Noninvasive temperature measurements during laser irradiation of the retina with optoacoustic techniques

Georg Schüle, Gereon Hüttmann, Ralf Brinkmann

Medical Laser Center Lübeck, Germany

ABSTRACT

In all laser treatments at the fundus of the eye the temperature increase is unknown. In order to optimize the treatment modalities, a noninvasive online temperature determination is preferable.

Method: Applying laser pulses to the fundus, thermoelastic stress waves are emitted based on the thermal expansion of the heated tissue, mainly the retinal pigment epithelium (RPE). The amplitude of the thermoelastic wave is proportional to the thermal expansion coefficient, which linearly depends on temperature between 30-80°C for water. The method was evaluated for selective RPE-treatment in vitro and clinically using the µs-laser pulses for treatment and temperature determination simultaneously. Conventional laser photocoagulation was investigated in vitro using an Ar Ion laser for coagulation and low-energy N_2-pumped dye laser pulses to probe the temperature.

Results: In all cases, sufficient pressure amplitudes were detected either by a needle hydrophon in vitro or by a contact lens with embedded transducer during treatment. Depending on the treatment parameter, temperature increase of 60°C were evaluated from the pressure transients. All temperatures detected are in close agreement to heat diffusion calculations.

Conclusion: We demonstrated a noninvasive online method to detect retinal temperatures during laser treatments. This technique can be adapted to photocoagulation, PDT and TTT.

Keywords: temperature measurement , optoacoustic, retinal pigment epithelium, RPE , selective microphotocoagulation

1. INTRODUCTION

The laser treatments of retinal diseases are widely used in ophthalmology. Laser therapies range from established cw photocoagulation [1] to new ophthalmic laser applications like photodynamic therapy (PDT)[2] and transpupilary thermo therapy (TTT)[3]. In all cases the laser induced temperature increase at the retina is only estimated by calculations or measured in animal experiments with high invasive techniques. No measurements were performed during patient treatment so far.

Temperature measurements in rabbits were performed with micro thermoelements which were placed near the retina during irradiation [4] and by the injection of a thermosensitive liposome [5]. Also the use of ultrasonics for temperature determination seems to be possible but has not been tested for the application at the eye [6, 7].

Optoacoustic (OA) techniques have been introduced for temperature measurements on tissue [8, 9] and in the eye [10]. On tissue, the work was focused on temperature mapping during laser induced thermo therapy (LITT)[11]. It has been shown, that with this technique it is possible to

Correspondence: e-mail: schuele@mll.mu-luebeck.de
tel:+49-451-500-6517
fax: +49-451-505486
www.mll.mu-luebeck.de

Ophthalmic Technologies XII, Fabrice Manns, Per G. Söderberg, Arthur Ho, Editors,
Proceedings of SPIE Vol. 4611 (2002) © 2002 SPIE · 1605-7422/02/$15.00

detect the tissue temperature distribution and also the extension of the coagulation zone.

The selective RPE cell treatment [12] is a promising method in ophthalmology for a variety of diseases, which are associated with a dysfunction of the RPE cells. In contrast to conventional photocoagulation with 200ms laser irradiation it is possible to spare the photoreceptor tissue[13], thus maintaining full vision in the treated area. Due to the repetition rate of 100-500Hz used, a baseline temperature is build up in the RPE [10] (fig 1). This effect is on the ms time scale, thus heat diffusion can reach other tissue layers like the photoreceptors. This makes the baseline temperature to an important factor, which interferes with the selective RPE effect.

The objective of this study was to introduce a novel method to determine noninvasively the laser induced temperature increase at the fundus by OA techniques. We present the feasibility of the technique during selective RPE treatment in vitro and patient treatment. Also in case of cw irradiation in vitro, the laser induced temperature increase was determined.

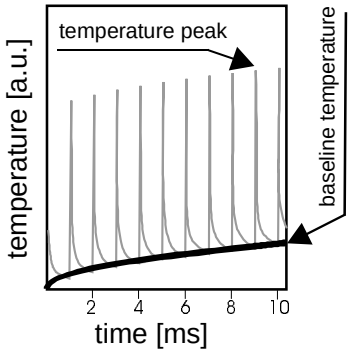

Figure 1: Temperature curve inside an RPE cell during pulsed irradiation. Due to a high repetition rate, a baseline temperature is build up.

