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Noninvasive optoacoustic temperature determination at the fundus of the eye during laser irradiation

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Abstract. In all fundus laser treatments of the eye, the temperature increase is not exactly known. In order to optimize treatments, an online temperature determination is preferable. We investigated a noninvasive optoacoustic method to monitor the fundus temperature during pulsed laser irradiation. When laser pulses are applied to the fundus, thermoelastic pressure waves are emitted, due to thermal expansion of the heated tissue. Using a constant pulse energy, the amplitude of the pressure wave increases linearly with an increase in the base temperature of between 30 and 80°C. This method was evaluated *in vitro* on porcine retinal pigment epithelium (RPE) cell samples and clinically during selective RPE treatment with repetitive microsecond laser pulses. During the irradiation of porcine RPE with a neodymium-doped yttrium (Nd:YLF) laser (527 nm, 1.7 μs, 500 Hz repetition rate, 160 mJ/cm^2) an increase in the base temperature of 30±4°C after 100 pulses was found. During patient treatments, a temperature increase of 60±11°C after 100 pulses with a 500-Hz repetition rate and 7±1°C after 30 pulses with 100 Hz at 520 mJ/cm^2 was found. All measured data were in good agreement with heat diffusion calculations. Optoacoustic methods can be used to noninvasively determine retinal temperatures during pulsed laser treatment of the eye. This technique can also be adapted to continuous-wave photocoagulation, photodynamic therapy and transpupillary thermotherapy, or other fields of laser-heated tissue. [DOI: 10.1117/1.1627338]

Keywords: photocoagulation; retinal pigment epithelium; selective microphotocoagulation; optoacoustic; thermoelastic expansion; selective retinal pigment epithelium treatment.

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1 Introduction

Treatment of the retina is one of the most common applications of lasers in medicine. The therapies range from established continuous wave (cw) photocoagulation[1] to new ophthalmic laser applications such as photodynamic therapy (PDT),[2] transpupillary thermotherapy (TTT),[3,4] and selective retinal pigment epithelium (RPE) treatment (SRT)[5] In all cases the laser-induced temperature increase at the retina can only be estimated by calculations. Accurate measurements, which are highly invasive, can only be performed in animal experiments, and so far no methods exist for patients. However, in most laser treatments, it would be very desirable to know the laser-induced temperature increase in order to optimize the treatment and to limit the damage to the target area.

In a variety of retinal diseases it is sufficient to damage only the RPE layer to induce the healing process.[5] However, in standard photocoagulation, the adjoining photoreceptor tissue is also destroyed. In contrast to this, SRT allows the photoreceptor tissue to be spared despite the damage to the RPE.[6] In SRT, a train of microsecond laser pulses rather than cw irradiation is used to spatially confine the heat to the strongly absorbing RPE. During the microsecond laser pulse, a high peak temperature is achieved at the light-absorbing melanosomes inside the RPE cell. The high temperature presumably leads to microbubble formation around the melanosomes,[7,8] which most probably results in a thermomechanical disruption of the RPE cell. Because of the geometrical arrangement of the tissue layers and the distribution of absorbing melanin granules, only a very small corresponding peak temperature is reached at the adjacent photoreceptors after single-pulse application. However, owing to a high repetition rate, the baseline temperature increases in both tissue layers during the application of a laser pulse train (Fig. 1). This effect is in the millisecond time scale, as in cw photocoagulation. It makes the baseline temperature an important factor that might interfere with the selectivity of the method. Especially in SRT, it is desirable to confine the laser-induced temperature rise to the RPE.

