Photothermal Tomography of Subcutaneous Chromophores

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ABSTRACT

Photothermal tomography (PTT) is applied to characterize diameter and depth of subcutaneous chromophores such as blood vessels that comprise port wine stain (PWS) birthmarks. PTT uses a fast infrared detector array to measure temperature rises in a PWS induced by pulsed laser radiation. A PTT record of PWS in response to pulsed laser exposure is composed of a sequence of infrared emission frames, each consisting of elevated temperature regions indicative of subcutaneous blood vessel heating. An analytic expression for recorded infrared emission frames is derived as a convolution integral of a PTT point spread function and the three dimensional temperature distribution in the PWS immediately following laser exposure. Diameters of blood vessels comprising the PWS are best resolved in early infrared emission frames when radial heat diffusion is relatively small. Blood vessel images in subsequent frames increase in amplitude due to heat generated in the subsurface PWS diffusing to the skin surface indicative of a "delayed thermal wave". Influence of diameter and depth of blood vessels on the PTT record is analyzed using an *in-vitro* PWS model consisting of multilayered collagen films.

1. INTRODUCTION

The laser provided the first major advance in therapy for port wine stain (PWS) birthmarks and has been used extensively in the past two decades. Light of the appropriate wavelength is preferentially absorbed by hemoglobin and converted to heat, causing thermal damage and thrombosis in the targeted vessels. Results of clinical studies using lasers are encouraging, but hypertrophic scarring, changes in the normal skin pigmentation, atrophy, or induration, which can occur in 20-40% of treated patients, remain worrisome complications[1-3]. Such complications are particularly likely in the population expected to gain the most benefit from laser therapy - infants and young children, due to the propensity for scar formation in younger age groups. Furthermore, only a small proportion of patients (10-20%) obtain 100% fading of their PWS, even after undergoing multiple treatments[4].

The reason for poor clinical results or complications seen after laser PWS therapy is the lack of specificity in choosing the optimal laser parameters on an individual patient basis. Presently, all patients are treated without taking individual variations in the biophysical, structural, optical and thermal properties of human skin and PWS into consideration. It is obvious that a method that does take these variations into consideration, would have decided advantages over existing methodology.

Photothermal tomography (PTT) uses a fast infrared detector array to detect temperature rises in a substrate, induced by pulsed radiation. In practice, a pulsed laser is used to produce transient heating of the object under study. The subsequent temperature rise, due to the optical absorption of the pulsed laser light, creates an increase in infrared (blackbody) emission which is measured by a fast infrared detector array. For the purposes of PTT, PWS in human skin can be modeled as a plexus of subsurface absorbing structures. In the PWS model, if a pulsed laser light source is used to irradiate skin, an immediate increase in infrared (blackbody) emission will occur due to optical absorption by hemoglobin contained within the blood vessels. The spatial distribution of the initial infrared emission, immediately after the laser pulse is delivered, provides a measure of the PWS blood vessel diameters (Figure 1).

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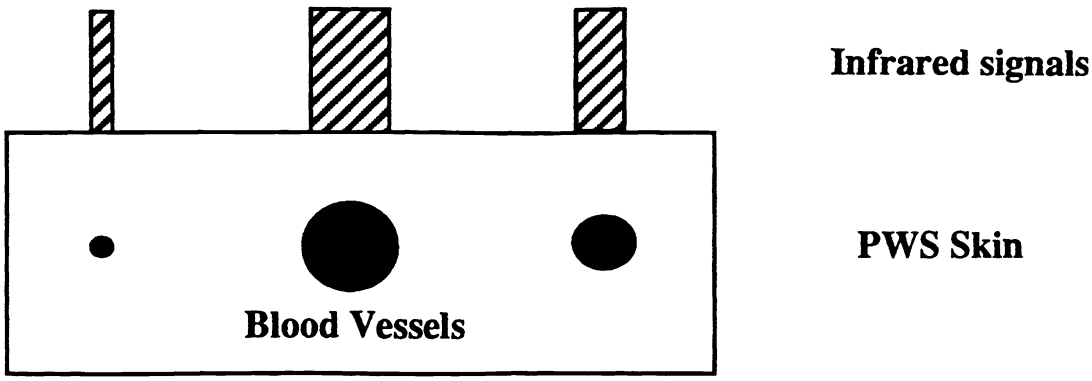

Figure 1: Initial infrared emission measurement of PWS skin.

