Dynamics of tissue optics during laser heating of turbid media

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The dynamics of the optical behavior of tissue during the photothermal interaction of laser radiation with tissue could significantly affect the optimization of light doses for effective and safe applications of lasers in medicine. Characterization of the dynamics of tissue optics during laser heating was performed by means of simultaneous measurements of the total transmittance, diffuse reflectance, and surface temperature of fresh and thermally coagulated human skin and canine aorta during long-pulsed Nd:YAG laser heating with a double integrating-sphere system and an infrared camera. Thermally induced changes in the optical properties of tissue caused a decrease in the total transmittance and an increase in the diffuse reflectance of both fresh and precoagulated skin and aorta samples. For fresh tissue, these changes were primarily reversible until photocoagulation occurred, then both the reversible, as well as the irreversible, changes were observed. However, for precoagulated tissue the reversible changes in the optical properties were dominant, whereas the irreversible changes were insignificant. Results from this study indicate the existence of the nonlinear behavior in the optics of turbid biological media during pulsed laser heating. Possible mechanisms responsible for this nonlinear optical behavior are discussed.

Key words: Tissue optics, reversible optical behavior, tissue coagulation, pulsed laser, laser heating, total transmittance, diffuse reflectance.

1. Introduction

The propagation of light in tissue is often modeled based on an approximate solution to the transport equation[1–4] or a Monte Carlo simulation.[4–7] Both methods use the absorption coefficient μ_a (in units of inverse meters), the scattering coefficient μ_s (in units of inverse meters), and the single-scattering phase function $p(\cos\theta)$ (in units of inverse steradians) to represent the optical properties of tissue. Various groups are investigating and developing methods to obtain the optical properties of tissue.[3,8] These properties are usually inferred from reflectance and transmittance measurements, which are performed under constant temperature (i.e., room or body temperature) by the use of low light doses. A critical question is whether optical properties determined under static conditions could truly describe the optical behavior of tissue during intense laser irradiation.

Several groups have demonstrated that thermally induced coagulation and dehydration irreversibly alter the optical properties of tissue.[9–17] An obvious example is the whitening of transparent egg white when cooked. The assumption that the optical properties of tissue remain constant during photothermal laser–tissue interactions is therefore inappropriate. Although the effects of photocoagulation and dehydration on tissue optics has been investigated for several years, most of these studies were restricted to either static or slow heating conditions. Therefore, these studies examined only thermally induced changes in the optical properties of tissue for a few limited stages in the process of laser–tissue interaction. Moreover, it has been reported that the absorption coefficient of water at mid-infrared wavelengths, as well as the refractive index of some transparent biological media, are temperature dependent, and these are often transient changes.[18–21] Hence we believe that photothermal laser interaction with tissue may cause both reversible as well as irreversible changes in the optical behavior of turbid tissue.

It is the aim of this study to explore the influence of laser-induced temperature rise on the optical

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behavior of tissue during laser heating. Transient changes in the total transmittance and in reflectance were monitored with a double integrating-sphere system to investigate the dynamics of the optical properties of human skin and canine aorta during high-power pulsed Nd:YAG laser irradiation. An infrared camera was used to quantify the laser-induced thermal field in the tissue. Thermally induced reversible and irreversible changes in the optical behavior of human skin and canine aorta, which represent two types of tissues of significantly different structure and static optical properties, are examined in this work.

2. Materials and Methods

Fresh human skin and canine aorta tissue were used in this study. These two types of tissue have significantly different static optical properties, and each contains one of the major tissue constituents, collagen and elastin, respectively. Human skin obtained from the tissue bank at a local hospital were preserved in a solution of RPMI 1640 (BioWhittaker) with HEPES (N'-2-hydroxyethylpiperazine-N'-2 ethane sulfonic acid), L-glutamine, penicillin G potassium, Grutamicin, and 0.9% sodium chloride and refrigerated at 2–6 °C. These samples contained both epidermal and dermal tissue (0.6 ± 0.2 mm thick, $n = 5$). Canine aortas were harvested immediately *post mortem* (1.2 ± 0.2 mm, $n = 5$). The canine aorta samples were wrapped in saline-moistened gauze, stored at 2–6 °C, and used within 24 h after the tissue was harvested. Prior to any measurements, the tissue was cut to 1.5 cm × 1.5 cm square samples. They were then mounted on a custom-made, U-shaped clamp and placed between two integrating spheres to conduct the measurement. Both sides of the sample were exposed to air to provide an air–tissue–air optical and thermal boundary condition.

For differentiating reversible changes from irreversible ones and determining the effect of thermal denaturation on the dynamics of the tissue optics, some tissue samples were thermally denatured prior to the performance of the optical measurements. In the preparation of these samples, fresh human skin and aorta were wrapped in water-tight aluminum foil packets and then submerged in a 75 ± 5 °C water bath for at least 45 min to fully coagulate the tissue samples.