Temperature measurements on the retina of rabbits have been performed with micro thermoelements placed near

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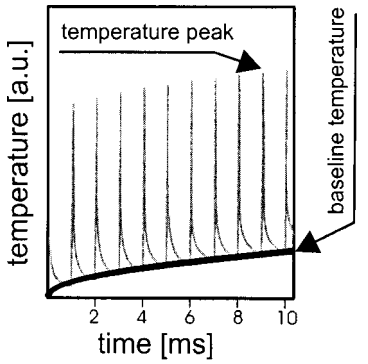

Fig. 1 Temperature curve inside an RPE cell during repetitive pulsed irradiation. A baseline temperature is built up, which depends on the pulse energy and repetition rate of the laser pulses applied.

the retina during irradiation[9,10] and by the injection of thermosensitive liposomes.[11] An ultrasonic temperature measurement seems to be possible as well, but has not been tested for this application.[12,13] Optoacoustic (OA) techniques have been used to measure the temperature of tissue[14–17] and focused on temperature mapping during laser-induced thermotherapy (LITT).[18] With this technique, it has been shown that it is possible to spatially resolve the tissue temperature and also the extent of the coagulation zone.

The objective of this study was to noninvasively determine the baseline temperature increase in the RPE during irradiation with repetitive laser pulses. The temperature measurements were performed using optoacoustic techniques with different repetition rates *in vitro* and during patient treatments. All data are compared with numerical temperature calculations of the different irradiation conditions.

2 Theoretical Background

2.1 *Optoacoustic Temperature Determination*

Laser-induced pressure waves can be generated in liquids by different physical mechanisms, i.e., dielectric breakdown, electrostriction, vaporization, thermoelastic expansion, and radiation pressure.[19,20] For absorbing media and low radiant exposure, the thermoelastic expansion of the heated volume dominates.[21]

Sigrist showed that the maximum peak pressure is proportional to the laser intensity I_0 and to the Grüneisen parameter Γ under conditions of no acoustic confinement but thermal confinement.[21] For small variations in the laser intensity I_0, it follows that

$$P^{\max}(T) \sim \Gamma(T) \times I_0 . \tag{1}$$

For water, Γ increases nearly linearly in the temperature range from 20 to 60°C.[22] Therefore the maximum pressure amplitude emitted after pulsed heating increases linearly with the base temperature in this range. A linear approximation of Eq. (1) leads to

$$P^{\max}(T) = \frac{I_0}{B_0} \times (T - T_{P=0}^{RPE}). \tag{2}$$

The temperature $T_{P=0}^{RPE}$ is the temperature where thermal expansion is zero and no effective thermoelastic expansion takes place. This temperature depends on the tissue and has to be determined experimentally. For water it is 4°C. B_0 is a sensitivity factor that includes the transducer sensitivity, signal amplification, and the amplitude of the acoustic transfer function. This value can be determined by the first laser pulse applied, if the start temperature T_0 and $T_{P=0}^{RPE}$ are known. Applying I_0 and measuring $P_0^{\max}$, B_0 is given by

$$B_0 = \frac{(T_0 - T_{P=0}^{RPE}) \times I_0}{P_0^{\max}}. \tag{3}$$

With known values of $T_{P=0}^{RPE}$ and B_0, the increase in the baseline temperature (Fig. 1) at the i'th laser pulse is given by

$$T_i(P_i^{\max}) = T_{P=0}^{RPE} + \frac{B_0 P_i^{\max}}{I_0}. \tag{4}$$

Therefore, when measuring temperature differences in the linear range of Γ, only T_0 has to be known, as long as the acoustic coupling (B_0) between tissue and transducer and the intensity I_0 do not change during irradiation.

2.2 *Numerical Temperature Calculations*

As the thermoelastic expansion takes place in the whole irradiated spot, the measured amplitude of the optoacoustic transient gives the mean temperature over the irradiated area. When performing numerical temperature calculations, this has to be taken into account. As a temperature model we use the solution of a quadratic light-absorbing layer irradiated with a spatially and temporally uniform laser profile.[23] The edge length equals the spot's diameter d and the homogeneous absorption thickness is 5 μm. Heat loss that is due to heat convection by choroidal blood vessels is neglected. To determine the mean temperature, we averaged over a circular area with a radius $d/2$ of this calculated rectangular area.

