Medical applications for ultrafast laser pulses

Holger Lubatschowski,*1 Alexander Heisterkamp,*1 Fabian Will,*1 Ajoy I. Singh,*2 Jesper Serbin,*1 Andreas Ostendorf,*1 Omid Kermani,*3 Ralf Heermann,*4 Herbert Welling,*1 and Wolfgang Ertmer*1

*1 *Laser Zentrum Hannover e.V, Hannover, Germany*

*2 *Union Park, Pali Hill, Mumbai, India*

*3 *LASERFORUM Köln, Germany*

*4 *Klinik für HNO-Heilkunde, Hanover Medical School, Germany*

Ultrafast lasers have become a promising tool for micromachining and extremely precise ablation of all kinds of materials. Due to the low energy threshold, thermal and mechanical side effects are limited to the sub m range. The neglection of side effects enables the use of ultrashort laser pulses in a broad field of medical applications. Moreover, the interaction process based on nonlinear absorption offers the opportunity to process transparent tissue three dimensionally inside the bulk. We demonstrate the feasibility of surgical procedures in different fields of medical interest: In ophthalmology intrastromal cutting and preparing of cornael flaps for refractive surgery in living animals is presented. Besides, the very low mechanical side effects enables the use of fs-laser in otoralyngology to treat ocecular bones. Moreover, the precise cutting quality can be used in fields of cardiovascular surgery for the treatment of arteriosklerosis as well as in dentistry to remove caries from dental hard tissue.

1. Introduction

Tissue processing with fs laser pulses has been of growing interest since its high precision was demonstrated on a variety of different tissue types. In dentistry for example, fs lasers have demonstrated their practical use to process hard tissue like enamel.[1)] Moreover, due to its sub μm precision, it is possible to perform surgical procedures like refractive surgery inside the human eye[2)] or even do 'nano surgery' of single biological cells.[3–5)]

The interaction mechanism of tissue processing with ultrashort laser pulses is based on photodisruption. Photodisruption takes place when laser light is focused to power densities in the range of 10^{11} to 10^{12} W/cm^2. At these intensities originally transparent material will be ionized by multiphoton absorption.[6)] This process is called optical breakdown. Due to the plasma ignition and its explosive expansion, a shock wave is generated and, if the process takes place in a fluid, a cavitation bubble develops. The shock wave as well as the cavitation bubble have a relevant mechanical damage potential. However, the aim of the surgeon is to induce minimal mechanical stress to the surrounding tissue during the operation.

Recently, turn key laser systems have become available emitting laser pulses in the fs range. Focussing the beam to a spot size of some μm in diameter, the threshold intensity is reached at pulse energies of only 1 μJ[7)] or, when focusing with extremely high numerical aperture even in the nJ regime.[4)] As a consequence, the secondary mechanical effects are reduced dramatically. Thus, femtosecond photodisruption offers the possibility to perform very precise surgical operations.

2. Ophthalmic applications

Femtosecond photodisruption offers the possibility to cut out an intrastromal lens, analogous to the so called LASIK procedure (Laser in situ keratomileusis) to correct the error of refraction of a patients eye. However, in contrast to the conventional LASIK procedure, the operation can be done without using a mechanical knife.

The principle of the fs-LASIK procedure is shown in Fig. 1. In a first step, a lamellar intrastromal cut is performed by scanning the laser in a spiral pattern. This procedure is analogous to the mechanical lamellar cut of a microkeratome (mechanical knife) in the conventional LASIK procedure. But not only the troublesome lamellar LASIK cut can be done with the fs-laser. In a second step, another cut prepare a stromal lenticule with the desired shape, depending on the refractive error of the treated eye. In the third step, the anterior corneal flap is opened, and the prepared lenticule can be extracted. Finally, the flap will be repositioned on the cornea. The surface of the cornea follows the missing volume of the lenticule, thereby leading to a change in refractive power.

In the experimental setup, the eyes of anaesthetized rabbits were fixed by a suction ring with a contact glass plate on its top. The anterior segment of the cornea is slightly flattened by the glass plate (Fig. 2). The glass plate has a fixed position relative to the focal plane of the laser beam. With this setup the focus of the laser beam can be well defined, with μm precision inside the corneal stroma.

