International Journal of Thermophysics, Vol. 26, No. 1, January 2005 (© 2005)
DOI: 10.1007/s10765-005-2372-0

A Novel Strategy For Monitoring Laser Thermal Therapy Based on Changes in Optothermal Properties of Heated Tissues[1]

W. M. Whelan,[2–4] S. R. H. Davidson,[5] L. C. L. Chin,[2] and I. A. Vitkin[2,5,6]

Laser thermal therapy uses near-infrared optical energy to heat and thereby treat diseased tissues such as solid tumors. A method to monitor the progress of laser thermal therapy by detecting temperature-induced changes in optical propagation has been developed. The advantage of a point optical monitoring strategy over a conventional point temperature monitoring approach is that optical intensity measurements are indicative of a larger 'sampling volume' of optothermal events. In porcine kidney *in vivo*, the optical intensity at 5 mm from a laser-coupled heating fiber decreased by 49% after 2.5 min of heating at 3 W. In bovine tissue *ex vivo*, the optical intensity at 8 mm from the heating fiber decreased by 62–83% during laser irradiation at 5 W. This substantial decrease in optical penetration is consistent with increased optical scattering by thermally damaged tissue (i.e., kidney and liver) around the heating fiber. This damage was not detected by a temperature sensor placed at the same distance from the heating

[1] Paper presented at the Fifteenth Symposium on Thermophysical Properties, June 22–27, 2003, Boulder, Colorado, U.S.A.

[2] Department of Medical Biophysics, University of Toronto, Canada.
[3] Department of Mathematics, Physics and Computer Science, Ryerson University, Toronto, Canada.
[4] To whom correspondence should be addressed. E-mail: bwhelan@ryerson.ca
[5] Medical Physics Division, Ontario Cancer Institute/Princess Margaret Hospital, University Health Network, Toronto, Canada.
[6] Department of Radiation Oncology, University of Toronto, Toronto, Canada.

fiber in kidney or liver. Furthermore, in the porcine kidney experiment, smoke production occurred, which is normally concomitant with high-temperature tissue charring around the heating fiber. This was observed as a complete loss in optical intensity but was not detectable in the temperature data. The measurements in this work indicate that point optical intensity may have a greater sensitivity to important optothermal events than do point temperature measurements for monitoring laser heating in tissues.

KEY WORDS: bovine liver; laser thermal therapy; light fluence; optical monitoring; porcine kidney; temperature.

1. INTRODUCTION

Laser thermal therapy (LTT) has been developed to destroy diseased tissue in a minimally invasive manner. The feasibility of this technique has been demonstrated in a number of sites including breast [1], brain [2,3], and liver [4,5]. Thermal therapy involves heating the target tissue to temperatures between 55 and 90 °C for several minutes in order to kill malignant cells. It is given as a stand-alone therapy and is different from hyperthermia, which involves lower temperature (41–45 °C) and longer time (tens of minutes) and which is used as an adjuvant to radiation therapy. During thermal therapy, tissue temperatures are typically measured using point sensors (e.g., thermocouples, fluoroptic probes) that yield temperature information at specific spatial locations. The use of point temperature measurements is complicated by the time delay in the conduction of thermal energy from a heating source to a temperature sensor. This is of crucial importance for laser thermal therapy as undesirable tissue charring can occur around the optical source fiber, yet go undetected by a temperature sensor 5–10 mm away.

As an alternative to point temperature monitoring, we have recently demonstrated a point optical monitoring strategy that measures temporal changes in interstitial optical intensity during heating [6,7]. This method takes advantage of the significant changes in tissue optical scattering that occurs due to thermal coagulation [8,9]. At temperatures above 60 °C, the thermal damage is due to denaturation of tissue proteins which is observed immediately as coagulation or 'whitening' of the tissue [10]. In this work, optical intensity and temperature measurements in porcine kidney *in vivo* and bovine liver *ex vivo* during laser heating at 810 nm are presented. The goal of this paper is to demonstrate that a major advantage of point optical monitoring over the conventional point temperature-based methods is that optical intensity measurements are indicative of a larger 'sampling volume' of optothermal events.

2. MEASUREMENTS

2.1. In vivo Porcine Liver

To demonstrate the utility of optical intensity measurements, a preliminary laser heating experiment was performed on porcine kidney *in vivo*, approved by the Animal Care Committee at the University Health Network.

