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Cryogen spray cooling for spatially selective photocoagulation: a feasibility study with potential application for treatment of hemangiomas

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ABSTRACT

The clinical objective in laser treatment of hemangiomas is to photocoagulate the dilated cutaneous blood vessels, while at the same time minimizing nonspecific thermal injury to the overlying epidermis. We present an in-vivo experimental procedure, using a chicken comb animal model, and an infrared feedback system to deliver repetitive cryogen spurts (on the order of milliseconds) during continuous Nd:YAG laser irradiation. Gross and histologic observations are consistent with calculated thicknesses of protected and damaged tissues, and demonstrate the feasibility of inducing spatially selective photocoagulation when using cryogen spray cooling in conjunction with laser irradiation. Experimental observation of epidermal protection in the chicken comb model suggests selective photocoagulation of subsurface targeted blood vessels for successful treatment of hemangiomas can be achieved by repetitive applications of a cryogen spurt during continuous Nd:YAG laser irradiation.

2. INTRODUCTION

Hemangiomas are benign vascular tumors that occur in up to 10% of children during the first year of life.<sup>1</sup> They differ from vascular malformations, such as port wine stains, in that they are not conglomerates of dilated vessels, but consist of plump, proliferating endothelial cells that may infiltrate the entire dermis, and extend several millimeters in depth.<sup>2</sup> Due to psychological and social factors, as well as functional impairments such as difficulty in eating, visual and breathing obstructions, early treatment is indicated.<sup>3,4</sup>

Apfelberg *et al*<sup>5</sup> and Hobby<sup>6</sup> first reported use of the argon laser ( $\lambda = 488$  and 514 nm) for treatment of hemangiomas in early infancy. However, due to relatively shallow penetration of the argon laser light into the tumor, therapeutic effect is restricted to superficial lesions. For thick hemangiomas, the Nd:YAG laser has been shown effective due to deep penetration of 1064 nm light.<sup>7-9</sup> A particularly problematic complication that can occur when using lasers is thermally induced damage to the epidermis and papillary dermis.<sup>10</sup>

Cooling of skin, using ice or chilled water in conjunction with laser irradiation, has been used to prevent epidermal thermal injury.<sup>11-13</sup> However, computed temperature distributions following sustained cooling (e.g., 15-60 s) by 0 °C ice at the skin surface show that in addition to cooling the epidermis, temperature of blood vessels is also reduced.<sup>14</sup> Thermal energy removed to protect the epidermis from injury will be offset by additional laser energy required to heat the blood vessels to a sufficiently high temperature for destruction.

When a cryogen is sprayed on skin surface, the epidermis can be cooled selectively.<sup>15-17</sup> For an appropriately short cryogen spurt duration (on the order of tens of milliseconds), the spatial distribution of cooling remains localized in the epidermis, while leaving the temperature of deeper vessels unchanged.

In a previous study performed ex-vivo on highly vascularized rabbit liver tissue, repetitive application of a 50 ms cryogen spurt during continuous Nd:YAG laser irradiation was shown to result in protection of the superficial tissue ( $\approx 400 \mu\text{m}$  in thickness) from thermal injury while still achieving photocoagulation of deeper structures.<sup>18</sup> In this paper, we present: 1) a theory to predict temperature distributions, and thicknesses of protected and photocoagulated tissue in response to repetitive cryogen spurts during continuous Nd:YAG laser irradiation; 2) experimental results of a study performed in-vivo utilizing the chicken comb animal model that demonstrate the feasibility of inducing deep tissue photocoagulation while protecting the epidermis from thermal injury; and 3) a preliminary case report on the use of cryogen spray cooling (CSC) in conjunction with Nd:YAG laser irradiation for treatment of hemangiomas.

### 3. THEORY

Temperature distributions in response to laser irradiation can be computed by solving the heat conduction equation,

$$\nabla^2 \Delta T_L(\mathbf{r}, t) + \frac{Q_L(\mathbf{r})}{k} = \frac{1}{\alpha} \frac{\partial \Delta T_L(\mathbf{r}, t)}{\partial t} \quad (1)$$

where  $\Delta T_L(^{\circ}\text{C})$  is the laser induced temperature increase,  $k (\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1})$  and  $\alpha (\text{m}^2\cdot\text{s}^{-1})$  are the tissue thermal conductivity and diffusivity, respectively;  $t$  (s) is time; and  $\mathbf{r}$  is the position vector in three dimensional coordinates. In turbid media, the volumetric rate of heat generation due to laser irradiation,  $Q_L (\text{W}\cdot\text{m}^{-3})$ , is defined as