In the case of repetitive laser irradiation with a repetition rate f_{rep}, the baseline temperature of the i'th laser pulse is determined at time $t_i = i \times 1/f_{\text{rep}}$. The mean temperature achieved by the previous laser pulses sums to $\overline{T}_{\text{rep}}(t_i)$, which is given by

$$\overline{T}_{\text{rep}}(t_i) = \frac{1}{\pi \times (d/2)^2} \times \sum_{n=1}^{i} \int_A T(\mathbf{r}, t_n) dA. \tag{5}$$

Using this solution, the temperature courses for all experiments performed were simulated with respect to their spot size, repetition rate, and radiant exposure. It has been shown that in humans about 60% of light in the green spectral range which reaches the fundus is absorbed by the RPE.[24] The absorption of porcine RPE was determined to be nearly 90% in transmission experiments with detached RPE.

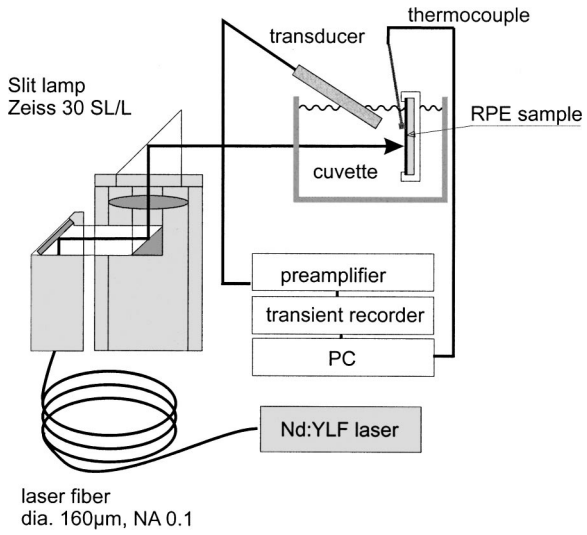

Fig. 2 Setup for optoacoustic measurements during irradiation of porcine RPE *in vitro*.

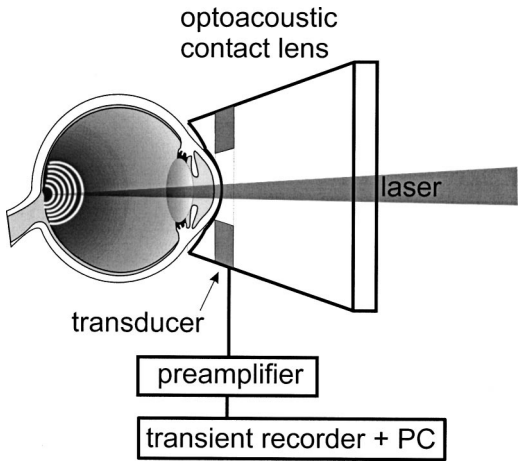

Fig. 3 Setup for optoacoustic measurements during selective RPE treatment. The laser and slit-lamp setup is the same as shown in Fig. 2. A standard contact lens is modified with a piezoelectric transducer.

3 Material and Methods

3.1 *Experiments for Temperature Determination in Vitro*

3.1.1 *In vitro setup*

The light of a frequency-doubled Nd:YLF laser (Quantronix, Inc., model 527DP-H, 527 nm, actively pulse stretched to 1.7 μs pulse duration, 600 μJ pulse energy, up to 1 kHz repetition rate)[7] was coupled into a 50-m long fiber (Ceram Optec GmbH, 105 μm, NA 0.1). This fiber was directly coupled to the slit lamp fiber (Zeiss, 160 μm, NA 0.1). The fiber tip was imaged with an ophthalmic laser slit lamp (Zeiss, 30 SL/L) to the sample surface. The beam diameter at the sample's surface was 160 μm and the beam profile was nearly tophat. The porcine RPE samples were fixed in a sample holder system and placed in a cuvette filled with physiological saline solution. A broadband ultrasonic transducer (Valpey-Fisher, VP-1093, DC-10 MHz) was placed approximately 3 mm beside the irradiated area. The OA transients were preamplified with an ultrasonic amplifier (Panametrics, preamplifier 5676, 50 kHz to 50 MHz) and recorded by a transient recorder (Sony/Tek, RTD710). The data were collected and analyzed with LabView (National Instruments) on a personal computer (PC). The cuvette temperature was measured by a thermocouple near the surface of the RPE sample (Fig. 2).