2. THEORETICAL BACKGROUND

2.1 Optoacoustic temperature determination

Irradiating liquids, solids and tissue, stress waves can be generated mainly by dielectric breakdown, electrostriction, vaporisation, thermoelastic expansion and radiation pressure [14, 15]. For absorbing media the thermoelastic effect is most important for sound generation [16]. It is associated with the thermal expansion of a heated volume. In case of acoustic and thermal confinement thermoelastic pressures of several hundred bars can be achieved [17].

Sigrist showed that the maximum peak pressure is proportional to the thermal expansion coefficient β [16]:

$$p^{\max}(T) \sim \beta(T) \tag{1}$$

For water β increase nearly linearly in the temperature range from 20 to 60°C [17]. Therefore the maximum pressure amplitude can be assumed as linear with temperature for this temperature range.

$$p^{\max}(T) \sim (T - T_{cal}) \tag{2}$$

Introducing two constants we can write eqn. 2 as:

$$T(P_i^{\max}) = T_{cal} + B_0 P_i^{\max} \tag{3}$$

The temperature T_{cal} depends on the tissue and has to be determined by calibration measurements with RPE. B_0 is a normalized value that includes the transducer sensitivity, signal amplification and the amplitude of the acoustic transfer function. This value has to be determined in every experiment by the first laser pulse applied, at known start temperature T_0 and T_{cal} by:

$$B_0 = \frac{(T_0 - T_{cal})}{P_0^{\max}} \tag{4}$$

Therefore measuring temperature differences in the linear range of β, only T_0 has to be known, as long as the laser pulse energy and the coupling between tissue and transducer do not chance during experiment.

2.2 Numerical temperature calculations

With this technique we determine the mean temperature over the irradiated area. When performing numerical calculations of heat diffusion, this has to be taken into account. As temperature model we use the solution of Freund et. al. [18]. To determine the mean temperature we avenue over a circular area with radius $d/2$. The homogenous absorption thickness is 5µm. Heat loss due to convection is neglected.

In case of repetitive laser irradiation, the baseline temperature of the n^{th} laser pulse was determined at point of time ($n * \tau_{rep}$). The mean temperature of the previous laser pulses was sum up to $\overline{T}_{rep}(n)$, which is given by:

$$\overline{T}_{rep}(n) = \sum_{i=1}^{n} \frac{\int_A T(\vec{r}, (i * \tau_{rep}))dF}{\pi(d/2)^2}, \tag{5}$$

with $\tau_{rep} = 1/$ (laser rep. rate).

With this solution all measured data were simulated with respect to their spot size, repetition rate and radiant exposure.

It has been shown, that in humans, 60% of the light, which reaches the retina is absorbed by the RPE [19]. The absorption of porcine RPE is 100% for dark pigmented eyes, which was determined in transmission experiments (Perkin Elmer, Lambda 14P) with detached RPE. The losses of light by light scattering were neglected.

3. MATERIAL AND METHODS

3.1 Temperature measurements in vitro

3.1.1 In vitro setup for calibration measurements and pulsed sample irradiation

A frequency doubled, pulse stretched Nd:YLF laser [20] (527nm, 1.5µs pulse duration, 100/500Hz rep. rate) was used as irradiation source. The fiber tip with top head beam profile was imaged with an ophthalmic laser slit lamp (Zeiss, 30 SL/L) to the sample which was fixed in a water filled cuvette (fig.2). Beam diameter at the sample was 160µm. The OA transients were received with an ultrasonic broadband transducer and recorded by a transient recorder. The distance between sample and transducer was approximately 3 mm. The sample cuvette temperature could be determined by thermocouple.

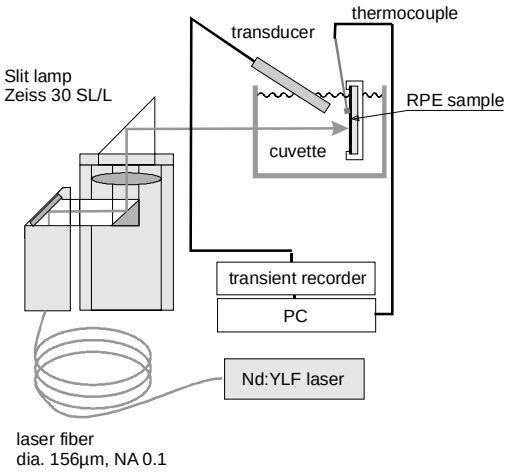

Figure 2: Setup for optoacoustic measurements during irradiation of porcine RPE with µs-laser pulses.