$$Q_L(\mathbf{r}) = \mu_a A_o(x, y) \exp(-\mu_{eff} z) \quad (2)$$

where  $A_o(x, y) (\text{W}\cdot\text{m}^{-2})$  is related to the irradiance and a factor that accounts for its augmentation at the surface due to back-scattering of light inside the tissue;<sup>19</sup>  $x$  (m) and  $y$  (m) are distances along the tissue surface;  $z$  (m) is the distance into the tissue;  $\mu_a (\text{m}^{-1})$  is the tissue absorption coefficient;  $\mu_{eff} = \sqrt{3\mu_a[\mu_a + \mu_s(1-g)]}$  is the effective attenuation coefficient ( $\text{m}^{-1}$ );  $\mu_s$  is the tissue scattering coefficient; and  $g$  is the anisotropy of scattering.<sup>20</sup>

The power density,  $P_d$  (power absorbed per unit area of laser irradiated site) ( $\text{W}\cdot\text{m}^{-2}$ ), is expressed as

$$P_d(x, y) = \int_0^{\infty} Q_L(\mathbf{r}) dz' = \frac{\mu_a A_o(x, y)}{\mu_{eff}}; \quad (3)$$

thus, we can rewrite equation (2) as

$$Q_L(\mathbf{r}) = \mu_{eff} P_d \exp(-\mu_{eff} z). \quad (4)$$

For a semi-infinite medium with surface temperature,  $T(z=0, t)$ , and initial temperature,  $T(z, t=0)$  both at a constant value,  $T_i$ , the one-dimensional solution to equation (1) is:<sup>21</sup>

$$\Delta T_L(z, t) = \frac{P_d}{\mu_{eff} k} \left\{ \text{erfc}(\tilde{z}) - \exp(-\mu_{eff} z) + \frac{\exp(-\tilde{z}^2)}{2} \left[ \text{erfcx}(\tilde{\mu}_{eff} - \tilde{z}) - \text{erfcx}(\tilde{\mu}_{eff} + \tilde{z}) \right] \right\} \quad (5)$$

with  $\tilde{\mu}_{eff} = \mu_{eff} \sqrt{\alpha t}$ ,  $\tilde{z} = z / 2\sqrt{\alpha t}$ , and  $\text{erfcx}(x)$  defined as  $\exp(x^2) \times \text{erfc}(x)$ , where  $\text{erfc}(x)$  is the complementary error function,  $1 - \text{erf}(x)$ .

We assume that repetitive application of a cryogen spurt during laser irradiation induces a periodic temperature variation at the surface, and write a thermal boundary condition as

$$T(z=0, t) = T_{trig} - \left[ \frac{T_{trig} - T_{min}}{2} (1 - \cos 2\pi f_{spurt} t) \right] \quad (6)$$

where  $T_{trig}$  is a pre-specified surface temperature above which a cryogen spurt is delivered,  $T_{min}$  is the minimum surface temperature achieved as a result of cooling, and  $f_{spurt}$  (Hz) is the cryogen spurt repetition rate.

Solution of equation (1) with no irradiation (i.e.,  $Q_L(r) = 0$ ), and with boundary condition (6) is:<sup>21</sup>

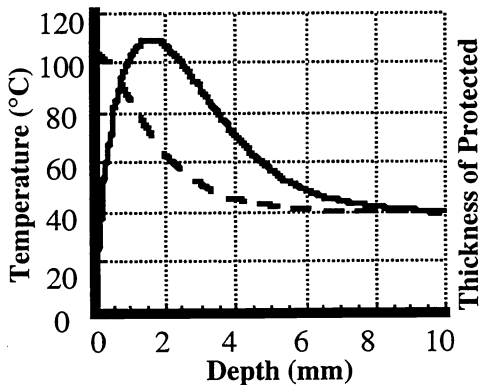
$$\Delta T_{CSC}(z, t) = \frac{T_{min} - T_{trig}}{2} \left\{ \text{erfc}(\tilde{z}) - \exp(-\beta z) \cos(2\pi f_{spurt} t - \beta z) \right\} \quad (7)$$

where  $\Delta T_{CSC}$  is the induced temperature decrease due to CSC, and  $\beta = \sqrt{\pi f_{spurt} / \alpha}$ . Temperature distributions within tissue can then be computed by superposition of thermal response to laser irradiation and CSC:

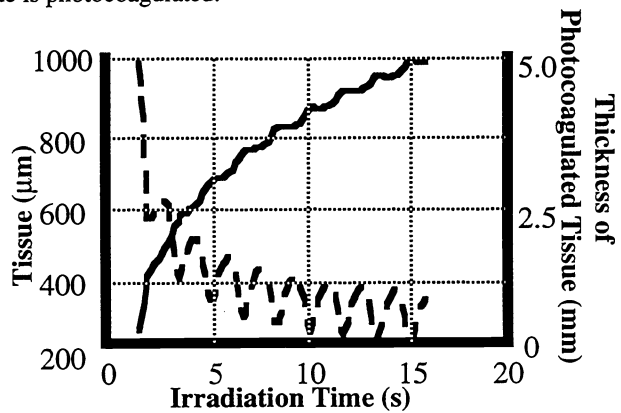
$$T(z, t) = \Delta T_L + \Delta T_{CSC} + T_{trig}. \quad (8)$$

In the absence of CSC, sufficiently high temperature within the superficial tissue structures is reached to cause laser induced thermal injury ( $P_d = 13 \text{ W}\cdot\text{cm}^{-2}$ , laser irradiation time,  $t_l = 4 \text{ s}$ ) (Figure 1). However, with repetitive CSC ( $f_{spurt} = 0.6 \text{ Hz}$ ) during irradiation ( $P_d = 13 \text{ W}\cdot\text{cm}^{-2}$ ,  $t_l = 17.5 \text{ s}$ ,  $T_{trig} = 40 \text{ }^\circ\text{C}$ ,  $T_{min} = 5 \text{ }^\circ\text{C}$ ), superficial tissue structures are protected from thermal injury even when a higher laser energy is used (Figure 1).

Assuming that the threshold temperature for photocoagulation is about  $55 \text{ }^\circ\text{C}$  when this temperature is maintained for seconds, we show the computed thicknesses of photocoagulated and protected tissues as a function of irradiation time (Figure 2). Physically unrealistic ripples in the curves result from the oscillatory boundary condition. Thickness of the protected superficial tissue decreases with irradiation time. With  $P_d = 13 \text{ W}\cdot\text{cm}^{-2}$ , and  $f_{spurt} = 0.6 \text{ Hz}$  approximately  $200 \text{ }\mu\text{m}$  of superficial tissue remains protected after  $16 \text{ s}$  of irradiation, whereas almost  $5 \text{ mm}$  of deeper tissue is photocoagulated.



**Figure 1.** Computed temperature distributions in response to Nd:YAG laser irradiation with (—) and without (---) CSC.

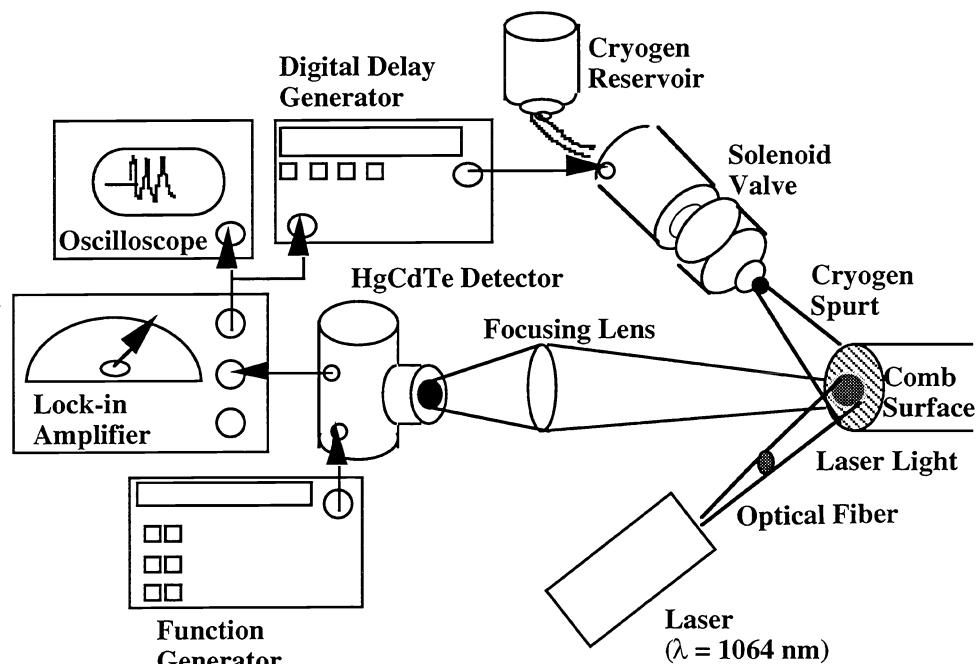


**Figure 2.** Computed thickness of protected (---), and photocoagulated tissue (—) in response to Nd:YAG laser irradiation and CSC.

