , while the temperatures within the PWS layer remain unaffected by cooling (figure 4). Postcooling the skin for 20 ms after 10 ms of precooling reduces the peak epidermal temperature by approximately 80°C , but also results in almost 40°C temperature reduction at the dermis-PWS interface.

Figure 4. Calculated temperature distributions in a category IIA PWS in response to an incident fluence of 7 J cm^{-2} : ---, no cooling and 1 ms after laser irradiation; —, 70 ms precooling and 1 ms after laser irradiation; —•—, at the end of 10 ms of precooling followed by 20 ms of postcooling. Cooling is with tetrafluoroethane. Evolution of uncooled and precooled responses at 20 ms is not shown.

Spraying with tetrafluoroethane does not sufficiently reduce the epidermal temperature when using fluences greater than 7 J cm^{-2} on category III PWSs. With a fluence of 8 J cm^{-2} on a category IIIB PWS, temperatures within the epidermal layer, 2 ms following the laser pulse, remain above 80°C even after precooling the skin for 100 ms with tetrafluoroethane (figure 5). By reducing T_∞ to -30°C , corresponding to the temperature of the chlorodifluoromethane-ice film at the skin surface (as measured by infrared radiometry in our laboratory), the peak temperature within the epidermal layer is reduced to 70°C when precooling the skin with a spurt duration of 80 ms. When using fluences greater than 8 J cm^{-2} on a category III PWS, relatively long spurts of chlorodifluoromethane are required that can result in cooling of PWS blood vessels as well.

Figure 5. Calculated temperature distributions in a IIIB PWS at 2 ms after deposition of the laser fluence (8 J cm^{-2}); - - -, no cooling; —, 100 ms precooling of skin with tetrafluoroethane; —•—, 80 ms precooling of skin with chlorodifluoromethane.

4. Discussion

Ideal laser treatment of PWS should result in irreversible thermal damage to blood vessels that compromise the PWS while preserving the overlying normal epidermis. Spray cooling of skin with a cryogen such as tetrafluoroethane has been suggested as a promising technique for eliminating thermal injury during pulsed laser treatment of PWSs (Nelson *et al* 1995a, b, Anvari *et al* 1995). The degree and spatial distribution of cooling has been shown to be directly related to the cryogen spurt duration (Anvari *et al* 1995). Although preliminary clinical results have indicated successful blanching of the PWS without any adverse epidermal thermal injury when using spray cooling in conjunction with flashlamp-pumped pulsed dye laser therapy, an optimum cooling modality should be selected on an individual patient basis based on knowledge of the PWS vessel depth distribution (Jacques *et al* 1993, Milner *et al* 1994). Recently, an algorithm has been developed to estimate the depth of PWS vessels from the recordings of time-resolved infrared radiometric measurements of the skin surface (Milner *et al* 1995). The appropriate cooling modality on an individual patient basis may be selected in conjunction with this algorithm or an alternative diagnostic technique.

Our calculations indicate that precooling of skin is sufficient to eliminate epidermal thermal injury. Although postcooling of skin enhances the heat sink capacity available for dissipation of the excessive heat generated within the epidermis, it can also result in cooling

of the PWS blood vessels when greater than 10–20 ms in duration.

For fluences greater than 9 and 7 J cm⁻² on patients with intermediate and high epidermal melanin content, respectively, spray cooling the skin by tetrafluoroethane is not sufficient to eliminate epidermal injury. A cryogen that has a lower boiling point than tetrafluoroethane (e.g., chlorodifluoromethane) may be more appropriate. Larger temperature drops can be obtained in a shorter time and the presence of a larger thermal gradient toward the surface allows for more rapid heat dissipation. Experiments utilizing our theoretical analyses are currently underway in our laboratory to optimize the cooling technique for clinical applications.

5. Conclusions

We have presented a theoretical study to examine the thermal response of skin to cryogen spray cooling in conjunction with pulsed laser treatment of PWS at 585 nm. Our calculations indicate that precooling the skin with tetrafluoroethane is effective in eliminating epidermal thermal injury when using fluences of less than 10 and 8 J cm⁻² on patients with intermediate and high epidermal melanin content, respectively. Chlorodifluoromethane is shown to be a potentially effective cryogen for eliminating epidermal injury when using fluences greater than those indicated.

