Nonlinear optical behavior of ocular tissue during laser irradiation

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A pump (cw Ho–YAG laser) and probe (He–Ne laser) system was used to study the dynamics of the optical behavior of ocular tissue during laser heating. The nonlinear optical behavior of porcine corneal and vitreous-humor tissue was characterized *in vitro* by means of measurements of the radial profile of a He–Ne laser beam transmitted through the tissue. Temperature gradients in the tissue created by the absorption of pump radiation caused the probe beam to diverge. For constant laser power, the rate of divergence was made dependent on the spot size of the pump beam. The profile of the transmitted probe beam returned to its original magnitude and shape after the tissue was permitted to cool. This reversible change in optical behavior was attributed to the formation of a negative lens owing to thermally induced local gradients in the refractive index of the tissue.

Key words: Thermal lensing, nonlinear optics, tissue optics.

1. Introduction

The optical properties of a biological medium are generally assumed to remain constant during laser irradiation unless the resulting temperature field alters the physical properties of the medium. Heating that produces either coagulation or dehydration will affect the absorption and the scattering properties of biological samples.[1–7] In addition to these irreversible changes, reversible changes in the optical behavior of tissue have been observed.[8,9] Thermally induced changes in the refractive index of water occur,[10] and for mid- and far-infrared wavelengths the absorption coefficients of water are temperature dependent and reversible.[11–16] Because water is the major component of soft tissue, we expect its optical behavior to be temperature dependent as well. To investigate irreversible and reversible changes in the optical behavior of tissue, we have selected the cornea and the vitreous humor. These media are ideal for pump–probe laser experiments because these tissues are normally transparent. In addition, transient changes in their optical properties might affect safety standards as well as dosimetry for ophthalmic laser applications, such as microsurgery with Nd:YAG lasers.[17,18]

We hypothesize that radial temperature gradients produced by laser heating will induce local changes in the index of refraction of tissue. These changes should alter the profile of a beam of light traveling through the tissue. To test this hypothesis, we studied the thermally induced, nonlinear optical behavior of porcine cornea and vitreous humor with a pump–probe laser system. An infrared, cw Ho–YAG laser rapidly increased the temperature in the tissue samples while a low-power He–Ne laser beam probed changes in the optics of the ocular media. This study examined the optical behavior of ocular tissue in a temperature range in which tissue heating did not induce any visible damage, such as whitening (coagulation) of the cornea. In addition, the optical behavior of water, which is frequently used to model the interaction of infrared laser radiation with tissue, was examined.

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2. Materials and Methods

Corneal and vitreous-humor tissue from porcine eyes were used in this study. After harvesting, the eyeballs were wrapped in saline-moistened gauze and stored at 4–6 °C to maintain the corneal water content. The cornea was excised and sandwiched between a microscope slide (1 mm thick) and a cover slip (0.2 mm thick). The cover-slip side was irradiated. The average thickness of the cornea was measured to be

1.2 mm ($n = 5$). The vitreous humor was drawn with a syringe after the cornea was removed and placed in a quartz container with a 2-mm path length. All specimens were used within 24 h post mortem. For comparative studies, the optical behavior of distilled water was also characterized through the use of the same setup and procedure.

The experimental system is shown in Fig. 1. A pump–probe system was employed to study the nonlinear optical behavior of cornea, vitreous humor, and water. Tissue heating was induced by a cryogenically cooled, cw Ho–YAG laser at $\lambda = 2.09$ µm (rare-earth medical) while a low-power He–Ne laser was used to detect the changes in optics of the sample. To change the spot size of the Ho–YAG laser beam, samples were placed at several locations in front of the focal plane of a plano–convex lens ($f = 11$ cm) that was used to focus both the pump and the probe beams. The optical alignment and the beam profile of both laser beams were measured after the lens by use of a knife-edge technique and a CCD camera. Although the pump and the probe laser beams were focused at different locations, their optical paths were almost identical in the range of 3–5 mm in front of the focal plane, where the experiments were conducted. The measured spatial distributions of both laser beams were Gaussian.

The profile of the He–Ne laser beam was monitored at the observation plane (20 cm behind the lens) with a standard-frame-rate (30 frames/s) CCD camera. Profile changes were assumed to indicate the extent of the nonlinear optical properties of the sample. The irradiance of the transmitted beam on the CCD array was adjusted with a neutral density (ND) filter to prevent image saturation. Video images were recorded through the use of a time-code generator that was synchronized with the laser shutter (video timer and VCR). Images were then digitized and analyzed, frame by frame, with a 33-ms temporal resolution to follow the dynamics of the probe-laser beam profile.