3.1.2 *In vitro RPE sample preparation*

The *in vitro* experiments were performed with freshly enucleated porcine eyes within 4 h postmortem. After equatorial dissection of the vitreous body, the neural and the neurosensory tissue, including the photoreceptors, was carefully removed. The sample with RPE as a superficial layer was fixed in a holder system and covered with physiological saline solution.

3.1.3 *Determination of $T_{P=0}^{RPE}$ for porcine RPE*

For determination of $T_{P=0}^{RPE}$, the temperature where no effective thermoelastic expansion takes place, the thermoelastic pressure maximum $p^{\max}$ in dependence of the RPE sample temperature [Eq. (4)] were measured on porcine RPE samples. The sample cuvette was filled with warm physiological solution at 45°C. During cooling, the RPE sample was irradiated with laser pulses of constant radiant exposure (50 mJ/cm^2, 250 ns, 1 Hz repetition rate). The pressure transients emitted were recorded with the transducer, and the maximum pressure was determined as the peak value of the positive (compressive) part of the OA transient. The sample temperature was measured with the thermocouple near the irradiated area. In this temperature range, no changes in the optical properties of the RPE were expected owing to a thermal denaturation of the samples. Measurements were performed on 17 samples from 17 eyes.

3.1.4 *Irradiation parameters*

The clinical treatment parameters for SRT, 100 laser pulses applied at a 500-Hz repetition rate and 30 pulses at 100 Hz, respectively, were also used in the *in vitro* experiments. Due to the lower damage threshold of porcine RPE[25] compared with that of humans, the maximum pulse energy was reduced from 100 μJ to 35 μJ for *in vitro* experiments.

3.2 *Setup for Temperature Determination during Patient Treatment*

Two different laser systems were used for the treatments. One system was the Nd:YLF laser slit-lamp system as described earlier with a 100-Hz laser pulse repetition rate and 30 laser pulses per pulse train. The retinal spot diameter was 160 μm. The second system was a clinical prototype [Carl Zeiss Jena, diode-pumped, frequency-doubled Nd:YAG 532 nm, 800 ns pulse duration, 500 Hz repetition rate, 100 pulses]. The same slit lamp was used with a 200 μm retinal spot diameter. Pulse energies between 50 and 140 μJ were used.

During treatment, a contact lens was placed on the patient's cornea to eliminate the eye's refraction and to fix the eye. We modified a standard contact lens (Haag Streit, laser lens 903L) with a piezoelectric transducer (Fig. 3). The signals from the transducer were preamplified with an ultrasonic

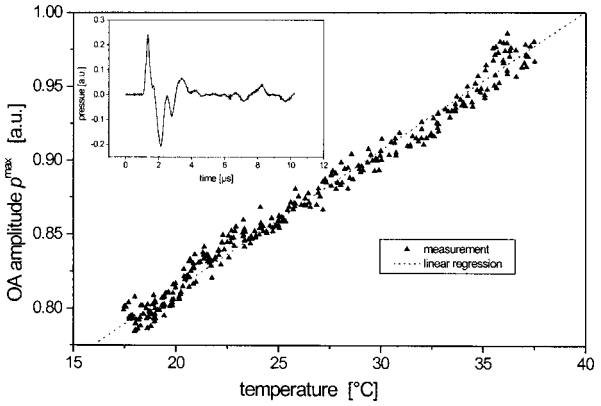

Fig. 4 One example of an RPE sample OA amplitude maximum $p_{RPE}^{\max}$ over temperature. The amplitude increase is linear with temperature. A typical OA transient is shown in the small inset.

amplifier (Panametrics, preamplifier 5676, 50 kHz to 50 MHz) and recorded by a transient recorder (data acquisition board, Datel PCI 431-B) in a PC. The data acquisition process and the analysis were programmed with LabView (National Instruments).

