Non invasive real-time temperature determination during laser treatments at the retina

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The first non-invasive method to determine the temperature increase at the retina in real-time during laser treatment is presented. In order to probe the temperature rise over time, nanosecond laser pulses are repetitively applied simultaneously to the heating laser light. The pulses lead to additional small transient temperature jumps which themselves cause the emission of thermo-elastic pressure waves at the chorio-retinal complex. The pressure waves are detected at the cornea using an ultrasonic transducer already embedded in the contact lens used for treatment. The pressure amplitudes are converted to temperature. The following article describes the method of opto-acoustic temperature determination in more detail and presents initial in vitro and in vivo results.

The therapeutic effect of almost all laser treatments at the retina is initiated by a local transient temperature increase. Variations in absorption and blood perfusion below the retina as well as in the light transmission through the eye can lead to different temperature increase at the retina and thus variable tissue effects for the same laser irradiation. This can result in either insufficient treatment without any benefit or inadvertently strong treatment with possible adverse effects.
The long term goal of this project is the use of the temperature information to appropriately regulate the treatment laser independent of the irradiated spot size. This method may promote the acceptance of new laser treatments such as Transpupilliary Thermotherapy (TTT), and can additionally speed such treatments as Laser Photocoagulation (LPC), also making them less invasive in the process and thus easing patient discomfort and improving safety.

1 Motivation

All therapeutic retinal laser treatments, with the exception of Photodynamic Therapy (PDT), are primarily based on the temperature increase caused by light absorption at the area of irradiation. The magnitude and time dependence of the temperature increase determine the strength and the extension of the thermal damage (coagulation). In addition to the adjustable laser parameters, the temperature increase in the target area is predominantly characterised by the unknown degree of light scattering within the eye as well as the individually differing pigmentation and pathology. Furthermore, for irradiation times of seconds to minutes, the choroidal circulation has also to be taken into consideration as it acts as heat sink. Since these anatomical and physiological parameters of the patients are not exactly determinable, the ideal dosimetry for irradiation can only be roughly estimated before treatment. For therapies without a clear visible endpoint, such as Transpupillary Thermotherapy (TTT) for closure of neovascularisations, predetermined dosimetry is especially critical. In TTT, diode laser radiation with a power of up to 800 mW is applied for one minute on to retinal spot sizes of up to 3 mm. This level of irradiation might produce no obvious effect for one particular patient, for another however, there may be unintentional coagulation in the central macula [1].
Laser photocoagulation (LPC) is an established procedure since the early 1970's, and is used to treat a variety of retinal diseases. Small spot sizes of 100 - 400 µm in diameter are typically irradiated with a power of 50 - 500 mW for 100 - 500 ms. The goal of the irradiation is a weak denaturation of retina, thus initiating a therapeutic response. Due to variable pigmentations of the fundi, the short irradiation time and the often high number of coagulations (up to 5000 in panretinal photocoagulation for diabetic retinopathy), a spot-oriented dosimetry with minimum coagulation sizes is impossible.
For most irradiation doses, a technique to control the temperature increase is desirable. So far, there have been no adequate methods available for online temperature monitoring at the retina during irradiation, and all known classic methods are not applicable. During the development of a new, pulsed laser treatment - selective retina therapy (SRT) [2] - we discovered and developed an optoacoustically based method which promises to realise this goal. During SRT we could determine the temperature dependence over time from the pulse train applied for patient treatment [3].