The optical sensor used in this study was fabricated in-house by first removing approximately 2 mm of the cladding from the end of an 800-μm core plane-cut fiber. The end was then dipped in a mixture of epoxy and titanium dioxide, creating an approximate sphere of diffusing material at the end of the fiber. The tip was irradiated with ultraviolet light for 10 min to fix the epoxy. The sensor fiber emission was measured and found to be not truly isotropic, with small null regions in the backward direction.

Before heating, the animal was anesthetized, then intubated and maintained by mechanical ventilation. The left kidney was then surgically exposed. Under ultrasound guidance, a 1-cm cylindrical diffusing heating fiber was inserted into the posterior lobe of the kidney to a depth of approximately 3.5 cm from the surface. The 800-μm optical detection fiber was inserted parallel to the heating fiber and positioned 5 mm from the center of the cylindrical tip. A fluoroptic temperature probe (Luxtron Corp., New Jersey) was inserted parallel to the heating fiber on the opposite side, and positioned 5 mm from the center of the cylindrical tip. The cylindrically diffusing heating fiber was coupled to a Diomed-15 laser (Diomed Ltd., Cambridge, United Kingdom) with a maximum power output of 15 W at 810 ± 20 nm. The 800-μm optical detection fiber was coupled to a PDA55 photodiode (Thorlabs Inc., Newton, New Jersey), and photovoltages were recorded at 30 s intervals using a handheld digital multimeter (Fluke Model 77, 1 s response time). Given the small diameter of the optical sensor, the large distance between the optical sensor and the heating fiber, and the highly scattering characteristic of tissues [11], it can be assumed that the spatial distribution of the light incident on the sensor was approximately uniform. Thus, photovoltage can be scaled by a calibration factor to obtain the optical fluence rate at the detector location. This calibration depends on the design of the sensor [12], including the numerical aperture, and is difficult to determine accurately. Hence, photovoltages were used in this study. Temperatures were recorded at 30 s intervals using a fluoroptic thermometry system (Model 7100, Luxtron Corp. NJ). The kidney irradiation was performed at 3 W.

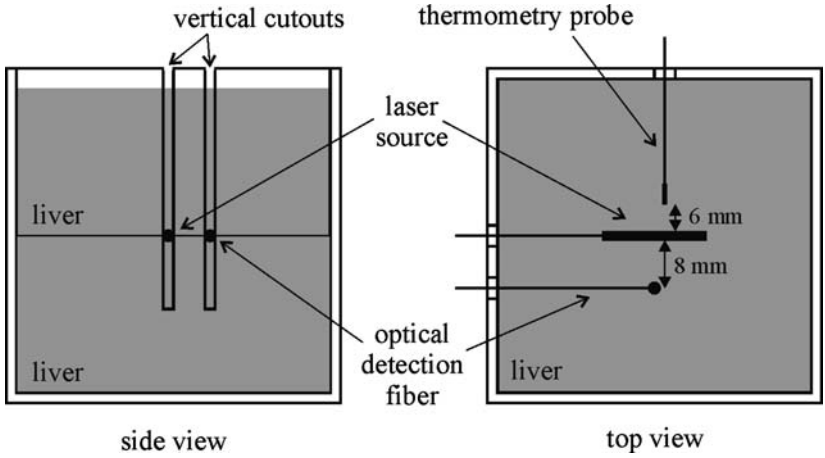

Fig. 1. Side- and top-view schematics of bovine liver *ex vivo* heating experiments showing thermometry probe, optical detection fiber, and cylindrical heating fiber placements.

2.2. Ex vivo Bovine Liver

Bovine liver was obtained from a local butcher shop and cut into slabs with approximate dimensions, 6 cm by 6 cm by 1.5 cm thick. In each experiment, one slab was placed at the bottom of an acrylic box, 6 cm on a side with vertical cutouts for positioning fibers, as shown in Fig. 1. A 2-cm cylindrical diffusing heating fiber (Resonance Optics, Massachusetts) was fed through the central vertical cutout on one side of the acrylic box and positioned at the center of the liver slab. A 800-μm orb-tipped optical detection fiber (numerical aperture of 0.37, Surgimedics, Texas) was fed through a parallel vertical cutout and was positioned parallel to and across from the center of the heating fiber, 8 mm away. A fluoroptic temperature probe (Luxtron Corp., New Jersey) was positioned perpendicular to the heating fiber 6 mm away from its center. A second liver slab was carefully placed on top of the first, followed by an acrylic plate. A weight was placed on top of the acrylic plate to ensure good coupling between the liver layers.