2. THEORY

Each infrared emission frame due to heating of subsurface PWS blood vessels, is a superposition of a PTT point spread function weighted by the initial temperature distribution in the skin immediately after laser exposure. Determination of the initial three-dimensional temperature distribution in PWS skin, $T(\xi,\eta,\zeta,t=0)$, immediately following exposure to a sub-therapeutic laser pulse, given only the time sequence of PTT infrared emission frames, $R(x,y,t)$, is the long term clinical goal of our research. The initial three-dimensional temperature distribution in the PWS is related to the PTT point spread function and infrared emission intensity by a convolution integral,

$$R(x,y,t) = \iiint T(\xi,\eta,\zeta,t=0)\cdot g(x-\xi,y-\eta,\zeta,t)\, d\xi\, d\eta\, d\zeta \qquad (1)$$

The PTT point spread function is the infrared emission intensity emanating from the skin surface ($z=0$) at position (x,y) at time t due to a delta function temperature distribution released from position (ξ,η,ζ), beneath the skin surface, at $t=0$. To apply eq. 1 it is necessary to derive an expression for the PTT point spread function, $g(x-\xi,y-\eta,\zeta,t)$.

2.1 Green's function temperature distribution

We assume a δ–pulse of energy, q, is released in an infinite medium at the origin at time $t=0$. The Green's function temperature distribution due to this pulse can be calculated from the heat diffusion equation as derived from the law of conservation of energy for an arbitrary infinitesimal volume,

$$div\,\vec{j} = -\frac{\partial}{\partial t}(\rho_t C_t T) - \rho_b C_b Q T + q\delta(t)\delta(r) \qquad (2)$$

Where,

$$\vec{j} = -\kappa \cdot grad\, T \qquad (3)$$

In eq. 2, $\rho_b C_b Q T$ is the energy loss due to blood perfusion, and q is the thermal energy contained in the δ–pulse source. The coefficients ρ_t, C_t, ρ_b and C_b are respectively the mass density and the specific heat capacity for the tissue (t) and the blood (b), and Q [1/s] is the blood perfusion rate, measured as the volume fraction of perfused blood (relative to the tissue) in unit time. Since the difference in mass density and heat capacity between the tissue and the blood is small, respective values are set equal. The function T is the increase in temperature in the tissue above normal background values. Using the relationship between the thermal diffusivity, χ, and the thermal conductivity, κ, and assuming that the thermal properties of the tissue are uniform, the heat diffusion equation becomes,

$$\nabla^2 T - \frac{1}{\chi}\frac{\partial T}{\partial t} - \frac{Q}{\chi}T = -\frac{q}{\kappa}\cdot\delta(t)\cdot\delta(r)$$
$$\text{where } \chi = \frac{\kappa}{\rho_t C_t} \tag{4}$$

Since the δ-pulse is released at a point in space, it is convenient to use spherical co-ordinates in the heat diffusion equation,

$$\frac{1}{r}\frac{\partial^2}{\partial r^2}(rT) - \frac{1}{\chi}\frac{\partial T}{\partial t} - \frac{1}{\delta_v^2}T = -\frac{q}{\kappa}\cdot\delta(t)\cdot\delta(r) \tag{5}$$

where the thermal penetration depth, δ_V, is defined as

$$\delta_v = \sqrt{\frac{\chi}{Q}} \tag{6}$$

Using the Laplace transformation, the transformed solution is,

$$T(s) = \frac{q}{4\pi\kappa r}\cdot e^{-\sqrt{\frac{s+Q}{\chi}}\cdot r} \tag{7}$$

The corresponding temperature distribution as a function of time, becomes

$$T(r,t) = \frac{q}{(4\pi t)^{3/2}\kappa(\chi)^{1/2}}\cdot e^{-\frac{r^2}{4\chi t}}\cdot e^{-Qt} \tag{8}$$