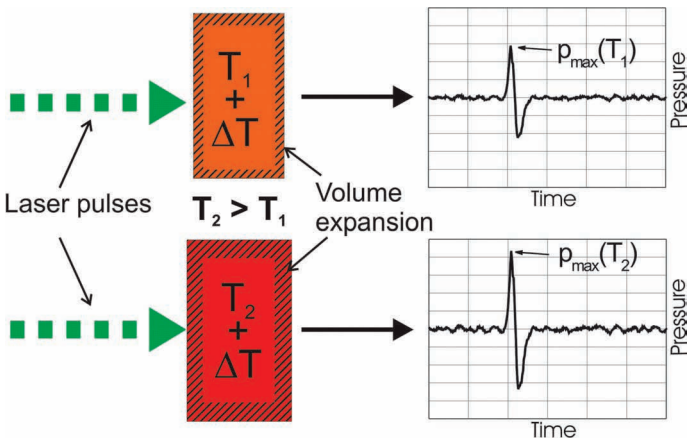

***Figure 1**: Principle of optoacoustic temperature determination*

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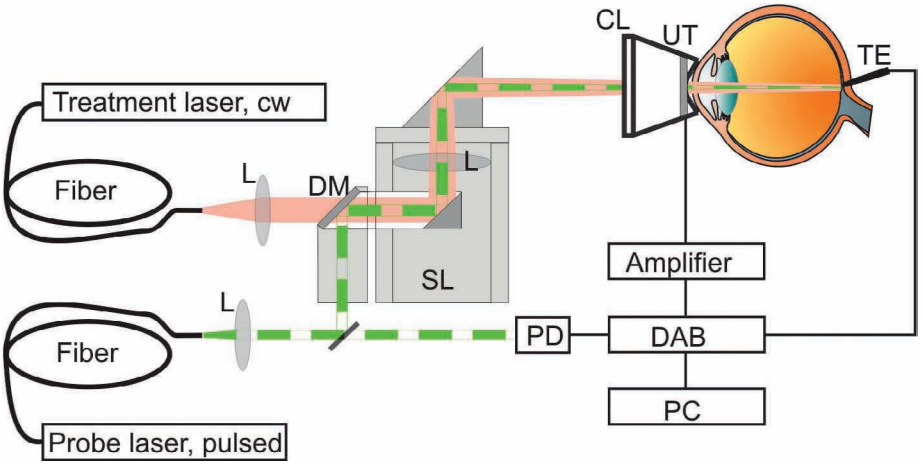


***Figure 2**: Experimental setup for optoacoustic temperature determination during cw-laser irradiation. L: lens, DM: dichroic mirror, SL: slit lamp, PD: photo diode, CL: contact lens, UT: ultrasonic transducer, TE: thermo couple (ex-vivo only)*

Subsequently, the technology has been further developed for TTT and is currently being made available for LPC.

2 Optoacoustic temperature determination

The therapeutic laser radiation is mainly absorbed at the retinal pigment epithelium (RPE) and the choroids at the fundus of the eye, where it leads to an instantaneous temperature increase. This results in a pressure increase within the tissue as its density is reduced with temperature. This pressure increase $\Delta P(\vec{r},t)$ is proportional to the temperature increase $\Delta T(\vec{r},t)$ and to the Grüneisen coefficient $\Gamma(T)$ which strongly depends on the temperature [4]:

$$\Delta P(\vec{r},t) \sim \Gamma(T) \cdot \alpha(\tau_p/\tau_{ak}) \cdot \Delta T(\vec{r},t) \quad \text{(Eq. 1)}$$

with $$\Gamma(T) = \frac{\beta(T) \cdot c_s(T)^2}{C_p(T)}$$

The dimensionless Grüneisen coefficient Γ contains the thermal expansion coefficient β, the speed of sound c_s and the specific heat capacity C_p at constant pressure. All the parameters depend on T, the most prominent being β. The highest pressure is obtained with $\alpha(\tau_p/\tau_{ac}) = 1$, if the pulse duration τ_p is much shorter than the acoustic transit time $\tau_{ac} = d/c_s$ of the wave through the heated volume of thickness d. If $\tau_p \gg \tau_{ac}$, an average pressure is obtained inside the absorber and α decreases hyperbolically with τ_p/τ_{ac}.

The local pressure increase results in a thermoelastic expansion with the emission of a bipolar pressure wave (**figure 1**), which can be described by the photoelastic wave equation [5]. Amplitude and frequency spectrum do not only depend on the laser radiation but also on the irradiated tissue volume and its consistence. If the laser irradiation is fixed, then the maximum pressure amplitude of the emitted wave $p_{max}(T)$ is proportional to the pulse energy E_0 and the Grüneisen parameter $\Gamma(T)$ and thus depends on the temperature [5].

$$p_{max}(T) \sim \Gamma(T) \cdot E_0 \quad \text{(Eq. 2)}$$

During tissue heating the pressure amplitude rises, because $\Gamma(T)$ increases with T although the same pulse energy E_0 is used (figure 1).

