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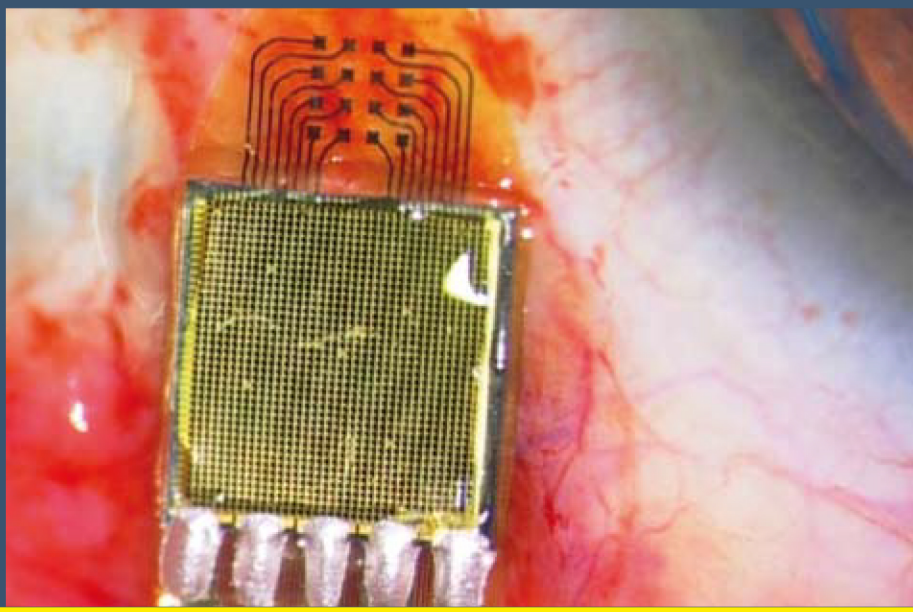
NEUE FOLGE, BAND 111, NUMMER 379

Intelligent Implants in Ophthalmology

Rudolf F. Guthoff, Klaus-Peter Schmitz,
and Eberhart Zrenner (Eds.)



Deutsche Akademie der Naturforscher Leopoldina –
Nationale Akademie der Wissenschaften, Halle (Saale) 2010
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NOVA ACTA LEOPOLDINA

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NEUE FOLGE NUMMER 379 BAND 111

Intelligent Implants in Ophthalmology

Leopoldina Symposium

Deutsche Akademie der Naturforscher Leopoldina

In cooperation with

Universität Rostock
Deutsche Ophthalmologische Gesellschaft
DFG-Sonderforschungsbereich Transregio 37
„Mikro- und Nanosysteme in der Medizin –
Rekonstruktion biologischer Funktionen“

April 23 to 25, 2009
Rostock/Warnemünde, Germany

Editors:

Rudolf F. Guthoff (Rostock)
Member of the Academy

Klaus-Peter Schmitz (Rostock)

Eberhart Zrenner (Tübingen)
Spokesperson and Vice-Senator of the Academy

With 106 Figures and 4 Tables

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Cover image:
Directly after explantation a first glimpse through the operating microscope reveals completely intact structures of the active subretinal implant: 16 direct stimulation electrodes at the top and the microphotodiode array with approximately 1600 diodes on the bottom are well preserved after 92 days within the subretinal space (see GEKELER et al. in this Volume p. 205).

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Contents

Accommodation – Young Eyes for Elderly People

The Retina Implant Project

Editorial

The Leopoldina Symposium "Intelligent Implants in Ophthalmology" was held in Rostock-Warnemünde April 23–25, 2009.

It was a collaborative effort together with the German Society of Ophthalmology (DOG), the German Research Foundation (DFG) SFB 37 'Micro- and Nanosystems in Medicine – Reconstruction of Biological Functions' and the University of Rostock.

The eye is the recipient organ for the majority of all medical implants worldwide. The continuing development of these implants presupposes high-quality interdisciplinary research, the current status and future prospects of which were outlined and discussed during the symposium.

The specialist technical content of the symposium was shaped by three novel developments at the interface between engineering science and medicine:

– *Glaucoma* and its risk factors, with particular emphasis on surgical management involving the use of micro-drainage systems. The controlled regulation of raised intraocular pressure is virtually inconceivable without employing these 'intelligent implants'. The wound healing processes that are a feature of conventional surgery often jeopardize success in the early postoperative phase.
– *Restoration of accommodation*. At least as far as the permanent restoration of the accommodative capability of the eye is concerned, the dream of eternal youth may perhaps turn into reality in years to come, especially since the results achieved with the accommodating intraocular lenses already in clinical use are still not entirely convincing. Rapid developments in the field of micro- and nanotechnology are likely to provide new solutions in the not-too-distant future.
– *The Retinal Implant Project*. The research team from Tuebingen has clearly achieved a breakthrough and this was demonstrated to a scientific audience for the first time at this symposium. – Electronic components implanted on or beneath the surface of the retina are now capable of transmitting electrical signals to the optic nerve, bypassing the photosensitive cells that no longer function in these patients, and thus of restoring rudimentary vision to individuals who had previously been completely blind.

The lively discussion generated between computer scientists, engineers and medical professionals showed that the anticipated new developments at this interface in the next few years may well be of fundamental importance for the field of ophthalmology as they open up novel therapeutic principles.

This volume should prove to be a valuable and stimulating resource for basic scientists of engineering disciplines, informatics as well as practicing surgically orientated ophthalmologists.

Rudolf F. GUTHOFF Klaus-Peter SCHMITZ Eberhart ZRENNER

Welcome Addresses

Nova Acta Leopoldina NF *111*, Nr. 379, 11–12 (2010)

Welcome Address

Udo Michallik (Schwerin)

State Secretary at the Ministry of Education, Science and Culture,
State of Mecklenburg-Vorpommern

Ladies and Gentlemen,

On behalf of the state government of Mecklenburg-Vorpommern, I am pleased to welcome you in Rostock-Warnemünde. I would like to thank the Leopoldina that they have chosen to organize their conference in Mecklenburg-Vorpommern, and I can assure you that Rostock, as the state's centre of excellence in science, is exactly the right venue to conduct scientific discussions on the latest advancements in clinical studies and improved methods of treatment and implants for eye diseases.

With this symposium, the Leopoldina sticks to its motto "To Explore Nature to the Benefit of the Human Being", which has been valid since its foundation in 1652. Health research is research for the human being and a major objective of public health care. Therefore, health research is widely promoted and financially supported by the federal and state governments. It is indeed a field where huge commitment and efforts are needed, because the expectations and hopes of affected patients and their families are extremely high due to the encouraging developments in clinical research.

Still, how should we handle scientific findings? In this respect, it is the main task of science and politics to carry a high degree of responsibility and weigh opportunities and risks. Therefore, the Leopoldina plays an outstanding role in this field and is widely acknowledged as Germany's exclusive institution in providing science-based advice to both politics and society. Moreover the Leopoldina is nothing less than the strategic link between science and other creative fields of our social development.

