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In-vitro investigations on 308 nm XeCl-excimer laser cataract ablation

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Abstract

The authors investigated the 308 nm XeCl-excimer laser ablation rate of human cataract nuclei of varying pigmentation. In a series of pre-investigations the intensity and spectral range of the laser induced fluorescence were analyzed. The authors then irradiated cataract tissue specimens of varying thickness and pigmentation and performed qualitative and quantitative analysis of transmitted radiation. Finally they evaluated the quantity and quality of radiation exposed to the retina during *in-vitro* surgery on a biologic eye model. The most important finding in our ablation rate study was the onset of saturation in ablation rate at energy fluences higher than 4 J/cm². The ablation time of whole cataract nuclei, therefore, could not come below 2.7 minutes. The use of optical fibers thinner than 1000 μm led to a significant decrease in the ablation rate and prolonged the ablation process far beyond clinical requirements. Significant transmission of 308 nm (primary) radiation was registered through irradiated cataract nuclei specimens of 0.5 to 1 mm thickness. Secondary radiation (fluorescence), analyzed by spectroscopy, peaked at 450 to 540 nm and was poorly absorbed in the cataract nuclei tissue. Open-sky cataract laser ablation on the authors' biologic eye model, however, showed that the intensity of fluorescence radiation, measured at the retina, did not reach toxic levels. On the contrary, primary 308 nm radiation reached intolerable intensities (>2 J/cm² within two seconds) at the peripheral retina when the remaining layer of ablated cataract nuclei became too thin (<0.5 to 1 mm) or when a posterior capsulotomy occurred.

Introduction

Since the early 1980s when Trokel and Srinivasan[1] presented the first study on cornea tissues treated with an excimer laser, the greatest emphasis has been directed to the development of different clinical applications and the design of a variety of delivery systems for UV lasers.

The ArF-excimer laser, emitting at 193 nm, has been proven to be a suitable tool for corneal surgery. High absorption in corneal tissue and high ionization power (single photon energy = 6.4 eV)

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are characteristics of 193 nm laser radiation. Application of ArF-excimer laser radiation on corneal tissue leads to decomposition of organic components to molecular fragments and elementary compounds in a merely photochemical process[2,3]. This process, termed photoablation[4], ensures most precise tissue treatment conditions. Adjacent deeper layers do not show any signs of damage due to tissue heating or mechanical irritation[5]. The most promising clinical application in ophthalmology seems to become photorefractive keratectomy (PRK). With this technique, refractive errors could be treated by remodelling the curvature of the corneal surface[6].

193 nm Excimer laser radiation can, however, only be delivered by dielectric mirrors and quartz lenses. The energy profile of the beam is inhomogeneous, the beam divergence is relatively high compared to conventional laser beams and, in addition, there is a significant pulse to pulse instability of laser energy in some laser systems. Therefore, the use of ArF-excimer laser radiation under clinical conditions is subject to a variety of technical problems[7].

Another field of investigation is the application of 308 nm XeCl-excimer laser radiation. 308 nm radiation shows relatively good transmission through optical fibers and, therefore, the beam inhomogeneity and divergence are minor problems. However, the ionization power (single photon energy = 4.0 eV) is lower compared to the 193 nm wavelength and investigations on observed thermal side effects of treated tissues indicate that the process of ablation with 308 nm radiation is not purely photochemical[8]. Since mid-UV-light, such as 308 nm laser radiation, shows relatively good transmission in water and can be delivered through optical fibers, it has been proposed for a variety of invasive medical applications of which angioplasty of coronary arteries is the most spectacular[9,10].

In ophthalmology, however, the intraocular application for vitreous surgery was tried and a procedure for fistulating glaucoma surgery was emphasized[11,12]. Other investigations showed promising qualities of the 308 nm laser in bovine and human lens ablation[13-17]. The experimental surgical procedure of laser ablation of the human lens was termed endocapsular excimer laser phacoablation[15]. An attempt was made to remove nucleus and cortex material through a small incision, sparing the entire lens capsule. At that time, models for artificial intraocular lenses were presented in which the capsular bag was refilled with optical material after nucleus removal. This gave accommodation power to the pseudophacos (phacoersatz)[18].

As cataract and implant surgeons who are experienced in small-incision cataract surgery, we were excited by the idea of developing an instrument that would enable us to safely remove sclerotic cataracts and would preserve, or even rehabilitate, the accommodative power of the patient. Any method to be developed, however, would have to come up to the safety and effectiveness of the well-established ultrasonic phacoemulsification procedure invented by Kelman[19].

A lack of valid data on the 308 nm laser ablation rate of human cataract lenses and investigations on 308 nm radiation transmission and toxicity that would go beyond theoretical considerations led us to begin our experimental work in this field in 1987. After evaluation of optimal laser and optical fiber parameters, we investigated specific ablation rates of 308 nm laser photoablation of human cataract nuclei in order to test the effectiveness of this energy source for clinical use in cataract surgery. Possible factors for improvement of ablation effectiveness should be pointed out, however, in order to develop a proper delivery system.

In addition, by taking the potential toxicity of 308 nm excimer laser radiation into consideration[20], we wanted to quantify retinal radiation exposure during an experimental procedure of XeCl-excimer laser cataract photoablation.

One effect of UV-laser application on tissue is the induction of fluorescence radiation[21], which in the case of cataract photoablation as well can be a source of potential toxicity. The laser induced fluorescence (secondary radiation), therefore, needed to be qualified as well. This was done by spectroscopic methods. The transmission of both primary (308 nm) and secondary radiation in nuclei tissue specimens of varying thickness and pigmentation was then evaluated in order to obtain specific safety margins for the surgical procedure. Finally, we analyzed the spectrum of transmitted radiation

and measured the energy fluence at the central and peripheral portions of the retina during nucleus photoablation on a biologic eye model.