Histological analysis demonstrate the smooth and precise character of fs tissue processing by ultrashort laser pulses.[7, 8, 10–12)] In Fig. 3 the light microscopic cross section of a porcine cornea shows the cutting line of 160 fs laser pulses. In this experiment, the corneal flap remains closed in order to analyze the cutting characteristics without mechanical in-

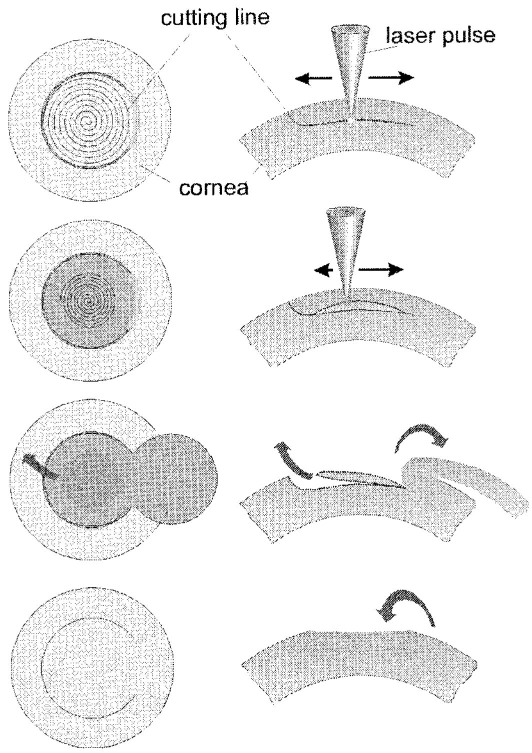

Fig. 1. Principle of fs laser keratomileusis: In a first step, a lamellar intrastromal cut is performed by scanning the laser in a spiral pattern. In a second step, another cut prepares a lenticule with the desired shape, depending on the refractive error of the treated eye. In the third step, the anterior corneal flap is opened, and the prepared lenticule can be extracted. Finally, the flap will be repositioned on the cornea. The surface of the cornea follows the missing volume of the lenticule leading to a change in refractive power.

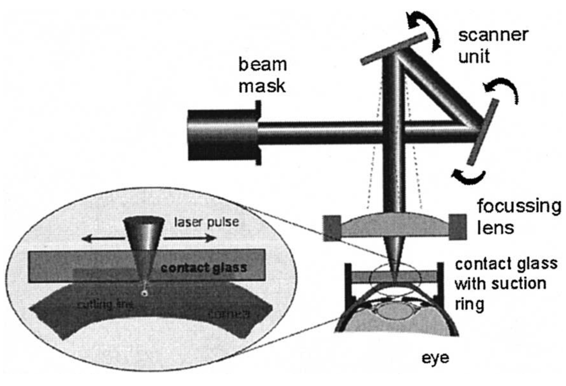

Fig. 2. Experimental setup for the beam delivery system. The laser light is guided to a scanner system and a focusing lens with 75 mm operating distance. The eyes are fixed below a suction ring with a contact glass plate on its top. The glass plate has a fixed position relative to the focal plane of the laser beam.

fluence due to any movements of the flap. The pulse energy of each laser pulse was $0.8\,\mu$J. The effective spot separation was set to $3\,\mu$m, whereas the spot diameter was estimated to be $4\,\mu$m. The mechanical as well as the thermal side effects caused by laser interaction are negligible small. The zone of visible thermal alteration of the adjacent tissue is below $1\,\mu$m.

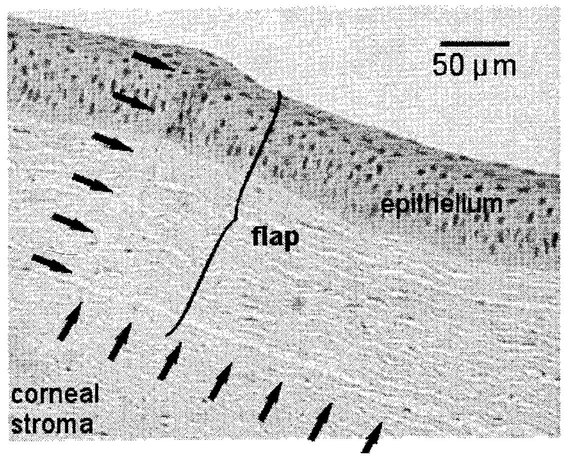

Fig. 3. Histological section (HE staining) of a porcine cornea, irradiated with 160 fs laser pulses (pulse energy $0.8\,\mu$J). The cutting line is indicated by the black arrows. On the left, the laser focus was moved upwards into the epithelium. Although optical breakdown takes place inside the corneal stroma and epithelium, no denudation or bursting of the tissue could be observed.