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Appendix A. Derivations of equations (9a), (9b), and (15)

Assuming a semi-infinite medium with an insulated boundary condition at the surface and an initial temperature distribution $\Delta T(z', 0)$ at $t = t_{laser}$, the resulting thermal response is given as (Carslaw and Jaeger 1959)

$$\Delta T(z, t) = \frac{1}{\sqrt{\pi}} \int_0^\infty \Delta T(z', 0) [e^{-(\tilde{z}' - \tilde{z})^2} + e^{-(\tilde{z}' + \tilde{z})^2}] d\tilde{z}' \quad (A1)$$

where $\tilde{z} = z/2\sqrt{\alpha t}$ and $\tilde{z}' = z'/2\sqrt{\alpha t}$. Substituting equation (1) for $\Delta T(z', 0)$ in (A1):

$$\begin{aligned} \Delta T_{epidermal}(z, t > t_{laser}) &= \frac{\Delta T_{0,epidermal}}{\sqrt{\pi}} \int_{\tilde{z}_1}^{\tilde{z}_2} [e^{-(\tilde{z}' - \tilde{z})^2} + e^{-(\tilde{z}' + \tilde{z})^2}] d\tilde{z}' \\ &= \frac{\Delta T_{0,epidermal}}{\sqrt{\pi}} \left\{ \int_{\tilde{z}_1}^\infty [e^{-(\tilde{z}' - \tilde{z})^2} + e^{-(\tilde{z}' + \tilde{z})^2}] d\tilde{z}' - \int_{\tilde{z}_2}^\infty [e^{-(\tilde{z}' + \tilde{z})^2} + e^{-(\tilde{z}' - \tilde{z})^2}] d\tilde{z}' \right\}. \end{aligned} \quad (A2)$$

Using the equality

$$\int_x^\infty e^{-(u+a)^2} du = \frac{\sqrt{\pi}}{2} \operatorname{erfc}(x+a) \quad (A3)$$

equation (A2) becomes

$$\Delta T(z, t) = (\Delta T_{0, \text{epidermal}}/2)[\operatorname{erfc}(\tilde{z}_1 - \tilde{z}) + \operatorname{erfc}(\tilde{z}_1 + \tilde{z}) - \operatorname{erfc}(\tilde{z}_2 - \tilde{z}) - \operatorname{erfc}(\tilde{z}_2 + \tilde{z})]. \quad (\text{A4})$$

By substituting the identity

$$\operatorname{erfc}(x) = 1 - \operatorname{erf}(x) \quad (\text{A5})$$

in (A4), and replacing t by $t - t_{\text{laser}}$ equation (9a) is obtained.

When $\Delta T(z', 0) = (\Delta T_{0, \text{PWS}}/f_{\text{area}})e^{-\mu_a(z' - z_3)}$, and letting $\tilde{\mu}_a^{\text{blood}} = \mu_a^{\text{blood}}\sqrt{\alpha t}$, equation (A1) becomes

$$\Delta T_{\text{PWS}}(z, t > t_{\text{laser}}) = \frac{\Delta T_{\text{PWS}} e^{2\tilde{\mu}_a^{\text{blood}} \tilde{z}_3}}{f_{\text{area}} \sqrt{\pi}} \int_{\tilde{z}_3}^{\tilde{z}_4} e^{-2\tilde{\mu}_a^{\text{blood}} \tilde{z}'} [e^{-(\tilde{z}' - \tilde{z})^2} + e^{-(\tilde{z}' + \tilde{z})^2}] d\tilde{z}'. \quad (\text{A6})$$