#### 4. METHODS AND MATERIALS

The highly vascular chicken comb was used as a model for hemangiomas since its histoanatomy is analogous to that found in selected vascular birthmarks, and has been extensively studied.<sup>22</sup> Five adult female leghorn chickens were anesthetized by intravenously injecting 0.3 ml of ketamine and xylazine in a 9:1 volumetric ratio 10-15 minutes prior to beginning each experiment. Experimental protocol and handling of the animals were approved by the Animal Research Committee at the University of California, Irvine.

The experimental set-up for laser irradiation and CSC is shown in Figure 3. Laser light was delivered through a 600  $\mu\text{m}$  core-diameter silica multimode optical fiber, and directly incident onto the comb. Diameter of the laser irradiated site,  $d$ , was maintained at 7 mm in all experiments. Incident laser power,  $P$ , ranged from 5 to 90 W; irradiation time,  $t_l$ , from 10 to 135 s; and the radiant exposure,  $E_o$ , from 130 to 3,500  $\text{J}\cdot\text{cm}^{-2}$ . Depending on the size of the comb, three to eleven sites were irradiated; combs with smaller surface areas allowed fewer irradiation sites.



**Figure 3.** Schematic of experimental set-up for CSC in conjunction with Nd:YAG laser irradiation. Measurements of surface temperature were made by infrared radiometry.

Chlorodifluoromethane (Aldrich Chemical Company, Milwaukee, WI) (boiling point (BP)  $\approx -40$   $^{\circ}\text{C}$ ), a hydrochlorofluorocarbon (HCFC-22) was used as test cryogen on the combs. Due to their relatively minimal ozone depletion potential, HCFCs are considered suitable alternatives to chlorofluorocarbons (CFCs).<sup>23,24</sup>

Cryogen was sprayed onto the comb through an electronically controlled standard automobile fuel injection valve positioned 4 cm from the surface at a  $30^{\circ}$  angle from the tissue normal. Cryogen spurt duration ( $\tau$ ) was set by a programmable digital delay generator (DG535, Stanford Research Systems, Sunnyvale, CA), and ranged between 30 and 100 ms. The cooled site on the comb surface was concentric with the laser irradiated site, and about 10 mm in diameter. No indications of cryogen induced thermal injury were observed outside the laser irradiated site.

Radiometric measurement of surface temperature at the center of the laser irradiated site was used to trigger the delivery of cryogen spurts. When the radiometric surface temperature reached a pre-specified trigger value,

$T_{trig}$ , (ranging between 36 and 41 °C), a cryogen spurt was delivered onto the comb. In this way, repetitive pulsed CSC during continuous laser irradiation was accomplished through a feedback system.

Infrared emission from the comb was detected using a 1 mm<sup>2</sup> liquid N<sub>2</sub> cooled HgCdTe detector (MDD-10E0-S1, Cincinnati Electronics, Mason, OH), optically filtered at the cold stop by a 10.6-14 μm bandpass filter. Because the infrared absorption coefficient of water in this range is approximately 60 mm<sup>-1</sup>,<sup>24</sup> we expect that contributions to the infrared signal originate predominantly from superficial depths (1/60 mm<sup>-1</sup> ≈ 0.017 mm).

The HgCdTe detector was placed at the focal plane of a 25 mm diameter f/1 Ge lens configured for unit magnification. For improved signal to noise ratio, pupil was stopped to 5 mm diameter, and the infrared signal was amplitude modulated by switching the detector on and off by a highly stable synthesized function generator (Model DS345, Stanford Research Systems) at a rate of approximately 25 kHz. Modulated signal was synchronously detected by a lock-in amplifier (Model SR850, Stanford Research Systems). The output signal of the lock-in amplifier was used to define the trigger level for the digital delay generator.