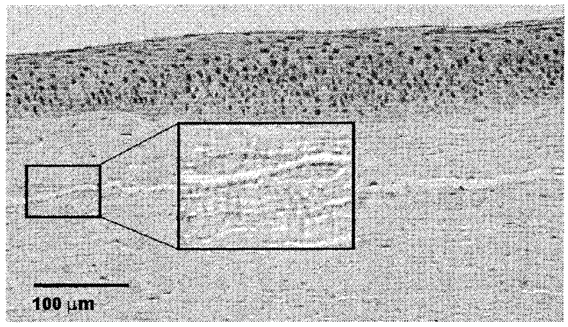

Fig. 4. Histological section (HE staining) of a porcine cornea, irradiated with 160 fs laser pulses at a pulse energy of $2\,\mu$J. Caused by the high intensities within the Rayleigh range of the laser beam, streaks were created inside the corneal tissue which image each single laser pulse. The corneal flap was opened and closed for better demonstration of the cutting line.

A new side effect was found when using small numerical apertures of the focusing lens. Caused by the high intensities within the Rayleigh range of the laser beam, streaks were created inside the corneal tissue which image each single laser pulse (Fig. 4). The strength of the streaks depends on the laser intensity. At a constant pulse energy of $2\,\mu$J almost no streaks could be observed at 930 fs, whereas at 160 fs the strongest streaks occurred. In the same way the intensity of the streaks increased with decreasing numerical aperture. In TEM, the streaks can be seen as a dark staining, crossing the picture in vertical direction (Fig. 5). The diameter of the streaks were estimated to be in the range of 200–500 nm, which is below the diffraction limit of the focused laser beam. The distance between two single streaks is equal to the separation of the laser pulses which is $3.5\,\mu$m. It is important to notice, that the streak appearance is obviously caused by accumulation of electron opaque material (contrast medium was uranyl acetate and lead citrate) and not by a change in the structure of the collagen fibrils how it would occur when thermal stress is exposed to the collagen.

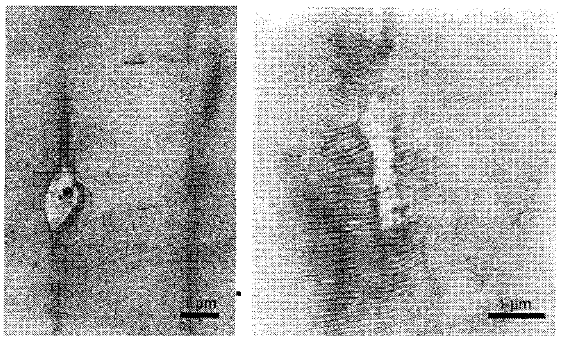

Fig. 5. In TEM the streaks can be noticed as a dark staining, crossing the picture in vertical direction. The diameter of the streaks were estimated to be in the range of 200–500 nm. The distance between two single streaks is equal to the separation of the laser pulses which is 3.5 μm. The left graph shows two streaks within the focusing plane of the cornea. On the left streak, optical breakdown occurred, which is indicated by the bubble. On the right streak, obviously no optical breakdown took place.

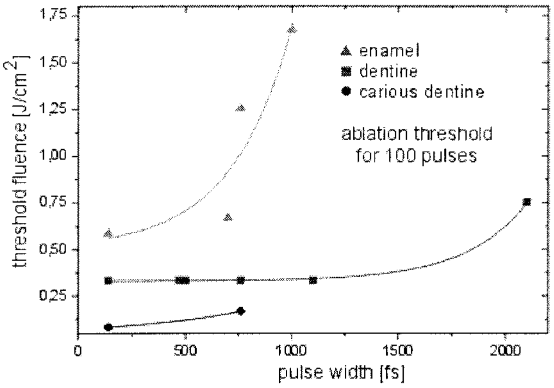

Fig. 6. The threshold fluence for ablation of dental tissue was determined with an SEM after exhibiting the tissue to 100 laser pulses.