I highly appreciate the fact that Rostock has been chosen by the Leopoldina as the venue to discuss important issues on the status quo and perspectives of ophthalmology. In addition, the successful interdisciplinary approach in biomedical engineering is being recognized in a special way and the scientific achievements in research and education of the University Eye Hospital Rostock and the Institute for Biomedical Engineering Rostock are being brought to public attention. This will strengthen the visibility of our state and provides us with the opportunity to show our achievements and the challenges that lie ahead. For that, Professor Guthoff (University Eye Hospital Rostock) and Professor Schmitz (Institute for Biomedical Engineering, University of Rostock) deserve our sincere thanks and recognition.

Mecklenburg-Vorpommern supports the rapidly developing research and technology in implants. Consequently, we do not exclusively focus on ophthalmology, because implant

technology opens up a wide range of extremely promising perspectives: on the one hand for medical science, which desperately needs new therapeutic concepts for organ regeneration, and on the other hand for our state, which we continue to develop as a technology location in the field of life sciences.

In addition, the state's subsidy policy in the scientific sector is not only directed at achieving regional economic effects, but primarily focused on strengthening the excellence and nationwide attention of our assets in research. Some may think of this process as slow-moving, but in my mind we are on the right path.

Rostock is, for instance, a highly attractive city. In this connection, the academic environment and the research activities outside the university play a major part in improving the quality of life in this region. This includes efficient and cross-faculty research areas in medical science and biomedical engineering. With its visible and economically verifiable added value, the research fields contribute significantly to the development of our state, because they have had great success in acquiring public and non-public third-party funds and provide an excellent basis for the nationwide and international profile through their numerous scientific presentations at conferences and in publications.

And also the state makes its contribution in promoting scientific excellence. For instance, currently the state supports the extension of the University Hospital Rostock into an advanced and functional medical institution under the public development planning. Additional funds were granted for the new building and restoration of the University Hospital. Thus a building project for a state-of-the-art and sustainable hospital could be launched. As a result, Rostock will be able to provide most favourable conditions for research, education, and health care.

I wish the Leopoldina Symposium every success and may the results convince both the scientific community and the medical sector.

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Nova Acta Leopoldina NF *111*, Nr. 379, 13–14 (2010)

Welcome Address

Eberhart Zrenner ML (Tübingen)

Spokesperson and Vice-Senator of the German Academy of Sciences Leopoldina

Magnifizenz,
Colleagues and friends,

It is my pleasure to forward to you, in behalf of Leopoldina's president, Volker ter Meulen and its Executive Board, best wishes for a successful meeting on a topic that is of increasing importance for medicine, society and visually impaired individuals. As society grows older, the necessity to replace damaged body structures and to restore function increases rapidly. Good vision is one of the greatest gifts, and to lose vision or to become blind poses – for many of us – the greatest threat. Ophthalmological implants provide rudimentary help in a number of cases but the complete loss of retinal function cannot be remedied yet; however, novel experimental concepts have opened new ways for therapy also in this area. This meeting brings together outstanding, critical scholars, competent in clinical vision research, who will discuss novel approaches and help find solutions to yet unsolved problems.

All this is in the best tradition of Leopoldina, the oldest continuously existing society of academic scholars in the world, founded in 1652 by four physicians in Schweinfurt. Its aim was and still is (I quote in English) "to advance elucidation in the field of Health Sciences and the resulting benefit for our fellow citizens" and this is just what we will do in this Leopoldina Symposium today and tomorrow. The Leopoldina was international from its very beginning. Emperor Leopold I, "Kaiser des Heiligen Römischen Reiches Deutscher Nation" who gave the academy its name, had elevated the Academy in 1677 to the Imperial Academy and had awarded among others the privilege of "Freedom from censorship", a privilege most important for the blooming of science and for maintaining "independence and dignity" even during the darkest times of the two dictatorships that Germany had to endure. The Leopoldina maintained its independence from state and government even in the most difficult times and served as an important link to international science by recruiting members from all countries, even under great difficulties during the cold war. Following Germany's reunification, the Society has grown to include 1,300 members from more than 30 countries. It was therefore a logical consequence that the Leopoldina had to be chosen in 2008 by the "Gemeinsame Wissenschaftskonferenz von Bund und Ländern" to become the German Academy of Sciences that

– Advises policy makers and informs the public in scientific matters;
– Represents Germany in international Academy affairs;
– Fosters many young scientists through Leopoldina-sponsored programs and awards;
– Organizes and supports symposia.

The Executive Board of Leopoldina expresses its most cordial thanks to the team that has so excellently organized this particular meeting under the dedicated leadership of Rudolf Guthoff and Klaus-Peter Schmitz and has assembled a group of most distinguished speakers in a scientific program of great interest for all of us.

Rostock is a most suited place given the fact that the University recently founded an interdisciplinary faculty that encompasses science and technology of Life, Light and Matter as well as Ageing Science and Humanities and this interdisciplinarity reflects the best tradition of the Leopoldina.

Finally: The German Academy of Sciences Leopoldina extends to all participants a warm welcome and its best wishes for a most successful meeting!

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Greetings

Gottfried O. H. Naumann ML (Erlangen)

Past President of the International Council of Ophthalmology

It is my privilege to bring you greetings and best wishes from the International Federation of Ophthalmological Societies and my successor as President of the International Council of Ophthalmology, Bruce Spivey.

In today's global economic environment the needs for restoration of vision and blindness prevention have to compete with acute infectious and chronic diseases that cause high mortality. It is not sufficiently appreciated that visual impairments increase worldwide in a universally aging population. In spite of the spectacular advances in ophthalmology in the last 50 years in the industrialized countries, the "Global Initiative for the Elimination of Avoidable Blindness Vision 2020: The Right to Sight", illustrates that cost effective microsurgery is still a huge task for our profession to develop eye-care for people in many developing countries. It is hard to believe that here unoperated cataracts is still a leading cause of avoidable blindness – although standardized extracapsular cataract surgery can cure this problem, according to the World Bank, the most cost effective surgical procedure.

In the industrial world the leading causes of blindness are chronic diseases like hereditary retinal dystrophies and age-related neurodegenerative diseases such as glaucomas, macula degenerations, and diabetic retinopathy.

Based on the excellent tolerance of optical implants within the lens capsule after extracapsular cataract surgery your workshop is going to investigate the potential of other intelligent implants within the delicate structures of the eye. Since 1949 hundreds of millions of patients have enjoyed satisfactory rehabilitation after lens implantation performed by well-trained ophthalmic microsurgeons.

The lens capsule is a particularly suitable support for such implants, because it lacks vascular supply and innervation. One requirement for a successful artificial lens implantation is an intact zonular apparatus which keeps it in place and stable. And of course the microsurgeon needs to respect features of the eyes normal function such as the relatively increased tissue pressure, the blood ocular barriers, avascularity of cornea, anterior chamber and vitreous.

Intelligent implants in front or below the sensory retina are a more recent advance that is more demanding intraoperatively because of the close vicinity to vascular system of the choroid and the retinal vessels as well as the potential for proliferative responses of the retinal pigment epithelium. The horizontal and vertical "Leitstrukturen" of the sensory retina assure a mechanical stable positioning guaranteed by the basal membranes of Bruch and

the internal limiting membrane of the retina as well as the middle and outer retinal "membrane". Together with the Müller cells they form a three dimensional structure that guides the microsurgical manipulation. The complexity of such procedures needs to be appreciated by the basic researchers.