The cylindrically diffusing heating fiber was coupled to a Diomed-60 laser (Diomed Ltd., Cambridge, United Kingdom) with a maximum power output of 60 W at 810 ± 20 nm. A PDA55 photodiode (Thorlabs Inc., Newton, New Jersey) was used to convert the light collected by the optical detection fiber into photovoltage signals proportional to the light intensity (fluence rate), and values were recorded using a Gen 2000 multifunction

data acquisition system (Labmate Sciemetrics, Nepean, Canada) displaying the average of 30 photovoltage signals at an update rate of 1 Hz. The effective integration time of the photodiode was 0.1–16.7 μs (0–40 dB gain setting). Temperatures were recorded every second using a fluoroptic thermometry system (Model 7100, Luxtron Corp. New Jersey). The liver irradiations were performed at 5 W for 600 s. Photographs of the induced tissue coagulation and source-sensor positions were taken following heating. A distance scale was placed within the field of each photograph. The coagulation diameter was measured at the mid-point of the cylindrical heating fiber.

3. RESULTS

Normalized temperature and optical intensity (photovoltage) measurements at 5 mm from a 1-cm cylindrical diffusing heating fiber are shown in Fig. 2 for a 3 W irradiation in porcine kidney *in vivo*. The temperature and optical intensity were normalized to their initial values. The uncertainty in photovoltage measurements was ± 0.1 mV, equal to 0.02 normalized units in Fig. 2. During the first 1–2 min of heating, a marginal 5 °C temperature increase was reported at 5 mm, and a maximum absolute temperature of 42.7 ± 0.5 °C. However, after approximately 1 min of heating, the optical intensity started to drop, decreasing by 49% after 2.5 min. This loss in optical intensity is characteristic of the onset of tissue coagulation at the heating source whereby the coagulated volume, with its increased scattering coefficient, acts as a light trap [7]. As a result of the substantial reduction in optical intensity, the input power to the heating fiber was reduced to 2 W at 2.5 min, which reduced both the temperature and optical intensity. At 3 min, the optical intensity was near zero, indicating that minimal light from the heating fiber was reaching the optical detector fiber. At 3.5 min, the acrid smell of tissue charring was observed and the treatment was immediately ended. Charring of the tissue adjacent to the heating fiber, an undesirable effect, has been observed by many [13,14] and has been reported to occur at 425 °C in porcine aorta [14]. The loss in optical intensity in Fig. 2 is consistent with published data in *ex vivo* bovine liver, where optically opaque, charred tissue was observed post treatment [6]. Hence, loss of optical intensity may be a good predictor of the onset of tissue charring. It is important to note that these significant treatment events were not detected by the temperature sensor placed at an analogous location to the optical sensor, on the other side of the cylindrical heating fiber, at the same radial separation. Furthermore, with point temperature measurements, tissue coagulation can only be assessed at the sensor locations, whereas a point optical measurement is

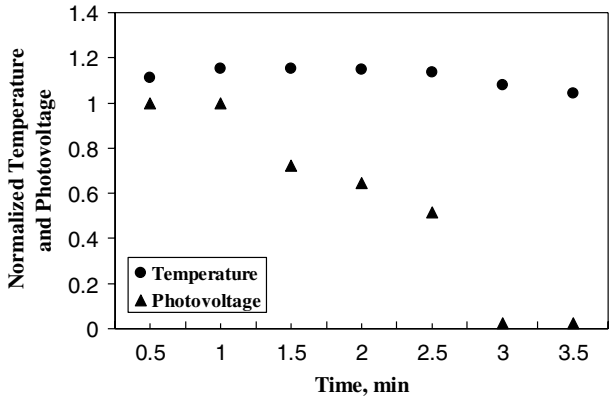

Fig. 2. Normalized temperature and optical intensity (photovoltage) measurements at 5 mm from a 1-cm cylindrical diffusing heating fiber for 3 W irradiation in porcine kidney *in vivo*. The uncertainty in photovoltage measurements was ±0.1 mV, equal to 0.02 normalized units.

an instantaneous representation of a larger volume of opto-thermal events, such as tissue charring at the heating fiber.