To minimize and account for artifacts we conducted control experiments. First, reference measurements were made with only the microscope slides or the quartz cuvette, i.e., without any sample. Next, measurements were performed with various tissue samples at different locations along the optical (z) axis. For each experiment the transmitted profile of the He–Ne laser beam at the observation plane was recorded in the absence of Ho–YAG radiation. This beam profile provided a reference for the normalization of the measurements that were performed during the laser-heating procedure. At each selected location on the sample the measurements were repeated three times. Sufficient time was allowed between irradiations for the sample to return to room temperature. The output power of the Ho–YAG laser was 500 ± 20 mW for all experiments. The exposure time, controlled by an external-cavity shutter with a 3-ms response time, was set at 500 or 300 ms, depending on the structure of the sample and the spot size (irradiance) of the heating beam. At the highest irradiance it was necessary to limit the exposure time to 300 ms to prevent visible coagulation at the cornea.

The incident irradiance was altered by a change in the position of the sample along the optical axis. Corneal samples were positioned at three different z-axis locations, resulting in spot sizes with a $1/e^2$ diameter D of 1.0, 1.2, and 1.4 mm for the Ho–YAG laser beam. The corresponding incident irradiances were 570, 400, and 290 mW/mm^2, respectively. Vitreous-humor samples were also tested at three different z-axis locations and had estimated incident irradiances of 850, 400, and 220 mW/mm^2 for $D = 0.8$, 1.2, and 1.6 mm, respectively. For water, one position was selected, resulting in an incident irradiance of 400 mW/mm^2 for $D = 1.2$ mm.

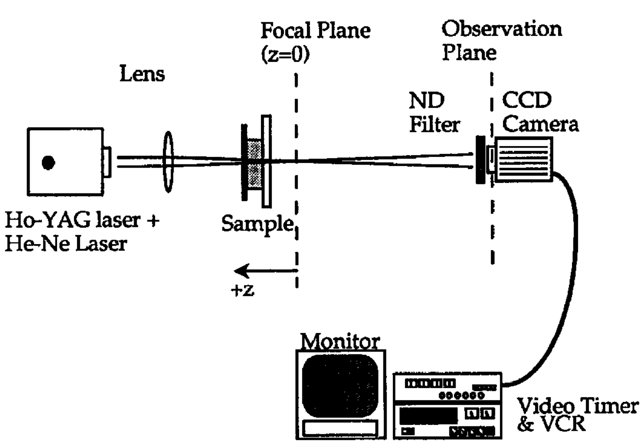

Fig. 1. Schematic diagram of the pump–probe laser system for monitoring the thermally induced nonlinear optical behavior of corneal and vitreous-humor tissue.

3. Results

In the absence of any absorbing media such as tissue, the transmitted He–Ne laser beam profile remained constant for all experiments during Ho–YAG irradiation of the microscope slides and the quartz container. After the sample was placed in the pump–probe setup and heated with the pump-laser radiation, the transmitted He–Ne laser beam began to diverge. This decreased the spot area of the transmitted probe beam at the observation plane. An illustration of the probe-laser beam trajectories extrapolated from this observation is presented in Fig. 2. The transmitted He–Ne laser beam returned to its original profile after the sample had cooled. A sequence of images of the beam profile of the transmitted He–Ne laser beam obtained from one of the corneal samples is shown in Fig. 3. Note that the spot area of the probe beam decreased and the central irradiance increased as the corneal sample was heated for 500 ms.

The optical behavior of corneal tissue for different pump-radiation spot sizes is shown in Fig. 4. Exposure of corneal tissue to high irradiance (of the order of 570 mW/mm^2 for $D = 1.0$ mm) induced a faster convergence in the spot area as compared with lower

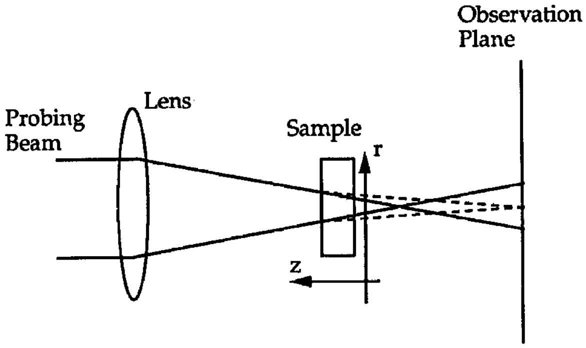

Fig. 2. Illustration of the self-defocusing action with the tissue located in front of the focal plane. The solid lines represent the original beam paths, and the dashed lines represent the modified beam paths that are due to thermal lensing.