The dynamics of tissue optics during laser irradiation were characterized by monitoring of the transient changes in the total transmittance and diffuse reflectance of laser radiation from the tissue. Two integrating spheres (Labsphere, 4 in. in diameter, time constant <20 ns) were used to collect the total transmitted $T(t)$ and reflected $R(t)$ light as a function of time (see Fig. 1). The fluence rate (in watts per millimeter squared) inside each sphere was measured with a photodiode (Hamamatsu Model S1087-01; rise time, $\sim$1 μs) located at the detector port (0.25 in. in diameter). Pinholes and density filters were used to limit the light flux incident on the photodiodes to ensure that the photodiodes operated in their linear region. For monitoring the temporal profile of the laser pulse and to provide a reference signal, a silica-glass microscope slide was placed in the beam path to deflect a small fraction ($\sim$15%) of the laser beam to a reference integrating sphere (see Fig. 1).

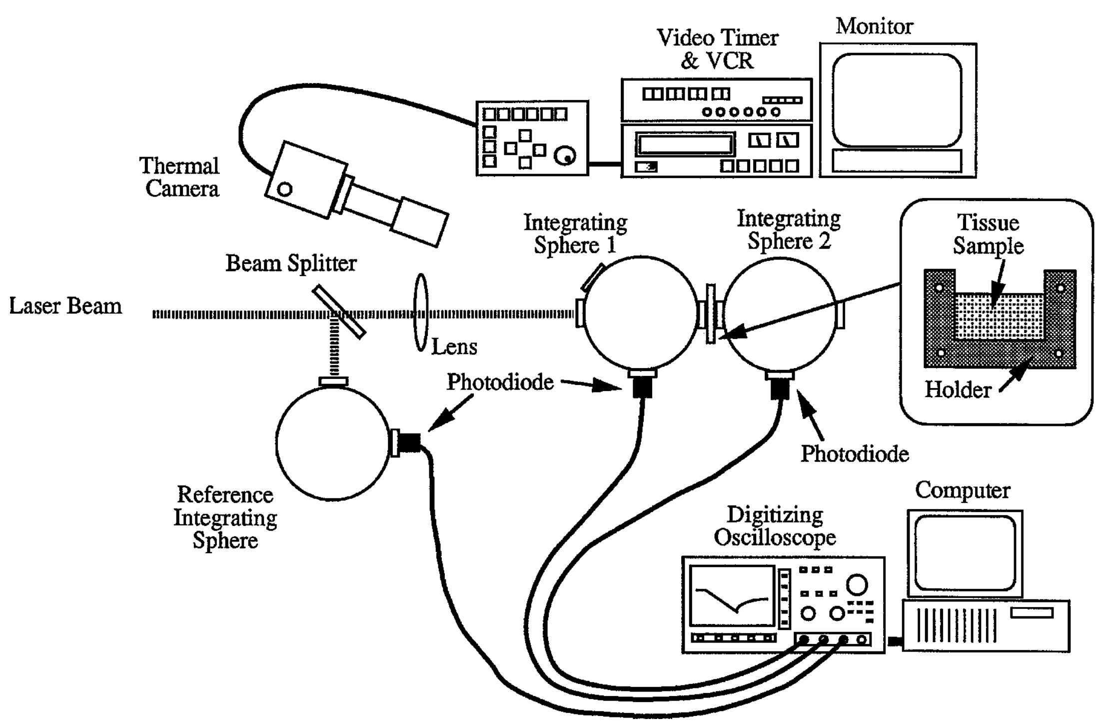

Fig. 1. Schematic diagram of the experimental setup for the *in vitro* measurements of the dynamics of optical behavior and the thermal response of tissue during pulsed laser irradiation.

With another fast detector, the reference signal Ref(t) was detected and recorded simultaneously along with $T(t)$ and $R(t)$ during laser heating by use of a digitizing oscilloscope (Tektronix, Model TDS-520) with general-purpose interface bus interface. Optically stable diffuse glasses and microscope slides were used to calibrate the system prior to each experiment.

A long (~200-µs) pulsed Nd:YAG laser emitting at 1064 nm (Lumonic Inc.) was used as a heat source. The laser was operated at 10 Hz producing 900 ± 20 mJ/pulse. After transmission through a microscope slide, the laser beam was focused onto the tissue surface by means of a long-focal-length biconvex lens (Newport; 0.5 in., $f = 50$ cm) illuminating a 1.5-mm spot.