Material and methods

Laser and optics

The laser used for all our experiments was an excimer laser (Technolas, Munich) filled with the mixture of xenon and chloride gas according to the manufacturer's instructions. The laser emits radiation at a wavelength of 308 nm with a pulse length of 40 nsec, whereby the repetition rate is adjustable at a single pulse mode and levels of 2, 10, 20, 40 Hz and a running mode (>60 Hz).

For our experiments, the laser beam was delivered over a dielectric mirror system to a bi-convex lens (f = 15 cm) that coupled the laser beam into an optical fiber (quartz). The optical fiber length ranged from 100 to 200 cm without significant influence on the energy transmission. Coated optical fibers of 600 and 1000 μm with varying angles of beam aperture from different manufacturers were used.

In order to evaluate the energy fluence (J/cm²) at the optical fiber output, the imprint size of the laser spot on developed photo-paper had to be measured. The maximum energy fluence which could be transmitted (OPHIR - laser power energy meter), came to 3 J/cm² for the 600 μm optical fibers and to 5 J/cm² for the 100 μm optical fibers. Higher energy fluences could not be transmitted for different reasons. For instance, when the laser beam was focussed directly on the optical fibers, the input surface could be destroyed by dielectric breakdown. This is an effect that occurs when high power laser energy activates the electrons of the optical fiber material itself. We therefore adjusted the focus of the laser beam ahead of the input surface so that the whole diameter of the optical core was illuminated. Unevenness of the optical fiber surface or contamination with particles, however, can cause color centers within the first parts of the optical fibers, again leading to an optical breakdown of fiber material and a subsequent decrease of transparency. Therefore, for ablation rate measurements at an energy fluence higher than 5 J/cm², we directly delivered the laser beam over dielectric mirrors and through a biconvex lens (f = 20 cm) on the target material (laser spot diameter = 0.8 mm). Because a significant decrease of energy output from the laser was noted in the running mode (>60 Hz), frequencies higher than 40 Hz were not used for ablation rate studies.

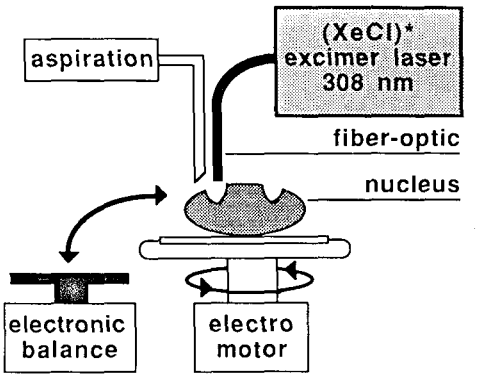

Fig. 1. The experimental setup used in our ablation rate studies is depicted. Opacified human lens nuclei were placed on a holder rotated by an electric-step motor. An optical fiber could be set at varying distances to the target and was directed paracentral to the nucleus pole. The ablation rate was evaluated under standardized conditions by electronic balance measurement before and after 308 nm excimer laser irradiation.

Biologic material

Human cataract lens nuclei (n = 160) were used for the *in-vitro* studies. Within 48 hours after extracapsular extraction, all nuclei which were kept in saline solution at a temperature of 4°C were used for experiment. One hundred and twenty nuclei were divided into two groups of either yellow or brown pigmentation for specific investigations. Porcine crystalline lenses were used to examine the sensibility of the lens capsule to direct 308 nm laser irradiation. Porcine eye globes were used in another study involving quantitative and qualitative radiation measurements. In order to simulate realistic conditions, human cataract nuclei were inserted into the porcine eyes. This eye model was used since human eyes with severe and variable opacification of the lens were not available to us in high quantities.

Ablation rate studies

The experimental setup for ablation rate studies is shown in Fig. 1. With an electronic balance (Sartorius analytic A 120 S, sensitivity: 10^{-4} g) we performed a quantitative analysis of the ablation rate of human cataract nuclei by measuring weight difference before and after 308 nm laser exposure. In order to determine a standard measurement of weight loss through evaporation of tissue water, however, evaluation of standardized experimental conditions, as described below, was necessary.

With the saline solution, the nuclei returned to room temperature. The nuclei were then taken out of their containers. Remaining soft cortex material attached to some of the nuclei was removed and the tissue was slightly dried with a cotton swab. The first weight measurement was then taken. Thirty seconds later, we started to irradiate the material. The second weight measurement was performed 2.5 minutes after the first. During irradiation, the nuclei were rotated on a specially constructed holder, driven by an electro-step-motor at three rotations per minute. The irradiation zone was paracentral to the nucleus pole in order to avoid heating of tissue and to reassure a constant distance between the optical fibers and the target tissue (fiber-target distance) throughout laser exposure time. Expelled nucleus material was aspirated by a vacuum tube placed over the zone of irradiation. The number of laser pulse exposures for ablation rate measurements was set constantly at 600 pulses while using varying repetition rates (10-40 Hz), increasing energy fluences (J/cm²), different optical fiber diameters (600 and 1000 μm) and setting various distances from the optical fibers to the target surface (fiber-target distance: 1-4 mm). Each experiment was performed on a series of two to five lens nuclei. The calculation of the single laser pulse ablation rate was based on the average data of this series. Some of the nuclei were used twice on one day. In these rare cases, both sides of the nucleus were used for irradiation.

In order to test the sensibility of the lens capsule to direct 308 nm excimer laser irradiation, we placed clear porcine lenses into a chamber (20 cm³) that was irrigated with balanced saline solution (150 mm H_2O, BSS). The setup is shown in Fig. 2. The average number of laser pulses necessary to lead to macroscopic visible capsule perforation was determined at varying distances (0.5-5 mm) of the optical fibers to the lens surface. Each variable was tested on five lenses. The energy fluence for this experiment was 2.1 J/cm² at a repetition rate of 2 Hz.