The risks of intraocular microsurgery both from anaesthesia and local effects must be kept in mind: With every microsurgical opening of the eye one cannot exclude with certainty very rare peculiar events such as expulsive choroidal hemorrhage, infectious endophthalmitis, and pupillary and ciliary block angle closure glaucomas, sympathetic uveitis, diffuse and cystic epithelial ingrowth, hemorrhage from vasoproliferative processes, toxic anterior segment syndrome (TASS), and intraoperative floppy iris syndrome (IFIS). All these special risks are extremely rare compared to the complications of surgery elsewhere. However, they should never be ignored if intraocular surgery is considered.

The program prepared by our colleagues GUTHOFF, SCHMITZ and all the participants in the program promises to give new insights into the field of intelligent implants with great potential. These studies are not only of academic interest, but shall also eventually be of practical value to the patients suffering from unnecessary blindness.

The task of the ophthalmologist is to prevent and treat visual loss. We must remember that 200 million people suffer from severe visual impairment and 35 million are blind.

This symposium may also stimulate a better awareness in the public about the significance of vision research and thus indirectly also help those that do not need these most exciting new innovations.

In the back of our mind we are conscious that priorities need to be respected in the practice of medicine as outlined by Paul KIRCHHOF, who distinguishes between emergency, necessity, comfort or the superfluous over-diagnosis and over-treatment.

We can expect an exciting symposium in the next two days demonstrating the enormous potential of miniaturization combined with neuro-biology. The choice of your topic illustrates again that ophthalmology continues to be on the cutting edge of bio-technology. It emphasizes again that visual research plays a significant role in pioneering contributions with significance to other areas in medicine.

I am convinced that your meeting will enjoy fruitful discussions that will lead to improvements of the lives of human beings suffering from impaired visual function.

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Nova Acta Leopoldina NF *111*, Nr. 379, 17–18 (2010)

Welcome Address

Peter Wiedemann ML (Leipzig)

President of the German Society of Ophthalmology

Dear Professor Guthoff,
Dear colleagues,

Thank for organizing this meeting on artificial implants in ophthalmology sponsored by the German Academy of Sciences Leopoldina together with the German Ophthalmological Society and the University of Rostock.

The eye is a small part of the body but of greatest importance for the quality of life. Due to highly successful cataract surgery worldwide most of all medical implants are placed in the eye. Other diseases such as glaucoma, characterized by loss of optic nerve fibers and degenerative retinal diseases will profit from implants in the future.

The development of these implants requires a high degree of interdisciplinary research and cooperation between clinicians, researchers, and industry. The current status and the development prospects of new implants for the diseased eye will be presented and discussed in this symposium. This meeting will help to foster the interdisciplinary collaboration in a fundamental area of ophthalmology and provide further synergies to secure lifelong good vision for our patients.

There are other reasons why this symposium is important: Excellent basic research in ophthalmology is not obvious due to great daily surgical clinical workload and success in our field. One learns recipes what to do and not to think about unsolved problems. Here we see that ophthalmological research is alive and produces results which can be used in clinical practice. Before we can construct an implant we need an idea what it should be. According to the *Fraunhofer-Gesellschaft* Munich one needs 1919 ideas to make 52 products accepted by the market, of which only eleven are actually successful in the real world. In plain English: to market a successful product, researchers need a hundred-fold in initial ideas. On the other side, failure does not mean necessarily that an idea is bad. There are enough ideas – they just need enough space and time in order to culminate in success. This should be possible by good cooperation between academic research and industry. At the end the aim of our cooperation is to inspire people and to give them a chance, to be successful.

The last remark I want to make with regard to cooperation between researchers and industry is a question. Who has today the authority to tell the truth when transporting information to the public? Whom do we believe as we cannot check all the advances in medi-

cal technology ourselves? Because we are overloaded by so many advertisements we need reliable carriers for accepted information. Here, Professor GUTHOFF, it was again a good choice that you have selected Leopoldina and DOG as sponsors of the meeting. These are credible and reliable opinion leaders in science and ophthalmology. They stand for competence, independence, and flexibility on new developments and expertise for special question.

We wish all participants of the symposium an intense and lively exchange with profitable discussions and talks.

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Nova Acta Leopoldina NF *111*, Nr. 379, 19–20 (2010)

Address

Wolfgang Schareck (Rostock)

Rector of the University of Rostock

Prof. Zrenner,
Prof. Guthoff,
Colleagues,

The University of Rostock is proud to host a Leopoldina symposium today, as we are all proud of Prof. Rudolf Guthoff who was elected as a member of this German National Academy of Sciences. The Leopoldina was founded in 1652 in Schweinfurt by four medical doctors who had travelled previously through Italy, where scientific academies were known since the early decades of the 17th seventeenth century. In 1682, during the reign of Leopold I, it became even an imperial academy. In those days, the University of Rostock had existed for more than 200 years, thus being the oldest university of the Baltic Sea Region – founded even before the universities of Greifswald, Copenhagen and Uppsala. Medicine as linking science was, along with the Faculty of Arts and the Faculty of Law, one of its foundation faculties.

In medicine, interdisciplinarity is commonplace. Cooperation with other disciplines was the four doctors' concern when they came back to Schweinfurt. The University of Rostock trusts in interdisciplinary networking to meet future challenges. For this purpose, three profile lines were established to interconnect the research within our nine faculties: Life, Light and Matter; Maritime Systems; and Aging Science and Humanities. The success achieved by our first profile line in recent national competitions encourages us to continue.

One hundred and seventy nine Nobel Prize laureates were also members of the Leopoldina, many of them long before they recieived the most prestigious award in the world in Stockholm. The University of Rostock has not produced that many Nobel Prize laureates, but we are very proud to have honored Albert Einstein in 1919. The *doctor honoris causa rostochiensis* awarded to him was the only one he ever got in Germany. And we are even prouder that this honour was not erased during the Nazi-dictatorship. Without a doubt, this was a merit of the University of Rostock at that dark time. Probably you are not aware of the fact that it was the Faculty of Medicine that initiated this tribute to Einstein.

Today I can only think of this as one early indicator of fruitful crossborder-thinking which took place at the University of Rostock some years ago. Interdisciplinarity is not only a slogan for us. As mentioned before, we are currently establishing real crossborder-

thinking with our interdisciplinary faculty. Scientists like Prof. Rudolf GUTHOFF are a guarantor and the living evidence of this successful path we intend to pursue. And it is not by accident that Mr. GUTHOFF is a member of the Leopoldina Society too.

So I wish your symposium good results and to all of you personally, all the best.

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Nova Acta Leopoldina NF *111*, Nr. 379, 21–23 (2010)

Welcome Address

Rainald VON GIZYCKI (Bad Nauheim)

Honorary President of Pro Retina Deutschland e. V.

Professor GUTHOFF,
Professor SCHMITZ,
Professor ZRENNER,
Ladies and Gentlemen,

I am very grateful for the invitation to speak to this Leopoldina audience since my doctoral thesis in 1974 dealt intensively with the foundation and development of the German Association for the Advancement of Science (*Gesellschaft Deutscher Naturforscher und Ärzte*) in the 19th century. This Association was founded in 1822 by the Leipzig philosopher ("Naturphilosoph") Lorenz OKEN after an attempt to reform the Leopoldina had failed a few years earlier. The scientific differentiation of this new Association into individual sections and subsections contributed significantly to the leading role of the German natural sciences. Indeed, most German scientific societies (including the DOG) have "split off" from these sections which became a starting point for "Privatdozenten" to establish new discipline-oriented university chairs and research institutes (see VON GIZYCKI 1979).