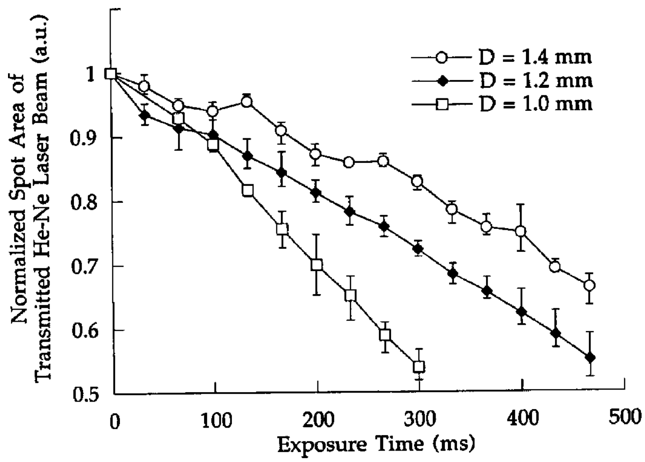

Fig. 4. Plot of the changes in the spot area of the transmitted He–Ne laser beam as a function of the exposure time for three different spot sizes for the pump laser (D = 1.0, 1.2, and 1.4 mm) for corneal tissue. The curves represent the averages of the measurements; the error bars indicate the maximum and minimum values.

irradiances (400 mW/mm^2 for D = 1.2 mm and 290 mW/mm^2 for D = 1.4 mm). After a 300-ms exposure time, the measured spot area of the probe beam decreased 50%, 27%, and 18% for pump-beam irradiances of 570, 400, and 290 mW/mm^2, respectively. An irradiance of 570 mW/mm^2 for 500 ms coagulated the cornea; the irradiated spot became white, which distorted the effects of thermal defocusing on the transmitted probe-laser beam profile.

The reversible feature of the thermally induced reduction in the spot area is seen in the small differences among the error bars on the curves shown in Fig. 4. Sufficient time for the tissue to cool off was provided between irradiances, and sites not coagulated were irradiated three times. The error bars represent the maximum and minimum spot-area values at different time intervals during pump-laser irradiation for the three exposures at each site. The change in the probe-beam spot area was highly reproducible.

Transient changes in the spot area of the He–Ne laser beam transmitted through vitreous-humor

