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Nonlinear absorption: intraocular microsurgery and laser lithotripsy

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Abstract. The paper reviews the principles of nonlinear absorption with reference to the present major clinical applications of plasma-mediated effects: intraocular microsurgery and laser lithotripsy. Emphasis is laid on the analysis of the working mechanisms, sources of collateral damage, and on strategies for both the optimization of efficacy and the minimization of side effects.

1. Background

'Nonlinear absorption' means that the absorption coefficient of a medium depends on the intensity of the incident light. It plays an important role in interactions of high-power laser beams with matter (Ready 1971). This review will be restricted to applications of pulsed lasers in medicine, where nonlinear absorption occurs in the form of moderate transient changes of the absorption coefficient, as observed in tissue ablation, or in the form of optical breakdown with plasma formation, as applied in intraocular photodisruption and laser lithotripsy.

Moderate transient changes of the absorption coefficient are observed in IR-laser ablation at wavelengths around 3 μm, i.e. close to the absorption peak of tissue water (Walsh and Cummings 1994). The rise of the water temperature during the ablation process can induce a decrease of the absorption coefficient by as much as one order of magnitude which is associated with a shift of the absorption peak towards shorter wavelengths (Vodopyanov 1991). The effect depends on the energy density reached during ablation and becomes important at values of about 1 kJ cm^{-3}. It has recently been postulated that the absorption characteristics of water also change during UV-laser ablation at $\lambda = 193$ nm (Walsh and Staveteig 1995). In this case, the absorption increases due to a shift of an absorption band at 163 nm to longer wavelengths. Free-radical formation during the laser–tissue interaction is another contributory factor to an increase of the absorption coefficient during UV-laser ablation (Pettit *et al* 1995). Consideration of the nonlinearity of tissue absorption may clarify the long-standing question of why the ablation depth observed in excimer laser ablation at 193 nm is about a factor of five smaller than with the Er:YAG lasers at 2.94 μm (Pettit *et al* 1995, Bende *et al* 1989), although the low-intensity penetration depth is five times larger at 193 nm than at 2.94 μm (Puliafito *et al* 1985, Walsh and Cummings 1994).

Very pronounced changes of the absorption coefficient are observed at light intensities above approximately 10^{10} W cm^{-2}, where plasma formation via 'inverse bremsstrahlung' and cascade ionization (Raizer 1966, DeMichelis 1969, Bass and Barrett 1972) occurs even in nominally transparent media like distilled water or the ocular media (Docchio *et al*

1986, 1988a). If some free electrons are present in the medium, they absorb photons by collisions with atoms. After acquiring an energy higher than the ionization potential, an electron may ionize an atom by impact, thus resulting in two electrons of lower energy being available to start the process again. An ionization cascade begins which results in plasma formation when a free electron density of 10^{18} cm^{-3} is exceeded during the laser pulse (Barnes and Rieckhoff 1968, Bloembergen 1974). For water, this electron density corresponds to a fractional ionization of about 1.5×10^{-5}. Attention is focused on water, because its breakdown threshold is very similar to that of transparent biological tissues like the ocular media (Docchio *et al* 1986).

Mechanisms for the generation of seed electrons for the ionization cascade are either thermionic emission by heating of linear absorbing chromophores in the target (in liquids these can be impurities), or multiphoton ionization. The multiphoton ionization rate is proportional to I^k, where I is the intensity of the beam and k is the number of photons required for ionization (Weyl 1989). The value of the proportionality constant decreases with increasing k, i.e. with increasing wavelength where more photons are needed to provide the energy necessary for ionization. Multiphoton ionization of water was recently discussed by Sacchi (1991). He suggested that one should not consider the ionization energy of single molecules (12.6 eV), but treat the medium as an amorphous semiconductor (Williams *et al* 1976) and look at the energy required for the excitation of electrons from the $1b_1$ molecular orbital to an exciton band (6.5 eV). This approach yields a higher probability for multiphoton processes than formerly assumed, which is in agreement with the work of Kennedy (1995) and Kennedy *et al* (1995).

When electron losses are neglected, the cascade ionization rate is proportional to the laser light intensity: $\eta_{casc} \propto I$ (Shen 1984). With decreasing pulse duration, I must increase for breakdown to occur during the shorter pulse duration. Since the multiphoton ionization rate has the much stronger intensity dependence $\eta_{mp} \propto I^k$, multiphoton processes become ever more important with decreasing pulse duration. Table 1 lists the intensity values I_{th} and the radiant energy values F_{th} required for optical breakdown in distilled water at various pulse durations, as well as the mechanisms dominating the breakdown process. It is interesting to note that I_{th} increases only moderately when the pulse duration is reduced from the ns range to the ps and fs range. This goes along with a pronounced decrease of the radiant energy F_{th} required for breakdown.

Table 1. Breakdown thresholds in distilled water at various pulse durations. The data for 6 ns and 30 ps are from Vogel *et al* (1997a), and the data for 100 fs are taken from Kennedy *et al* (1995).

Pulse duration	Breakdown mechanism	Spot size (μm)	I_{th} (10^{11} W cm^{-2})	F_{th} (J cm^{-2})
6 ns	Cascade ionization	11.6 ± 0.5	0.79 ± 0.08	472 ± 47
30 ps	Cascade/multiphoton ionization	19.5 ± 0.4	3.70 ± 0.14	11.1 ± 0.4
100 fs	'Pure' multiphoton ionization	17.0	57.7	0.577

With short pulses of 200 ps or less, the role of multiphoton absorption is strong enough such that the breakdown process is no longer influenced by the presence of impurities, and the thresholds in tap water and distilled water are the same (Docchio *et al* 1988a, Kennedy *et al* 1995).With pulses of 6 ns duration, the threshold is by a factor of three to seven lower in tap water than in distilled water, because linear absorbing impurities provide seed electrons for cascade ionization at intensities lower than required for multiphoton ionization. The thermionic emission of the seed electrons depends on the density of the deposited energy, i.e. on the radiant energy F of the laser beam and the absorption coefficient α of the impurities (or the target medium). The contributions of thermionic emission and cascade ionization to plasma formation vary depending on α, F and the laser pulse duration τ. With μs pulses and absorption coefficients typical for intracorporeal stones, thermionic emission may even dominate during a major part of the laser pulse, and cascade ionization starts to play an important role only after a high electron density has been created by heating of the target (Teng *et al* 1987a). The threshold for plasma formation is therefore determined by the radiant energy incident on the stone rather than the intensity.