The clinical treatment parameters with 100 laser pulses at 500Hz repetition rate were applied to the RPE sample. Due to the lower damage threshold of porcine RPE [21] compared to humans, the pulse energy was reduced to 5-35µJ.

3.1.2 Calibration measurements

For determining the calibration constant T_{cal} of RPE, the maximum peak pressure of the OA transients was measured for different RPE temperatures. The sample cuvette was filled with warm physiological solution at 40°C and then slowly cooled down. The OA transients generated with laser pulses at repetition rate of 1 Hz and 50

mJ/cm² were recorded during cooling. The RPE sample temperature was measured with a thermocouple near the sample surface.

3.1.3 In vitro RPE sample preparation

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

3.1.4 cw irradiation setup

As cw laser source an external AOM modulated Argon cw laser (Spectra Physics, 2030-15S) was used. The laser light was coupled into a 50 m long fiber (Ceram Optec GmbH, 50µm, NA 0.22) which was connected to the slit lamp fiber. The tip of the slit lamp fiber was imaged 4 times magnified (640µm) to the sample surface with ophthalmic laser slit lamp (Zeiss, Visulas). As probe pulse for temperature determination a N_2-laser pumped dye laser (Laser Science, Inc. VSL-337ND, 580nm, 6ns, 6µJ) was coupled with a dichroic mirror to the fiber (fig. 3). The transducer and sample arrangement follow the pulsed in vitro experiment (fig 2).

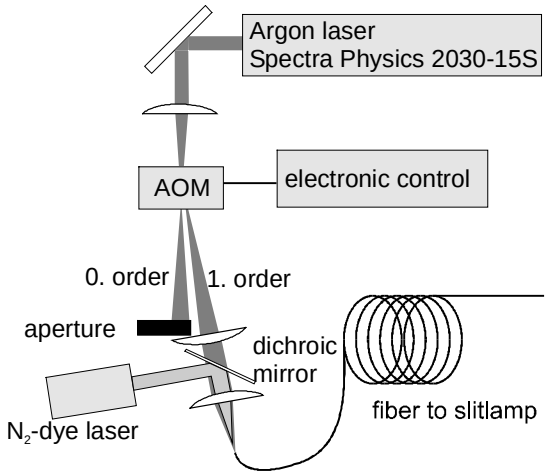

Figure 3: Setup for optoacoustic measurements during cw irradiation of RPE. As probe laser for temperature measuerments a N_2-pumped dye laser was coupled with a dichroic mirror to the fiber.

3.1.5 cw irradiation experiments

For the experiments with cw laser irradiation, less pigmented porcine RPE samples were chosen. The samples were prepared as described above. The spot diameter was 640µm and power of 134mW was applied to the sample for up to 800ms. Because of the low repetition rate of the probe laser, the probe pulse was applied in multiple experiments by shifting the delay time between the cw laser onset and the probe pulse. Every delay point was averaged over 10 measurements.

3.2 Temperature determination during patient treatment

3.2.1 Treatment setup

We used the same pulsed laser/slitlamp system as described above. During treatment a contact lens is placed on the patient's cornea to eliminate the corneal refraction and to fix the eye. We modified a standard contact lens with a piezzo electric transducer (fig 4)[21]. The signals from the transducer were recorded by data acquisition board in a PC. The data acquisition process and the analysis were programmed with LabView (National Instruments, 6i).

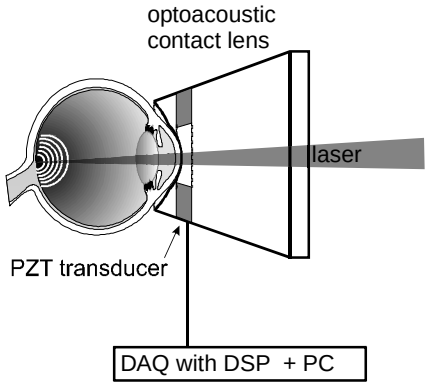

Figure 4: Setup for optoacoustic measurements during patient treatment with µs-laser pulses.