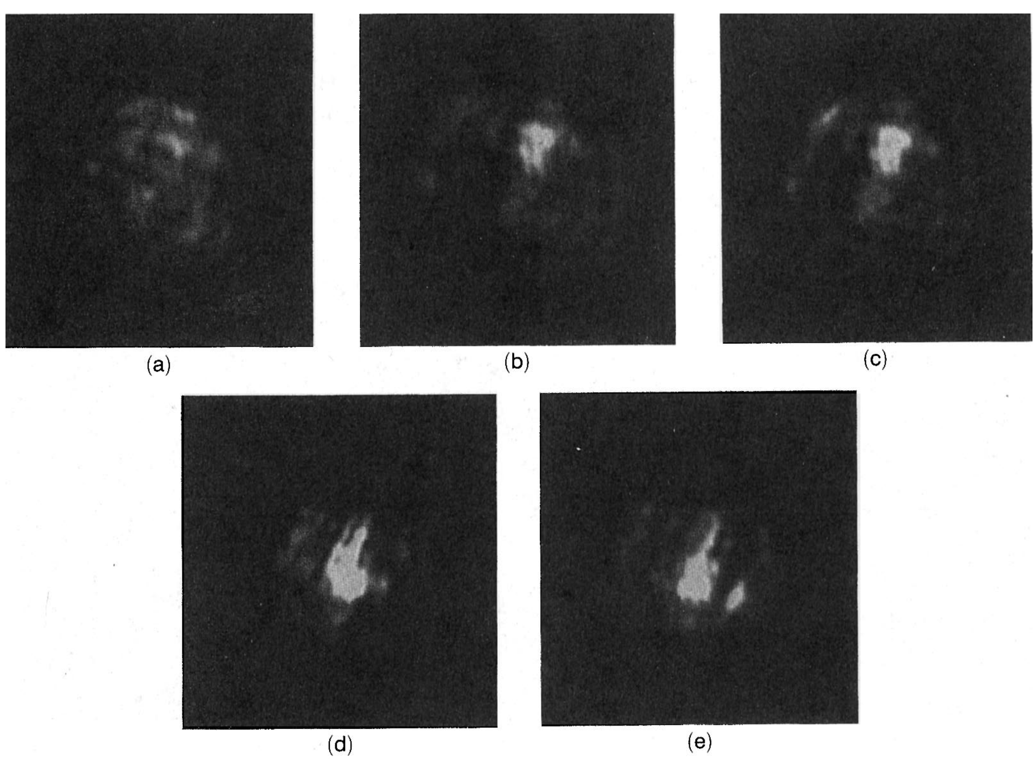

Fig. 3. Sequence of images showing the changes in the profile of the probing beam transmitted through the cornea, which was heated with a Ho–YAG laser (D = 1.2 mm, at 400 mW/mm^2 for 500 ms): the reference image taken at (a) t = 0 ms, (b) t = 33 ms, (c) t = 165 ms, (d) t = 330 ms, and (e) t = 500 ms.

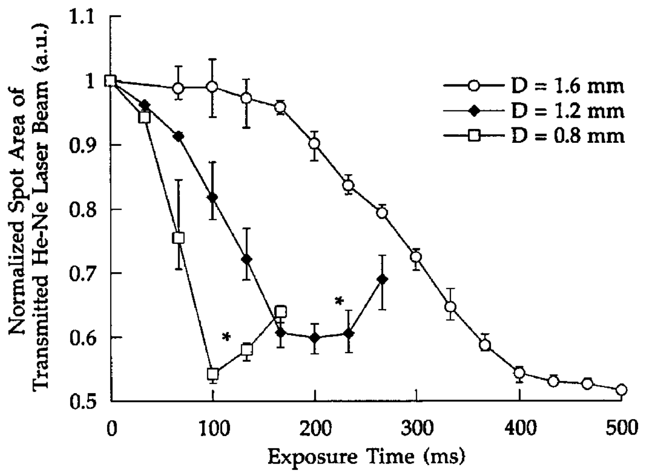

Fig. 5. Plot of the changes in the spot area of the transmitted He–Ne laser beam as a function of the exposure time for three different spot sizes for the pump laser ($D = 0.8$, 1.2, and 1.6 mm) for vitreous-humor tissue. The curves represent the averages of the measurements; the error bars indicate the maximum and minimum values. The asterisks indicate the onset of distortion of the probe-laser beam profile.

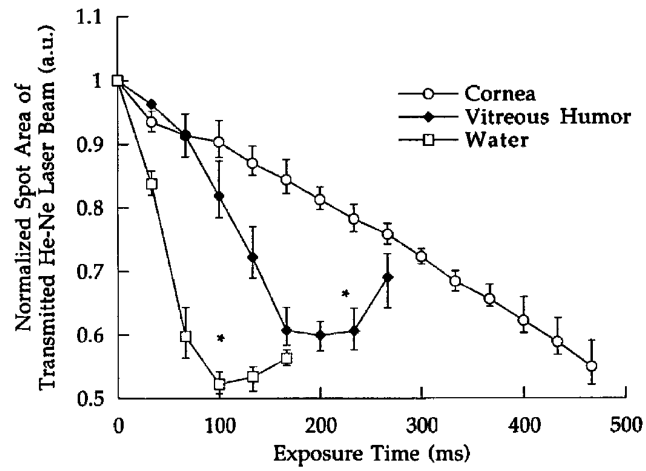

Fig. 7. Plot of the changes in the spot area of the transmitted He–Ne laser beam with 400 mW/mm^2 of the pump laser on cornea, vitreous humor, and water. The curves represent the averages of the measurements; the error bars show the maximum and minimum values in these measurements. The asterisks indicate the onset of convection-induced distortion of the probe-laser beam profile. An irradiance of 400 mW/mm^2 for 500 ms did not coagulate the cornea.