2.2 PTT point spread function

For the purpose of PTT point spread function computation we assume a semi infinite medium with an air boundary so that infrared emission at the surface can be calculated due to the release of a δ-pulse at the point (ξ=0, η=0, ζ_O) at t=0. The co-ordinate system is placed (Figure 2) at the point of release such that z=0 is coincident with the insulating boundary surface and the distance from the origin to the observation point is $r^2=x^2+y^2$. With no energy loss across the boundary, a solution[5] is found with equivalent image an actual point sources positioned at equal distances above and below the surface. The temperature distribution at position (ξ,η,ζ) ($\rho^2=\xi^2+\eta^2$) is then given by,

$$T(\rho,\zeta,t) = \frac{q}{(4\pi t)^{3/2}\kappa(\chi)^{1/2}}\cdot e^{-\frac{\rho^2}{4\chi t}}\left(e^{-\frac{(\zeta-\zeta_o)^2}{4\chi t}} + e^{-\frac{(\zeta+\zeta_o)^2}{4\chi t}}\right)e^{-Qt} \tag{9}$$

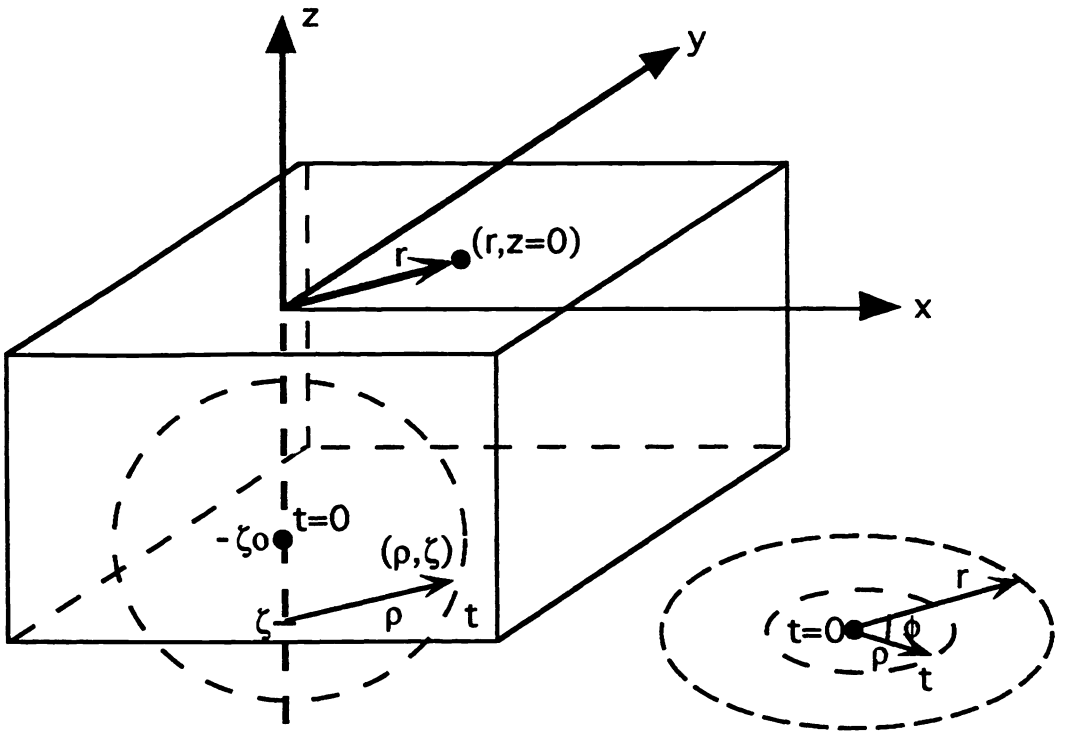

Figure 2: Geometry assumed for PTT point spread function computation.