Pro Retina, since its foundation in 1977, represents the interests of patients affected by retinal degenerative diseases, in particular patients with Retinitis Pigmentosa and age-related macular degeneration, but also patients with rare retinal diseases like cone-rod degeneration, Choroideremia, or Usher Syndrome (see VON GIZYCKI et al. 2010). These are progressive, mostly incurable eye diseases, leading in most cases to blindness and reducing significantly the quality of life of patients and relatives.

Today Pro Retina has more than 6,000 members whose main motivations for membership are the search for a cure and the coping with the disease together with peers. We therefore are very grateful to all those clinicians and researchers, in particular to Professor ZRENNER, chairman of our scientific and medical advisory board, who fosters close cooperation with us and supports our goals.

In 1986 we jointly organized the Retina International Conference in Bad Nauheim under the following motto which is still valid today: "Researchers help patients – patients help researchers".

You, the researchers, have meanwhile helped us to detect the genetic causes of inherited retinal degenerations, to apply successfully gene therapy for patients with LCA (Leber's Congenital Amaurosis), to test growth factors and nutritional supplements in clinical

studies, and, last but not least, to develop Retina Implants up to their application to patients. It is estimated that worldwide about 200 to 300 retina patients have already received an implant on a long-term or short-term basis.

We, the patient organizations, have helped researchers and clinicians by providing access to probands for clinical trials, by public advocacy activities, by direct involvement in research projects, and in particular by funding and promoting research. We fund tutorships and colloquia for young researchers, the development of a front-edge DNA-"RetChip", the development of patient registries, purchase of laboratory equipment and our two annual RP- and AMD-research awards. In order to concentrate these activities and to make the public aware of our research needs and profile, Pro Retina established in 2007 the independent Pro Retina Foundation Fighting Blindness. And I am very happy and proud, as member of the Board of Trustees, to announce to you that our Foundation has decided a few days ago to establish two "Stiftungsprofessuren" (sponsored university chairs) in the area of retinal degenerative diseases.

Here again, it was due to our traditionally good cooperation with Professor ZRENNER that a second sponsor was found, enabling us to finance these two chairs for an initial period of five years after which the two host universities (Bonn and Regensburg) will take them over. With this decision our Foundation has clearly set the tone towards strengthening therapy-related research for inherited retinal diseases.

We also consider this effort to be an invitation to all stakeholders (clinicians, researchers, politicians, sponsors) to cooperate with us to achieve our mission, the prevention of blindness.

Ladies and Gentlemen, Pro Retina has an assembly of delegates representing its members; half a year ago I talked to a delegate colleague who is wearing a subretinal implant. He reported about the surgical intervention as well as the positive visual impressions and phosphenes he experienced during the experiments after the operation. My question, why he was participating and why he was still wearing the implant, was answered as follows:

– For him, this short revival of vision has been personally extremely gratifying, although it was of negligible practical value;
– He hopes that his participation will be useful for future generations of RP patients;
– By his participation he wants to support the continuation of research and development in the field of visual prostheses.

This pattern of motivation was also found in a study of more than 50 potential implant carriers in 2005 (VON GIZYCKI 2005).

I think it is very encouraging for clinicians to know that their work may produce such positive feedback from patients. Also, I am convinced that in the future "patient-pioneers" will continue to promote the application of retina research not only for themselves, but also for the benefit of their peers.

I am sure the Leopoldina Symposium will be a productive meeting and will make a substantial contribution to the success of future implant research.

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Welcome Lecture

Nova Acta Leopoldina NF *111*, Nr. 379, 27–30 (2010)

Medicine, Technology, and the Danger of Doctor's Dependencies

Klaus Bergdolt (Köln)

Abstract

We should all accept the new technical possibilities. They are a wonderful gift for many suffering people. But doctors should insist on their independence, on their liberty. Fund-raising will be more and more important in the future, but a total transparency is necessary to avoid any temptation. If the patient gets the impression that a certain surgeon or a certain hospital does not look, first of all, at his subjective, personal situation but at the income of the institution, he will lose his confidence and prefer another hospital.

Zusammenfassung

Wir alle sollten die neuen technischen Möglichkeiten annehmen. Sie sind ein wundervolles Geschenk für viele kranke Menschen. Die Ärzte jedoch sollten auf ihrer Unabhängigkeit und Freiheit bestehen. Die Einwerbung von Finanzmitteln wird in Zukunft mehr und mehr an Bedeutung gewinnen, aber eine vollständige Transparenz dabei ist erforderlich, um jede Art von Versuchung zu vermeiden. Gewinnt der Patient nämlich den Eindruck, dass ein bestimmter Chirurg oder eine bestimmte Klinik nicht zuallererst auf seine persönliche Situation achtet, sondern vielmehr auf die Einnahmen der Einrichtung, wird er das Vertrauen verlieren und eine andere Klinik vorziehen.

The technical progress in ophthalmology is overwhelming. Nobody who knows the desperation of visually impaired people will protest against innovations which could relieve their difficult situation. It would be a dubious as well as unjust presumption to speak of a *greed for technology* which ignores – to follow the arguments of those who criticize a "cold, technical medicine" – the real needs of the patients. An ethical problem, however, exists if an eye surgeon is ready to carry out operations which will not eliminate an illness or ailment but improve – more or less modestly – the quality of seeing in patients (or should one speak of *clients*?) with good visual faculties. Such surgical interventions represent services which improve vision in a way adequate glasses would also do. They are, to speak openly, useful for the optician as well as the eye doctor who can charge extra fees because such surgical corrections are – very rightly – not covered by the German health funds and insurances. The ethical conflict is intensified by the fact that most of these services involve (certainly few) risks for the health of the patients which not are at all compensated or legitimated by a (promised) better quality of life which is often sublimely suggested – especially by those who earn money carrying out these operations.

Apart from this financial seduction, that eye doctors can succumb to the technical progress of modern ophthalmology (and medicine in general) is one of the main reasons that surgical treatment has reached, in the beginning of the 21st century, its extremely high level in which ill people place all their hopes. Many eye diseases can be healed. In other cases – at least the complaints of the patients can be reduced. Helping suffering or desperate people by bold operations became a pillar of modern ophthalmology. But modern technology can also raise the quality of life. We all agree that glasses fitted with cataract lenses, heavy and rather ugly, are no longer reasonable to Western people. Even more: The refusal of new technologies would logically imply the refusal of most of the surgical innovations since Graefe's ingenious breakthroughs. Cataract operations with or without plastic implant? – ethically there are no problems, apart from the fact that the implanted lens is more comfortable because the patient can reject complicated spectacles which in the 1970s still replaced the refraction of the removed lenses. We do not discuss in this context the interesting fact that in some countries of the third world obviously the implantation of lenses is cheaper – and therefore the preferred method! – than the production and distribution of glasses!