Through an extra port in integrating sphere 1, the surface temperature of the tissue during laser irradiation was monitored with an infrared camera (Inframetrics, Model 600L). Although it was not possible to infer accurately the peak temperature during laser heating because of the slow temporal response (33 ms) of the infrared camera, the average temperature increase and the temperature relaxation after each laser pulse were measured.

The time courses of the relative total transmittance $T(t)/\mathrm{Ref}(t)$ and the diffuse reflectance $R(t)/\mathrm{Ref}(t)$ were used to analyze the dynamics of the optical behavior of the tissue samples. Each experiment in this study was repeated at least five times to examine the reproducibility of the optical response. Because Nd:YAG laser radiation provided both pump (heating) and probe (monitoring the changes in tissue optics) functions, the optical behavior of the tissue between laser pulses was not documented.

For facilitation of observation and analysis, a special sequence of laser pulses was used to characterize the dynamics of tissue optics during pulsed laser heating (see Fig. 2). The sequence started with the application of a single laser pulse during which the temporal distribution of both reflected and transmitted signals was recorded. The purpose of this measurement was to establish the initial values, T_{init} and R_{init}, needed to determine the optical behavior of tissue following the application of subsequent pulses. T_{init} and R_{init} were defined as

$$T_{\mathrm{init}} = \frac{T(t_{\mathrm{init}})}{\mathrm{Ref}(t_{\mathrm{init}})}, \tag{1}$$

$$R_{\mathrm{init}} = \frac{R(t_{\mathrm{init}})}{\mathrm{Ref}(t_{\mathrm{init}})}, \tag{2}$$

respectively, where t_{init} is defined as the time interval corresponding to the first few microseconds of the laser pulse applied prior to the observation of any significant increase in tissue temperature.

For elevating tissue temperature, a few seconds after the application of a single laser pulse, 20 laser pulses were delivered at the rate of 10 pulses/s to the same site of the tissue where the initial values for reflectance and transmittance were measured. The number of laser pulses and the repetition rate were chosen to induce a significant surface-temperature rise (20–30 °C at least) in the tissue. During pulsed laser heating, the average surface temperature of the irradiated site at the start of each pulse increased as a result of the superposition of temperature fields produced by the previous pulses. The time-varying total transmittance and diffuse reflectance of laser radiation from the heated sample were recorded during the last laser pulse (20th). The minimum value in the total transmittance $T_{20}(t_{\mathrm{min}})$ and the time of its occurrence were recorded. The maximum value in the diffuse reflectance $R_{20}(t_{\mathrm{max}})$ and the time of its occurrence were also recorded. The normalized terms $T_{20,\mathrm{min}}$ and $R_{20,\mathrm{max}}$ were defined as

$$T_{20,\mathrm{min}} = \frac{T_{20}(t_{\mathrm{min}})}{\mathrm{Ref}_{20}(t_{\mathrm{min}})}, \tag{3}$$

$$R_{20,\mathrm{max}} = \frac{R_{20}(t_{\mathrm{max}})}{\mathrm{Ref}_{20}(t_{\mathrm{max}})}, \tag{4}$$

respectively, where the subscript 20 implies the measurement within the 20th pulse and $t_{\mathrm{min}}(t_{\mathrm{max}})$ represents the time of the occurrence of the maximum change in the transmittance and reflectance, respectively, within the 20th pulse.

After the tissue was permitted to cool off and return to room temperature, another single pulse was delivered to document the optical behavior of tissue following laser heating. To assess the optical properties of tissue at this stage, T_{final} and R_{final} were defined by

$$T_{\mathrm{final}} = \frac{T(t_{\mathrm{init}})}{\mathrm{Ref}(t_{\mathrm{init}})}, \tag{5}$$

$$R_{\mathrm{final}} = \frac{R(t_{\mathrm{init}})}{\mathrm{Ref}(t_{\mathrm{init}})}, \tag{6}$$

respectively. For quantifying the dynamics of the tissue optics during laser heating, the percent tran-

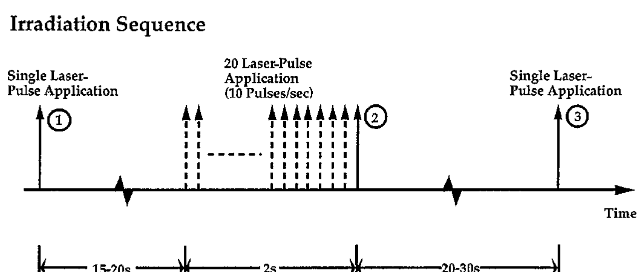

Fig. 2. Illustration of the irradiation sequence used in the study of the dynamics of tissue optics during pulsed laser irradiation. The numbers 1, 2, and 3 that are circled denote the pulses at which the measurements were taken.