The temperature dependence of water, the main constituent of tissue, can be described with a second order polynomial up to a temperature of 100°C. Eq. 2 can thus be approximated by

$$P_{max}(T) = \varepsilon \cdot E_0 \cdot ((T^2 - T_0^2) - 2T_{max}(T - T_0)) \quad \text{(Eq. 3)}$$

The temperature T_0, which gives $\Gamma(T) = 0$, corresponds to water at its highest density at 4°C. T_{max} is the maximum temperature of the polynomial fit. The pressure wave travels through the eye and can be measured with an appropriate transducer at the cornea. The transfer constant ε in eq. 3 accounts for the pressure propagation and impedance mismatches in the eye as well as for the geometry and sensitivity of the pressure transducer including the signal amplification.

The tissue parameter T_0 and T_{max} have to be determined experimentally for the fundus tissue, wherefore we used enucleated porcine and rabbit eyes. Tissue was placed in a cuvette filled with saline solution. The whole cuvette was heated up while it was irradiated with probe pulses of a N_2-dye laser (λ = 500 nm, τ_p = 3 ns, E_0 = 5 µJ). The pressure waves were detected with an ultrasonic transducer. In the range of 15 to 50°C, average values of T_0 = -20.5°C and T_{max} = 114.4°C were determined [6].

The transfer constant ε strongly depends on the individual eye and the position of the irradiation spot at the retina as well as the transducer contact at the cornea. Consequently it has to be determined directly prior to each measurement. Therefore probe laser pulses are applied just before switching on the treatment laser, thus P_{max} is normalised to T_{body} and ε is fixed according to eq. 3. After switching on the treatment laser the actual temperature T can be calculated online by eq. 3 according to the rising pressure amplitude P_{max}.

3 Measurements on the eye

For a determination of retinal temperature increases during continuous (cw) laser irradiation of the ocular fundus, the beam of the treatment laser (diode laser, λ = 810 nm, $P \leq 3$ W) was superposed concentrically with the beam of the pulsed measurement laser by means of a dichroic mirror. The coupled radiation was transmitted through a laser slit lamp and a contact lens with embedded transducer onto the retina of enucleated porcine eyes (*ex-vivo*) and rabbit eyes (*in-vivo*), respectively (**figure 2**). Contact lenses are generally used in oph-

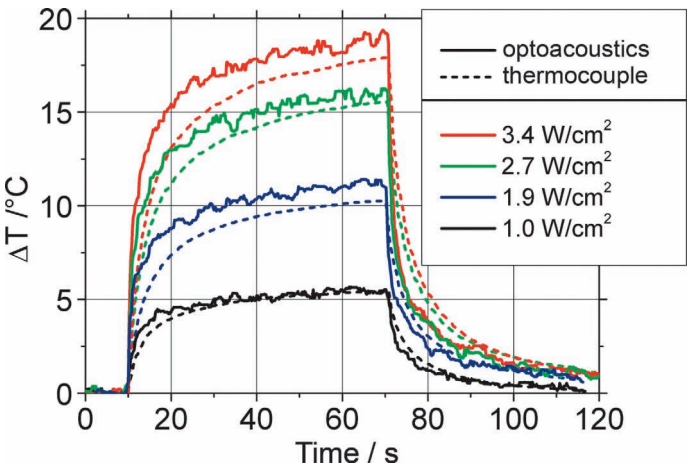
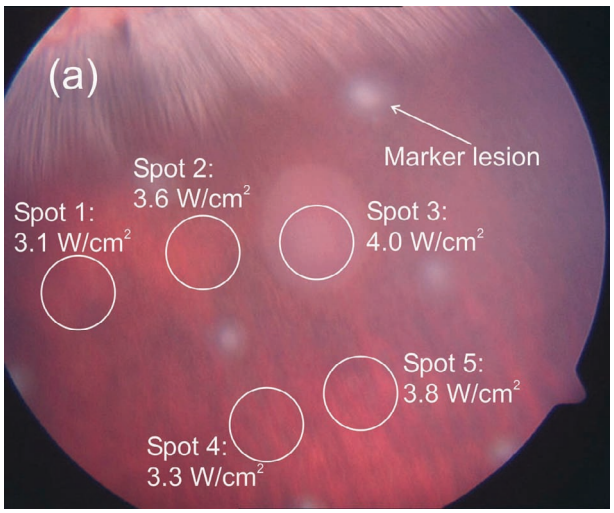


***Figure 3**: Temperature increase at the fundus of a porcine eye during cw-laser irradiation (ex-vivo). Thermoelectric measurement (dotted line) and optoacoustic determination (solid line)*