samples when various incident irradiances were used to heat the samples are shown in the Fig. 5. The rate of change of the spot area of the transmitted probe beam increased as the diameter of the heated spot decreased. This change was similar to that seen in the corneal-tissue results. When a vitreous-humor sample was located 3 cm in front of the focal plane of the 850-mW/mm^2 pump-laser beam with $D = 0.8$ mm, the spot area reached a minimum, which was approximately 45% of its original size, within 100 ms after the onset of exposure. After 100 ms, the transmitted spot became distorted; its beam profile lost its symmetry as the irradiation continued. We attribute the distortion of the He–Ne laser beam profile to the laser-induced free convection in this sample. When the vitreous-humor sample was moved 1 cm forward (for a 400-mW/mm^2 pump-laser beam with $D = 1.2$ mm), between 150 and 200 ms were necessary to reach a minimum spot area, which was approximately 40% of the initial value. After that, the distortion of the probe beam as described for the case above was observed (see Fig. 6). When the sample was located 5 cm in front of the focal plane (a 220-mW/mm^2 pump-laser beam with $D = 1.6$ mm), the observed spot size decreased by 50% by the end of the 500-ms irradiation.

In the experiments with water, dynamic optical behaviors similar to those seen during irradiation of the corneal and vitreous-humor samples for the transmitted He–Ne laser beam was observed. During irradiation with the 400-mW/mm^2 pump-laser beam with $D = 1.2$ mm, the spot area of the probe-laser beam decreased rapidly within the first 100 ms of the irradiation (see Fig. 7). After a maximum decrease of 50% in the spot area was observed at approximately 100 ms, the beam profile of the transmitted probe-laser beam spot gradually became dis-

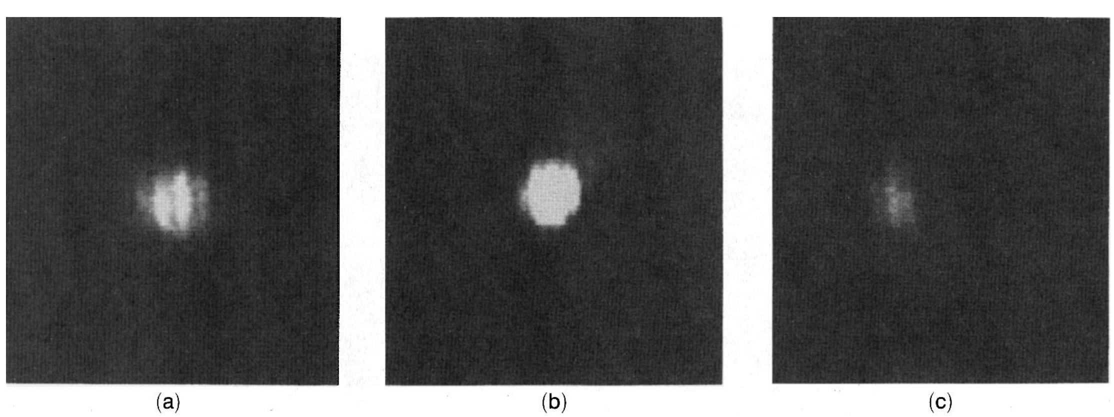

Fig. 6. Sequence of images showing the distortion, caused by free convection, of the He–Ne-laser beam profile as the beam travels through vitreous humor for images taken at (a) $t = 0$ ms (the reference beam profile), (b) $t = 233$ ms (the beam profile before the onset of distortion), and (c) $t = 400$ ms (the distorted beam profile).

torted until the end of the irradiation. A comparison of the nonlinear optical behaviors of water, vitreous humor, and cornea made with data from an irradiance of 400 mW/mm^2 for $D = 1.2$ mm over 500 ms showed changes in the spot area of the transmitted He–Ne laser beam during the irradiation. The results are shown in Fig. 7.

4. Discussion

The important phenomenon observed in this study was that the transmitted probe-laser beam undergoes reversible self-defocusing when the ocular sample is heated with the pump-laser beam. We believe this reversible optical behavior is due to the temperature dependence of the refractive index[19–25] of ocular media, which is approximately governed by

$$n(r, z) = n_0 + \Delta T(r, z, t)\left(\frac{dn}{dT}\right), \quad (1)$$

where n_0 is the background refractive index, $\Delta T(r, z, t)$ is the change in temperature, and dn/dT is the total change in the index of refraction with a change in temperature. Because the probe laser beam converges during the heating process of ocular media, the dn/dT of corneal and vitreous-humor media must be negative: the higher the temperature, the lower the refractive index. The slightly temperature-dependent value of the dn/dT for water is known to be $-1.2479 \times 10^{-4}/°C$ at 30 °C (see Fig. 8). Although the dn/dT for the cornea and the vitreous humor are not available, we might anticipate that they should be close to the value of water because of the high water content of these ocular media (78% for the cornea[26] and 98% for the vitreous humor[27]).