sient change in optical behaviors was first determined by

$$\Delta T_{\min}\% = \left(\frac{T_{20,\min} - T_{\text{init}}}{T_{\text{init}}}\right)100\% \tag{7}$$

$$\Delta R_{\max}\% = \left(\frac{R_{20,\max} - R_{\text{init}}}{R_{\text{init}}}\right)100\%, \tag{8}$$

respectively. Furthermore, differentiating the reversible and irreversible components of the thermally induced changes in the optical behavior of the tissue was accomplished by the use of the following equations:

$$\Delta T_{\text{rv}}\% = \left(\frac{T_{20,\min} - T_{\text{final}}}{\Delta T_{\min}}\right)100\% \tag{9}$$

$$\Delta T_{\text{ir}}\% = \left(\frac{T_{\text{final}} - T_{\text{init}}}{\Delta T_{\min}}\right)100\% \tag{10}$$

$$\Delta R_{\text{rv}}\% = \left(\frac{R_{20,\max} - R_{\text{final}}}{\Delta R_{\max}}\right)100\% \tag{11}$$

$$\Delta R_{\text{ir}}\% = \left(\frac{R_{\text{final}} - R_{\text{init}}}{\Delta R_{\max}}\right)100\%, \tag{12}$$

where values of $\Delta T_{\min} = T_{20,\min} - T_{\text{init}}$ and $\Delta R_{\max} = R_{20,\max} - R_{\text{init}}$ were used. The reversible and irreversible changes are represented by the subscripts rv and ir, respectively.

3. Results

We observed that, in general, the total transmittance decreased and the diffuse reflectance increased gradually as surface temperature of skin or aortic specimens was elevated during pulsed laser heating. A typical profile of the time-varying total transmittance of laser radiation through fresh human skin samples at different pulses (i.e., the 1st, 5th, 10th, and 20th pulses) is shown in Fig. 3. The optical behavior of skin exhibited both reversible and irreversible changes during high-power pulsed Nd:YAG laser irradiation (510 mJ/mm^2). The maximum changes in both the total transmittance and diffuse reflectance were observed at the end of the 20th pulse. When the skin sample returned to room temperature after laser heating, its optical behavior had partially recovered. Figures 4(a) and 4(b) illustrate the time-resolved optical behavior of fresh human skin irradiated with the pulse-irradiation sequence described in Fig. 2. The difference between the initial values (T_{init} and R_{init}) and the final values (T_{final} and R_{final}) of the total transmittance and reflectance represents the irreversible modification of the optical properties of skin. The maximum surface-temperature rise observed during laser heating of skin after the 20th laser pulse was approximately 71 ± 2 °C (see Table 1). The corresponding

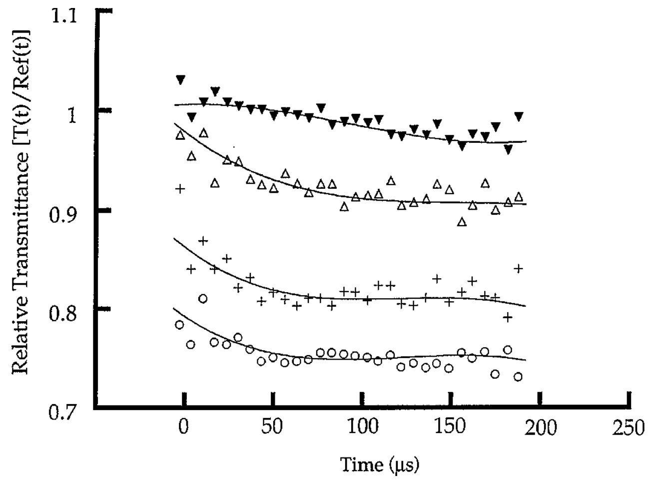

Fig. 3. Dynamics of the total transmittance of fresh skin (thickness of 0.6 mm) irradiated with a sequence of Nd:YAG laser pulses (510 mJ/mm^2). Changes in transmittance within the 1st, 5th, 10th, and 20th pulses are presented. The solid curves are the third-order polynomial least-squares fits to the data. Zero on the time axis represents the start of each laser pulse: Inverted solid triangles represent the 1st pulse, open triangles the 5th pulse, crosses the 10th pulse, and open circles the 20th pulse.

maximum decrease in the total transmittance $\Delta T_{\max}\%$ was 36% ± 3%. This change contained both reversible $\Delta T_{\text{rv}}\%$ and irreversible $\Delta T_{\text{ir}}\%$ components, of which the irreversible part was approximately one third of the maximum change. Under the same conditions the maximal increase in the diffuse reflectance $\Delta R_{\max}\%$ was 58 ± 7%, of which approximately 36% ± 5% of this change was irreversible $\Delta R_{\text{ir}}\%$. However, for the precoagulated human skin samples, the changes in optical behavior during laser heating were mainly reversible (at least 90%). In this case the deposition of 20 laser pulses raised the surface temperature to ~72 ± 4 °C and caused a 21% ± 5% decrease in the total transmittance $\Delta T_{\min}\%$, as well as a 30% ± 10% increase in the diffuse reflectance $\Delta R_{\max}\%$.