The OA data were taken during treatment in a clinical pilot study for SRT at the eye clinics of the Medical University Lübeck and the University of Regensburg. All patients gave written informed consent to the measurements and treatment.

3.3 *Data Analysis*

The first probe laser pulse has to be applied at a known RPE temperature to calculate the sensitivity factor B_0. In the case of patients, T_0 is the body temperature and is the cuvette water temperature for *in vitro* experiments. With a known start temperature T_0, the material constant $T_{P=0}^{RPE}$ and pressure peak $P_1^{\max}$ from the first probe pulse, B_0 was calculated according to Eq. (3). All following pressure values $P_i^{\max}$ for the *i*'th laser pulse were then used to calculate the temperature T_i with this predetermined value B_0 [Eq. (4)].

4 Results

4.1 *Temperature Dependence of the Thermoelastic Pressure Maximum in RPE*

To determine $T_{P=0}^{RPE}$, the temperature dependence of the OA amplitude $p^{\max}$ for porcine RPE was measured. The peak pressure increases linearly with temperature (Fig. 4). A linear fit according to Eq. (2) was applied to calculate the calibration temperature $T_{P=0}^{RPE}$ of the porcine RPE. Averaged over seventeen samples, $T_{P=0}^{RPE} = -52.3(\pm 20.5\,\mathrm{STD})°\mathrm{C}$.

4.2 *Results of Temperature Determination in Vitro*

During irradiation of porcine RPE with 1.7-μs Nd:YLF laser pulses at 32 μJ pulse energy, which corresponds to a radiant exposure of 160 mJ/cm^2, the OA transients were recorded. After determining the $p^{\max}$ of each OA transient and B_0 for the first pulse, the temperature increase was calculated [Eq. (4)] using the material constant $T_{P=0}^{RPE}$. The temperature curve starts at a cuvette water temperature of 18°C (Fig. 5). After 100 pulses, the baseline temperature had increased to 55°C.

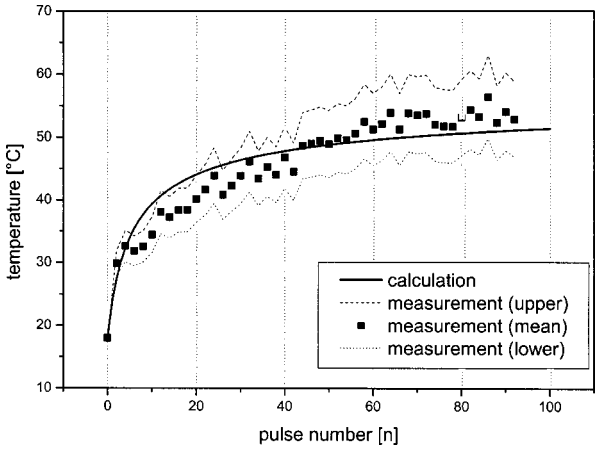

Fig. 5 Baseline temperature increase during irradiation of porcine RPE with 160 mJ/cm^2 at a repetition rate of 500 Hz. The spot diameter was 160 μm. The results of the heat diffusion calculations were adjusted to the measured data to 87% absorption in the RPE. The upper and lower limits of the measured results reflect the standard deviation of $T_{P=0}^{RPE}$.

The upper and lower limits of the measured results reflect the standard deviation of $T_{P=0}^{RPE}$. The heat diffusion calculations were performed with the set of parameters used in the experiment and 87% absorption in the RPE, which gives the best least-squares fit to the measured temperature values.