Things are, however, a considerable problem when bio-engineering becomes, as it did during the last decades, financially pressured. Under the new constraint to raise money for research (which is an important precondition to climb up the ladder of the researcher's career!) the patient risks ceding his central position to economic calculations. As in the 1860s, when Claude Bernard declared the patient to be the *vestibule* of the "temple of medical science", whereas the laboratory was seen – in a bold imagery – as a kind of *inner sanctum* (the famous French physiologist had no doubts about that ranking!), today the patient risks, a second time, to be subordinated to interests of others. This time he is a victim of the economic paradigm. Once more he was degraded to a *means to an end* which is, for Kant, incompatible with human rights and human dignity. In both cases suffering people are no longer regarded as the focal point of the medical world but as economic or scientific quantities! To avoid this degradation it should be guaranteed that the surgeon – although this seems very difficult (and there exists a disquieting grey area!) – does not, in any way, benefit financially on the part of the producer. It should never be allowed to be rewarded by those who support financially one's study – neither as a private incoming nor (many researchers refuse to accept this!) in favor of the involved institute or the so-called "researcher group" beyond the actually running study! The dependence is one of the great dangers which threaten the liberty of our scientists. It is too tempting to play down the negative sides of a technical innovation if you can expect great recompenses from those who have developed, for instance, new surgical equipment you have to judge or write about. The danger is great as – at least for the German situation – Hans Weiss recently showed us in his book about the supposed *corrupted medicine* (*Korrupte Medizin*). The networks are immense, the interdependencies too. The problem applies to heart valves as well as to eye lenses. Even more, the heads of the innumerable scientific "studies" which are going on, including their collaborators, should not be informed – in the ideal case – about the economic intention and market strategies of the producers. Moreover, there should be, also for the public, an absolute transparency as to the relationship between the initiator of a study and the source of the money supporting the study.

This sounds very removed from the reality, even naïve. The problem is, indeed, that without a close cooperation between industry and universities (or other research institutes) the scientific progress would be in danger. The Western governments require and reward

such cooperation, euphemistically (sold as "joint ventures"), because the public sources of money are exhausted. "Private commitment" is, just in the field of science, a new magic word which silences nearly every doubt or objection. The conception is not new. We know from medical history: Even (and just) at those glorious times when Germany (about 1900) was the leading power in medical research – in the era of VIRCHOW, KOCH, BEHRING or EHRLICH – universities and industries did research work in close cooperation. The success was enormous, and the method was copied in many countries. However, this ethical problem is more threatening, more pressing than ever. In the times of bio-patents (a very delicate issue whose dangers have not at all been cleared up until to the present day!) a breathtaking bio-business exists, promising gigantic profits for employers and shareholders. The situation is no longer comparable with the one around 1900. It is more dangerous. In countries with a clearly utilitarian tradition, such as the UK or the United States, this way of making money has a long tradition going back to the beginning of the 20th century. The question is now – and the discussion goes on also in America! –, if manipulations of the human genome or the organization of organ banks are the right means to become rich for people who do not contribute their *know how* or competence, but their money. In other words: There are indeed great doubts if ill people are the right objects for the stock market.

To realize the economic implications we should insist on strict controls and probing questions in the ethical commissions which have been prescribed for all German medical faculties. In reality these commissions, as experience has shown, do not ask for every detail. Of course, the source of the funding must be declared. But in most cases the consequences remain undiscussed in detail. A prior control is not easy. The increasing pressure on the faculties and universities to raise external funds is seductive. There is the suspicion that those who have conceived the idea that researchers could organize external money to reduce the debts of their institutes or hospitals did not intend to produce a better medicine. They wanted, first of all, to close the huge financial gaps. For this aim they are paid. The governments were happy about the new chance to reduce the holes in the public finances. In meantime, nearly all German university hospitals have been transformed into (let us hope independent) companies whose executive and supervisory boards are judged by their economic success – and only by this. The (never proven) dogma that the economically successful clinic offers automatically top humane medicine on the basis of a top scientific level has become more and more accepted because it implies – in a seductive way – a simple solution to resolve the immense problems of our health system. This model consisting in raising money for hospitals not only by excellent treatment of patients (which should amplify the good image of the involved doctors and nurses), but also by external funds (whose origins are various), is really alarming because it programs a lasting dependence and demands among physicians and surgeons talents and skills which are not those which define the good doctor or surgeon. On the contrary!

One may be induced to say that the expensive high-tech medicine remains absolutely uncontested if the patient wishes explicitly the treatment with such ultra modern equipment – also if economic interests which he cannot overlook are the real motivating forces favoring this kind of operation and not another one that the treating doctor does not mention. Ethically this is unacceptable because the concept of the *informed consent* has been violated. The patient must also know if he is object of a study which promises a lot of money to those who have initiated it. Furthermore, he must be informed about all the dependencies of his doctors. Another problem is, however, the question whether the patient's

decisions and wishes were expressed truly autonomously and how far he is sometimes really able (also intellectually) to assess the pro and con. This question should also be put before more harmless interventions. Should his decision to be ascribed to the pressure put on him by his family, by the social environment, by the media, suggesting – to return to ophthalmology – that one has to be as beautiful, as young, as sporty as possible, without glasses of course? Is he, in this case, open to the information that a correction of the cornea also implies some risks and side effects?

But just at this point of the discussion we should ask ourselves if there is not anything like a voluntary self-restriction? Many people fear – and we must wonder if they are right! – a "mystification" of new technologies in the context of the delusional idea that everything is feasible. This ideal needs a simple, purely technically interpretable concept of man. When DESCARTES, in the 17th century, applied the concept of the *machine* to biological entities as the human organism, he was convinced that the body as *res extensa* is ensouled (and awakened to life) by the *res cogitans* which we call soul. Such a phenomenon, which distinguished men from animals, is not popular in the current science communities. But reducing the patient's dignity to a certain quantity within a pure economic calculation is not better than degrading him to a purely scientific object as Claude BERNARD did. Of course we can say that everybody has to decide for himself. In a modern society autonomy is an ethical and political key word, even a magic term. But if we give up the suffering man who needs our help and trusts in our competence as the deciding factor in the medical system, all science risks becoming a money-orientated profession. This argumentation does not at all mean a hard criticism of technical progress in medicine. On the contrary! But all who are involved should see the danger that they become themselves – as doctors! – more and more like little economic quantities or pieces who work within an opaque and incalculable system, at the risk and mercy of others who represent another world and think in a different way. It must not be mentioned that such an existence would not be at all compatible with the tradition of medical ethics, which began with the oath of HIPPOCRATES.

We should all accept the new technical possibilities. They are a wonderful gift for many suffering people. But doctors should insist on their independence, on their liberty. Fundraising will be more and more important in the future, but a total transparency is necessary to avoid any temptation. If the patient gets the impression that a certain surgeon or a certain hospital does not look, first of all, at his subjective, personal situation but at the income of the institution, he will lose his confidence and prefer another hospital. By the way, the media will increasingly not hesitate to write about these intertwinements. High-tech medicine is a wonderful chance if its financing remains transparent and accountable.

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Glaucoma and Intraocular Pressure – from Goldmann to Telemedicine

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The Role of Intraocular Pressure in Primary Open Angle Glaucoma

Franz Grehn (Würzburg)

With 5 Figures

Abstract

The various forms of glaucoma are still some of the most frequent causes of avoidable blindness in the world. Among the risk factors that lead to the development and progression of glaucoma, intraocular pressure is the only risk factor that can be influenced by therapy. As glaucoma results from the irreversible degeneration of axons of retinal ganglion cells, the screening for glaucoma, the strict application of therapeutic measures, as well as a thorough follow up are crucial to avoid blindness. Several large multicenter studies showed that glaucoma can be halted or slowed by sufficient pressure lowering therapy if diagnosed in an early stage.