The infrared radiation emanating from subsurface thermal sources is scattered and absorbed while exiting the skin. Assuming a Gaussian scattering mechanism, with a scattering coefficient σ_s, and an exponential absorption loss, with attenuation coefficient μ, the infrared emission at $r^2=x^2+y^2$ at the skin surface due to a differential element of thermal energy located in the skin at position (ρ,ϕ,ζ) is proportional to,

$$\frac{1}{(2\pi\sigma_s^2)} e^{-(\rho^2+r^2-2\rho r\cos\varphi)/2\sigma_s^2} \cdot e^{\mu\zeta} \cdot \mu$$

By integrating over a differential volume element $(d\rho \cdot (\rho \cdot d\varphi) \cdot d\zeta)$ and assuming that the inverse blood perfusion rate is much longer than the time of measurement (t<<(1/Q)), the PTT point spread function becomes

$$\begin{aligned} g(r,t) = \iiint_V [(&\frac{1}{(2\pi\sigma_s^2)} e^{-(\rho^2+r^2-2\rho r\cos\varphi)/2\sigma_s^2} \cdot e^{\mu\zeta} \cdot \mu) \\ &\times (\frac{q}{(4\pi t)^{3/2}\kappa(\chi)^{1/2}} e^{\frac{\rho^2}{4\chi t}} (e^{\frac{(\zeta-\zeta_o)^2}{4\chi t}} + e^{\frac{(\zeta+\zeta_o)^2}{4\chi t}})] \, d\rho \cdot (\rho \, d\varphi) \cdot d\zeta \\ &= \frac{q}{(2\pi\sigma_s^2)} \cdot \frac{\mu}{(4\pi t)^{3/2}\kappa(\chi)^{1/2}} \cdot [-\int_{\zeta=o}^{-\infty} e^{\mu\zeta} (e^{\frac{(\zeta-\zeta_o)^2}{4\chi t}} + e^{\frac{(\zeta+\zeta_o)^2}{4\chi t}}) d\zeta] \\ &\times (\int_{\rho=o}^{\infty} e^{\frac{\rho^2}{4\chi t}} \rho (\int_{\varphi=o}^{2\pi} e^{-(\rho^2+r^2-2\rho r\cos\varphi)/2\sigma_s^2} d\varphi) d\rho) \end{aligned} \quad (10)$$

The analytical solution to this equation is,

$$g(r,t)=\frac{q\mu/(\rho_t C_t)}{(2\sigma_s^2+4\chi t)2\pi}e^{-\frac{r^2}{4\chi t+2\sigma_s^2}}e^{-\frac{\zeta_o^2}{4\chi t}}(e^{u_+^2}\mathrm{erfc}(u_+)+e^{u_-^2}\mathrm{erfc}(u_-)) \quad (11)$$

where,

$$u_\pm=\mu\sqrt{\chi t}\pm\frac{\zeta_o}{2\sqrt{\chi t}} \quad (12)$$

Since $q/\rho_t C_t$ is the initial temperature rise at ζ_o, the PTT point spread function corresponding to a unit temperature rise at t=0 is,

$$g(r,t)=\frac{\mu}{(2\sigma_s^2+4\chi t)2\pi}e^{-\frac{r^2}{4\chi t+2\sigma_s^2}}e^{-\frac{\zeta_o^2}{4\chi t}}(e^{u_+^2}\mathrm{erfc}(u_+)+e^{u_-^2}\mathrm{erfc}(u_-)) \quad (13)$$

Determination of the PTT point spread function allows computation of the convolution integral (Eq. 1) relating the infrared emission frames, R(x,y,t), to the initial temperature distribution, $T(\xi,\eta,\zeta,t=0)$, in the PWS.

3. METHODS AND MATERIALS

3.1 *In-vitro* PWS model

We have developed an *in vitro* model using collagen films consisting of variable amounts of absorber to simulate individual blood vessels in multilayered composite PWS skin. This model makes use of thin (i.e. 50-100 μm) collagen films and an organic optical absorbing dye. The collagen films (Collatec, Plainview, NJ) are prepared to different thicknesses and optical absorption to simulate various PWS. Each phantom is prepared by staining collagen films with Brilliant Blue® [triphenylmethane dye (Aldrich Chemical Co., Milwaukee WI)] which absorbs optimally at a wavelength of 585 nm, the wavelength often utilized for PWS therapy. The variation of the dye absorbance with concentration is calibrated spectrophotometrically. When masked collagen films are placed in a dye solution, the blue dye binds to the collagen fibers in specific areas outlined by the mask - resulting in films with well defined patterns that simulate PWS blood vessels. With this technique, collagen layers corresponding to epidermis, dermis and PWS are prepared.