Using the equalities

$$\int_{x_1}^{x_2} e^{-2\tilde{x}\tilde{z}' - (\tilde{z}' \pm \tilde{z})^2} d\tilde{z}' = e^{\tilde{x}^2 \pm 2\tilde{x}\tilde{z}} \int_{x_1}^{x_2} e^{-(\tilde{z}' \pm \tilde{z})^2} d\tilde{z}' \quad (\text{A7})$$

and (A3), equation (A6) becomes

$$\begin{aligned} \Delta T_{\text{PWS}}(z, t > t_{\text{laser}}) = & (\Delta T_{\text{PWS}} e^{\tilde{\mu}_a^2 + 2\tilde{\mu}_a \tilde{z}_3} / 2f_{\text{area}}) \{ e^{-2\tilde{\mu}_a^{\text{blood}} \tilde{z}} [\operatorname{erfc}(\tilde{\mu}_a^{\text{blood}} + \tilde{z}_3 - \tilde{z}) \\ & - \operatorname{erfc}(\tilde{\mu}_a^{\text{blood}} + \tilde{z}_4 - \tilde{z})] + e^{2\tilde{\mu}_a^{\text{blood}} \tilde{z}} [\operatorname{erfc}(\tilde{\mu}_a^{\text{blood}} + \tilde{z}_3 + \tilde{z}) \\ & - \operatorname{erfc}(\tilde{\mu}_a^{\text{blood}} + \tilde{z}_4 + \tilde{z})] \}. \end{aligned} \quad (\text{A8})$$

Substituting the identity (A5) in (A8), and replacing t by $t - t_{\text{laser}}$ equation (9b) is obtained.

When $\Delta T(z', 0) = \Delta T_s e^{(-kz')}$ and letting $\tilde{k} = k\sqrt{\alpha t}$, equation (A1) becomes

$$\Delta T_{\text{cooling}}(z, t > t_{\text{laser}}) = \frac{\Delta T_s}{\sqrt{\pi}} \int_0^\infty e^{-2\tilde{k}\tilde{z}'} [e^{-(\tilde{z}' - \tilde{z})^2} + e^{-(\tilde{z}' + \tilde{z})^2}] d\tilde{z}'. \quad (\text{A9})$$

Using equalities (A6) and (A3) and the short-hand notation $\operatorname{erfcx}(x) = e^{x^2} \operatorname{erfc}(x)$, equation (A9) becomes equation (15).

Appendix B. Derivations of equations (16a) and (16b)

With the initial temperature distribution (1) at $t = t_{\text{laser}}$ and the boundary condition (6), the resulting thermal response due to epidermal melanin or blood absorption can be written as (Carslaw and Jaeger 1959)

$$\Delta T(z, t) = \frac{1}{\sqrt{\pi}} \int_0^\infty \Delta T(z, t_{\text{laser}}) \left\{ e^{-(\tilde{Z}' - \tilde{Z})^2} + e^{-(\tilde{Z}' + \tilde{Z})^2} \left[1 - 2\sqrt{\pi} \tilde{H} \operatorname{erfcx}(W) \right] \right\} d\tilde{z}' \quad (\text{B1})$$

where $\tilde{Z} = z/2\sqrt{\alpha(t - t_{\text{laser}})}$, $\tilde{Z}' = z'/2\sqrt{\alpha(t - t_{\text{laser}})}$, $\tilde{H} = (h/k)\sqrt{\alpha(t - t_{\text{laser}})}$, and $W = \tilde{Z}' + \tilde{Z} + \tilde{H}$. Using the equalities (A3) and

$$\int_x^\infty e^{-(u+a)^2} \operatorname{erfcx}(u) du = \frac{e^{-(x+a)^2} \operatorname{erfcx}(x) - \operatorname{erfc}(x+a)}{2a} \quad (\text{B2})$$

which is obtained by integration by parts, the thermal response due to epidermal melanin absorption becomes