Since plasma formation by ns or ps laser pulses enables localized energy deposition largely independent of the absorption coefficient of the target tissue, it is ideally suited for non-invasive microsurgery in the transparent media of the eye. The localized energy deposition leads in a very short time to evaporation of the tissue within the plasma volume followed by shock wave emission and cavitation bubble generation. The latter effects are often not intended in intraocular surgery, but they are used in laser lithotripsy for the fragmentation of urinary, biliary and salivory calculi. Both applications of nonlinear absorption are described in the following sections.

2. Intraocular microsurgery

2.1. Working mechanisms and sources of collateral damage

2.1.1. Sequence of events. For intraocular microsurgery (Krasnov 1973, Aron-Rosa *et al* 1980, Fankhauser *et al* 1981), ns or ps laser pulses are focused into the eye via an ophthalmic slit lamp microscope which allows visual control of the surgical procedure. Plasma formation starts at the laser focus, and during the laser pulse the plasma grows into the cone angle of the laser beam (Docchio *et al* 1988b). The temperature of the plasma reaches a value of about 10 000 K (Barnes and Rieckhoff 1968) causing immediate evaporation of the tissue or liquid within the plasma volume. The rapid temperature rise during breakdown leads to an explosive expansion of the plasma which drives a shock wave and generates a cavity within the intraocular fluid, as shown in figure 1. After 5 mJ laser pulses often used in clinical practice the initial shock wave pressure is 5000–10 000 MPa (Vogel and Busch 1994, Noack and Vogel 1995), and the cavity reaches a radius of about 1 mm (Vogel *et al* 1994a). The bubble expands beyond its equilibrium radius and, as a result of the hydrostatic pressure, implodes within less than a millisecond. The bubble content of vapour and gas is thereby strongly compressed so that pressure and temperature rise again to values similar to those achieved during optical breakdown. Hence, the bubble rebounds and a second acoustic transient is emitted into the surrounding liquid (Vogel *et al* 1986). This cycle can repeat itself several times until the bubble energy is dissipated. Within the eye, the bubble dynamics is influenced by the ocular structures in the surroundings of the bubble. When the bubble collapses in the vicinity of a rigid boundary, for example the cornea, iris or an artificial intraocular lens, a high-speed liquid jet (maximum speed $\approx$100 m s^{-1}) directed toward this boundary is produced (Vogel *et al* 1990). The jet (figure 2) can cause a high impact pressure when it hits the boundary (Vogel and Lauterborn 1988).

For clinical purposes, a sequence of laser pulses is always needed, and therefore the interaction between subsequent pulses must also be considered. After each pulse, small gas bubbles remain from the cavitation bubble produced during optical breakdown. They

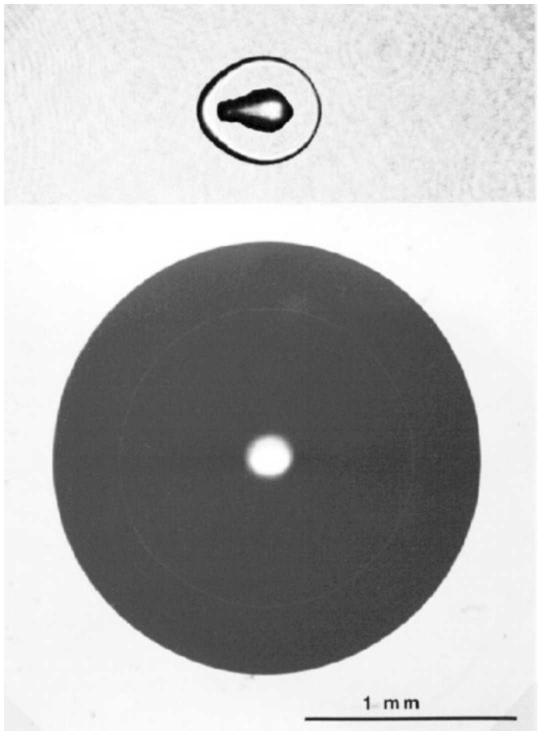

Figure 1. Laser plasma, shock wave and cavitation bubble created by a 5 mJ Nd:YAG laser pulse with 6 ns duration. The upper picture was taken 90 ns after the laser pulse, and the lower picture 130 μs after the laser pulse, when the cavitation bubble was maximally expanded. Both are printed with the same magnification. Figure taken from Vogel *et al* (1994a).

are filled partly with evaporated tissue and partly with air which was dissolved in the intraocular fluid and diffused into the oscillating cavity (Crum 1984). The residual bubbles are often expelled quite far from the application site but are, of course, trapped within the eye. They can be collapsed by the acoustic transients and the expanding cavitation bubbles from subsequent laser pulses (Vogel *et al* 1990). A liquid jet is thereby formed which penetrates the gas bubble in the propagation direction of the pressure waves. This process is independent of any boundary in the vicinity of the bubble. If the bubble is close to sensitive tissue structures they can be affected by the jet impact.