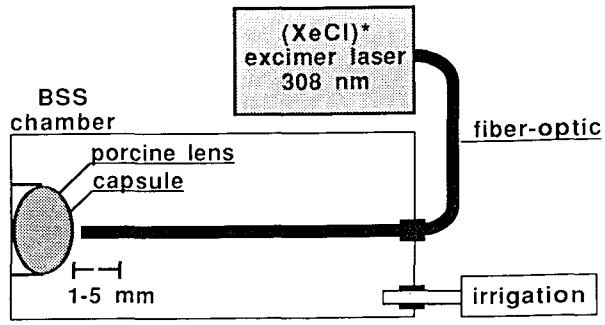

Fig. 2. The experimental setup for testing the sensitivity of the lens capsule to direct irradiation with 308 nm excimer laser radiation is depicted. Porcine lenses were placed into a chamber irrigated with balanced saline solution (BSS). An optical fiber was introduced and the number of laser pulses which led to visible perforation of the lens capsule was registered at varying fiber-target distances.

Qualitative and quantitative radiation measurements

We qualitatively analyzed the spectrum of radiation that was transmitted through 308 nm excimer laser irradiated medium yellow-brown human lens nuclei specimens involving 308 nm (primary) radiation and the laser induced fluorescence (secondary) radiation. In a second experimental series, quantitative investigation of energy transmission in yellow and brown pigmented nuclei specimens was performed. The experimental setup is shown in Fig. 3. The human nuclei were cut into tissue specimens of varying thickness (0.5-4 mm) and then placed on a quartz platelet. An optical fiber (1000 μm optical fiber, 1.33 J/cm²) was then set at a 1 mm distance over the target tissue. For qualitative transmission analysis, a light detector was placed under the platelet and coupled with an optical fiber to an optical multichannel analyzer (OMA-ELSIS-Technolas, 300-800 nm). The spectras were computed and depicted on a monitor and could be printed out. For

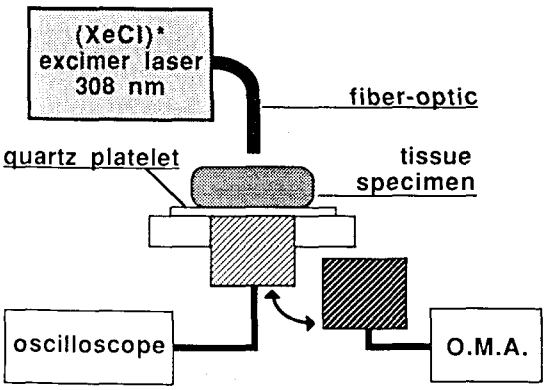

Fig. 3. The experimental setup for investigation of quantitative and qualitative radiation transmission in 308 nm laser irradiated yellow and brown pigmented cataract nuclei tissue specimens of varying thickness is shown. For qualitative transmission analysis, a light detector coupled to an optical multichannel analyzer (OMA) was placed under the quartz platelet. Spectras were computed and depicted on a monitor and could be printed out. For quantitative measurements, an energy detector that could be placed at the same site was coupled to an oscilloscope. The average energy measured without a tissue specimen on the quartz platelet was taken as reference.

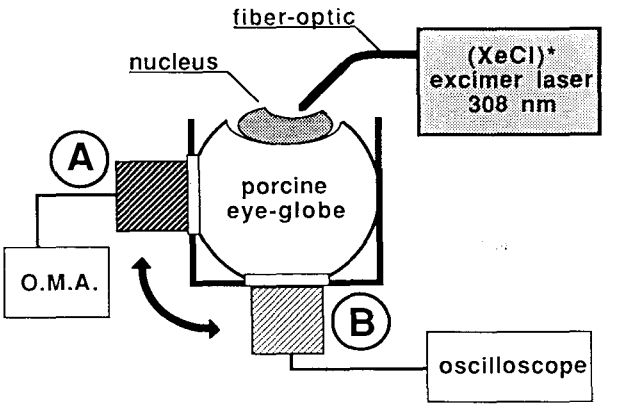

Fig. 4. The experimental setup for qualitative and quantitative analysis of retinal exposure to primary (308 nm) and secondary (fluorescence) radiation during 308 nm excimer laser nucleus ablation in a biologic eye model is shown. The globe equator and the posterior pole were trephined and used as measure-points A and B. The eye globe was then fitted into a holder that had quartz windows corresponding to the trephined holes of the eye globe. After the cornea was removed, the clear porcine lens was replaced by an opacified human lens nucleus. For qualitative transmission analysis, the light detector coupled to the spectroscopic system (OMA) was fastened to either of the windows. Spectra were computed at various states of the ablation procedure. For quantitative measurements, the energy detector coupled to the oscilloscope was fastened to the same sites in separate experiments. The average energy measured in the aphakic eye model was taken as reference.

quantitative measurements, an energy detector (Gentech - Pex 4, 10^{-3} - 19 mJ; conversion factor: 529 V/J, detector size: 10.18 mm²) now placed at the same site, was coupled with an oscilloscope (Hameg 20 MHz). The average energy fluence measured without a tissue specimen on the quartz platelet was 601 mJ/cm². This value was taken as reference. Irradiation was performed within 3.5 minutes after taking the lenses out of their containers. Each experiment was performed on five tissue specimens.

Qualitative and quantitative analysis of retinal exposure to primary and secondary radiation during 308 nm excimer laser nucleus ablation was investigated by using a constructed biologic eye model. The experimental setup is shown in Fig. 4. A hole was trephined (r = 5 mm) into a porcine eye globe at either of the following two sites: the globe equator, used as measure-point A, and the posterior pole, used as measure-point B. This prepared eye globe was fitted into a holder that had quartz windows corresponding to the pretrephined holes. The cornea was then removed and the clear porcine lens nucleus was replaced by an opacified human lens nucleus. Either the light- or energy-detector was fastened to either of the windows in separate experiments. Similar to operation conditions, an optical fiber, emitting 308 nm laser radiation (3.54 J/cm², 2 and 10 Hz) was then positioned at a 35-45 degree angle to the pupillary plane and open-sky ablation was performed by photoablation of the nucleus tissue layer by layer down to the plane of the porcine capsule.