Normalized optical intensity measurements at 8 mm and absolute temperature changes at 6 mm from a 2-cm cylindrical diffusing heating fiber for 5 W irradiation in *ex vivo* bovine liver are shown in Fig. 3a and b, respectively. The optical intensity curves for the three repeated experiments are qualitatively similar in that each exhibits three important trends. First, there is a rise in optical intensity early in the heating protocol. This is consistent with our previous work whereby the magnitude of the rise in optical intensity increased as the initial (ambient) temperature of the *ex vivo* liver sample decreased [6]. Our results indicate that tissue optical property changes may occur prior to the onset of coagulation in *ex vivo* bovine liver. However, the biomolecular mechanism behind this effect is not clearly understood. Walsh and Cummings [15] have demonstrated shifts in the absorption spectrum at mid-infrared wavelengths (1440–2940 nm) due to temperature changes. The second trend observed in Fig. 2 is a decrease in optical intensity consistent with the onset of tissue coagulation at the heating source [6]. Finally, the observed continuous decrease in optical intensity is consistent with the propagation of the coagulation boundary as heating is maintained. The reductions in optical intensity (from initial values) for the three trials were 83, 62, and 73%, corresponding to post-heating coagulation diameters of 13, 12, and 14 mm, respectively, with a measurement uncertainty of ±0.5 mm. Tissue

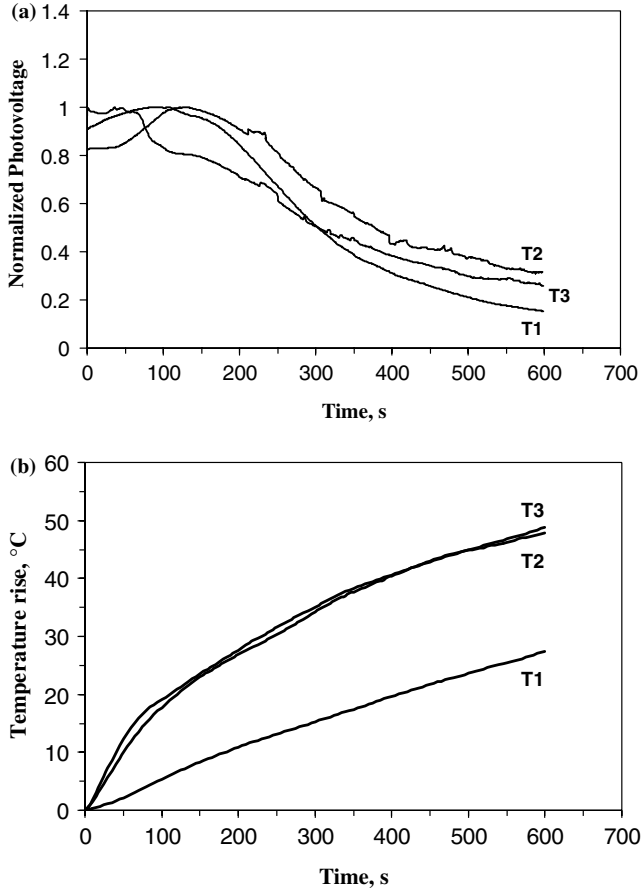

Fig. 3. (a) Normalized optical intensity measurements at 8 mm and (b) absolute temperature change at 6 mm from a 2-cm cylindrical diffusing heating fiber for 5 W irradiation in bovine liver *ex vivo*. (T1, T2, and T3 refer to trials 1, 2, and 3, respectively).

charring was not observed in any of the heated liver samples. The variation in optical intensity profiles is likely a result of inter-sample variability in the liver optical properties. However, such variation seems to have a minimal affect on the final coagulation diameter. Optical absorption coefficients and effective optical penetration depths for native and coagulated porcine kidney and bovine liver at 810 nm are not available in the literature. However, for *ex vivo* porcine liver, a 21% increase in optical

absorption and a 68% reduction in effective optical penetration depth at 830 nm have been reported due to coagulation [16].