A PWS model phantom was constructed to test the spatial resolution of PTT (Figure 3A). The simulated PWS consisted of five closely spaced 250 μm diameter stained collagen strips positioned underneath two non-absorbing 125 μm thick type-I collagen films and overlying a 10 mm thick collagen sponge. After the model PWS phantom was exposed (Figure 3B) to a 1 J flash lamp pumped dye laser pulse (λ=585 nm, pulse width (τ_p)≈450 μs), a PTT time sequence of infrared emission was recorded with a fast 128 x 128 infrared detector array optically filtered for sensitivity in the 3-5 μm range.

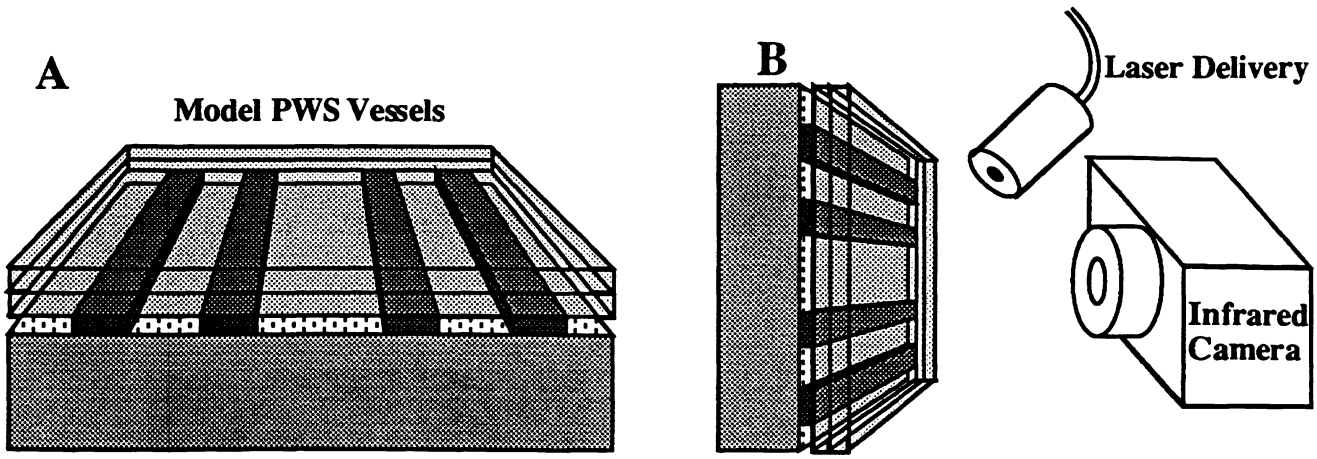

Figure 3: (A) Model collagen phantom simulating buried PWS blood vessels. (B) Experimental arrangement to test resolution of PTT.

3.2 PWS Patient PTT measurements

Recently, we have verified the functionality of our PTT system with infrared emission measurements of a PWS patient with light normal skin color and corresponding low epidermal melanin concentrations. A PTT time sequence of infrared emission frames of the patient's PWS were recorded (Figure 4) following administration of a 7.5 Jcm^{-2} light dose from a flash lamp pumped dye laser (λ=585 nm, τ_p≈450 μs). A typical PTT acquisition consisted of one hundred image frames, taken 4.6 ms apart over 460 ms.