$$\begin{aligned}
 \Delta T_{\text{epidermal}} &= \Delta T_{0,\text{epidermal}} \left[\frac{1}{2} \operatorname{erfc}(\tilde{Z}_i - \tilde{Z}) + \frac{1}{2} \operatorname{erfc}(\tilde{Z}_i + \tilde{Z}) \right. \\
 &\quad \left. - 2\tilde{H} \int_{\tilde{Z}_i + \tilde{Z} + \tilde{H}}^{\infty} e^{-(W - \tilde{H})^2} \operatorname{erfcx}(W) dW \right]_{\tilde{Z}_i = \tilde{Z}_2}^{\tilde{Z}_i = \tilde{Z}_1} \\
 &= (\Delta T_{0,\text{epidermal}}/2) \{ \operatorname{erfc}(\tilde{Z}_i - \tilde{Z}) + \operatorname{erfc}(\tilde{Z}_i + \tilde{Z}) \\
 &\quad + 2[e^{-(\tilde{Z}_i + \tilde{Z})^2} \operatorname{erfcx}(\tilde{Z}_i + \tilde{Z} + \tilde{H}) - \operatorname{erfc}(\tilde{Z}_i + \tilde{Z})] \}_{\tilde{Z}_i = \tilde{Z}_2}^{\tilde{Z}_i = \tilde{Z}_1} \\
 &= (\Delta T_{0,\text{epidermal}}/2) \{ \operatorname{erfc}(\tilde{Z}_i - \tilde{Z}) - \operatorname{erfc}(\tilde{Z}_i + \tilde{Z}) \\
 &\quad + 2e^{-(\tilde{Z}_i + \tilde{Z})^2} \operatorname{erfcx}(\tilde{Z}_i + \tilde{Z} + \tilde{H}) \}_{\tilde{Z}_i = \tilde{Z}_2}^{\tilde{Z}_i = \tilde{Z}_1}. \tag{B3}
 \end{aligned}$$

By substituting the identity (A5) in (B3), and replacing t by $t - t_{\text{laser}}$, equation (16a) is obtained.

With $\tilde{M} = \mu_a^{\text{blood}} \sqrt{\alpha(t - t_{\text{laser}})}$, the thermal response due to blood absorption is

$$\begin{aligned}
 \Delta T_{\text{PWS}} &= \frac{\Delta T_{0,\text{PWS}}}{f_{\text{area}}} e^{2\tilde{M}\tilde{Z}_3} \left\{ \frac{e^{\tilde{M}^2}}{2} [e^{-2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} - \tilde{Z}) + e^{2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} + \tilde{Z})] \right. \\
 &\quad \left. - 2\tilde{H} \int_{\tilde{Z}_i + \tilde{Z} + \tilde{H}}^{\infty} e^{-(W + \tilde{M} - \tilde{H})^2 + 2\tilde{M}\tilde{Z} + \tilde{M}^2} \operatorname{erfcx}(W) dW \right\}_{\tilde{Z}_i = \tilde{Z}_4}^{\tilde{Z}_i = \tilde{Z}_3} \\
 &= \frac{\Delta T_{0,\text{PWS}}}{f_{\text{area}}} e^{2\tilde{M}\tilde{Z}_3 + \tilde{M}^2} \left\{ \frac{1}{2} [e^{-2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} - \tilde{Z}) + e^{2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} + \tilde{Z})] \right. \\
 &\quad \left. - \frac{\tilde{H} e^{2\tilde{M}\tilde{Z}}}{\tilde{M} - \tilde{H}} [e^{-(\tilde{Z}_i + \tilde{Z} + \tilde{M})^2} \operatorname{erfcx}(\tilde{Z}_i + \tilde{Z} + \tilde{H}) - \operatorname{erfc}(\tilde{Z}_i + \tilde{Z} + \tilde{M})] \right\}_{\tilde{Z}_i = \tilde{Z}_4}^{\tilde{Z}_i = \tilde{Z}_3} \\
 &= \frac{\Delta T_{0,\text{PWS}}}{f_{\text{area}}} e^{2\tilde{M}\tilde{Z}_3 + \tilde{M}^2} \left\{ \frac{1}{2} [e^{-2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} - \tilde{Z}) + e^{2\tilde{M}\tilde{Z}} \operatorname{erfc}(\tilde{Z}_i + \tilde{M} + \tilde{Z})] \right. \\
 &\quad \left. - \frac{\tilde{H} e^{2\tilde{M}\tilde{Z}}}{\tilde{M} - \tilde{H}} [e^{-(\tilde{Z}_i + \tilde{Z} + \tilde{M})^2} \operatorname{erfcx}(\tilde{Z}_i + \tilde{Z} + \tilde{H}) - \operatorname{erfc}(\tilde{Z}_i + \tilde{Z} + \tilde{M})] \right\}_{\tilde{Z}_i = \tilde{Z}_4}^{\tilde{Z}_i = \tilde{Z}_3} \tag{B4}
 \end{aligned}$$

By substituting the identity (A5) in (B4), and replacing t by $t - t_{\text{laser}}$, equation (16b) is obtained.

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