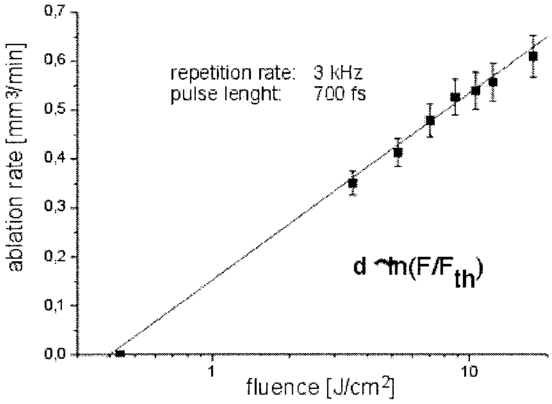

Fig. 7. The ablation rate increases logarithmically with the laser fluence. To measure the ablation rate, cavities of 1 mm×1 mm were ablated in dentine and the depth was determined with an optical microscope.

Thus, it is more likely that the high photon density leads to multi photon absorption and consequently induces UV damage by photodissociation. This assumption competes with the hypothesis, in which the authors assume, that due to the high intensity a significant amount of free electrons is produced[13] which do not reach plasma density. However, the free electrons might have induced radical reactions which damage the collagen and lead to the streak formation.

With respect to recently performed in-vivo-experiments, these tissue-alterations seemed to be permanent. The streaks could be found even 7 and 14 days after treatment of the animals.[10, 14] Nevertheless, the cornea of these animals was clear and no haze during observation of the eyes by a slit lamp could be detected.

3. Dental applications

Minimal invasive treatment of carious tissue has become an increasingly important aspect in modern dentistry. State of the art methods like grinding using turbine-driven drills[15] or ablation by Er:YAG-Lasers[16] generate mechanical and thermal stress, thus generating microcracks of several tens of microns in the enamel. These cracks are starting points for new carious attacks and have to be avoided for long term success of the dental treatment. Femtosecond laser ablation offers a tool for crack-free generation of cavities in dental tissue.

In a first experiment, the threshold fluence for ablation of dental tissue was determined with an SEM after exhibiting the tissue to 100 laser pulses (Fig. 6). It could be verified, that the threshold fluence increases with the pulse length, since the initialization of the plasma is a multiphoton process that depends on the intensity of the laser radiation. Furthermore, the threshold fluence of sound enamel was found to be the highest (>0.5 J/cm^2) followed by sound dentine (>0.3 J/cm^2). The relatively low threshold fluence of carious dentine ($<$ 0.25 J/cm^2) can be used as a discrimination effect, which supports the removal of only carious tissue, while leaving healthy tissue intact.

Consistently to theory the ablation rate depends logarithmically on the laser fluence. To measure the ablation rate, cavities of 1 mm×1 mm were ablated in dentine and the depth was determined with an optical microscope (Fig. 7).

The laser induced plasma was used to distinguish carious from healthy tissue. The peaks in the spectra are caused by Calcium. Since the Calcium concentration decreases in carious tissue, the intensity of the spectra gives information about the condition of the tissue.

Due to low mechanical and thermal stress to the material, precise structuring of oral tissue with fs pulses is possible. Micro cracks and molten zones cannot be found (Fig. 8).

4. Ear surgery

Small dimensions and low range to sensory cells and nerve structures are special demands in treating auditory ossicles and cochlea in middle ear surgery. Due to its high precision and low thermal and mechanical stress on bone and inner ear, fs laser pulses are also well suited for many applications. Potential applications are the reconstruction of defect auditory ossicles, perforation of stapes foot plate (stapedioplasty) and modeling of ossicles as an alternative docking methods of active middle ear implants or positioning of cochlea implants.

The threshold fluence on bone tissue ranges from 0.7 J/cm^2 (@ 130 fs) to 1.13 J/cm^2 (@ 1 ps) depending on laser pulse duration . The ablation rate per pulse is in the nm-range near threshold energy (Fig. 9). However, using kHz repetition rate, the high precision ablation can be combined with sufficient ablation speed.