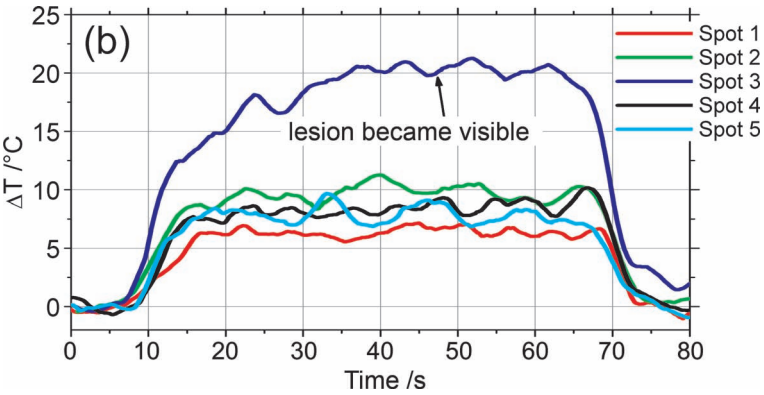


***Figure 4**: (a) White light fundus image of a rabbit's eye after TTT. The circles indicate the irradiated areas, the arrow shows a marker lesion for orientation. (b) Measured temperature increases (in-vivo). The arrow marks the point in time when the lesion became visible*

thalmology for retinal laser therapies. In combination with a slit lamp, a clear view into the eye can be obtained.

The used setup allows for an independent adjustment of the two spot diameters. To compensate energy fluctuations of the laser source, the detected pressure signals were normalised to pulse energy. With a repetition rate of 5 Hz , the applied pulse energy of 5 µJ leads only to transient small temperature peaks which do not contribute to an increase of the baseline tissue temperature.

3.1 Ex-vivo temperature determination

By means of the experimental setup (figure 2) the temperature increase during cw laser irradiation of a porcine eye was determined. The retinal diameter of the cw laser spot was 2 mm with irradiation between 1.0 and 3.4 W/cm^2. The absorption of the radiation at the fundus causes a volumetric temperature increase. Due to heat conduction, the dimension of the heated volume is hereby larger than the irradiated volume, with the highest temperature increase in the centre of the irradiated area. By using a spot diameter for the measurement laser of only 300 µm and positioning it in the centre of the cw laser spot the maximum temperature increase is obtained. The transfer constant ε was determined before the measurement by applying 20 laser pulses and detecting the according pressure maxima. For a comparison of the optoacoustically determined temperature increases with thermoelectric data, a thermocouple (type T, diameter 250 µm) was positioned subretinally in the centre of the irradiated volume.

The cw exposure started 10 s after beginning the calibration procedure and lasted for 60 s. The resulting temperature developments are depicted in **figure 3** for the thermoelectric measurement (dotted line) and optoacoustic determination (solid line). Immediately after switching on the cw laser, the irradiated volume heats up to the maximum reached at the end of the exposure time, with the temperature increase being linearly dependent on the irradiation. The average temperature increase after 60 s was found to be 5.8°C/(W/m^2) as determined optoacoustically and 5.5°C/(W/m^2) according to the thermocouple measurement. A comparison of both temperature developments shows good agreement with a maximum deviation of 1.2°C at the end of the laser exposure. This deviation is at least partially attributable to the very difficult positioning of the thermocouple inside the retina.

3.2 In-vivo temperature determination

The following experiment was carried out under the national and European guidelines (86/609/EEC) for the treatment of animals, with permission of the competent authority. A rabbit was anesthetised and positioned in front of the slit lamp. The contact lens with embedded transducer was placed on to the rabbit's eye. By means of a diode laser, a pattern of small coagulations were induced on the retina as marker lesions. Subsequently, five laser exposures were carried out on five different areas with irradiations between 3.1 and 4.0 W/cm^2 with a retinal spot diameter of 2 mm [6]. **Figure 4a** shows a white light fundus image taken after the laser exposures. The light spots indicate the lesion pattern, the white circles mark the treated areas. The appropriate temperature developments, determined optoacoustically, are depicted in **figure 4b**.