For aortic specimens the total transmittance decreased, but the diffuse reflectance remained approximately constant when the samples were heated by laser radiation. Typical profiles of the time-resolved transmittance and reflectance during pulsed laser heating are shown in Figs. 5(a) and 5(b). The close correlation between the initial states (T_{init} and R_{init}) and final states (T_{final} and R_{final}) of the optical behavior indicates that the changes in aorta optics observed during laser heating were nearly fully reversible. For the fresh canine aorta samples, the surface temperature reached 58 ± 1 °C at the end of laser irradiation, and there was not any visible sign of coagulation such as blanching. The maximum decrease in the total transmittance $\Delta T_{\min}\%$ was ~23% ± 3%. This change was mainly reversible ($\Delta T_{\text{rv}}\% > 90\%$). Under the same conditions, the maximum increase in diffuse reflectance $\Delta R_{\max}\%$ was approximately a 7% ± 2%, of which two thirds of

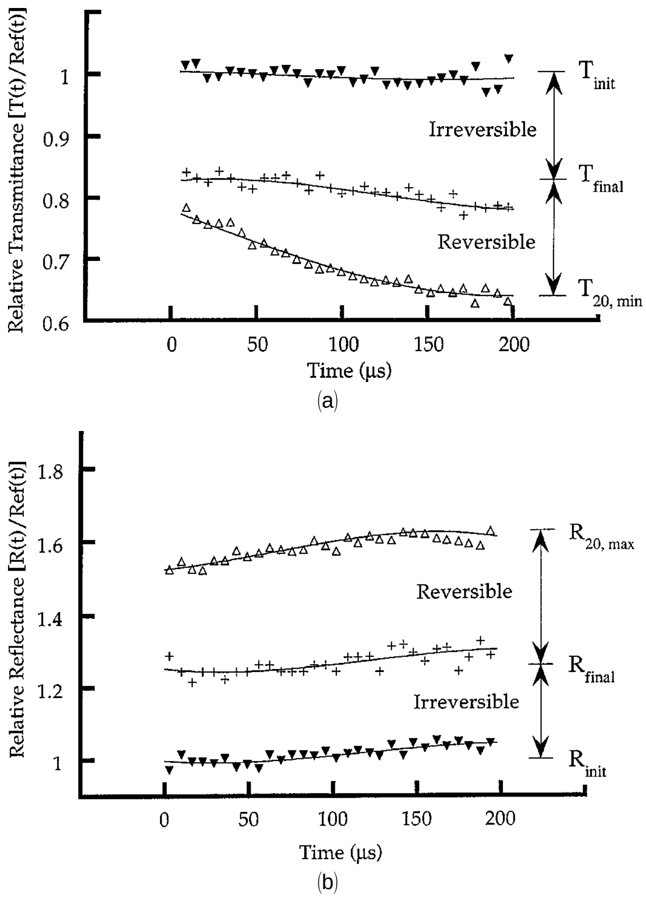

Fig. 4. Example of the dynamics of (a) the total transmittance and (b) the diffuse reflectance of a fresh human skin sample (thickness, 0.8 mm) irradiated with a sequence of 20 Nd:YAG laser pulses (510 mJ/mm^2). The inverted solid triangles represent the time-resolved optical behavior of human skin within the first single laser-pulse application (①), the open triangles the last pulse (20th, ②) in the irradiation sequence, and the crosses the last single laser-pulse application (③). The solid curves are the third-order polynomial least-squares fits to the data. Zero on the time axis represents the start of each laser pulse.