Zusammenfassung

Das Glaukom stellt nach wie vor eine der häufigsten Ursachen vermeidbarer Erblindung dar. Unter den nachgewiesenen Risikofaktoren ist der erhöhte Augeninnendruck der einzige Faktor, der therapeutisch beeinflusst werden kann. Da es sich um eine irreversible Degeneration von Axonen retinaler Ganglienzellen handelt, sind die Vorsorgeuntersuchung zur Erkennung des Glaukoms, die konsequente Therapie sowie eine lückenlose Nachkontrolle von besonderer Bedeutung. Große Studien haben gezeigt, dass mit ausreichender Therapie der Verlauf des Glaukoms sehr stark verlangsamt werden kann und dass Erblindung nicht eintritt, wenn das Glaukom rechtzeitig diagnostiziert und konsequent behandelt wird.

By definition, primary open angle glaucoma is a chronic progressive optic neuropathy which shows a typical excavation of the optic disc. Glaucoma leads to, when not treated, progressive paracentral visual field defects eventually resulting in blindness. According to the optic nerve properties, these defects are irreversible because regeneration of neurons in the optic nerve does not occur. This is due to the complex topographic connections of retinal neurons with the cerebral visual centers. As far as we know, regeneration is efficiently suppressed in optic nerves of higher mammals and primates.

Increased intraocular pressure is the main risk factor for the development and the progression of glaucomatous optic nerve damage. The intraocular pressure results from the equilibrium between aqueous humor production and aqueous humor outflow. The aqueous humor is produced by the two-layered epithelium of the ciliary body at a constant flow rate of approximately 2.4 µl/min. This volume flows through the pupil into the anterior chamber and then exits the eye via the trabecular meshwork, Schlemm's canal, the collector channels, and the intra- and episcleral vein system. The intraocular pressure is determined by the resistance in the trabecular meshwork which adapts to flow rate changes

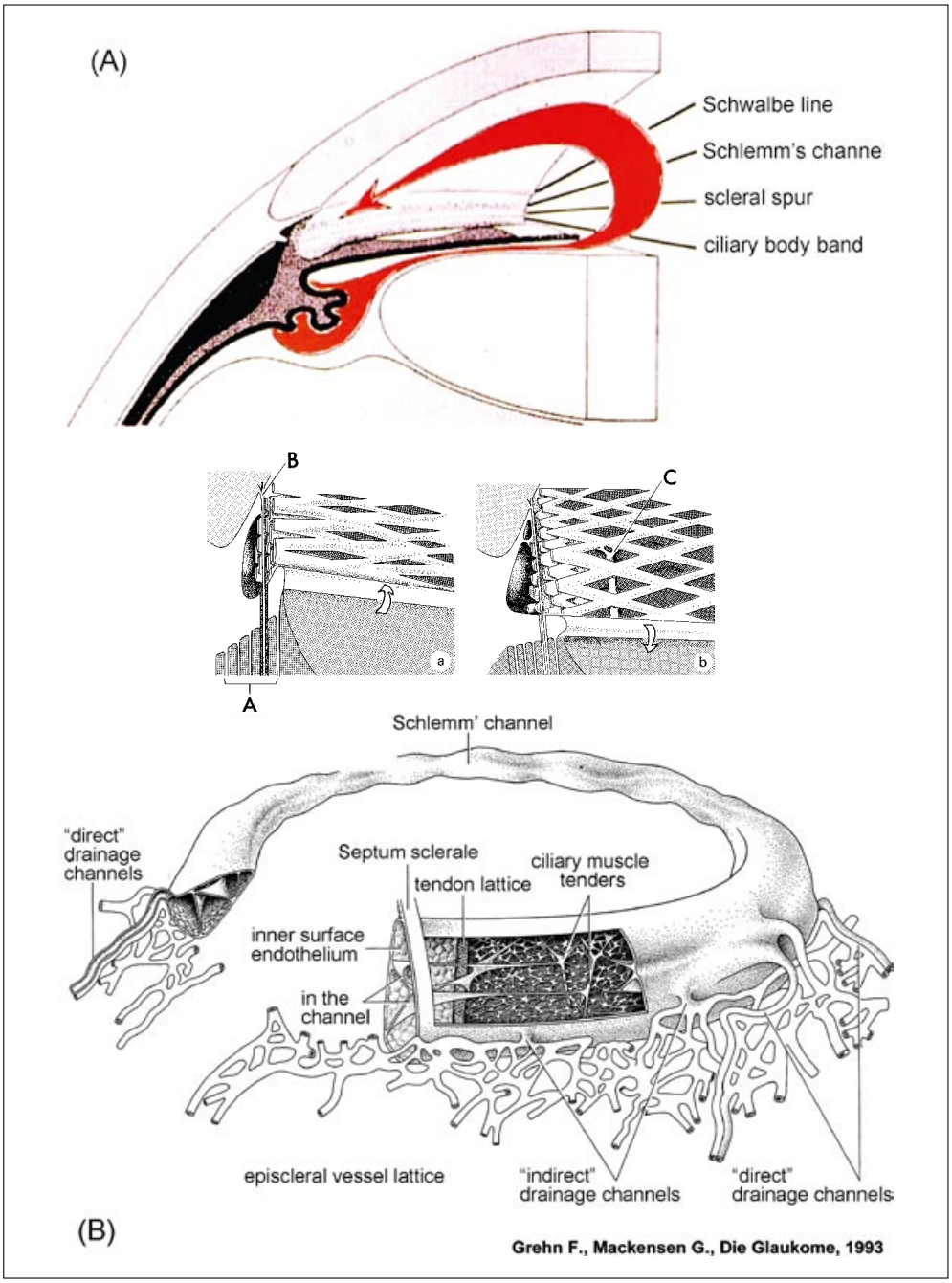


Fig. 1 Schematic representation of aqueous humor flow through the posterior chamber into the anterior chamber (*A*) and through the trabecular meshwork (*B*) into Schlemm's canal. Upper left: depending on the state on contraction of the ciliary muscle, the trabecular meshwork is unfolded or collapsed. (From Grehn and Mackensen 1993)

in healthy eyes (Fig. 1). In glaucoma, however, the increase of outflow resistance within the trabecular meshwork results in an increase of intraocular pressure while the production of aqueous humor is constant and pressure-independent. However, a close correlation between intraocular pressure level and the degree of damage does not exist. The frequency distribution of intraocular pressures in glaucomatous eyes overlaps considerably with the frequency distribution of intraocular pressures in healthy persons. Therefore, the level of intraocular pressure does not allow to distinguish between glaucoma or non-glaucoma. Hence, the modern definition of glaucoma relates only to the damage seen at the optic nerve head and the corresponding visual field defects. The term "ocular hypertension" that describes elevated intraocular pressures without damage of the optic nerve and the term "normal pressure glaucoma" that describes glaucomatous damage at statistically normal intraocular pressures are both misleading as they are not describing separate disease entities (Fig. 2).