Results

A basic consideration for UV-laser ablation rate studies on biologic material is the effect of the tissue humidity. For instance, if the target material is ablated in an aqueous environment, as it would be done in real cataract surgery, reproductive and valid results would not be attainable. Therefore, in our experiments the nuclei were ablated under semi-dry conditions. Thus, high reproducibility of our

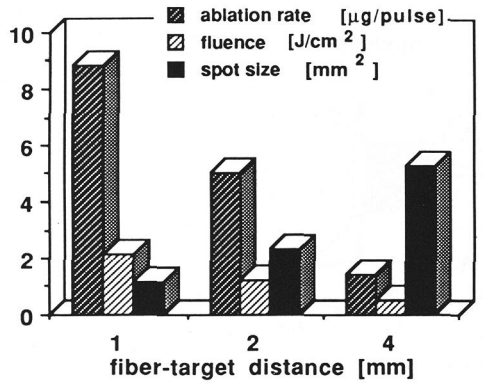

Fig. 5. The influence of increasing fiber-target distances on the average ablation, the size of the laser spot and the energy fluence, is shown. Due to high beam divergence at the optical fiber output, the energy fluence (J/cm²) decreased in correlation to the increase of the laser spot size. Subsequently, a decrease in average ablation rate was noted.

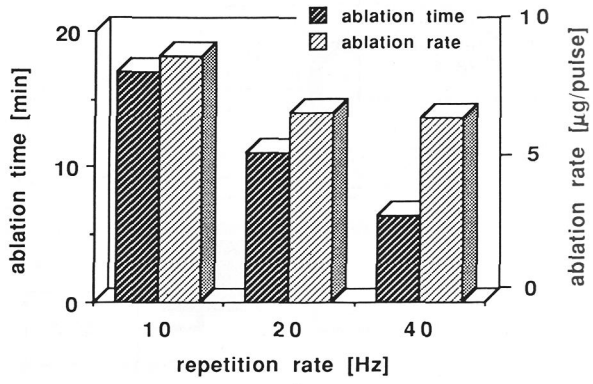

Fig. 6. The influence of varying repetition rates on the average single laser pulse ablation rate is shown. The average overall time necessary to ablate whole cataract nuclei was shortest at repetition rates of 40 Hz.

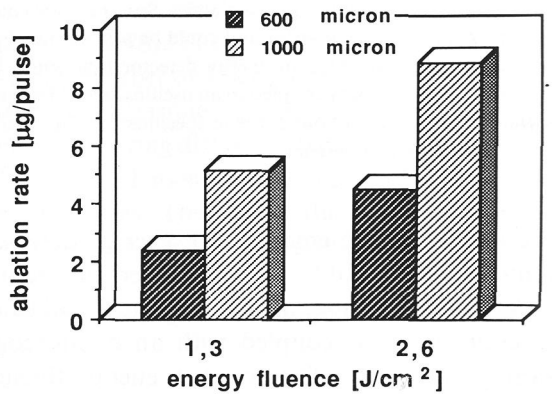

Fig. 7. The influence of different optical fiber core diameters (600 *vs.* 1000 µm) on the average ablation rate is depicted. The average single laser pulse ablation rate for a 600 µm optical fiber was found to be 52% (± 0.5%) of the rate attained by using a 1000 µm optical fiber at energy fluences of 1.3 and 2.6 J/cm² at a 1 mm fiber-target distance.

results is ensured. However, under the standardized conditions that we have evaluated, the effect of evaporation of tissue water is considered. The validity of our results, therefore, is based on conditions that are very close to a realistic situation.

Ablation rate studies

Optimal parameters, such as the optical fiber target distance, the pulse repetition rate and the core diameter of the optical fibers, were evaluated in a series of pre-investigations. The average ablation rate per single laser pulse was calculated on the ablation rate data of nuclei of varying pigmentation. The results were then considered in the following studies.

In Fig. 5, it is shown that by increasing the distance of the optical fibers from the target tissue, a decrease of ablation rate occurs. The highest ablation rate was measured at a fiber-target distance of 1 mm, using a 1000 µm optical fiber at 10 Hz repetition rate. The size of the irradiated area expanded with an increasing fiber-target distance whereby the energy fluence and subsequently the evaluated average ablation rate decreased.

In another series of experiments, we found that the average single laser pulse ablation rate at 10 Hz was higher compared to the ablation rate at 20 or 40 Hz applying the same energy fluence per pulse. However, the average overall time necessary to ablate whole nuclei was shortest at repetition rates of 40 Hz (Fig. 6). At higher repetition rates, ablation rate studies were not useful since a striking decrease of energy output from the laser cavity was noted.

The influence of the core diameter of tested optical fibers on the ablation rate was then measured for both 600 and 1000 µm optical fibers at energy fluences of 1.3 and 2.6 J/cm² (10 Hz). The average ablation rate for the 600 µm optical fibers was found to be 52.2% (2.52 µg/pulse) at 1.3 J/cm² and

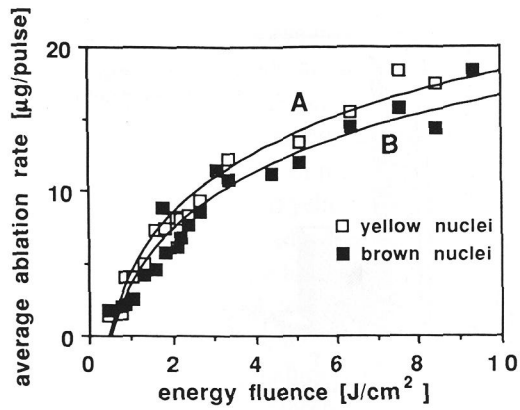

Fig. 8. The effect of increasing energy fluences was evaluated (10 Hz, 1000 µm optical fibers, 1 mm fiber-target distance) and is shown. We differentiated yellow (curve A) and brown (curve B) pigmented cataract nuclei. The dots correspond to the average single laser pulse ablation rates of two to five irradiated nuclei. The ablation rate rose continuously with slightly higher rates for the yellow nuclei up to levels of 4 J/cm². Beyond fluence levels of 5 J/cm² the increase of ablation rate came close to a level of saturation.