3.2.2 Treatment parameters

The clinical used treatment parameters for selective RPE treatment are 100 laser pulses at repetition rate of 500 Hz. Pulse energies between 50µJ and 140µJ were used.

3.3 Data analysis

The first probe laser pulse has to be applied at known RPE temperature to calculate the normalization value B_0. This has to be done directly before the irradiation so that the acoustic transfer function of the system does not chance during experiment. In case of treatment, T_0 will be the body temperature, or cuvette water temperature for RPE samples. With known start temperature T_0 , calibration constant T_{cal} and pressure peak maximum P_0 from the first probe pulse, B_0 can be calculated according to eqn. 4. All following pressure values $P_i^{\max}$ from the $i^{\text{-th}}$ probe laser pulse are used to calculate the temperature T with normalization value B_0 (eqn. 3). As pressure peak maximum the first peak of the bipolar transients are fitted by a peak find algorithm of LabView (National Instruments, 6i).

4. RESULTS AND DISCUSSION

4.1 Temperature dependence of the thermoelastic pressure maximum in RPE

For determination of the values T_{cal} from eqn. 3 the temperature dependence of the OA amplitude $p^{\max}$ on RPE was measured. As expected the amplitude increases linearly with temperature (fig. 5). A linear fit with $T(P) = T_{cal} + B_0 P^{\max}$ lead to $T_{cal} = -52.3\,°\text{C}$.

At higher temperatures, the optical properties of the PRE sample chance during experiment. Thus, the calibration measurement was only performed up to 40°C.

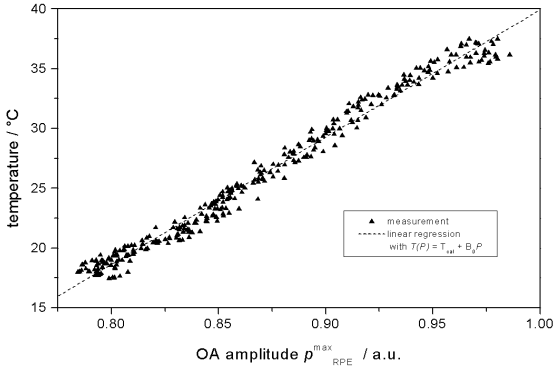

Figure 5: OA amplitude maximum over RPE sample temperature. The amplitude increase linear with temperature

4.2 Results during cw irradiation in vitro

The temperature increase during cw irradiation was determined by analyzing the pressure peaks, induced by the 6µJ Dye laser pulse. The temperature starts at cuvette temperature of 18°C and increases up to 45°C (Figure 6). Heat diffusion calculations, assuming 33% absorption at the RPE, are close to the measured data.

This experiment demonstrates the possiblity to measure the temperature increase during cw irradiation by applying additional low energy probe laser pulses. The low radiant exposure of 0.1 mJ/cm² of the probe laser makes it possible to use this technique also during standard cw treatments at the fundus. The radiant exposures for cell damage is 3 orders of magnitudes higher than the applied probe energy. The individual and also intraindividual differences of conditions like optical transmission of the eye, absorption of the RPE and light scattering at drusen wont affect the temperature detection method.

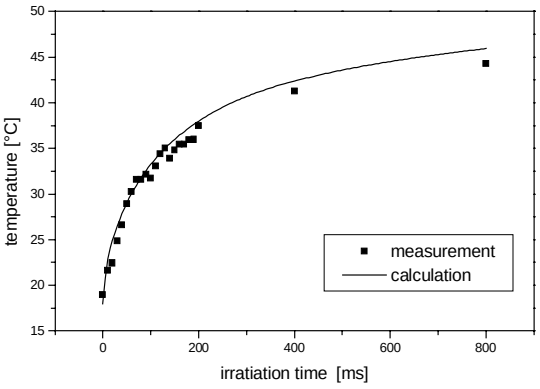

Figure 6: Temperature increase during irradiation of porcine RPE with 134mW Argon laser with 640µm spot diameter. All data points were averaged over 10 measurements. Calculations were performed assuming 33% absorption in the RPE.