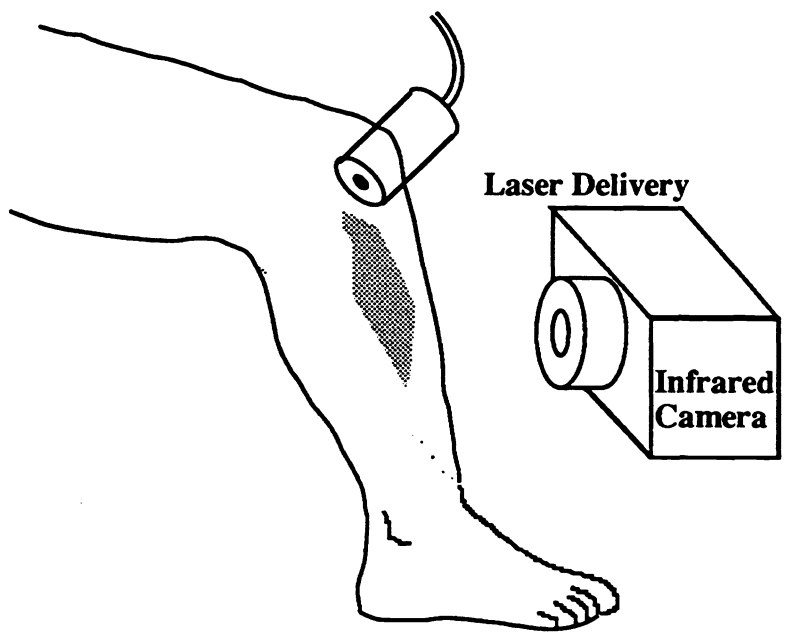

Figure 4: PTT measurement of patients PWS located on leg.

4. RESULTS AND DISCUSSION

4.1 *In-vitro* PWS measurements

In the experiment referred to in Figure 3B, each laser heated collagen strip is visible in recorded PTT infrared emission frames. Two representative frames recorded at 40 and 200 ms after the laser pulse was delivered are illustrated in Figures 5A and 5B, respectively. At early time points, five laser-heated stained collagen strips are resolved (Figure 5A). At later times, infrared emission increases as heat from model PWS blood vessels diffuses toward the collagen surface. Adjacent collagen strips are resolved less clearly (Figure 5B) at later times as radial heat diffusion begins to blur images in subsequent infrared emission frames.

Figure 5: Infrared emission frames of model PWS blood vessels at (A) 45 ms and (B) 230 ms after the laser pulse was delivered.

The results of this preliminary investigation allow two important conclusions to be drawn: (1) the diameters of stained collagen strips that simulate PWS blood vessels are optimally measured with large signal-to-noise ratios at early time points after the laser pulse was delivered; (2) model PWS blood vessels with diameters of 250 μm can be detected and distinguished with our prototype PTT system. However, in principle, with appropriate reconfiguration of the infrared collection optics, subsurface PWS blood vessels as small as 5-10 μm in diameter could be detected.

4.2 PWS Patient PTT measurements

Two representative infrared emission frames of a patient's PWS recorded at 230 and 460 ms after the laser pulse was delivered illustrate important features of a PTT acquisition. High temperature regions in the early frame (Figure 6A) correspond to laser heating of PWS blood vessels. In this frame, small groups of distinct PWS blood vessels can be identified as small elliptical shaped regions which, over time, merge into a larger composite structures (Figure 6B) as a result of radial thermal diffusion.