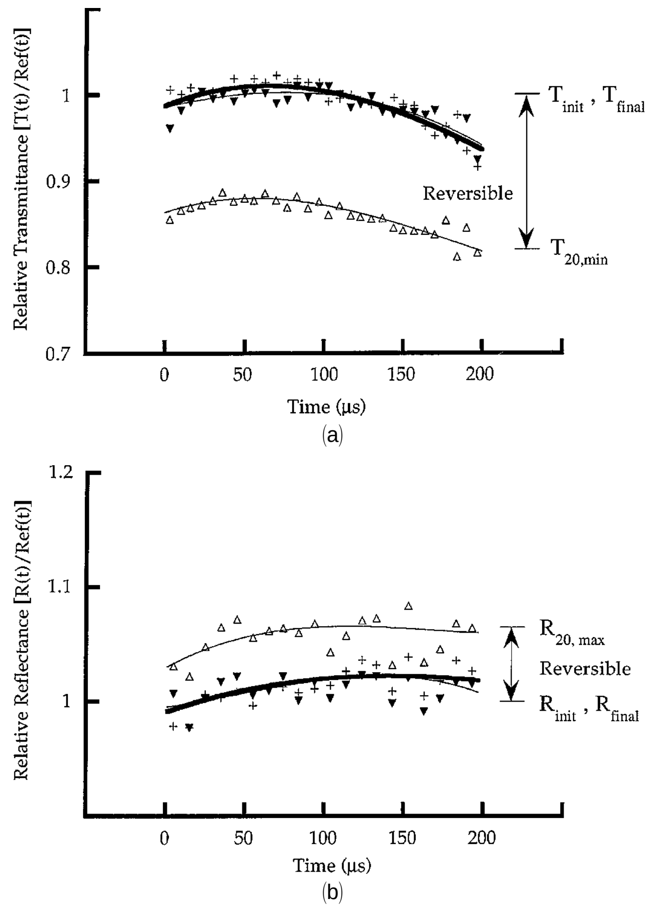

Fig. 5. Example of the dynamics of (a) the total transmittance and (b) the diffuse reflectance of a fresh aorta sample (thickness 1.2 mm) irradiated with a sequence of 20 Nd:YAG laser pulses (510 mJ/mm^2). The inverted solid triangles represent the time-resolved optical behavior of canine aorta within the first single laser pulse application (①), the open triangles the last pulse (20th, ②) in the irradiation sequence, and the crosses the last single laser-pulse application (③). The solid curves are the third-order polynomial least squares fits to the data. Zero on the time axis represents the start of each laser pulse.

this change was recovered after the laser application.

For the precoagulated canine aorta samples, the changes in the optical behavior arising from laser heating were also mainly reversible. The deposition of 20 laser pulses induced a peak surface temperature of ~69 ± 2 °C in the coagulated canine aorta samples and caused an 18% ± 1% decrease in the total transmittance $\Delta T_{\min}\%$. This change was almost entirely reversible. In contrast, in the dif-

Table 1. Final Surface Temperatures and Corresponding Optical-Behavior Changes of Human Skin Irradiated with a Sequence of 20 Nd:YAG Laser Pulses at 510 mJ/mm^2[a]

Sample	Final Surface Temperature (°C)	Percent Change		
		Maximum	Reversible Part	Irreversible Part
Fresh skin				
T	71 ± 2	$\Delta T_{\min}\% = -36 \pm 3$	$\Delta T_{\rm rv}\% = 64 \pm 6$	$\Delta T_{\rm ir}\% = 36 \pm 6$
R	71 ± 2	$\Delta R_{\max}\% = +58 \pm 7$	$\Delta R_{\rm rv}\% = 64 \pm 5$	$\Delta R_{\rm ir}\% = 36 \pm 5$
Coagulated skin				
T	72 ± 4	$\Delta T_{\min}\% = -21 \pm 5$	$\Delta T_{\rm rv}\% = 95 \pm 5$	$\Delta T_{\rm ir}\% = 5 \pm 5$
R	72 ± 4	$\Delta R_{\max}\% = +30 \pm 10$	$\Delta R_{\rm rv}\% = 89 \pm 8$	$\Delta R_{\rm ir}\% = 11 \pm 8$

[a]The mean values plus and minus the standard deviation of five measurements for each result are presented.

fuse reflectance $\Delta R_{max}\%$ a small increase of $4\% \pm 1\%$ was detected.

4. Discussion

The dynamics of the optical behavior of human skin and canine aorta have been analyzed *in vitro*. The results demonstrate that the optical properties of these turbid tissues undergo reversible and irreversible changes during 1064-nm pulsed laser heating. Some general characteristics of the dynamics of the optical behavior of turbid tissue were observed in this study. First, the reversible changes in optical behavior were temperature related; they vanished as the temperature of the sample returned to room temperature. Second, in the temperature range reported here, the reversible and irreversible changes in the optical behavior of human skin and canine aorta shared a common trend: the total transmittance decreased and diffuse reflectance increased during laser radiation. However, the extent of the changes in the optical behavior of these two types of tissue was different, especially for the change in the maximum diffuse reflectance (see Tables 1 and 2). Third, the mechanisms of thermally induced reversible changes in optical behavior seemed to be independent from those of the irreversible changes. This difference was at least partially supported by the experimental results obtained from precoagulated samples cooked in a constant-temperature water bath prior to laser heating. When the coagulated samples were irradiated, the irreversible component expressed as $\Delta T_{ir}\%$ and $\Delta R_{ir}\%$ became relatively insignificant (see Tables 1 and 2). However the reversible component in terms of the maximum percent change was approximately the same for the fresh and the precoagulated tissue samples.