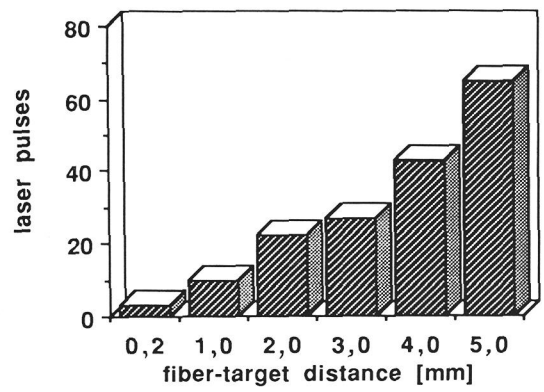

Fig. 9. The sensibility of porcine lens capsules to direct 308 nm irradiation was investigated and the result is depicted. At a fiber-target distance of 1 mm, perforation of the capsules occurred after exposure to only ten pulses. The number of laser pulses necessary to lead to such an effect increased with higher fiber-target distances.

52.3% (4.63 µg/pulse) at 2.6 J/cm² energy fluence of the rate attained by using a 1000 µm optical fiber at a 1 mm fiber-target distance (Fig. 7). Subsequently, the total ablation time of a whole nucleus with a 600 µm optical fiber (40 Hz, 2.6 J/cm²) extended to approximately 11 minutes compared to approximately six minutes when a 1000 µm optical fiber (40 Hz, 2.6 J/cm²) was used.

Considering the results of the pre-investigations, the effect of increasing energy fluences was then evaluated at repetition rates of 10 Hz using a 1000 µm optical fiber. The fiber-target distance was held at 1 mm. For this study, we differentiated both groups of cataract nuclei (yellow and brown pigmentation) in order to obtain information about the influence of tissue composition and pigmentation. The onset of effective ablation (threshold) was noted at an energy fluence of approximately 0.2 J/cm², at which no significant difference in the yellow or brown types of nuclei could be observed. In Fig. 8, one can see that the ablation rate rose continuously with slightly higher rates for the yellow nuclei up to levels of 4 J/cm². Beyond fluence levels of 5 J/cm², however, the increase of ablation rate seemed to come close to a level of saturation.

The investigation of the sensibility of the lens capsule to direct 308 nm laser irradiation showed that, in an aqueous environment (BSS), at an optical fiber target distance of 1 mm, perforation of the tested porcine lens capsules occurred after exposure to ten pulses (1000 µm optical fibers, 2 Hz, 2.1 J/cm²). Approximately 70 pulses were necessary to lead to visible capsule perforation at 5 mm distance (Fig. 9).

Qualitative and quantitative radiation measurements

Qualitative analysis of fluorescence (secondary radiation), induced by irradiation of cataract nuclei of medium yellow-brown pigmentation with a 308 nm laser (1000 µm optical fiber, 1.33 J/cm²), showed a spectral range of 400-650 nm. Maximum intensities were found at 450-510 nm. Transmission of secondary radiation (400-650 nm) was detectable during 308 nm laser irradiation of nuclei tissue specimens of 4 mm thickness (10% relative integrated intensity). No primary 308 nm laser radiation was transmitted down to a tissue specimen thickness of 2 mm. The intensity of the transmitted secondary radiation, however, increased up to 12% (at 3 mm specimen thickness), 35% (at 2 mm speci-

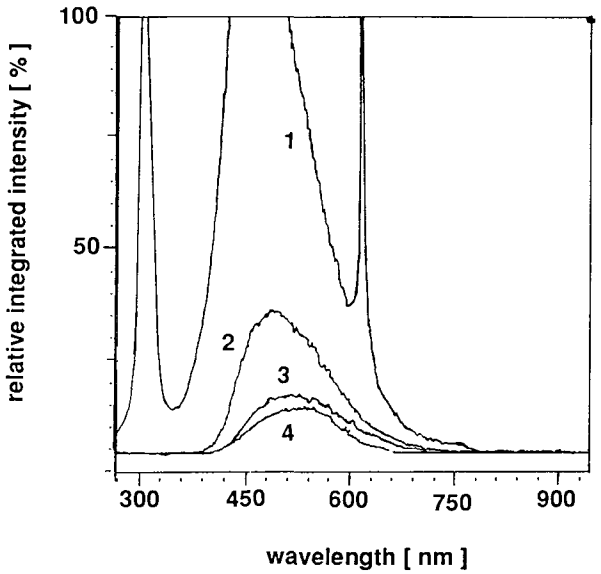

Fig. 10. Spectroscopic analysis (OMA) of 308 nm laser induced fluorescence (secondary radiation) in cataract nuclei of medium yellow-brown pigmentation showed a spectral range of 400-650 nm with maximum intensities at 450-510 nm. Transmission of secondary radiation was detectable through nuclei tissue specimens of 4 mm thickness (curve 4). No primary 308 nm laser radiation was transmitted down to a tissue specimen thickness of 2 mm (curves 4, 3 and 2). The intensity of the transmitted secondary radiation, however, increased up to relative intensities of over 100% when the thickness of the irradiated tissue specimen was only 1 mm (curve 1). At this level a high peak at 308 nm was detectable. The high peak at 616 nm is an artefact due to second order registration of the initial 308 nm peak.

men thickness) and finally up to relative intensities of over 100% when the thickness of the irradiated tissue specimen was only 1 mm. At this point, a high peak at 308 nm as well was detectable (Fig. 10).