The temperature profiles at 6 mm for trials 2 and 3 in Fig. 3b are highly similar with a maximum temperature rise of 48 °C. In trial 1, the temperature probe did not remain fixed at the desired distance of 6 mm from the heating fiber, but had shifted to a final separation of 9 mm. This increased distance is reflected in the temperature data such that the maximum temperature rise for trial 1 was 27 °C and the shape of the profile is indicative of temperatures sampled at a distance further from the source compared to trials 1 and 2. Again, we note that the occurrence of important optothermal events such as the onset and propagation of tissue coagulation are evident in the optical intensity data but not in the temperature data.

If thermal therapy is delivered by a laser, the optical monitoring approach is obvious; however, even for microwave and ultrasound interstitial thermal therapies, the resulting tissue changes can still be probed optically by placing a non-heating optical source adjacent to the energy source and an optical detection fiber at some distance from the heat source/optical source pair [17]. The major advantages of a point optical monitoring strategy over the conventional point temperature-based methods are (1) the occurrence of thermal damage in the target volume can be detected immediately due to the speed of light in tissues, (2) optical signal changes are large, and (3) optical readings are indicative of a larger 'sampling volume' of optothermal events.

ACKNOWLEDGMENTS

Financial support for this work was provided by the Natural Sciences and Engineering Research Council of Canada, the National Cancer Institute of Canada (with funds from the Canadian Cancer Society), and the Canada Foundation for Innovation. The authors would like to thank Michael Sherar, Arthur Worthington, and Ed Sinofsky for experimental assistance.

REFERENCES

1. S. A. Harries, Z. Amin, M. E. F. Smith, W. R. Lees, J. Cooke, M. G. Cook, J. H. Scurr, M. W. Kissin, and S. G. Bown, *Br. J. Surgery* **81**:1617 (1994).
2. O. Schrottner, P. W. Ascher, and F. Ebner, *Proc. Fifth Int. Congress Eur. Laser Assoc.* (1990), p. 66.
3. F. X. Roux, L. Merinne, and B. Leriche, *Lasers Med. Sci.* **7**:121 (1992).
4. J. Hahl, R. Haapiainen, J. Ovaska, P. Puolakkainen, and T. Schroder, *Lasers Surg. Med.* **10**:319 (1990).

5. K. Dowlatashi, A. K. Bhattacharya, B. Silver, T. Matalon, and J. W. Williams, *Surgery* **112**:603 (1992).
6. L. C. L. Chin, W. M. Whelan, M. D. Sherar, and I. A. Vitkin, *Phys. Med. Biol*. **46**:2407 (2001).
7. L. C. L. Chin, W. M. Whelan, and I. A. Vitkin, *Phys. Med. Biol*. **48**:543 (2003).
8. J. P. Ritz, A. Roggan, C. Isbert, G. Muller, H. G. Buhr, and C. T. Germer, *Lasers Surg. Med*. **29**:205 (2001)
9. M. G. Skinner, S. Everts, A. D. Reid, I. A. Vitkin, L. Lilge, and M. D. Sherar, *Phys. Med. Biol*. **45**:1375 (2000).
10. J. Pearce and S. Thomsen in *Rate Process Analysis of Thermal Damage. Optical-Thermal Responses of Laser-Irradiated Tissue*, A. J. Welch and M. J. C. van Gemert, eds. (Plenum Press, New York, 1995).
11. W. F. Cheong, S. A. Prahl, and A. J. Welch, *IEEE J. Quantum Electronics* **26**:2166 (1990).
12. H. J. Van Staveren, J. P. A. Marijinisson, M. C. G. Aalders, and W. M. Star, *Lasers Med. Sci*. **10**:137 (1995).
13. C. Sturesson, *Lasers Surg. Med*. **22**:51 (1998).
14. G. L. LeCarpentier, M. Motamedi, L. P. McMath, S. Rastegar, and A. J. Welch, *Proc. IEEE Eng. in Medicine and Biology* (1989), pp. 1209–1210.
15. J. T. Walsh, Jr. and J. P. Cummings, *Lasers Surg. Med*. **15**:295 (1994).
16. J. P. Ritz, A. Roggan, C. Isbert, G. Muller, H. J. Buhr, and C. T. Germer, *Lasers Surg. Med*. **29**:205 (2001).
17. L. Chin, M. Pop, W. Whelan, M. Sherar, and A. Vitkin, *Rev. Sci. Instrum*. **74**:393 (2003).