By normalizing the induced temperature increase to the applied pulse energy, the accuracy of this method was tested for different laser pulse energies from 21 to 32 μJ at a 500 Hz repetition rate (Fig. 6). The graphs show a good correspondence in slope and amplitude.

4.3 *Results during Treatment of Patients*

With the use of the OA contact lens it is possible to measure the OA transients during selective treatment of the RPE. By analyzing the $p^{\max}$ following each laser pulse, the baseline temperature increase was determined with the material constant $T_{P=0}^{RPE}$ of porcine RPE. For the treatment parameters of

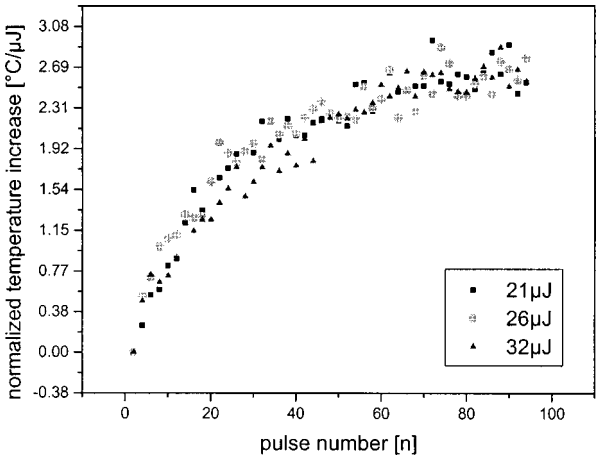

Fig. 6 The pulse energy normalized temperature increase for different applied pulse energies on porcine RPE. Since the induced baseline temperature increase is linear with the applied pulse energy, the normalized temperatures are the same for different pulse energies.

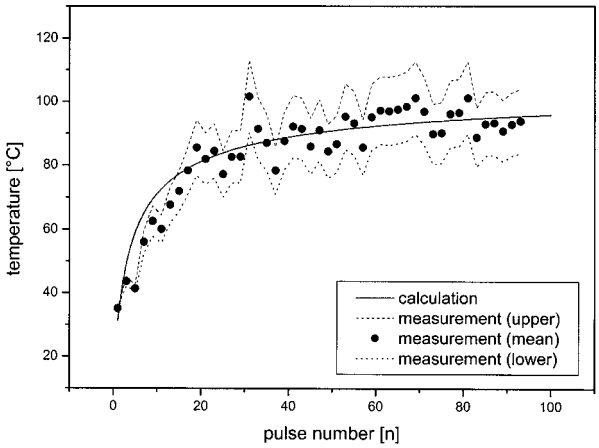

Fig. 7 Baseline temperature increase during selective RPE treatment with 100 pulses at a 500 Hz repetition rate. In this case the treatment parameters are a 800 ns, 523 nm Nd:YAG laser pulse, 100 μJ pulse energy, and a 200 μm spot diameter. For calculations, 52% absorption in the human RPE were used. The upper and lower limits of the measured results reflect the standard deviation of $T_{P=0}^{RPE}$.

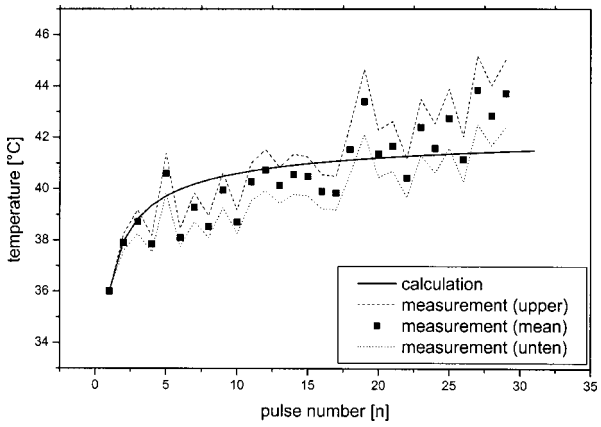

Fig. 8 Baseline temperature increase during selective RPE treatment with 30 pulses at a 100 Hz repetition rate. In this case the treatment parameters are a 1.7 μs, 527 nm Nd:YLF laser pulse, 100 μJ pulse energy, and a 160 μm spot diameter. For heat diffusion calculations, 32% absorption in the human RPE was used. The upper and lower limits of the measured results reflect the standard deviation of $T_{P=0}^{RPE}$.