The spectral range of radiation transmitted through the lens capsule and vitreous during 308 nm laser nucleus ablation in our constructed eye model also depended on the thickness of the remaining nucleus tissue and on the target direction of the optical fibers. The spectral range of transmitted radiation detected at the retina (measure-points A and B) correlated to the previously analyzed spectra. When the remaining nucleus layer became thinner than approximately 1 mm towards the end of the ablation process, the relative intensity of transmitted primary radiation (308 nm) increased to values of over 100% relative integrated intensity

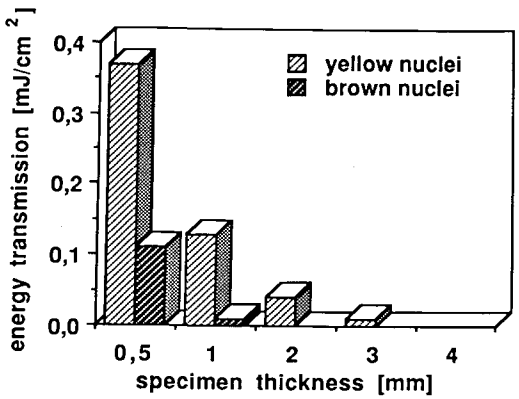

Fig. 11. The results of quantitative measurement of transmitted energy through 308 nm laser irradiated cataract nuclei specimens depended on their pigmentation (yellow or brown) and thickness (0.5-4 mm). The intensity of transmitted radiation was in the range of 0.018-0.061% of the reference value (601 mJ/cm²). Higher energy values were found in the yellow group. However, the transmission threshold was found to be at a nucleus specimen thickness of 0.5-1 mm.

only in the target direction of the optical fibers (measure-point A) and at the central retina (measure-point B).

The results of quantitative energy measurements of radiation (primary and secondary) transmitted through 308 nm laser irradiated (1.33 J/cm²) cataract nuclei specimens depended on their pigmentation (yellow or brown) and thickness (0.5-4 mm). Significant energy transmission was detectable through brown pigmented nuclei specimens of 0.5 mm thickness and through yellow pigmented specimens of 1 mm thickness. However, the intensity of transmitted radiation was in the range of 0.018-0.061% of the reference value (601 mJ/cm²). In yellow nuclei, slight energy transmission could be measured up to 2 mm specimen thickness. The critical transmission threshold was, therefore, found to be at a nucleus specimen thickness of 0.5-1 mm (Fig. 11).

For quantitative evaluation of retinal exposure to radiation (primary and secondary), we used the energy values measured during irradiation (3.54 J/cm² per pulse) of an aphakic porcine eye as reference. The measured reference value was 36.61 mJ/cm² per pulse at measure-point A and 1.7 mJ/cm² per pulse at measure-point B. A considerable amount of energy must have been absorbed in

the vitreous. In the phakic eye model, however, the average energy measured at measure-point A decreased to 0.122 mJ/cm² per pulse and to 0.64 mJ/cm² per pulse at measure-point B. These values were evaluated by a series of 21 measurements using different nuclei (brown and yellow) and have to be regarded as average data under standardized conditions. When the remaining layer of the nucleus became thinner than 1 mm towards the end of the procedure, the measured energy at the central and peripheral retina reached values that came up to the previously determined reference values of the aphakic eye model.

Discussion

The first results in the field of XeCl-excimer laser lens ablation were presented by Puliafito[14]. He found that ablation characteristics of bovine clear crystalline lenses confirmed high 308 nm radiation absorption and he discussed the possibility of excimer laser application for cataract surgery. Detailed ablation rate studies were presented by Nanevicz[16]. She also used weight measurements for ablation rate studies but investigated bovine lens material. Papers published by Bath[15], Buchwald[22] and Hunkeler[23] reported on 308 nm laser photoablation of human cataract material. Quantitative ablation rate studies were done by measuring the ablation depth, rather than measuring the amount (weight) of tissue that is ablated by a single laser pulse. Furthermore, apart from the recently published work of Maguen[17], there was no information available on the influence of varying laser and optical fiber parameters or different lens pigmentation on 308 nm excimer laser lens ablation.

By investigating the ablation rate of cataract lenses by weight measurement, however, as performed in our study and that by Nanevicz[16] on bovine lenses, we received more valid information. The weight loss through evaporation of tissue water and the heating of material through laser irradiation must be considered, as was done in our experiments. Conclusions can then be made with respect to the total time necessary to photoablate whole lens nuclei. Subsequently, the total energy can be calculated.

The best fiber-target distance, optical fiber core diameter and most effective laser pulse repetition rates were determined. The relation of the fiber-target distance and the laser spot diameter determines the energy fluence and subsequently the ablation rate. The relative ablation effect of a 600-μm optical fiber is comparable to the effect of the 1000-μm fiber when the same energy fluence is applied. However, the effect of a larger zone of irradiation using a 1000-μm optical fiber leads to a significantly higher ablation rate. If the zone of irradiation is enlarged by using a higher fiber-target distance, a significant reduction of applied energy fluence results and the ablation rate decreases. High beam divergence at the optical fiber output is apparently the reason for this. Considering these findings, we then evaluated 40 Hz to be the most effective in ablating a whole lens nucleus. It is important to move the optical fiber over the target tissue at such high repetition rates, otherwise heating of the irradiated tissue could occur. In respect to the cooling effect of irrigation in a closed chamber cataract procedure, this would, however, be a minor problem. For technical reasons, we could not perform investigations using higher repetition rates than 40 Hz. But it must be considered that higher repetition rates would only shorten the total ablation time significantly, as long as it is ensured that primary ablation products are removed from the site of irradiation before the following laser pulse reaches the target. Therefore, the effect of increasing pulse repetition rate (Hz) on the ablation rate is probably limited by an onset of saturation at certain frequency levels. This, however, requires further investigation.