2.1.2. Working and damage mechanisms. Ionization and evaporation of the tissue within the plasma volume are the primary working mechanisms of intraocular microsurgery. Nevertheless, thermal damage to adjacent tissue is, at low repetition rates, restricted to a layer around the evaporated volume with less than 1 μm thickness (Vogel *et al* 1990). The limited role of heat conduction from the plasma into the surrounding tissue is partly due to the short laser pulse duration and partly a consequence of the rapid adiabatic cooling of the plasma during its expansion. Collateral effects are mainly mechanical, in the form of tissue disruption due to the explosive character of the plasma expansion. The disruptive effects are sometimes useful, as in posterior capsulotomy (see below), but are more often not intended, especially if precise tissue cutting is desired or if the target is located near sensitive ocular structures.

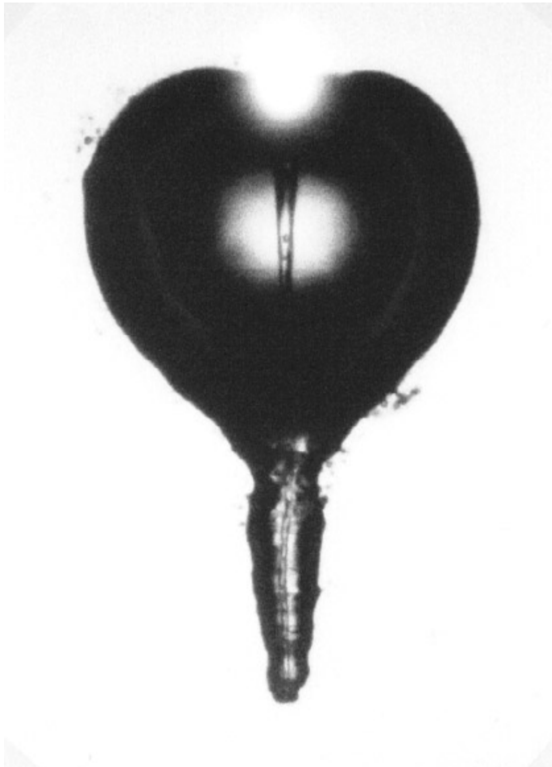

Figure 2. Cavitation bubble with a high-speed liquid jet directed toward a solid boundary located slightly below the bottom of the frame. The picture was taken during rebound of the bubble after its first collapse. Horizontal bubble diameter 0.8 mm.

In the early days of intraocular microsurgery, photodisruption was mostly attributed to the action of the shock wave. It is now known, however, that cavitation is responsible for all gross tissue effects (Vogel *et al* 1990, 1994a), and that shock waves cause damage merely on a subcellular level which may consist of rupture of cell membranes, injury to cell organelles and bond breaking in biomolecules (Cleary 1977, Doukas *et al* 1993, Teshima *et al* 1995). This is explained by the very short interaction time with the shock waves due to their duration of less than 100 ns (Vogel *et al* 1996b). The short interaction time prevents tissue displacement of more than a few μm which could lead to macroscopic tissue disruption. Doukas *et al* (1993) showed that the threshold for functional cell damage caused by laser-induced pressure transients is about 100 MPa. After a 1 mJ laser pulse of 6 ns duration, this pressure is surpassed up to a distance of about 200 μm from the plasma (Vogel and Busch 1994c, Vogel *et al* 1996b). The cavitation bubble expands to a radius three times as large and therefore dominates the tissue effects.

Jet formation during the bubble collapse concentrates the bubble energy at a location away from the application site and has a damage range slightly larger than the maximal bubble radius (Vogel *et al* 1990). The range of a 1 mJ laser pulse, for example, is 0.8 mm. The damage range of single laser pulses scales in the same way as the cavitation bubble size: it is proportional to the cube root of the laser pulse energy. The physical effect with the largest damage range is the jet formation occurring when a gas bubble remaining from earlier laser exposures is collapsed by the pressure transient produced by a subsequent laser pulse. The interaction of a 4 mJ pulse with a gas bubble attached to the cornea can result in an endothelial lesion, even if the laser focus is located 3.5 mm away from the bubble (Vogel *et al* 1990).

When the application site is located in the posterior part of the eye, a further potential hazard is irradiation of the retina, because the retinal pigment epithelium is a tissue with strong linear light absorption. The transmission of laser light through the focal region is, however, very much reduced when the plasma is formed ('plasma shielding') (Steinert and Puliafito 1983, Dochio and Sacchi 1988, Nahen and Vogel 1997), and the amount of transmitted light hardly increases with increasing pulse energy once the breakdown threshold is surpassed (figure 3(*a*)). Figure 3(*b*) shows, on the other hand, that the plasma shielding is compromised in the presence of optical aberrations which often occur in clinical practice. With ns pulses of 3–5 mJ pulse energy, damage to the retina has been observed at up to a distance of 3 mm between focus and retina (Bonner *et al* 1983, Brown and Benson 1985).

2.1.3. Plasma size. To assess the extent of the plasma-mediated evaporation, one needs to know the scaling laws for the plasma length as a function of laser pulse energy, focusing angle and pulse duration. A good starting point is the 'moving breakdown model' developed by Raizer (1965) and refined by Docchio *et al* (1988b) which describes how the location of optical breakdown moves from the beam waist upstream toward the laser during a superthreshold laser pulse. Based on this model, one can derive the following relations for the plasma length z as a function of laser pulse intensity and focusing angle θ:

$$z = z_0\sqrt{I/I_{th} - 1} \qquad \text{for } \theta = \text{const.} \tag{1}$$

$$z = \frac{\lambda}{\pi \tan^2(\theta/2)}\sqrt{\frac{I}{I_{th}} - 1}. \tag{2}$$

Figure 4 shows measurements of the plasma length for various focusing angles at 30 ps and 6 ns pulse duration. The plasma length is plotted as a function of $(I/I_{th} - 1)$ on a logarithmic scale to check the validity of equation (1). For the ps pulses one obtains straight lines with a slope of about 0.5 (figure 4(*a*)) as predicted by the model, and the data agree to within ±30% with the values given by equation (1). The agreement is not as good for the ns pulses (figure 4(*b*)), neither with respect to the slope nor with respect to the absolute values for the plasma length. At equal I/I_{th}, ns plasmas should, according to (1), have the same length as ps plasmas, but they are considerably longer. At $I/I_{th} = 10$ and $\theta = 22°$, for example, the ns plasma is 100 μm long, whereas the ps plasma measures only 25 μm. The deviation from the model is probably due to the UV radiation emitted by the plasma produced at the beginning of the laser pulse (Vogel *et al* 1997a). This radiation creates free electrons in the liquid near the plasma which act as seed electrons for further cascade ionization. The breakdown threshold is thus lowered during the laser pulse, and the plasma grows larger than predicted by the moving breakdown model which assumes a constant threshold. The situation is different in ps breakdown where multiphoton ionization always provides sufficient seed electrons for the cascade ionization part of the breakdown. The threshold is therefore hardly influenced by the plasma radiation and remains constant during the whole breakdown process, as assumed by the model.

2.2. Clinical applications

The laser of choice for intraocular microsurgery is an Nd:YAG laser with a wavelength of 1064 nm, or another pulsed laser emitting in the IR at a wavelength around 1 μm.

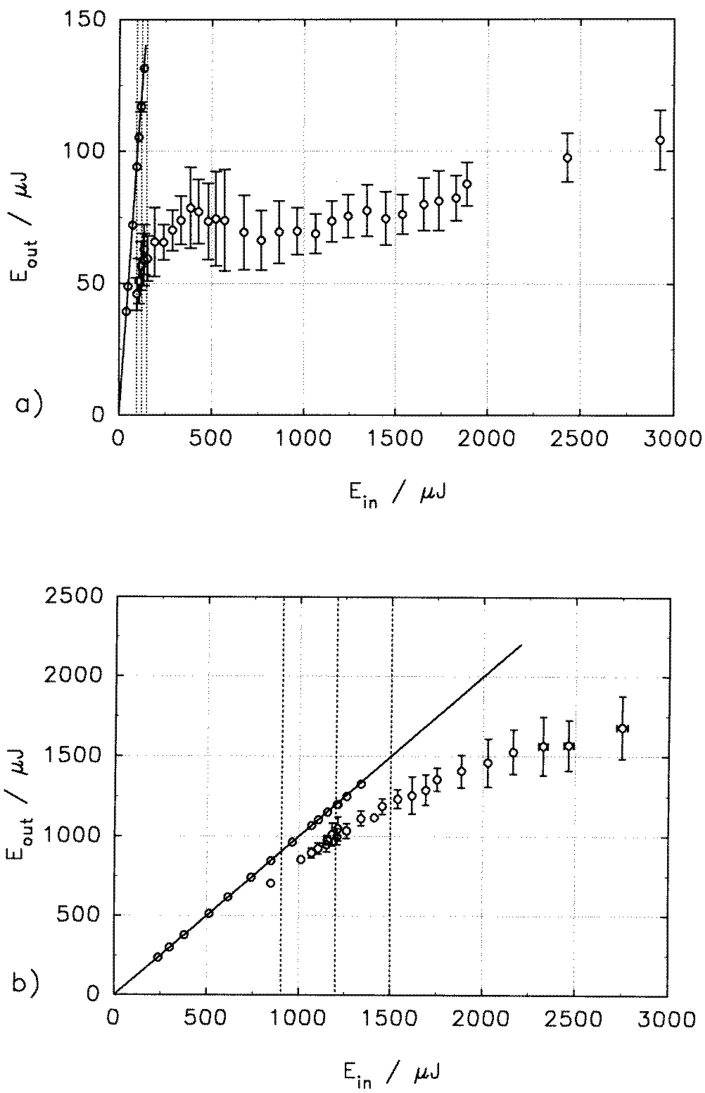

Figure 3. Nd:YAG laser energy transmitted through the focal region at subthreshold and superthreshold pulse energies; (*a*) with miminal aberrations, (*b*) with a phase difference of 19λ between the centre and periphery of the laser beam. Pulse duration 6 ns; focusing angle 22° in (*a*) and 24° in (*b*). Breakdown energy E_{th} and the range between 10% and 90% breakdown probability are indicated by broken lines. Unpublished results of Nahen (1995).

At these wavelengths the patient is not dazzled, the light is transmitted well into the eye, and the risk of retinal damage is minimal, because the absorption coefficient of the retinal pigment epithelium is small. The typical clinical instrument is, at present, a small passively Q-switched Nd:YAG laser with 2–5 ns pulse duration and up to 10 mJ pulse energy attached to an ophthalmic slit lamp. The most common and important applications of intraocular photodisruption are posterior capsulotomy and iridotomy. Posterior capsulotomy is frequently necessary after extracapsular cataract surgery where the lens nucleus and cortex