Because of the Gaussian profile of the Ho–YAG laser beam and the axial absorption of its radiation, a temperature gradient in the radial, as well as the axial, direction of the tissue is generated. This temperature gradient results in a gradient in the refractive index for both axes. In this study, the incident-ray trajectories are approximately parallel to the axial direction; thus the effect of the axial gradient of the refractive index on the probe laser beam is small and can be neglected.[28] It is known that the local variation in the refractive index is directly proportional to the incident power and is inversely related to the square of the spot size of the pump laser beam.[21] Thus the smaller the spot size of the Ho–YAG laser on the sample, the higher the irradiance and the resulting temperature. The lensing effect in the media is more pronounced as a result of the steeper gradient of the refractive index. This increase explains why the defocusing rate of the probe beam shown in Figs. 4 and 5 increases as the spot size of the pump laser decreases. Local variation in the refractive index eventually vanishes as the temperature gradients disappear. However, irreversible changes in the transmitted probe-laser beam profile occur if the heat induces permanent changes in the structure of the corneal sample.

The temperature dependence of the refractive index comprises two components: temperature- and stress-dependent variations. The dn/dT hence can be separated into two independent terms, that is,

$$\frac{dn}{dT} = \left(\frac{\partial n}{\partial T}\right)_\rho + \left(\frac{\partial n}{\partial \rho}\right)_T \frac{\partial \rho}{\partial T}, \quad (2)$$

where ρ is the density of the medium.[19] The first term (right-hand side) of Eq. (2) represents the temperature-dependent change in the refractive index at a constant density. This term is related to the absorption coefficient and can be either positive or negative, depending on the characteristics of the thermally induced shift of the absorption spectrum of the medium. The second term on the right-hand side of Eq. (2) characterizes the change induced by thermal expansion, which is negative. Because the cooler surrounding tissue constrains the hotter tissue during laser heating, a gradient in density is produced. This density gradient in turn produces refractive-index variations.[19,20] Because photoelastic and thermal-expansion coefficients for the ocular media are not available, we could not evaluate the significance of thermal expansion in dn/dT. Although thermal-expansion-induced bulging, which causes a lensing effect,[20] of the front face of samples has been reported in nonbiological media, in the current study the surfaces of ocular samples were constrained to be flat by the container or the holder.

In the experiments with the vitreous humor, the rate of defocusing increased after a certain point in the heating process (see Fig. 5). This phenomenon was not observed in the experiments with water and cornea and may be due to heat-induced liquefaction of the vitreous humor.[29,30] This liquefaction process causes major changes in the mechanical properties of vitreous humor, especially its viscosity. Furthermore, the optical and thermal properties of vitreous humor may also be affected by this process. These heat-induced variations in the physical properties of vitreous humor therefore change the rate of the self-defocusing action of the probe-laser beam.

The thermal-defocusing phenomenon is known to be very sensitive to free-convection currents in liquid

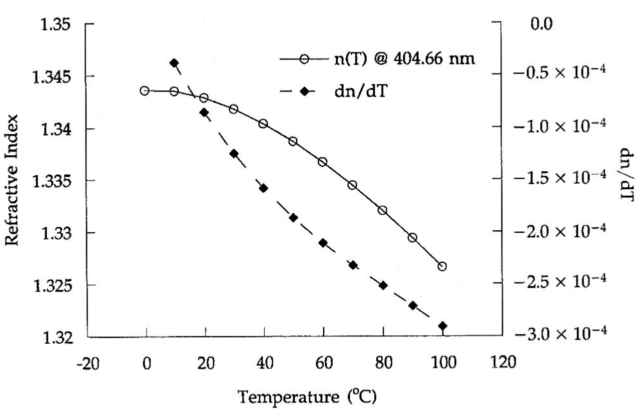

Fig. 8. Plot of the temperature dependence of the refractive index and the dn/dT value for water at 404.66 nm (see Ref. 10).

media.[19] High absorption of 2.09-μm laser radiation by water and by ocular media leads to the formation of a steep density gradient that is due to thermal expansion. This expansion initiates free convection for low-viscosity media, such as water at 0.8904 cp at 25 °C,[10] and heated vitreous humor. A free-convective flow in a medium leads to an asymmetric temperature profile. As a consequence, an asymmetric lens is formed that causes beam deflection and distortion of the laser beam profile, as seen in Fig. 6.