The infrared detection system was calibrated by measuring the lock-in amplifier output voltage as a function of the surface temperature of an aluminum block coated with highly emissive ( $\epsilon \approx 0.97$ ) black paint (TC-303 black, GIE Corp., Provo, UT) and heated by a resistive element from 23 °C to 75 °C. Surface temperature of the aluminum block was measured using a precision thermistor (8681, Keithley Instruments, Cleveland, OH) attached to the block; the measured output voltage varied linearly with temperature.

Following each experiment, irradiated and cooled sites were examined grossly for surface protection due to CSC, while the opposite sides of the combs were examined for blanching due to laser induced photocoagulation. Chickens were euthanized at various times (1 h - 21 days) following the experiments. Combs were removed and prepared for histologic analysis.

## 5. RESULTS AND DISCUSSION

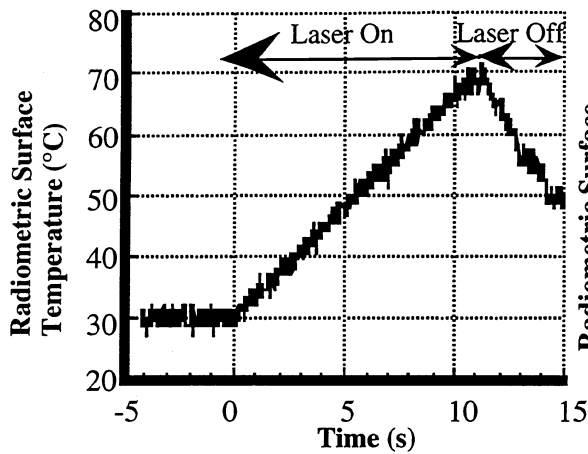
### 5.1. Temperature measurements

Temperature measurement in response to laser irradiation ( $P = 20$  W,  $t_l = 12$  s,  $d = 7$  mm) without CSC showed a linear increase to 70 °C (Figure 4a). The observed linear increase indicates that both thermal diffusion and heat loss at tissue-air interface were negligible during irradiation. Under these conditions, surface temperature is directly related to the radiant exposure, tissue thermal properties, and absorption coefficient.<sup>26</sup> Once the laser was turned off, surface temperature decreased monotonically.

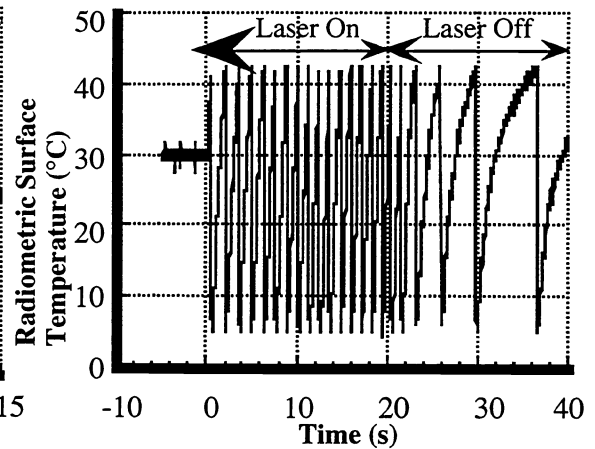
Rapid surface temperature reductions to approximately 5 °C were observed in response to 50 ms chlorodifluoromethane spurts sprayed onto the comb during laser irradiation ( $P = 35$  W,  $t_l = 20$  s,  $d = 7$  mm,  $T_{trig} = 42$  °C) (Figure 4b). When the infrared radiometry feedback system remained on after the laser was turned off, cryogen spurts (with decreasing frequency) were released in response to heat diffusing from within the comb to the surface (Figure 4b).

### 5.2. Gross and Histologic Observations

Without CSC, the irradiated comb surface was always blanched in response to laser irradiation at  $E_o$  as low as 520 J•cm<sup>-2</sup> ( $P = 20$  W,  $t_l = 10$  s,  $d = 7$  mm). With CSC, however, protection of superficial tissue structures from thermal injury was achieved even when irradiating the comb surface at higher values of  $E_o$  ranging from 910 ( $P = 35$  W,  $t_l = 10$  s,  $d = 7$  mm) to 2,600 J•cm<sup>-2</sup> ( $P = 50$  W,  $t_l = 20$  s,  $d = 7$  mm). The thickest comb site that was blanched on the opposite surface ( $P = 40$  W,  $t_l = 20$  s,  $d = 7$  mm;  $E_o = 2,080$  J•cm<sup>-2</sup>), and protected on the irradiated surface due to CSC was 6.1 mm. Superficial tissue structures were not protected by CSC when  $E_o$  exceeded 2,340 J•cm<sup>-2</sup> ( $P = 60$  W,  $t_l = 15$  s,  $d = 7$  mm).