Using optimal laser and optical fiber parameters, we investigated the effect of increasing energy fluence on the ablation rate. The most important finding was that the ablation rate increased up to an energy level of 4 J/cm². Exceeding an energy fluence level of 5 J/cm² did not improve the ablation rate proportionally to the increase of applied energy fluence. Based on the values we found in the ablation rate studies, we used the following formula to calculate the total time for photoablation of

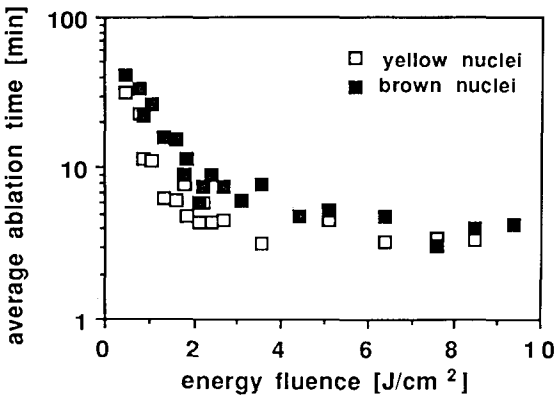

Fig. 12. The average total ablation time at 40 Hz was calculated for yellow and brown pigmented nuclei. It ranged from 52 minutes (0.4 J/cm²) to 2.7 minutes (7.6 J/cm²). Ablation of yellow pigmented nuclei is considerably faster than of brown pigmented nuclei.

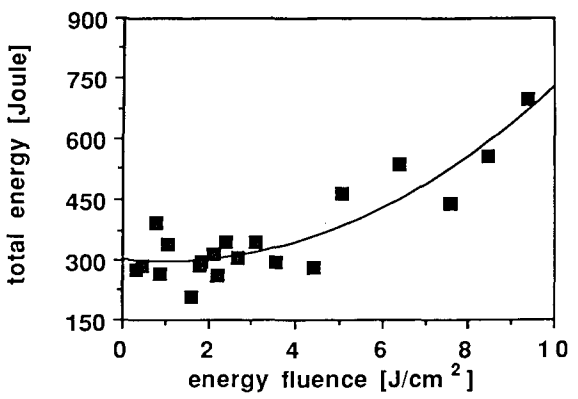

Fig. 13. The calculation of the total energy (Joule) needed for whole nucleus ablation shows a disproportional increased of applied total energy (up to 700 J) at energy fluences higher than 4 J/cm². This is due to an onset of saturation of ablation rate at high fluences.

whole nuclei in relation to the applied energy fluence (J/cm²):

$$\text{total ablation time (min)} = \frac{\text{weight of nucleus (mg)}}{\text{ablation rate (mg} \times \text{min}^{-1})}$$

The total ablation time at 40 Hz ranges from 52 minutes (0.4 J/cm²) to 2.7 minutes (7.6 J/cm²) as shown in Fig. 12.. It must also be considered that these values are idealized, for we were not able to conduct an energy fluence higher than 5 J/cm² through any optical fibers. Even at fluences of 3-4 J/cm², transmission quality of the optical fibers sometimes decreased significantly after three to five minutes. Careful preparation of the optical fibers was time consuming and sometimes frustrating, since optical breakdown at high energy fluences often destroyed the input surfaces.

The calculation of the total energy (Joule) needed for whole nucleus ablation was done using the following formula:

$$\text{total energy (J)} = \frac{\text{weight of nucleus (mg)} \times \text{energy/pulse (J)} \times \text{pulses (min}^{-1})}{\text{ablation rate (mg} \times \text{min}^{-1})}$$

The onset of saturation of the ablation rate at an energy fluence higher than 4 J/cm² leads to a disproportional increase of the applied total energy (up to 700 Joules) as one can see in Fig. 13. The average total energy of a phacoemulsification procedure is in the range of 200-300 Joules. By application of this amount of energy, an average nucleus can be removed within 60 seconds by ultrasonic fragmentation. With this amount of energy, however, 308 nm excimer laser cataract photoablation would take at least three minutes at an energy fluence of 4-5 J/cm² and a repetition rate of 40 Hz.

We can conclude from these tests and calculations that a reduction in the total ablation time cannot be expected through an increase in energy fluence. Possible improvement can be attained by using pulse repetition rates higher than 40 Hz, assuming that the energy output of the laser remains stable. Another way to improve radiation transmission in the optical fiber, ablation rate and thereby the total ablation time, could be the use of laser pulse durations of longer than 40 nsec. Thermal side effects would then, however, have to be a matter of consideration.

Due to the high absorption of UV light in the lens, the phakic eye is well protected against retinal light damage[24]. In the cataract laser ablation procedure, however, both primary (308 nm) and secondary (fluorescence) radiation are present since emission of fluorescence radiation is induced by direct lens irradiation with a 308 nm laser. Therefore, investigations on retinal radiation exposure during laser phacoablation needed to be quantitative and qualitative.

The toxicity of 308 nm laser radiation and its potential danger, if used for intraocular procedures, was considered by Marshall and Sliney[20]. The action threshold for retinal UV-light damage is both energy fluence and time dependent[25]. The action threshold for minimal damage to the rhesus retina determined on fundus photographs is 30 J/cm² when the retina is exposed to 440 nm light. The threshold for retinal damage decreases with shorter UV-light wavelengths. Therefore, the threshold is only 5 J/cm² when the retina is exposed to 325 nm light[25]. Based on the findings of Ham *et al.*[25], we extrapolated the action threshold for 308 nm to be approximately 2-3 J/cm².*

It is known that damage to blue-light sensitive cones is induced by 463 nm light and to green-light sensitive cones by 530 ± 80 nm light[26]. The qualitative analysis of 308 nm laser induced fluorescence showed that the highest spectral intensities in our study were in the range of 450-540 nm. Therefore, fluorescence radiation also has to be regarded as being potentially retinotoxic. The results we found contribute to the considerations of Nanevicz[16] who pointed out that specific lens chromophores were found to have an absorption maximum of 360-420 nm emitting fluorescence light at a wavelength of 440-520 nm[27].