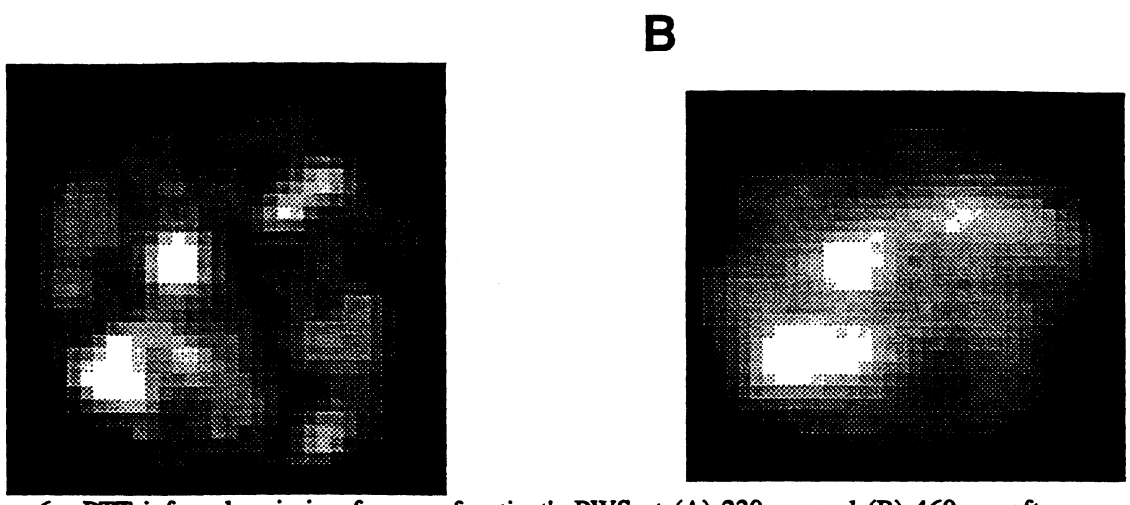

Figure 6: PTT infrared emission frames of patient's PWS at (A) 230 ms and (B) 460 ms after exposure to a sub-therapeutic laser dose.

The time evolution of the infrared emission intensity of a single pixel in the measured (Fig. 4) PTT time sequence coincident with a PWS blood vessel, shows (Figure 7) a characteristic "delayed thermal wave"[6,7], whereby an initial temperature rise is followed by a peak as laser-generated heat diffuses toward the skin surface.

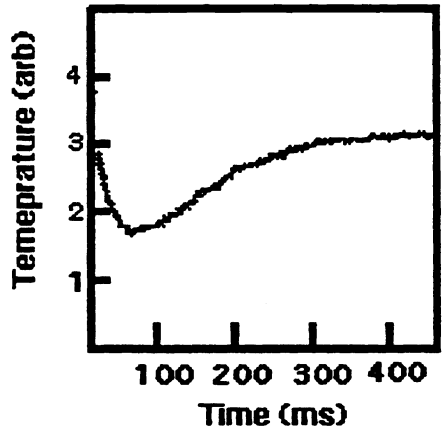

Figure 7: Infrared emission intensity at single pixel coincident with PWS blood vessel

Absorption of infrared radiation by water in skin is an important physical property that determines the PTT signal amplitude in response to laser heating of PWS blood vessels. Since the attenuation coefficient of water is large[8] (~10,000 cm^{-1}) at 3 μm, infrared emission intensity measurements at this wavelength probe the most superficial (~1-3 μm) layer of the skin. In contrast, at 4 μm, the water attenuation coefficient is substantially smaller[8] (~100 cm^{-1}) and hence infrared emission intensity measurements probe deeper (100-300 μm) cutaneous layers. We expect that laser heated PWS blood vessels appearing in early infrared emission frames are detected in the 4 μm transmission window, while at 3 μm only time delayed temperature increases at the skin surface are observed. In skin, the scattering coefficient and average cosine are respectively[9] approximately 0.1 mm^{-1} and 0.9 , which in the 3-5 μm range implies an absorption dominant process. Best lateral resolution could be obtained at 3 μm where the absorption to scattering ratio is greatest. However, direct observations of buried cutaneous structures in early frames at this wavelength are limited by small signal to noise ratios. A compromise between good lateral resolution and a high signal to noise ratio should be found in the 3-5 μm band where the water attenuation coefficient varies by two orders of magnitude.

From these experiments we conclude it is possible, using state of the art fast infrared detector arrays, to: (1) measure distinct diameters of blood vessel heating in response to laser exposure; and (2) observe a "delayed thermal wave" characteristic of laser heated PWS blood vessels at specific locations within the recorded infrared emission frame.

5. CONCLUSIONS

Results of studies described can lead to the development of a new method which will provide a much more rational approach to the selection of laser parameters appropriate on an individual patient basis for treatment of PWS. Prior to the institution of laser PWS therapy, measurements provided by PTT will provide information regarding (1) diameter and depth of laser-heated blood vessels comprising the PWS; and (2) optimal laser parameters to heat sufficiently and destroy the targeted subcutaneous PWS blood vessels. Studies underway seek to clarify the spectral dependence of infrared scattering in skin and its functional dependence. Future work will construct a tomographic computer algorithm that transforms a time sequence of infrared emission frames into a three-dimensional image showing diameter and depth of laser-heated blood vessels that comprise the PWS. It is believed that many of the questions encountered during the clinical management of PWS patients will be answered once a better understanding of the individual variations in the biophysical, structural, optical and thermal properties of human skin and PWS are achieved using PTT.

6. CITED LITERATURE

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