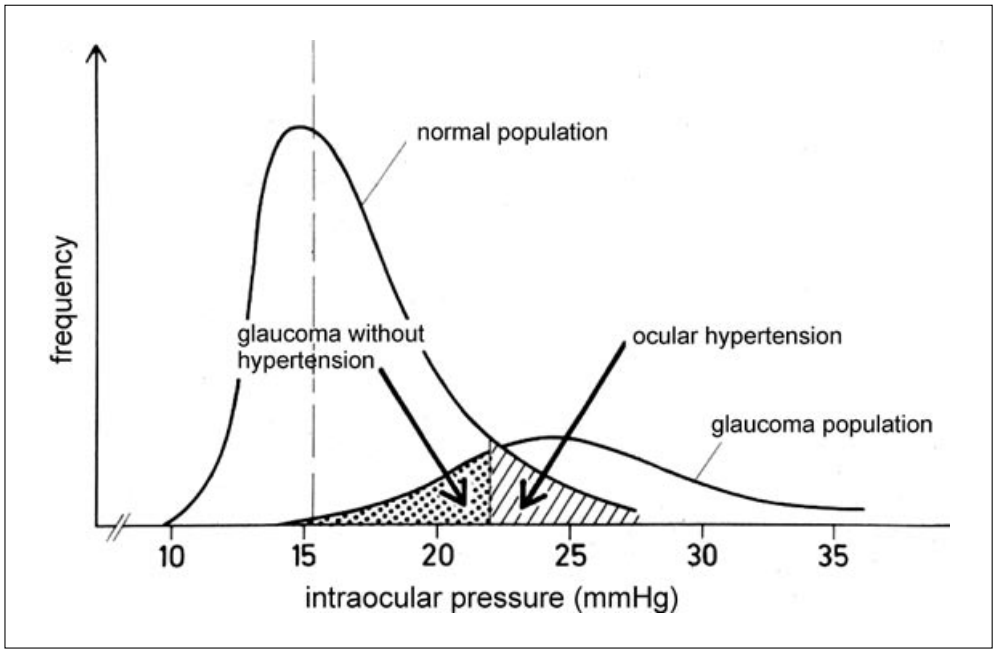


Fig. 2 Frequency distribution of intraocular pressures in the normal population and in the glaucoma population. "Ocular hypertension" is defined as values above 21 mmHg of the normal population. Normal tension glaucoma (*Glaukom ohne Hochdruck*) is defined as patients with glaucoma damage but intraocular pressures below 21 mmHg. Schematic drawing with logarithmic ordinate. (From Grehn and Mackensen 1993)

The mechanical factors that lead to excavation of the optic disc with damage to the axons of the retinal ganglion cells are not completely understood. In the very long axons of the retinal ganglion cells which form the optic nerve, the axoplasmic organelles are transported in both directions. Hence, the transition zone between the intraocular high pressure compartment and the extraocular low pressure compartment is the critical area that may block the axoplasmic flow and interrupt nutritional signals to the ganglian cell soma if the intraocular pressure is elevated. Various theories blame mechanical factors such as kinking

of the axons, steep pressure gradient in the lamina cribrosa from the intraocular to the extraocular compartments, weak collagen structure of the eye wall, or vascular factors such as capillary blood flow impairment. However, there is not one single mechanism that can be clearly shown to be responsible for the damage (Fig. 3). However, if we look at secondary glaucomas where the intraocular pressure is very high and other predisposing factors are absent it becomes clear the elevated intraocular pressure by itself can cause typical and severe glaucomatous damage of the optic disk and the visual field. It is therefore generally accepted that the intraocular pressure should be decreased in cases of glaucoma by various approaches (topical medication, laser, surgery). Recent studies have clearly shown that a therapeutic decrease of intraocular pressure can reduce the risk of developing glaucoma or decrease the rate of progression in established disease. Other risk factors such as age, corneal thickness and genetic factors cannot be influenced. The large therapeutic clinical studies that now prove that the incidence of glaucoma can be reduced by half when the intraocular pressure is sufficiently lowered are the Ocular Hypertension Treatment Study (Kass et al. 2002), and the European Glaucoma Prevention Study (Miglior et al. 2005). Similarly, it was proven that the therapeutic reduction of intraocular pressure can slow down the progression of glaucoma damage compared to a non-treated control group in the Early Manifest Glaucoma Treatment Study (Heijl et al. 2009), Advanced Glaucoma Intervention Study (*AGIS Investigators* 2000 a, b), and Collaborative Normal Tension Glaucoma Study (Drance et al. 2001). The benefit of lowering intraocular pressure is also demonstrated in glaucomas with statistically normal intraocular pressure (Normal Tension Glaucoma; 10–21 mmHg).

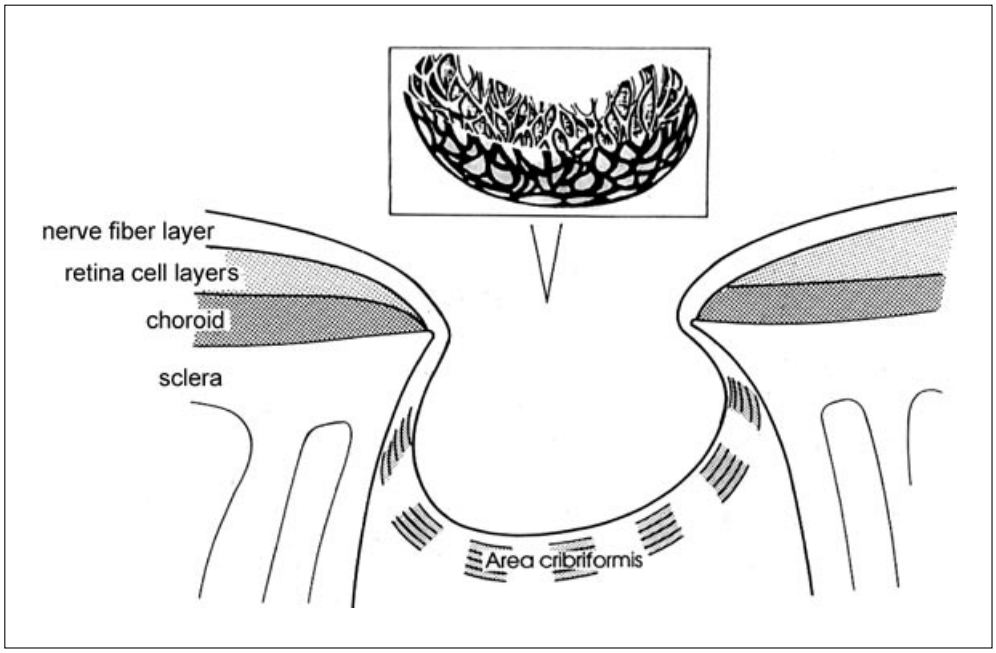


Fig. 3 Schematic drawing of the changes of the lamina cribrosa where the axons of the retinal ganglion cells (nerve fibers) are damaged in glaucoma. (From Grehn and Mackensen 1993)

The therapeutic strategy, however, should not only aim at a pre-defined intraocular pressure (target pressure), but should include a meticulous follow up of functional parameters and morphologic parameters. With this concept in mind, glaucoma care needs to verify that the pre-defined target pressure will in fact prevent progression of glaucomatous damage. This proof is difficult to provide within a short time period. Therefore, a two step approach is recommended: (*i*) Defining a target pressure for the individual patient according to the large clinical studies and according to the individual risk factors of the patient. (*ii*) Follow up of the visual field with multiple measurements until statistical significance of visual field trend is reached.