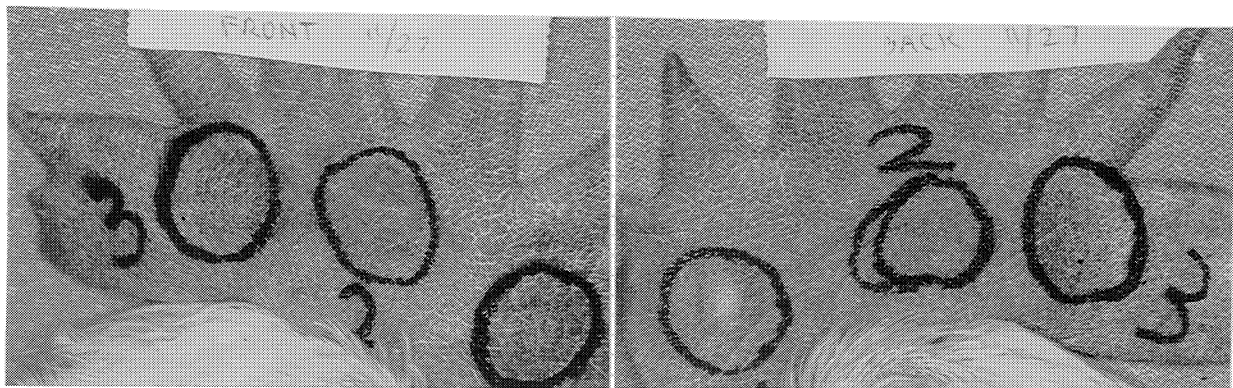


**Figure 4a.** Radiometric surface temperature of the chicken comb in response to Nd:YAG laser irradiation without CSC.



**Figure 4b.** Radiometric surface temperature of the chicken comb in response to Nd:YAG laser irradiation, and 50 ms repetitive chlorodifluoromethane spurts.

Photographs of irradiated and opposite surfaces of a comb taken immediately after the experimental procedure are shown in Figure 5. Laser irradiation parameters were:  $P = 35 \text{ W}$ ,  $t_l = 20 \text{ s}$ ,  $d = 7 \text{ mm}$  on sites 1 and 2;  $P = 35 \text{ W}$ ,  $t_l = 30 \text{ s}$ ,  $d = 7 \text{ mm}$  on site 3. Sites 1 and 2 were cooled by repetitive application of 50 ms chlorodifluoromethane spurts. On site 3, the spurt duration was 80 ms. Tissue thickness was 4.0, 9.1, and 7.0 mm for sites 1-3, respectively. Surface of the comb was not blanched since with CSC temperature was maintained below the necessary threshold required for thermal damage (Figure 5a). However, the surface opposite to radiation at site 1 was blanched (Figure 5b); indicating a sufficient laser induced temperature increase was obtained at this location to cause thermal damage. The opposite surfaces at sites 2 and 3 were not blanched due to greater tissue thickness at these locations.



(a)

(b)

**Figure 5.** Photographs of a chicken comb irradiated with the Nd:YAG laser and repetitively cooled with 50 ms chlorodifluoromethane spurts. (a) irradiated surface is not blanched due to CSC, (b) on the opposite side of the comb, site 1 was blanched.

Histologic sections obtained from site 1 are shown in Figure 6. Euthanasia time was 21 days after the experimental procedure. Epidermis is intact; papillary and reticular dermis are clearly distinguished (Figure 6a). The opposite side of the comb is shown in Figure 6b. Most of the dermal venules are occluded, and the necrotic tissue appears as a homogeneous structure. Histologic sections obtained from comb sites that were irradiated without CSC showed detachment of epidermis.