On treatments spots 1, 2, 4 and 5 an almost constant temperature plateau between 6.4 and 9.7°C is reached after approx. 5 s [6]. In contrast to the *ex-vivo* results, the temperature rise is not linearly dependent on the applied laser power, indicating intra-individual differences in retinal pigmentation and choroidal blood flow. On treatment spot 3, an immense temperature increase of more than 20°C was observed, even though the applied power was only slightly higher than on spot 5. During this laser exposure an extensive whitening of the retina occurred – this must be avoided at all costs in clinical treatment, as it indicates irreparable damage to the retina with extended vision loss. The point in time when the lesion became visible to the physician is marked by an arrow in the diagram – too late to prevent the patient's eye from damage. If this strong temperature rise were visible online during clinical treatment, the physician could either cease treatment or at least have reduced the laser power much earlier.

3.3 Temperature determination during laser photocoagulation

In first *ex-vivo* experiments the technical feasibility of an online temperature determination during retinal laser photocoagulation (LPC) was investigated. In LPC the exposure time and spot diameters are considerably decreased compared to TTT. For these parameters it is practicable to apply the radiation of the treatment laser and the measurement laser through the same optics and fiber. In an experimental setup, similar to the one shown in figure 2, a continuously emitting Nd:YAG laser (λ = 532 nm) was used for LPC. Probe and LPC radiation were coupled and transmitted through the same optical fiber. By means of the slit lamp optics, the fiber tip was imaged onto the retina, generating a top-hat spot profile with a diameter of 400 µm. Due to the axial and lateral temperature gradient over the spot, an averaged temperature increase ΔT over the absorbing volume is determined. The maximum temperature increase in the centre of the spot ΔT_{max} is time-dependent and exceeds ΔT by a factor of 1.5 to 2.

In different areas of an enucleated porcine

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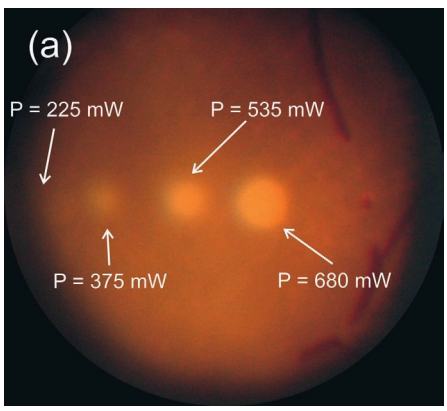
eye four laser exposures were performed consecutively with laser powers ranging from 225 to 680 mW and an exposure time of 680 ms. The according fundus image (**figure 5a**) shows visible coagulations for applied laser powers of 375 mW and up. The simultaneously determined ΔT's are depicted in **figure 5b**. The temperature rise ΔT, as well as the dimension of the thermal retina damage, increase with the applied laser power. Based on the Arrhenius theory for thermal damage and with the knowledge of the temperature development over time, the appropriate constants for retinal denaturation can be directly calculated from the corresponding coagulation thresholds [7]. Additionally, a specific temperature/time history can be defined at which a certain coagulation stage (e.g. minimal visible) is reached. Using proper dosimetry control of the coagulation, the risk of retinal bleeding or unwanted large and painful lesions could be significantly reduced.

4 Summary and Outlook

The optoacoustic method developed here allows for a non-invasive real-time measurement of temperature during retinal laser therapies. This technique carries the potential to correlate the degree of thermal lesion with the induced retinal temperature, and thus better predict the therapeutic outcome of the treatment. This correlation can be used to evaluate an optimum temperature profile for retinal laser treatments to achieve the best therapeutic effect. A further step is the development of an automatically regulated feedback system to adjust the laser power to achieve the desired thermal damage individually for every spot and patient.

The non-invasive online determination of retinal temperature increases during laser photocoagulation of the retina was awarded the „Innovation Prize for Medical Technology 2006" by the German Ministry for Education and Research. The associated project is designed to run for three years and started end of 2007.



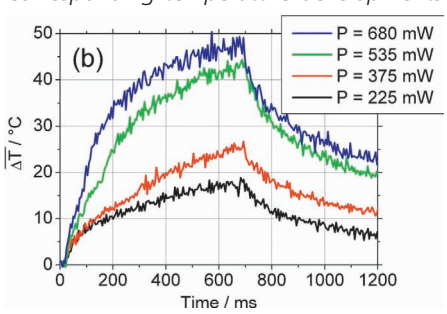


***Figure 5**: (a) White light fundus image of a porcine eye after laser photocoagulation. (b) Corresponding temperature developments*

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