Analyzing laser generated cavities in human ossicles by electron microscopy, the outstanding precision can be demonstrated. Even at pulse repetition rates of 3 kHz, no thermal effects like melting zones can be found. At the cavities wall, still the opend bone channels can be seen (Fig. 10).

5. Extraluminal Laser Angioplasty (ELAN)

The main cause of cardiovascular disease is a process known as atherosclerosis, which decreases the elasticity of the vessel and also encroaches on the internal dimensions of the vessel reducing blood flow. This thickening of the arterial walls is caused by the formation of atheroma within the inner layers of the vascular walls, and over time may result in total occlusion of the vessel. Such a blockage may result in acute myocardial infarction (heart attack) or stroke (brain attack). Traditionally the cure is predominantly by internal surgical procedures (CABG - Coronary Artery Bypass Grafting) and balloon angioplasty (PTCA).[17–21)]

A new procedure which uses ultrafast laser technology is called ELAN. The purpose of ELAN - an acronym for Extraluminal Laser Angioplasty is an intervention at the site of arterial stenosis to remove tissue from the external surface of the artery wall in order to reduce the effective wall thickness and to restore arterial wall flexibility. The blood pressure inside the artery ensures an increase in vessel diameter and relief of obstruction as soon as flexibility of the arterial wall is restored (Fig. 11). This is in comparison to Balloon angioplasty and Stenting methods that force the arterial wall outwards. The ELAN system will use Optical Coherence Tomography (OCT) to acquire near real-time three-dimensional (3D) images of the diseased artery. At the same time, the process of ablation is controlled on-line through OCT.[22–24)]

As a first ex vivo study, human atherosclerotic vessel were held under pressure of 120 mm HG with saline solution and irradiated with 160 fs laser pulses with a repetition rate of 1 kHz. Three parallel lines were cut which results in an clear dilatation of the vessel (Fig. 12). The histological analysis

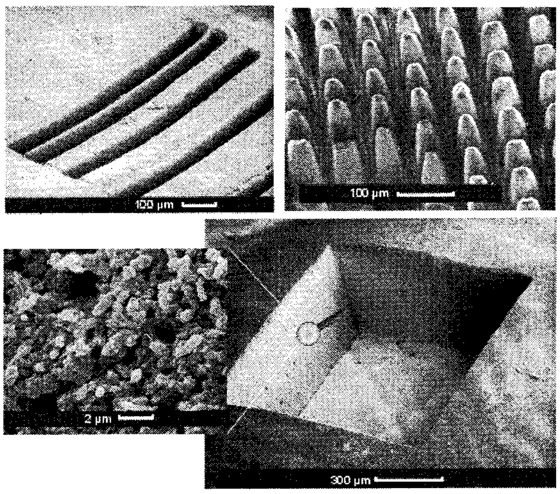

Fig. 8. Due to low mechanical and thermal stress to the material, precise structuring of oral tissue with fs pulses is possible. Micro cracks and molten zones cannot be found.

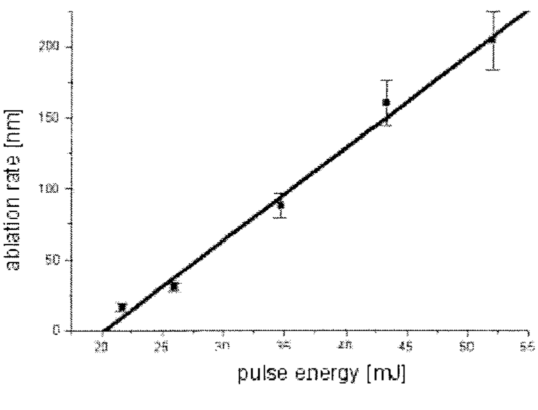

Fig. 9. Ablation rate of bone tissue as a function of laser pulse energy (pulse duration 180 fs, spot size 0.0024 mm^2).