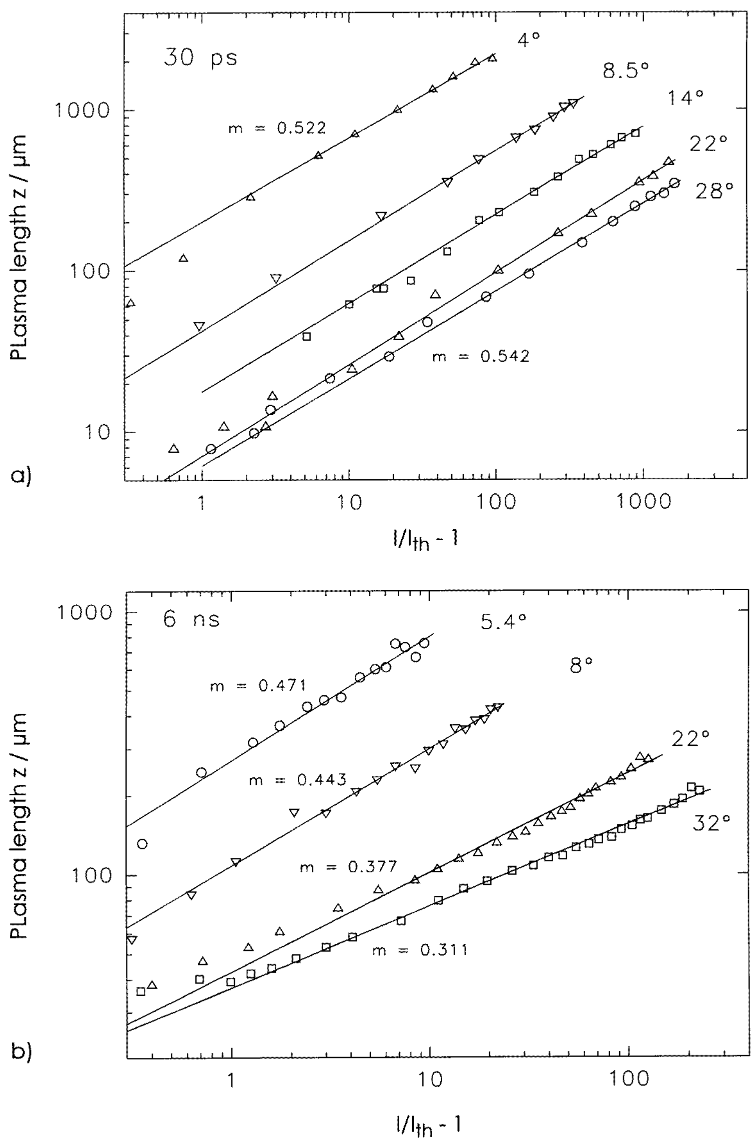

Figure 4. Plasma length z as a function of $I/I_{th} - 1$ for various focusing angles at a pulse duration of (a) 30 ps, (b) 6 ns. From Vogel *et al* (1997a).

are removed and an artificial intraocular lens (IOL) is implanted into the capsular bag. The posterior lens capsule may become turbid some time after the operation. In this case, an incision is made by focusing a sequence of laser pulses on the lens capsule. During the procedure, one has to take great care to avoid pitting of the IOL by considering the distance the plasma extends from the laser focus toward the IOL. An iridotomy, i.e. the creation of a hole through the iris, is one of the methods for glaucoma treatment. It facilitates the flow of aqueous from the posterior chamber into the anterior chamber angle where it is drained out of the eye. Other applications of photodisruption are the lysis of anterior and posterior synaechiae, pupillary membranectomy, and the cutting of vitreous strands and membranes. For a detailed description of clinical applications of intraocular microsurgery the reader is referred to the book by Steinert and Puliafito (1985) and the reviews by Fankhauser and Kwasniewska (1989) and Gabel (1992).

2.3. Optimization strategies

Fine tissue effects with little collateral damage can be achieved if the characteristics of the laser pulses and the delivery system are adjusted to minimize the energy threshold E_{th} for optical breakdown. E_{th} is proportional to F_{th} and the focal area. It can be reduced by operating the laser in fundamental mode, or by using a 'Gaussian' resonator with variable reflectivity mirrors (Magni *et al* 1989), because both techniques provide a minimal spot size of the laser focus. A small spot size requires furthermore that the focusing angle is as large as possible without causing vignetting at the pupil. This can be achieved by using an appropriate contact lens for each segment of the eye (Rol *et al* 1986). The perfectly smooth optical surface of the contact lens leads to a further improvement of the focus as compared to focusing through the corneal surface without a contact lens

Laser pulses with 30–40 ps pulse duration have a much lower breakdown threshold F_{th} than ns pulses (see table 1) and are therefore suitable for performing intraocular surgery with pulse energies in the microjoule range (Zysset *et al* 1989, Vogel *et al* 1994b). This may enable applications requiring more localized tissue effects than can be achieved with ns pulses. To fulfil the surgical task with such a small individual pulses energy, a sequence of many pulses has to be applied. Clinical ps lasers emit either single pulses or pulse series with repetition rates between 10 Hz and 1 kHz which can be applied in a scanning mode with various pre-programmed patterns (spot, line, circle, spiral, rectangle, etc). This also offers new treatment modalities for some 'classical' Nd:YAG laser applications. An iridotomy, for example, should ideally have a diameter of about 1 mm to avoid reclosure and ensure a continuous flow of aqueous into the anterior chamber. An attempt to produce this opening with only one laser pulse of high energy could harm the adjacent corneal endothelium and disperse debris which may cause a transient intraocular pressure rise. Generation of the opening by many single pulses with small energy is possible, but tedious and time-consuming. Application of a series of low-energy (150 μJ) ps pulses in a spiral pattern, however, has proved to be a fast procedure with minimal side effects, because the iris tissue is mainly evaporated and not torn apart (Vogel *et al* 1996c)

Picosecond pulses are attractive for the cutting of vitreous strands and membranes, since the retinal damage range at 200 μJ pulse energy is only 0.5 mm (Vogel *et al* 1994b). This application is, however, limited to the central fundus region, because in the periphery the focus is distorted by optical aberrations and no cutting effect is achieved (J Roider, personal communication).