4.3 Results during pulsed irradiation

4.3.1 Results of pulsed irradiation in vitro

During irradiation of porcine RPE with 1.7µs Nd:YLF laser pulses at radiant exposure of 160mJ/cm² the OA transients were recorded. Determining $p^{\max}$ of each OA transient and B_0 from the first pulse, the temperature increase could be calculated (eqn.3) with calibration constant T_{cal}. The temperature curve starts at cuvette water temperature of 18°C (fig 7). After 100 pulses the temperature increases up to 55°C. The heat diffusion calculations were performed with the set of parameters which was used in the experiment assuming 100% absorption in the RPE (eqn.5).

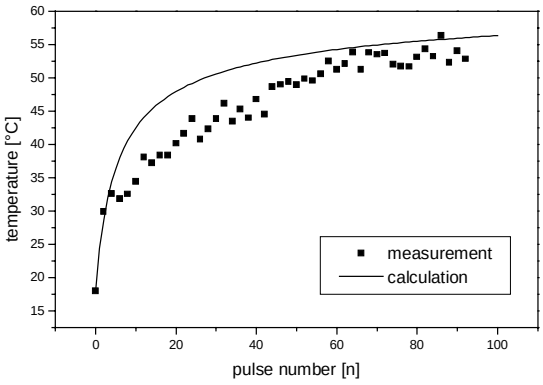

Figure 7: Baseline temperature increase during irradiation of porcine RPE with 160mJ/cm² at a repetition rate of 500Hz. The spot diameter was 160µm. For calculations 100% absorption in the RPE was used.

4.3.2 Results during patient treatment

By the use of the OA contact lens it is possible to measure the OA transients during selective treatment of the RPE. By analysis of the p^{max} of each OA signal, the temperature increase could be determined with the calibration constant T_{cal} of porcine RPE experiments. For the treatment parameters 100µJ, 100 pulses, 200µm spot diameter and 500 Hz repetition rate a high temperature build up was measured (fig 8). The start temperature is the body temperature of 37°C. The temperature increases up to 90°C. The calculations with 60% energy absorption at RPE give temperature of 110°C. In this case, the absorption at the fundus can be lower than assumed in the temperature calculation.

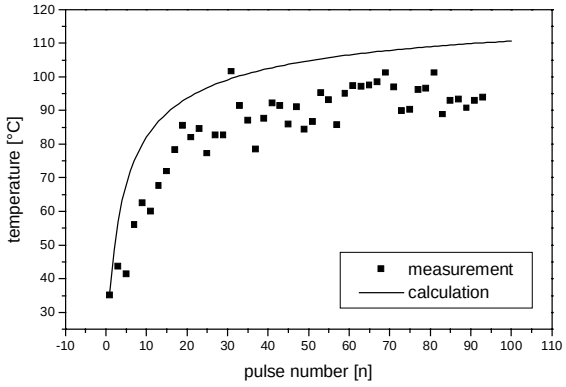

Figure 8: Temperature increase during selective RPE treatment with 100 pulses at 500Hz repetition rate. Calculations were performed assuming 60% absorption in human RPE.

The measured temperature data during treatment were calculated with the calibration constant T_{cal} of porcine RPE. For further, more detailed experiments during treatment, T_{cal} has to be determined with human RPE samples. However, large deviations are not expected.

5. CONCLUSIONS

It has been demonstrated, that with an optoacoustic technique it is possible to determine non-invasively the temperature increase at the fundus of the eye during laser irradiation in vitro and during patient treatment. This technique is applicable in treatments with pulsed lasers, as well as during cw irradiation. The minimal time between two temperature probe is limited to the acoustic transit time of the RPE to 6µs.

The calibration constant T_{cal} has to be evaluated for numerousness RPE samples. Also T_{cal} has to be determined for human RPE. The linearity of the pressure amplitude with temperature for porcine RPE was only measured up to 45°C. Nevertheless, the results in vitro and during treatment are in close agreement with the temperature calculations also for high temperatures.

For the case of selective treatment it was detected by this technique that the induced temperature is to high to ensure no damage of the photoreceptors at higher radiant exposures. The treatment parameters chanced to 100Hz, where only a low baseline temperature is build up.