100 μJ, 100 pulses, a 200 μm spot diameter, and a 500 Hz repetition rate with the Nd:YAG system, a high baseline temperature builds up during treatment. An example of this is shown for a single treatment spot in Fig. 7. The upper and lower limits of the measured data reflect the standard deviation of $T_{P=0}^{RPE}$. The initial temperature is the body temperature of 37°C. The baseline temperature increases to 90°C. However, in the treated area, no thermal damage such as a grayish lesion was visible with an ophthalmoscope. By fitting the temperature calculation results to the experimental data, 52% absorption in the RPE gave the best least-squares fit, which is in quite good agreement with the literature data range of 50[26] to 60%.[24]

For treating a patient with the Nd:YLF laser, 30 pulses at a lower repetition rate of 100 Hz were used. A pulse energy of 100 μJ on a spot with a 160 μm diameter was applied. The temperature curve starts at body temperature and increases to only 44°C (Fig. 8). As expected, the baseline temperature increase is much lower than that for 500 Hz. The irradiated spot was also ophthalmoscopically invisible. Fitting the absorption to 32% gave the best match between the experimental data and the temperature calculations. By adjusting the calculated curve to the measured final temperature of 44°C, nearly 50% absorption is achieved.

5 Discussion

It has been demonstrated that optoacoustic techniques can be used to noninvasively determine the baseline temperature increase of the laser-irradiated fundus of the eye *in vitro* and during treatment of patients. In the case of a pulsed treatment laser, the treatment pulse itself can be used to probe the temperature. The measured temperatures are in agreement with temperature calculations and in the range of commonly known RPE absorption.

5.1 *Determination of* $T_{P=0}^{RPE}$

The measurements show that the $p_{RPE}^{\max}$ is linearly related to the porcine RPE sample temperature in the measured temperature range of 18 to 40°C. In this temperature range we did not observe any structural changes of the porcine RPE. In the baseline temperature measurements, the temperature dependence of $p_{RPE}^{\max}$ was assumed to be linear also for higher temperatures. This assumption is supported by comparing our measured results with temperature calculations at higher temperatures. Neither in the *in vitro* measurement nor during patient treatment was a systematic temperature deviation at higher temperatures observed.

The temperature stability of the transducer is given by the temperature of thermal depolarization, the Curie temperature. The lead zirconium titanate material used has a Curie temperature of 310°C.[25] The water temperature of 40°C that was used is far below this critical temperature.

The material constant measured for porcine RPE of $T_{P=0}^{RPE} = -52.3$°C is in good agreement with values found for other tissues. The measured data from Larin et al.[16] and Esenaliev et al.[15] can be interpolated to a value of between $T_{P=0}^{\text{liver}} = -50$°C[16] and -54°C[15] for canine liver. For canine myocardial tissue a $T_{P=0}^{\text{myocard}} = -118$°C was found.[15]

The measurements were made with a radiant exposure of 50 mJ/cm^2. During treatment, radiant exposures up to 600 mJ/cm^2 were applied to the eye. Different pulse energies should not affect the determined temperature $T_{P=0}^{RPE}$. It was shown for water that the temperature of the vanishing pressure varies by less than 0.5°C by varying the laser pulse energies up to vaporization.[20] This small variation of 0.5°C can be accepted in our application owing to the relatively large standard deviation of $T_{P=0}^{RPE}$.

5.2 *In Vitro Temperature Determination on Porcine RPE*

If 100 laser pulses are applied at 160 mJ/cm^2 on porcine RPE, the baseline temperature increases up to 55°C (Fig. 5). This

result can also be verified by calculations, taking into account that the average temperature over the irradiated area is determined.