It has been suggested that corneal intrastromal refractive surgery be performed with the ps laser (Niemz *et al* 1993) The idea is to correct myopia by evaporation of a stroma layer in the central cornea without damaging the corneal epithelium, endothelium or Bowman's layer. Evaporation of stromal tissue should reduce the thickness of the central cornea and thus decrease the curvature of the corneal surface. One problem of the technique is that the minimal plasma length near breakdown threshold is as large as 10 μm (figure 4). This results in a less accurate ablation than is possible with the excimer laser where an ablation depth well below 1 μm can be achieved (Pettit *et al* 1995). The actual displacement of the anterior corneal surface can be considerably smaller than the intrastromal plasma length, but it depends in a complicated way on the distance between ablated layer and corneal surface, and on the mechanical properties of the cornea. Another problem is the cavitation accompanying plasma-mediated evaporation. The disruptive effects of cavitation are very strong when the plasma is completely surrounded by tissue, as in the corneal stroma. The volume of the evaporated tissue (which approximately equals the plasma volume) is therefore small compared to the tissue displacement caused by the expansion of the laser plasma (Vogel *et al* 1994b, c, 1997b). Furthermore, the energy deposition acquires statistical character, because the laser light is scattered by the cavitation bubbles produced by earlier pulses. In experiments on cats performed by Habib *et al* (1995) and in a clinical study by Marchi *et al* (1996), no clear relationship could be established between laser parameters and refractive outcome.

Disruptive surgical effects may be diminished by applying a concept recently developed for the reduction of cavitation in pulsed laser ablation (Vogel *et al* 1996a). The laser pulse energy is divided into a pre-pulse with low and an ablation pulse with higher energy. The pre-pulse creates a small bubble at the application site, and the ablation pulse is applied when this bubble is maximally expanded and can be filled by the ablation products of the main pulse. With a suitable energy ratio between the pulses, the ablation products will not enlarge the bubble generated by the pre-pulse, and the maximal bubble size remains much smaller than after a single ablation pulse. In water, for example, this method works well with an energy ratio between about 1:7 and 1:30. The concept should not be confused with the high repetition rate burst mode available in many clinical Nd:YAG lasers. The bursts consist of several pulses with equal energy and can therefore not considerably reduce cavitation effects. Moreover, the large cavitation bubble generated by the first pulse may push aside the target tissue thus preventing plasma formation by subsequent pulses (Jungnickel and Vogel 1992). This effect lowers the efficiency of photodisruption.

3. Laser lithotripsy

3.1. Working mechanisms and sources of collateral damage

Laser lithotripsy (Mulvaney and Beck 1968, Fair 1978, Watson *et al* 1987) requires delivery of laser light into the body. For this procedure to be minimally invasive, the light is transmitted through an optical fibre in a catheter which should be as small as possible. Focusing devices at the fibre end increase the catheter diameter, are easily damaged during the fragmentation process of the stone, and require the surgery to be performed in a non-contact mode. It is therefore preferable to use the bare fibre in direct contact with the calculus. Damage to the tip of the bare fibre is, of course, not desirable either, but will not prevent continuation of the procedure. Since the irradiated spot at the fibre tip has a diameter of 200 μm or more, pulse energies of 40–70 mJ are necessary to surpass the breakdown threshold at the stone surface and efficiently fragment the calculus (Thomas *et al* 1988b). Nanosecond pulses in this energy range are difficult to transmit through optical fibres without causing damage to the fibre, especially near the fibre tip where microcracks develop due to the pressure transients from the laser plasma. As a consequence, plasma forms inside the fibre, and fragments of the exploding fibre are driven into the surrounding tissue (Fleming *et al* 1991, Strunge *et al* 1991). Since plasma formation inside the fibre depends on the intensity of the laser pulse, it can be markedly reduced if, at the same energy, the pulse duration is prolonged (Strunge *et al* 1991). A longer pulse duration does not compromise plasma formation on the linear absorbing stone, because that depends on the radiant energy applied (Teng *et al* 1987a). Laser pulses with a duration of about 1 μs can thus efficiently fragment stones while causing little damage to the fibre. Attention will therefore be focused on this parameter range. Other attempts to perform lithotripsy with pulse durations of a few ns (Schmidt-Kloiber *et al* 1985, Thomas *et al* 1988b, Shi *et al* 1990) will not be discussed here in detail.

3.1.1. Sequence of events. The sequence of events is plasma formation, emission of a pressure transient, and generation of a cavitation bubble, as in intraocular microsurgery (Teng *et al* 1987a, Lo *et al* 1990, Ihler 1992, Rink *et al* 1995, Rudhart 1995). The details of the process are, however, quite different. Plasma formation at clinically reasonable energy levels requires linear absorption of the stone, or of pigmented microinclusions (Berenberg *et al* 1994). It is therefore advantageous to choose a laser wavelength at which the absorption coefficient of the stone is high, usually in the short visible and UV wavelength range (Watson *et al* 1987, Nishioka *et al* 1987, Thomas *et al* 1988a). Plasma is formed when enough free electrons are produced by heating of the stone to support cascade ionization. Near threshold, this occurs only at the end of the laser pulse, but well above threshold it occurs further at the beginning of the pulse (Teng *et al* 1987a). This leads to an extended energy range in which the coupling of light energy into the plasma and thus the transformation into mechanical energy grows with increasing pulse energy (Rink *et al* 1995, Rudhardt 1995). The fast temperature rise within the plasma creates a high pressure, whereby the peak pressure is limited by the plasma expansion during the laser pulse. Confinement of the plasma by the surrounding liquid and the fibre tip is therefore important to allow the development of pressures high enough to fragment the stone. With liquid confinement, the peak pressure is about 10 times higher than during plasma formation in an air environment (Teng *et al* 1987b). The peak pressure amounts to about 250 MPa at 1.5 μs pulse duration, 100 mJ pulse energy, and 400 μm fibre diameter (Ihler 1992). Due to the relatively long laser pulse duration, the pressure transient has a rise time and duration in the range of several hundred nanoseconds, and no shock front develops (Rink *et al* 1995, Ihler 1992).