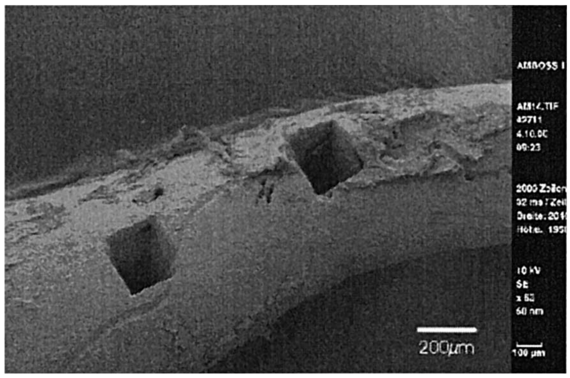

Fig. 10. Processing of a human malleus with 130 fs laser pulses and a pulse energy of 30 μJ.

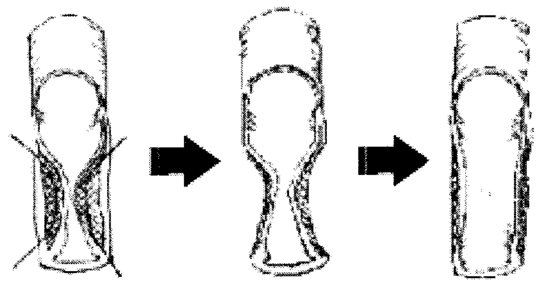

Fig. 11. Principle of the ELAN procedure. An increase in thickness due to cholesterol and other deposits causes narrowing of arteries with loss of flexibility. Tissue from the external surface of the artery wall is removed in order to reduce the effective wall thickness and to restore arterial wall flexibility. The blood pressure inside the artery ensures an increase in vessel diameter and relief of obstruction as soon as flexibility of the arterial wall is restored.

Fig. 12. Three parallel cuts 2 cm long, performed in a segment of a vessel (carotis of a pig). The vessel was held under pressure of 120 mm Hg with saline solution. The laser spot was 100 μm in diameter. The Vshaped expansion of the cut demonstrates the dilatation of the vessel.

yield an expected low thermal damage of the irradiated tissue.

The main advantages of the ELAN procedure can be found in providing a higher success rate as measured by infrequency of vascular re-blockage by maintaining the tunica intima in its pristine condition. Often, damage to this layer caused by other methods of angioplasty leads to re-blockage.

6. Conclusion

Mechanical and thermal side effects caused by fs photodisruption are comparable to what is known from excimer laser ablation, which has been used in refractive surgery since more than 20 years and acts as a gold standard for laser ablation. Cavitation and laser induced pressure transients, which limits the precision of the surgical procedure when using ns and ps photodisruption, is reduced dramatically with fs pulses.

With respect to the required laser parameters such as pulse energy and average power fs-LASIK seems to be the first profitable application of ultrashort laser pulses in medicine. In the nearest future, turn key fs laser systems will be available, which meets the demands for refractive intrastromal surgery to a price which is comparable to excimer laser systems. The advantage of such a system would be the easier and more flexible management of the surgical procedure, without using a mechanical knife.

Another advantage of fs-LASIK would be its speed of operation. Recently, ultra short pulsed lasers systems with a repetition rate of 300 kHz and sufficient output power are available as turn key systems. With such a repetition rate, the surgical procedure to correct the visual acuity within an aperture of up to 9 mm on the cornea would take less than 20 sec, which is much faster than conventional excimer laser procedures. At the moment, the authors are working on a scanner system which guarantees a sufficient precision in launching the laser pulses into the corneal stroma at such a high repetition rate.

Ear surgery as well as vascular surgery needs some more pulse energy and average power due to the larger amount of tissue which has to be removed. As a consequence, the available laser systems will be more expensive. However, if the surgical procedures, were no alternatives can be found with other lasers are successful, fs laser systems will also find their market in that field.

Dental tissue processing needs by far the most powerful laser systems to have a chance in competing with conventional mechanical devices. On the other hand, there is a large market which motivates the physicists and engineers to develop reliable, compact and economically priced systems. Based on laboratory systems it was already demonstrated that it is possible to remove dental hard tissue with an adequate efficiency.

However, the accuracy and reproducibility of the surgical outcome in all demonstrated applications has to be investigated as well as the post op wound healing process. Then, compact and low priced laser fs laser sources have the potential to be an attractive tool for many application in surgery.

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