By normalizing the induced temperature increase to the applied pulse energy, it is shown in Fig. 6 that this increase is linear for different pulse energies. This was expected, since the results achieved with water show similar behavior.[19]

5.3 *Temperature Determination during Patient Treatment*

In selective RPE treatment, the photoreceptors and neural tissue should be spared by minimizing heat conduction from the absorbing RPE layer. By applying short laser pulses, only the RPE cell layer is heated up until cell damage occurs. The laser repetition rate must be low enough to allow effective cooling of the RPE preventing a high baseline temperature (Fig. 1). With the OA technique described here, the baseline temperature increase induced by different repetition rates can be monitored during treatment. At a repetition rate of 500 Hz, the baseline temperature increases up to 90 ± 13°C, which is at the damage threshold of the RPE (Fig. 7). In this case, thermal damage of the photoreceptors seems possible. However, even microperimetry did not show skotoma.[6] At higher radiant exposure, a mild white lesion appears, which is typical for thermal denaturation of the retina. At a lower repetition rate of 100 Hz, the baseline temperature increase is negligibly low—up to only 44 ± 2°C (Fig. 8) at the same pulse energy used for the 500 Hz repetition rate. Only 30 laser pulses were applied, owing to the limited irradiation time of 300 ms in order to minimize movements of the eye during irradiation. With the 100-Hz treatment modality, a much higher range of safety between selective RPE treatment and thermal damage of the photoreceptors can be assumed. Further experiments have to prove this.

The temperatures measured during treatment were calculated with the material constant $T_{P=0}^{RPE}$ of porcine RPE. For further, more detailed studies, $T_{P=0}^{RPE}$ should be determined with human RPE samples as well. However, large deviations are not expected because of the similar structure of the RPE.[26]

5.4 *Precision of OA Temperature Measurement*

Owing to the standard deviation of the measured material constant $T_{P=0}^{RPE} = -52.3(\pm 20.5)$°C, the determined temperature changes have a standard error of 17%. This error can be reduced by decreasing the deviation of $T_{P=0}^{RPE}$ with a higher number of measurements, especially with human RPE samples. The measurements during patient treatment with a 100 Hz repetition rate showed that it is possible to detect temperature changes in the range of 1°C. This precision is sufficient for application in most laser irradiation modalities at the eye. Increasing the pulse-to-pulse stability of the laser will increase the measurement precision. However, more accurate results can also be achieved by measuring the energy of each pulse in the train and normalizing each OA transient to the pulse energy (compare Fig. 6).

5.5 *Application During cw Irradiation Modalitiy*

It has been shown principally for *in vitro* experiments that it is also possible to determine the laser-induced increase in fundus temperature during cw irradiation.[27] In this case an additional low-energy probe laser pulse was applied to determine the temperature increase. The radiant exposure was below the maximum permittable exposure (MPE) for application on human eyes. With use of the OA laser contact lens, it should be possible to perform temperature measurements during cw laser treatment of the retina.

6 Conclusion

A new method for noninvasively determining the laser-induced temperature increase at the fundus is presented. It was possible to determine the baseline temperature increase during selective RPE treatment *in vitro* and also during treatment of a patient. The treatment laser pulse itself was used to probe the increased fundus temperature. Comparing the measured results with temperature calculations, a retinal absorption between 32 and 52% for humans and nearly 90% for porcine RPE was found. This is in good agreement with established values. The temperature accuracy is about 17% based on the standard deviation of the material constant $T_{P=0}^{RPE}$ of porcine RPE. Temperature changes as low as 1°C can be detected. This technique can be applied during cw laser treatment of the retina and will be a step toward real-time temperature-controlled cw photocoagulation and TTT. OA temperature determination can be used in all fields of laser–tissue interaction and also in nondestructive testing (NDT) in metrology.

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