The similarity between the self-defocusing action of the probe beam (He–Ne laser) in the experiments with water, vitreous humor, and cornea suggest that water might be the key component responsible for this nonlinear optical behavior. However, the validity of the use of water to model the response of ocular media during infrared laser radiation is questionable. The rate of the self-defocusing action in the experiments with water, vitreous humor, and cornea as shown in Fig. 7 indicates the variations in the thermal responses among these media that result from the differences in their optical and their physical properties. Water has a greater absorption coefficient[11,12,31] (μ_a = 35–40 cm^{-1}) and a penetration depth (285–333 μm) at the 2.09-μm wavelength compared with vitreous-humor and corneal tissue, with an absorption coefficient[32–34] $\mu_a = 20$ cm^{-1} and a penetration depth of 500 μm. Heat deposition during Ho–YAG laser irradiation in water is more superficial compared to that in the ocular media. Water has a relatively greater thermal diffusivity[35] (1.4433×10^{-7} m^2/s) than do other ocular media (1.4143×10^{-7} m^2/s or less[35,36]), and water responds more quickly to changes in the thermal environment. In contrast, the vitreous humor and the cornea, which have a lower thermal diffusivity, take a longer time to reach a new equilibrium condition. In addition, free convection occurs in water and in vitreous humor because of their low viscosities, which distort the temperature profile in the medium as well as in the laser beam. All these factors introduce considerable deviations in the thermal response between water and ocular media. Hence we believe that water may not serve as a good model to evaluate the thermal response or the thermally induced nonlinear optics of ocular media, especially the cornea, during Ho-YAG laser irradiation, or for any tissue and any pump laser.

The nonlinear optical properties of ocular media reported in this paper may influence some ophthalmic laser applications and their safety considerations. Safety standards assume that a laser beam is represented as a point source and a minimum spot occurs at the retina. For wavelengths from 0.95 to 1.3 μm the penetration depth ($1/e$) in water is 1–2 cm. Absorption by the cornea, lens, and vitreous humor in this wavelength band will undoubtedly affect the spot size at the retina and thus estimates of retinal irradiances. In Ho–YAG laser photothermal keratoplasty, success relies on the precision one has to control collagen shrinkage in the treated cornea and on the capability to maintain the integrity of the surrounding tissue, especially the endothelium. The thermally induced lensing effect in corneal tissue, as demonstrated in our study, will lead to the changes in the local fluence rate. This in turn alters the rate of heat generation inside the cornea and may change the therapeutic results. In a laser posterior capsulotomy, a nanosecond or picosecond Nd:YAG laser pulse is focused into the transparent tissue to produce optical breakdown, which disrupts the tissue. The size of the area of tissue disruption is controlled by the variation of the energy of each pulse. If a stronger destructive effect is needed, a burst of laser pulses with a high repetition rate (e.g., 50 Hz) may be used.[17,18] Applying laser pulses to the anterior target in the eye at such a high repetition rate could potentially induce a small, nonuniform temperature elevation in the cornea and create some degree of the thermal-lensing effect. The outcome of this laser application therefore could be changed because the lensing effect alters the spot size of the laser beam on the target. Besides, the strong light (electromagnetic) field could also induce the observed changes in the refractive index by means of other mechanisms such as the Kerr effect,[19,37] which also leads to a lensing effect in the cornea. The significance of the influence of the nonlinear optical properties of ocular media in ophthalmic laser applications needs further investigation, and we will report the results of our further investigation in the future. For any mathematical model[36] that simulates the thermal response of ocular tissue to laser radiation, the influence of temperature-dependent thermal lensing should be taken into consideration to achieve accurate predictions.

5. Conclusion

This study demonstrated the nonlinear, thermo-optical behavior of the cornea and the vitreous humor during laser heating. The local index of refraction of these ocular media decreases as the temperature increases. A self-defocusing phenomenon in the transmitted probe laser beam is transient and disappears as the temperature gradient vanishes. The existence of temperature-dependent optical nonlinearities of ocular tissue could affect the outcome of various laser applications in ophthalmology.

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