In terms of the thermal response of tissue, with heat conduction neglected, during each pulse, the temperature rise at the end of the 200-μs pulse would be

$$\Delta T(t) = \frac{\phi(0)\mu_a t}{\rho c}, \tag{13}$$

where $\phi(0)$ is the fluence rate just below the sample surface, μ_a is the absorption coefficient, t is the pulse length, ρ is the density of the sample, and c is the volumetric heat capacity. If one assumes values of $\phi(0) = E = 2.55 \times 10^5$ W/cm^2, $\mu_a(\text{skin}) = 1.0$ cm^{-1}, $\rho c = 4.18$ (W s/(cm^3 °C), the transient temperature rise during a 200-μs laser pulse is approximately

$$\Delta T(t) = (6.1 \times 10^4)t = 12\ °\text{C}. \tag{14}$$

At the end of each 200-μs pulse, the temperature is partially relaxed until the next laser pulse. The estimated diffusion time for a spot radius of 0.75 mm is ~500 ms,[20] which is longer than the 100-ms time interval between heating laser pulses delivered at 10 Hz. This resulted in a buildup of temperature between the laser pulses. Thus the measured temperature is the accumulation of the temperature increases during each laser pulse and the relaxation responses between pulses. The difference between the final temperature rise observed during laser heating of skin ($\Delta T = 50$ °C) and that documented during laser heating of aorta ($\Delta T = 37$ °C) is essentially attributed to the lower absorption coefficient of fresh canine aorta at 1064 nm.

Thermal coagulation is a well-known rate process through which the exposure of tissue to heat above a threshold temperature and over a period of time may irreversibly denature the tissue samples. During laser heating of skin, a surface temperature of >70 °C produced by 20 Nd:YAG laser pulses of 510 mJ/mm^2 was sufficient to coagulate the human skin and induce thermal lesions that could be easily seen with the naked eye. The irreversible decrease in the total transmittance and increase in the diffuse reflectance suggest an increase in the scattering coefficient of the tissue, which is consistent with the findings of previous studies.[9–14]

However, the thermal response of canine aorta to the heating pulsed sequence utilized in this study appeared to be quite different. The temperature did not rise high enough to induce any visible thermal lesions. Thus the changes in transmittance and reflectance were essentially reversible. We believe the small irreversible component observed throughout these measurements (see Table 2) were produced by surface dehydration or water evaporation during laser heating.[12,13]

The existence of reversible optical changes in tissue during laser heating implies that the temperature rise in tissue can affect tissue optical behavior through mechanisms other than coagulation and

Table 2. Final Surface Temperatures and Corresponding Optical-Behavior Changes of Human Skin Irradiated with a Sequence of 20 Nd:YAG Laser Pulses at 510 mJ/mm^2[a]

Sample	Final Surface Temperature (°C)	Percent Change: Maximum	Reversible Part	Irreversible Part
Fresh aorta				
T	59 ± 1	$\Delta T_{min}\% = -23 \pm 3$	$\Delta T_{rv}\% = 93 \pm 6$	$\Delta T_{ir}\% = 7 \pm 6$
R	59 ± 1	$\Delta R_{max}\% = +7 \pm 2$	$\Delta R_{rv}\% = 61 \pm 35$	$\Delta R_{ir}\% = 40 \pm 35$
Coagulated aorta				
T	69 ± 2	$\Delta T_{min}\% = -18 \pm 1$	$\Delta T_{rv}\% = 96 \pm 5$	$\Delta T_{ir}\% = 4 \pm 5$
R	69 ± 2	$\Delta R_{max}\% = +4 \pm 1$	$\Delta R_{rv}\% = 70 \pm 40$	$\Delta R_{ir}\% = 30 \pm 40$

[a]The mean value plus and minus the standard deviation of five measurements for each result are presented.

dehydration. Possible mechanisms and their influences on the dynamics of the optical behavior of the tissue are listed in Table 3. All of these mechanisms, we believe, could coexist in the laser-heating process and could contribute in varying degrees to the overall dynamics of the optical behavior of tissue during laser irradiation.

One possible mechanism for the reversible changes in the optical behavior of tissue is the temperature dependence of the local index of refraction. In general, the effect of temperature on the index of refraction can be approximated by

$$n(r, z, t) = n_0 + \Delta T(r, z, t)\frac{\mathrm{d}n}{\mathrm{d}T}, \tag{15}$$

where n_0 is the index of refraction at room temperature and it is assumed that the local fluence rate is only r and z dependent. Radial and axial temperature gradients that are due to nonuniform heating result in gradients in the index of refraction, which lead to a lensing effect in the heated medium. The thermal-lensing phenomenon has been demonstrated in various transparent biological media[21,22] whose optical properties are dominated by absorption. Because the gradient of the index of refraction deviates the trajectories of photons away from their original paths, the optical path length for each photon is anticipated to increase. Thus for turbid media, any analysis of the laser–tissue interaction must account for the gradient of the index of refraction in the propagation direction. Overall thermal lensing in tissue is expected to induce a nonlinear response in the optical behavior of tissue by decreasing the transmittance and increasing the effective absorption. More efforts, both theoretical and experimental, are needed to clarify the link between thermal lensing and the reversible optical behavior in a turbid tissue.