The pressure pulse from the cavitation bubble collapse is shorter but can have a higher amplitude than that from optical breakdown with μs pulses (Ihler 1992, Rink *et al* 1995). In experiments with a flat model stone or a brass target in the bulk of liquid, the peak amplitude of the bubble pulse was about 750 MPa after a 100 mJ laser pulse, and the energy content of the bubble pulse (1.4 mJ) was higher than that of the breakdown pulse (0.6 mJ) (Ihler 1992). An optical fibre used as a test object was fragmented during bubble collapse, but not by the pressure pulse from optical breakdown (Rink *et al* 1995). Rink *et al* (1995) and Ihler (1992) concluded from these observations that cavitation bubble collapse is the main fragmentation mechanism in lithotripsy with μs pulses. Neither research group, however, investigated how the bubble dynamics is changed if it takes place in a tube like the ureter or bile duct. The pressure developed during bubble collapse near a solid boundaries depends very strongly on the geometry of the boundary conditions (Vogel and Lauterborn 1988, Chahine 1982, Ihler 1992). It is maximal for hemispherical collapse on a plane surface and may drop considerably under clinical conditions where this symmetry is not present.

3.1.2. Working and damage mechanisms. The action of pressure transients on elastic tissue and on brittle stones is very different. The pressure pulses do not harm tissue unless the peak pressure exceeds a value of about 1 kbar and the pulses exhibit a very steep rise time or a shock front (Doukas *et al* 1993, Delius 1994). They can, however, fragment stones, because in a brittle material a very small relative displacement will lead to crack formation. The selectivity of the shock wave action on brittle material is the rationale behind laser lithotripsy and extracorporeal shock wave lithotripsy (Delius 1994).

Intracorporeal stones are usually a conglomerate of crystalline and organic components, and small voids (Johrde and Cocks 1985, Pittomvils *et al* 1994). They are acoustically inhomogeneous, with many zones of different acoustic impedance. Whenever the pressure pulse coming from a zone with high impedance propagates into a zone with smaller impedance it is partially reflected as a tensile stress wave. These waves have a high damage potential, since stones are about five times more susceptible to tensile stress than to pressure (Ihler 1992). The very localised coupling of the pressure transient into the stone and the inhomogeneity of the pressure wave propagation may additionally lead to shearing forces (Brunton 1966, Peterson 1972). Tensile stress and shearing forces will create cracks, enlarge pre-existing cracks and voids, and finally lead to fracture. Since crack formation takes time, longer cracks can develop after μs laser pulses than after ns pulses, where the pressure transients are much shorter (Peterson 1972). Stone fragments are therefore larger after irradiation with μs pulses than with ns pulses, where powdery fragments are produced (Thomas *et al* 1988b, Rink *et al* 1995) and a larger number of pulses is required to break up the stone (Rink *et al* 1995). The creation of very small fragments requiring a large amount of acoustic energy is not required to allow excretion of the fragments. Microsecond pulses are thus an efficient means for lithotripsy. Pulse durations much longer than 1 μs are, however, again disadvantageous, because the pressure developed during plasma formation and the coupling of energy into the cavitation bubble decreases leading to a diminished efficacy of stone fragmentation (Nishioka *et al* 1987, Bhatta and Nishioka 1989, Rudhardt 1995).

The primary source of collateral tissue damage is misaiming of the laser pulses leading to plasma formation at the tissue instead of on the stone, often with the consequence of a haemorrhage (Thomas *et al* 1988b). Tissue damage can also arise from the expanding cavitation bubble, which at very large pulse energies may even rupture the ureter or bile duct (Tidd *et al* 1976). Another potential damage mechanism is the interaction between residual gas bubbles and pressure transients from subsequent laser pulses, which was described in section 2. An upper limit for clinically useful pulse energies of μs pulses seems to be in the order of 150 mJ (Vandeursen *et al* 1991).

3.2. Clinical applications

Laser lithotripsy is mainly used for the fragmentation of urinary stones and biliary stones. It is at present mostly performed with flash-lamp-pumped dye lasers emitting pulses with up to 150 mJ energy, 1–2 μs duration, and a wavelength of 504 nm (Coumarin) or 590 nm (Rhodamin 6G). It competes with extracorporeal shock wave lithotripsy (ESWL) which is usually the first method of choice for urinary stones, because it is less invasive than laser lithotripsy. However, for conditions like ‘steinstrasse’, where a line of urinary stones are stuck in the ureter, laser lithotripsy is advantageous (Watson *et al* 1987, Copcoat *et al* 1988, Dretler 1988, Bhatta and Dretler 1989). While more invasive and often requiring general anaesthesia, utereroscopic manipulation of distal ureteral calculi offers significantly greater stone-free rates, with a lesser need for retreatment and auxiliary procedures (Vandeursen *et al* 1993). Biliary stones are often fragmented by ESWL or removed together with the gall bladder by means of laparoscopic cholecystectomy, but for retained common bile duct stones laser lithotripsy is a suitable method (Nishioka *et al* 1987, Ell *et al* 1993, Neuhaus *et al* 1994). Laser lithotripsy has also been successfully applied for fragmentation of salivary calculi (Sterenborg *et al* 1990, Zenk *et al* 1994).