Regarding the potential toxicity of both 308 nm and fluorescence radiation, we calculated the cumulative energy fluence that is transmitted through the lens nucleus during 308 nm laser ablation. However, such quantification lacks perfect reproducibility since the measured energy values, on which is it based, are merely random samples of the total radiation exposure. Furthermore, there are a great number of factors influencing the measurements. Two factors which we have found to be of major importance are the pigmentation and remaining thickness of the ablated nucleus. We therefore randomized our evaluation by using nuclei of different pigmentation and by taking values measured during various states of the ablation procedure. We then calculated the cumulative energy that would reach the retina using average values (see *Results*) in a theoretical 308 nm laser cataract ablation procedure under idealized conditions based on the data of our ablation rate studies. In such a procedure, the total ablation time could be four minutes (40 Hz) using an energy fluence of 3.54 mJ/cm². As a result, the cumulative energy would then be approximately 1.2 J/cm² in the peripheral portion of the retina and 6.2 J/cm² in the central portion. Regarding the qualitative analysis of transmitted radiation through the nucleus during the ablation procedure in our eye model, we believe that these energy values are mainly due to secondary (fluorescence) radiation. This assumption is supported by the fact that we found higher radiation intensities in the central portion of the retina although the optical fibers were directed towards the peripheral portion of the retina in the 35-45 degree angle position. Fluorescence radiation leads to a less directed illumination of the whole retina compared to beam aperture dependent primary (308 nm) laser radiation. However, if the primary (308 nm) radiation is insufficiently absorbed and transmitted through the remaining thinner nucleus (< 1.0 mm), 100-200 laser pulses (3.54 mJ/cm²) are enough to reach a cumulative energy value of 5 J/cm² in the peripheral portion of the retina. The central portion of the retina would, however, be less endangered in such a case since the laser beam is directed towards the retinal periphery in the 35-45 degree angle position.

Since the action threshold for retinal damage by exposure to radiation in the range of approximately 440 nm within four minutes is as high as 30 J/cm²[25], we concluded that a toxic intensity of the time integrated laser induced fluorescence radiation is not reached within the time of laser application. On the contrary, retinal damage is induced within two to five seconds at a repetition rate of 40 Hz when the retina is exposed to 308 nm radiation since the action threshold is only 2-3 J/cm²[25]. Furthermore, side effects on the close-by lens capsule or the vitreous cannot be excluded.

The lens capsule cannot function as a shield for toxic radiation since 90% of radiation in the range of 300-400 nm wavelength is transmitted[28]. However, an important finding in our tests was that the

* Such extrapolation lacks perfect validity, however, since Ham investigated continuous radiation rather than light pulses in the range of nanoseconds (308 nm) to microseconds (fluorescence).

lens capsule is sensitive to direct 308 nm irradiation. Even at a fiber-target distance of 4 mm, perforation could be observed, due to the good transmission of 308 nm radiation in water. The quantification of a specific ablation rate for the lens capsule seems to be a very theoretical concern in view of the fact that only ten laser pulses (2.1 J/cm²) affect a visible perforation at a fiber-target distance of 1 mm.

Other ocular tissues are sensitive to UV-light exposure as well. The cornea, for instance, is transparent only for radiation of wavelengths higher than 400 nm. Damage to the cornea can, thus, be experimentally induced by shorter wavelengths. Reversible changes in rabbit corneas were found at a wavelength of 305 nm (0.04 J/cm²). Defects such as endothelial cell loss were observed when applying 305 nm light at a higher energy fluence (0.3 J/cm²). In addition, irradiation at an energy fluence of 1 J/cm² (305 nm) led to uveitis and visible iris defects[29]. 308 nm excimer laser irradiation induced damage on rabbit and porcine corneas, showing that application of energy fluences of 3-6 J/cm² leads to epithelial defects, consecutive stromal scar formation and endothelial cell loss[30]. Again we must stress the fact that the lens nucleus shields toxic 308 nm radiation. It must then be considered, however, that if laser radiation is transmitted through or passed the nucleus shield, harmful action to intraocular structures must be expected.

Another aspect of intraocular XeCl-excimer laser application that is sometimes a matter of concern is the potential mutagenicity of UV light. Epidemiologic studies have shown that solar ultraviolet radiation can cause skin cancer in humans. Germicidal 254 nm ultraviolet lamps can also cause cell mutation. Mutation is probably caused at all ultraviolet wavelengths, but the effect is highly dependent on wavelength. The lowest mutagenic threshold is observed at 254 nm, owing to the avid absorption of this wavelength by DNA[31,32].

There is little information about the potential mutagenicity of excimer radiation. Colella[33] attempted to induce mutation with irradiation at 308 nm and energy densities of 0.4-1.6 mJ/mm² (80-4000 pulses) in Chinese hamster cells. The dose of 308 nm required to induce a number of equivalent mutations to 254 nm was in the range of ten times higher. Another important factor in induction of mutagenic effects by UV light is the exposure time. High doses applied within a short time, such as in a surgical procedure, should be well tolerated. *In vivo* healing studies showed no histopathologic evidence of mutagenic effects in animals[9].

We came to the conclusion that at the present state of laser and optical fiber technology, cataract surgery by 308 nm XeCl-excimer laser is not yet practicable. Photoablation of a lens within a range of three to five minutes is only possible using optical fibers of 1000 μm thickness. Therefore, a handpiece tip that would have to deliver 1000 μm optical fibers plus a sufficient irrigation-aspiration system to perform the surgery would be larger than the tip used in the ultrasonic phacoemulsification procedure. The shortness of time when intraocular structures are exposed to a variety of possibly traumatizing effects is one of the main advantages of small-incision surgery. However, the use of optical fibers of 600 μm diameter would extend the ablation time to at least ten to 15 minutes. Even longer ablation times could be expected when a 400 μm fiber is used. This extension of time would obviously be disadvantageous in the performance of the surgical procedure. Therefore, we cannot yet see any advantages to the established ultrasonic small-incision method. Furthermore, we cannot rely on the radiation shielding effect of the opacified lens alone, since we actually photoablate the only protective material as the target of the procedure itself. Knowing that even short time and low energy irradiation with 308 nm laser light is highly toxic, we are very concerned about the safety of the procedure.

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