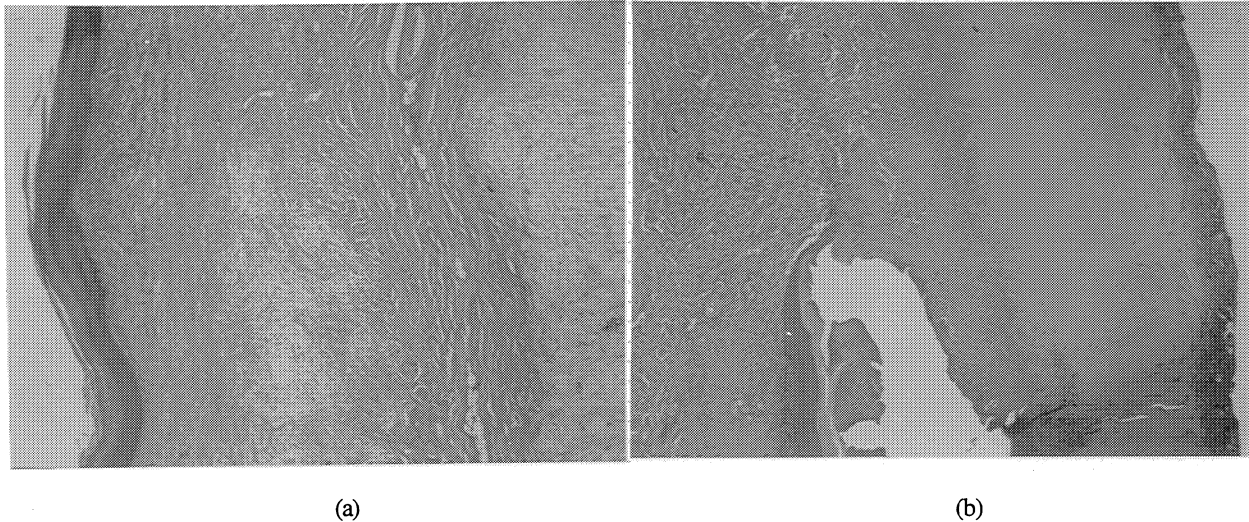


Figure 6. Histologic sections of site 1 (chicken euthanized 21 days after the experiment). (a) epidermis is intact on the irradiated and cooled surface, (b) deeper tissue structures are photocoagulated (magnification: 73X).

### 5.3. Clinical implications and a preliminary case report

Light emitted from the Nd:YAG laser ( $\lambda = 1064 \text{ nm}$ ) penetrates deeply (5-7 mm) into tissue, and has been used to photocoagulate thick hemangiomas.<sup>4,7-9</sup> However, laser induced thermal damage to the epidermis remains a major concern.<sup>10</sup>

As demonstrated in experiments using the chicken comb model, epidermal protection and deep tissue photocoagulation can be achieved by repetitive application of a short cryogen spurt during continuous Nd:YAG laser irradiation. In addition to protecting the superficial tissue structures from thermal injury, CSC can potentially reduce the irradiation time during laser treatment of hemangiomas. Relatively high incident powers (that might otherwise result in photothermal destruction of superficial tissue) may be applied over a short time (e.g.,  $t_l = 10\text{-}20 \text{ s}$ ).

Although in this study, up to approximately 6 mm of tissue was photocoagulated, successful treatment of hemangiomas might be achieved by inducing smaller coagulation depths to initiate the "involution" process.<sup>10</sup> In a preliminary clinical evaluation, a six month old male child with a hemangioma on his lower lip was treated under general anesthesia using Nd:YAG laser irradiation in conjunction with CSC at Chang Gung Memorial Hospital in Taipei, Taiwan. Six sites were irradiated with  $P$  ranging from 30 to 45 W, and  $t_l = 15$  or 20 s ( $E_o = 1,170$  to  $2,340 \text{ J}\cdot\text{cm}^{-2}$ ). Diameter of irradiated sites was 7 mm. Chlorodifluoromethane spurts ( $\tau = 50 \text{ ms}$ ) were released during the irradiation at a non-uniform frequency ranging between 0.9 and 2.0 Hz.

Five weeks after the procedure, considerable shrinkage of the hemangioma was observed. When a hemangioma is located on the lip, it is plausible that similar results could have been obtained without CSC. However, with CSC no open wounds were formed, and a rapid healing response in 10 days was observed. Additional experiments are underway to optimize the irradiation and CSC parameters for successful clinical application.



## 6. CONCLUSIONS

Spatially selective photocoagulation of subsurface targeted blood vessels by repetitive application of a short cryogen spurt during continuous Nd:YAG laser irradiation has been demonstrated in the chicken comb animal model, and in one human case. This procedure may be effective for treatment of thick hemangiomas which requires photocoagulation of subsurface blood vessels while protecting the epidermis.

## 7. ACKNOWLEDGMENTS

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