Table 3. Possible Mechanisms Responsible for Inducing Reversible Changes in Tissue Optical Behavior during Laser Heating

Mechanism	Description	Influence on Optical Behavior
Thermal lensing $n(T)$	Gradient in the index of refraction caused by nonuniform heating	Decrease in T and increase in R
Temperature dependence of the reduced scattering coefficient: $\mu_s'(T) = \mu_s(T) \cdot [1 - g(T)]$	Changes in the size and/or shape of scatterers due to temperature rise	Increase in T and decrease in R (as μ_s' decreases)
Water transport	Temporary local dehydration during laser heating	Increase in T and decrease in R
Thermal expansion	Decrease in tissue density and increase in tissue thickness caused by thermal expansion of tissue	Decrease in T and increase in R

Thermally induced changes in the shape or size of the scatterers in a tissue is considered to be another cause of the reversible behavior of the tissue optics during laser heating. Such changes can affect the reduced scattering coefficient μ_s', which is the combination of the scattering coefficient μ_s and the anisotropy factor g. If the changes in shape or size of the scatterers results in a decrease in the reduced scattering coefficient, an increase in the total transmittance and a decrease in the diffuse reflectance will be expected as a consequence. On the other hand, if the reduced scattering coefficient increases because of the changes in the physical characteristics of the scatterers, an opposite phenomena in optical behavior will be observed.

We also suspect that the laser pulses induce transitory water diffusion that cause local dehydration in the irradiated zone. Local dehydration may enhance the forward-scattering characteristic of the cell,[23] which increases the anisotropy factor. Thus forward scattering is increased, which consequently causes a rise in the total transmittance and a drop in the diffuse reflectance.

Thermally induced physical expansion of the biological medium is another consideration. Because the heated area is restrained by the surrounding cold region, thermal expansion is more pronounced along the axial direction as compared with that along the radial direction (i.e., a bulging effect). The increase in tissue volume lowers its density, which decreases the refractive index of the tissue. Thermally induced increases in tissue thickness result in enlarging the optical depth, which causes a decrease in transmittance and an increase in the reflectance. Because the thermal expansion coefficients for human skin and canine aorta are not available, a quantitative evaluation cannot be made.

For the exposure parameters used in the current study, thermally induced changes in the diffuse reflectance of aortic specimens were less pronounced as compared with those for the skin samples. This difference may be due to a combination of factors including: (1) A lower absorption of the 1064-nm radiation by vascular tissue, resulting in less of a temperature rise compared with that of skin tissue. In the reported experiments, no attempts were made to achieve similar temperature increases in both aortic and skin samples by adjustment of the exposure parameters. Thus direct comparisons of the optical behavior of vascular and skin tissues at similar elevated temperatures is not possible. (2) Aortic tissue is optically thicker because of its high scattering coefficient at 1064 nm ($\mu_s = 200\ \mathrm{cm}^{-1}$ for aorta versus $\mu_s = 73\ \mathrm{cm}^{-1}$ for skin).[1,24,25] Therefore, a small thermally induced increase in the effective scattering of vascular tissue does not significantly alter the observed diffuse reflectance. (3) Human skin and canine aorta are substantially different in their structures, as well as their constituents. The contribution of each mechanism listed in Table 3 to the dynamics of the optical behavior of each tissue may vary depending on the physical properties of the tissue.

Although several mechanisms have been identified that may induce nonlinear optical behavior in tissue, our experiments did not generate the necessary data for establishing the relative importance of each mechanism. However, our study clearly shows the presence of both reversible and irreversible changes in tissue optics during laser heating and demonstrate the need for developing a more comprehensive understanding for laser–tissue interactions and for modeling this process. Considerations of these issues will have a crucial impact on the optimization of light doses for laser therapy, as well as on the development of real-time feedback, such as reflectometry for the control of laser therapy.

5. Conclusion

The dynamics of the total transmittance and diffuse reflectance of human skin and canine aorta during long-pulsed Nd:YAG laser irradiation have been characterized. The laser-induced temperature rises in tissue cause reversible and irreversible changes in the optical properties of tissue. The observed nonlinear optical behavior of tissue during laser heating demonstrates the need for developing means to account for the dynamics of tissue optics during laser therapy.

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