This method seems to be well applicable for temperature measurements during standard cw treatments of the fundus like photocoagulation, PDT and TTT.

ACKNOWLEDGEMENT

The authors would like to thank the FAZIT-Foundation for financial support.

REFERENCES

1. *Laser photocoagulation of subfoveal recurrent neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group.* Archives of Ophthalmology, 1991. **109**(9): p. 1232-1241.
2. *Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group.* Archives of Ophthalmology, 1999. **117**(10): p. 1329-1345.
3. Reichel, E., et al., *Transpupillary thermotherapy of occult subfoveal choroidal neovascularization in patients with age-related macular degeneration.* Ophthalmology, 1999. **106**(10): p. 1908-1914.
4. Birngruber, R., *Choridal Circulation and Heat Convection at the Fundus of the Eye*, in *Laser Applications in Medicine and Biology*, M.L. Wolbarsht, Editor. 1991. p. 277-361.
5. Desmettre, T.J., et al., *Diode Laser-Induced Thermal Damage Evaluation on the Retina With a Liposome Dye System.* Lasers in Surgery and Medicine, 1999. **24**: p. 61-68.
6. VanBaren, P. and E.S. Ebbini, *Multipoint temperature control during hyperthermia treatments: theory and simulation.* IEEE Trans Biomed Eng, 1995. **42**(8): p. 818-827.
7. Seip, R. and E.S. Ebbini, *Noninvasive estimation of tissue temperature response to heating fields using diagnostic ultrasound.* IEEE Trans Biomed Eng, 1995. **42**(8): p. 828-839.
8. Larin, K.V., et al. *Monitoring of temperature distribution in tissues with optoacoustic technique in real time*. in *SPIE*. 2000. San Jose,CA: SPIE.
9. Esenaliev, R.O., et al., *Real-time optoacoustic monitoring of temperature in tissues.* Proc. SPIE, 1999. **3601**: p. 268-275.
10. Schüle, G., et al. *Optoacoustic measurements during µs-irradiation of the retinal pigment epithelium.* in *SPIE 2000*. 2000. San Jose, CA.
11. Esenaliev, R.O., et al. *Real-time optoacoustic monitoring during thermotherapy*. in *SPIE*. 2000. San Jose, CA: SPIE.
12. Roider, J., et al., *Subthreshold (retinal pigment epithelium) photocoagulation in macular diseases: a pilot study.* British Journal of Ophthalmology, 2000. **84**(1): p. 40-47.
13. Roider, J., et al., *Retinal sparing by selective retinal pigment epithelial photocoagulation.* Archives of Ophthalmology, 2000. **117**(8): p. 1028-34.
14. Jacques, S.L., *Laser-Tissue Interactions. Photochemical, photothermal, and photomechanical.* Surgical Clinics of North America, 1992. **73**(2): p. 531-558.
15. Sigrist, M.W., *Laser generation of acoustic waves in liquids and gases.* Journal of Applied Physics, 1986. **60**(7): p. R83-R121.
16. Sigrist, M.W. and F.K. Kneubühl, *Laser-generated stress waves in liquids.* Journal of the Acoustical Society of America, 1978. **64**(6): p. 1652-1663.
17. Paltauf, G. and H. Schmidt-Kloiber, *Microcavity dynamics during laser-induced spallation of liquids and gels.* Applied Physics A, 1996. **62**: p. 303-311.
18. Freund, D.E., et al., *A Theoretical Comparison of Retinal Temperature Changes Resulting from Exposure to Rectangular and Gussian beams.* Lasers in the Life Sciences, 1996. **7**(2): p. 71-89.
19. Hammond, B.R. and M. Caruso-Avery, *Macular Pigment Optical Density in a Southwestern Sample.* Investigative Ophthalmology and Visual Science, 2000. **41**(6): p. 1492-1497.
20. Brinkmann, R., et al., *Origin of retinal pigment epithelium cell damage by pulsed laser irradiance in the nanosecond to microsecond time regimen.* Lasers in Surgery and Medicine, 2000. **27**(5): p. 451-464.
21. Schüle, G., et al. *Optoacoustic Control System for Selective Treatment of the Retinal Pigment Epithelium.* in *SPIE*. 2001. San Jose, CA.