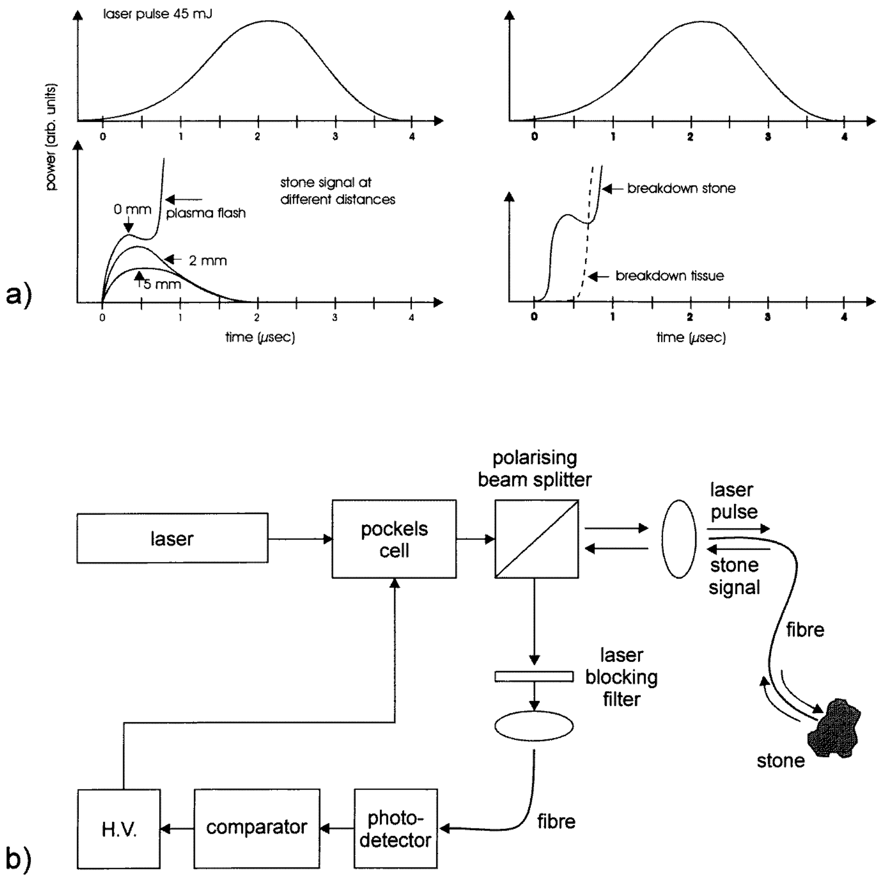

Figure 5. (*a*) Light signals re-emitted from the stone surface when the fibre tip is located at various distances from the stone (left), and comparison of the signals re-emitted from stone and tissue (right). One can define a threshold which is surpassed within the first 500 ns only if the fibre tip is directed at a stone and located at a distance of $\leqslant 2$ mm from the stone. (*b*) Set-up for stone/tissue discrimination and pulse interruption. If within 500 ns the intensity of the light collected by the fibre does not surpass the required threshold, the rest of the laser pulse is blocked out by means of the Pockels cell. After Engelhardt *et al* (1988) and Thomas *et al* (1988b).

3.3. Optimization strategies

One approach to minimize the risk of collateral tissue damage in laser lithotripsy is to look for a wavelength which is strongly absorbed by the stone and only weakly absorbed by tissue or blood. Wavelengths longer than 650 nm, i.e. with minimal blood absorption, are unfortunately also weakly absorbed by most stones (Thomas *et al* 1988a). Therefore a wavelength of 504 nm was chosen for lithotripsy by Watson *et al* (1987). Although blood absorption has a relative minimum at this wavelength, the absorption coefficient is still quite high. At energy values used for fragmentation, tissue damage can therefore not be avoided when the tissue is directly irradiated by the laser pulses (Thomas *et al* 1988b). A way out which avoids the need for endoscopic access is the real-time discrimination between stone and tissue at the fibre tip first described by Engelhardt *et al* (1988) and later followed by Rosen *et al* (1993). The method is outlined in figure 5. The fluorescence signal during the first part of the laser pulse before plasma formation is much stronger on a stone than on tissue, especially when the fibre tip is close to the stone. The laser emission is therefore stopped before plasma formation starts, if the fluorescence signal does not exceed a certain threshold. This way tissue damage is avoided even if the fibre tip is in direct contact with tissue. The technique has been successfully applied in clinical practice (Ell *et al* 1993, Neuhaus *et al* 1994). Other feedback techniques relying on differences of the acoustic signals or plasma spectra from stone and tissue (Bhatta *et al* 1989) have the disadvantage that they recognize tissue only after damage has already been produced by at least one laser pulse.

It would be desirable to replace the pulsed dye laser by a more compact and reliable solid state laser source with approximately 1 μs pulse duration. A good candidate for this is the alexandrite laser, because normal Q-switch pulses from this laser already have a duration of about 100 ns. The pulses can be stretched to up to several μs and formed to a rectangular shape by appropriate control of the Pockels cell voltage (Brinkmann *et al* 1990, Simmons and Koschmann 1992). The pulse stretching can easily be combined with the stone/tissue discrimination and feedback system described above.

The absorption of some hard stones is so low that fragmentation is virtually impossible when wavelengths in the visible and near-IR part of the spectrum are used (Bhatta and Dretler 1989). It has therefore been proposed to create absorption independent of the stone by adding an absorbing dye to the saline solution used for flushing of the application site during the surgical procedure (Reichel *et al* 1992, Cecchetti *et al* 1993, Rudhart 1995). Schafer *et al* (1994) suggested the use of holmium lasers emitting light at wavelengths near 2 μm where the absorption of water and cholesterol is high. Cholesterol is a chromophore contained in virtually all biliary stones, and the high water absorption supports plasma formation in the liquid between fibre tip and stone. The use of free-running holmium lasers with 350 μs pulse duration and 0.5–1 J pulse energy for the fragmentation of ureteric calculi has, however, led to significant damage to the ureter (Watson and Smith 1993, Sayer *et al* 1993). A real alternative to the dye laser would only be given by holmium laser pulses with a duration of approximately 1 μs. Such pulses could probably be produced by Q-switching and pulse forming by means of an FTIR modulator as described for an ErCr:YSSG laser by Könz *et al* (1993) and Högele *et al* (1996). Another approach to improve the energy deposition at the stone surface is the use of two wavelengths from a frequency-doubled alexandrite laser. At 375 nm the threshold for plasma formation is considerably lower than at the fundamental wavelength of 750 nm (Steiger and Geisel 1994). If both wavelengths are used simultaneously, the UV component starts the plasma formation, and the first harmonic provides the energy for further heating of the plasma.

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