The target pressure can be defined according to guidelines of the European Glaucoma Society. In these guidelines the intraocular pressure should be lowered by 20, 30, or 40% with an upper cut off limit of 21, 18 or 16 mmHg both depending on the amount of damage present when therapy is started (*European Glaucoma Society* 2003) (Fig. 4). A previous pilot study demonstrated a correlation between visual field preservation and the EGS target pressure definition (Funk und Frank 1996). For assessment of the prognosis of an individual case it is important to know whether the optic nerve damage occurred at a high

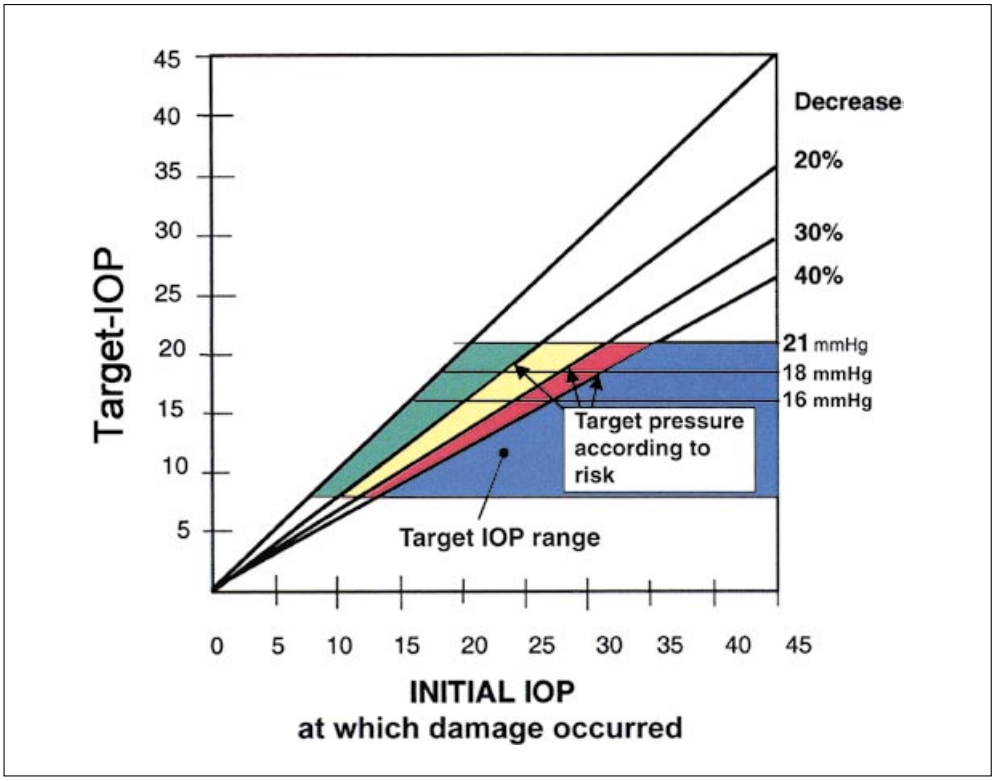


Fig. 4 Definition of target pressure according to the criteria of the European Glaucoma Society: X-axis: Initial IOP at which damage occurred; Y-axis: Target IOP. Depending on the degree of damage and the presence of risk factors, the range of target pressure is bordered by a varying percentage of pressure decrease and a varying upper cut off line. (Copyright: European Glaucoma Society)

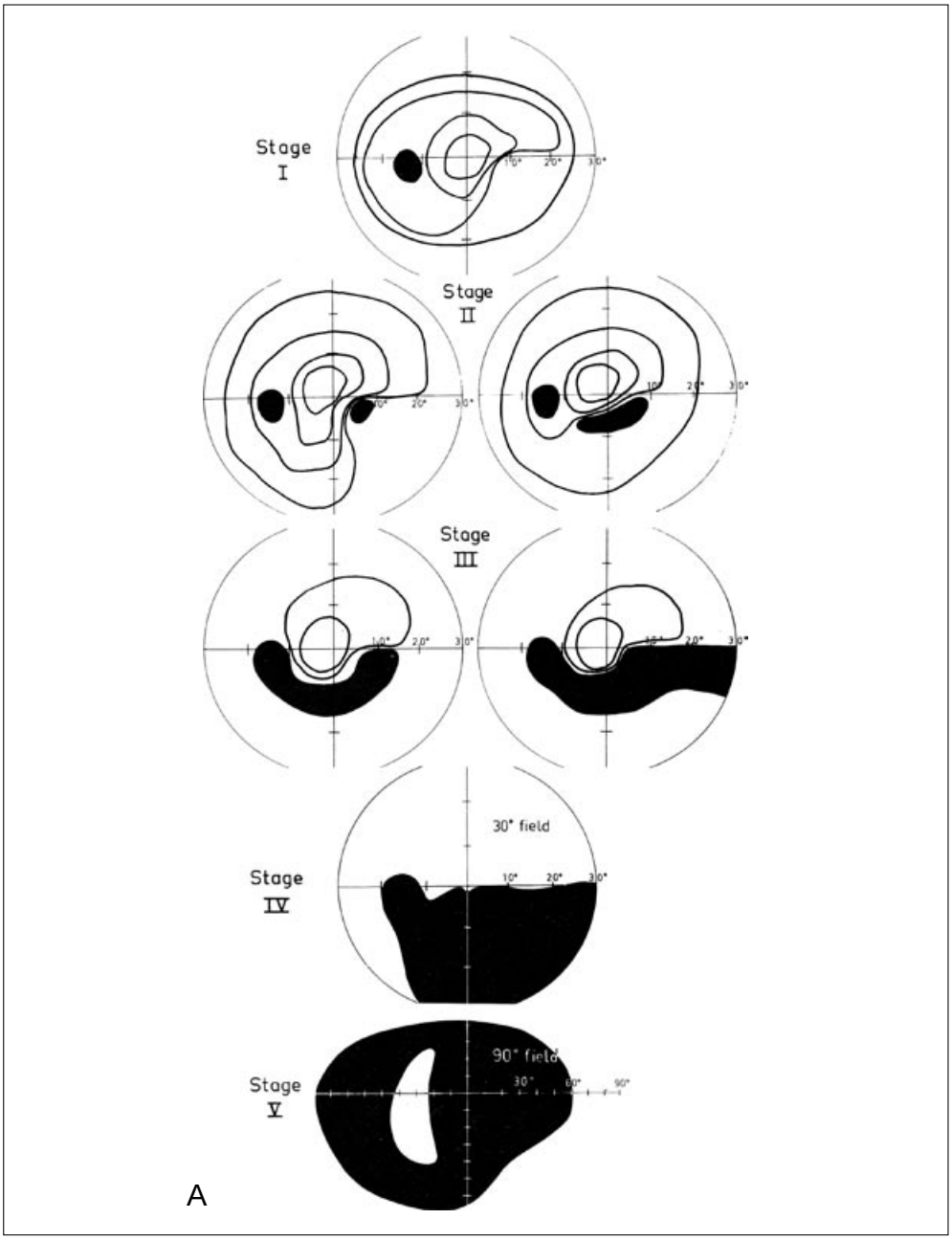
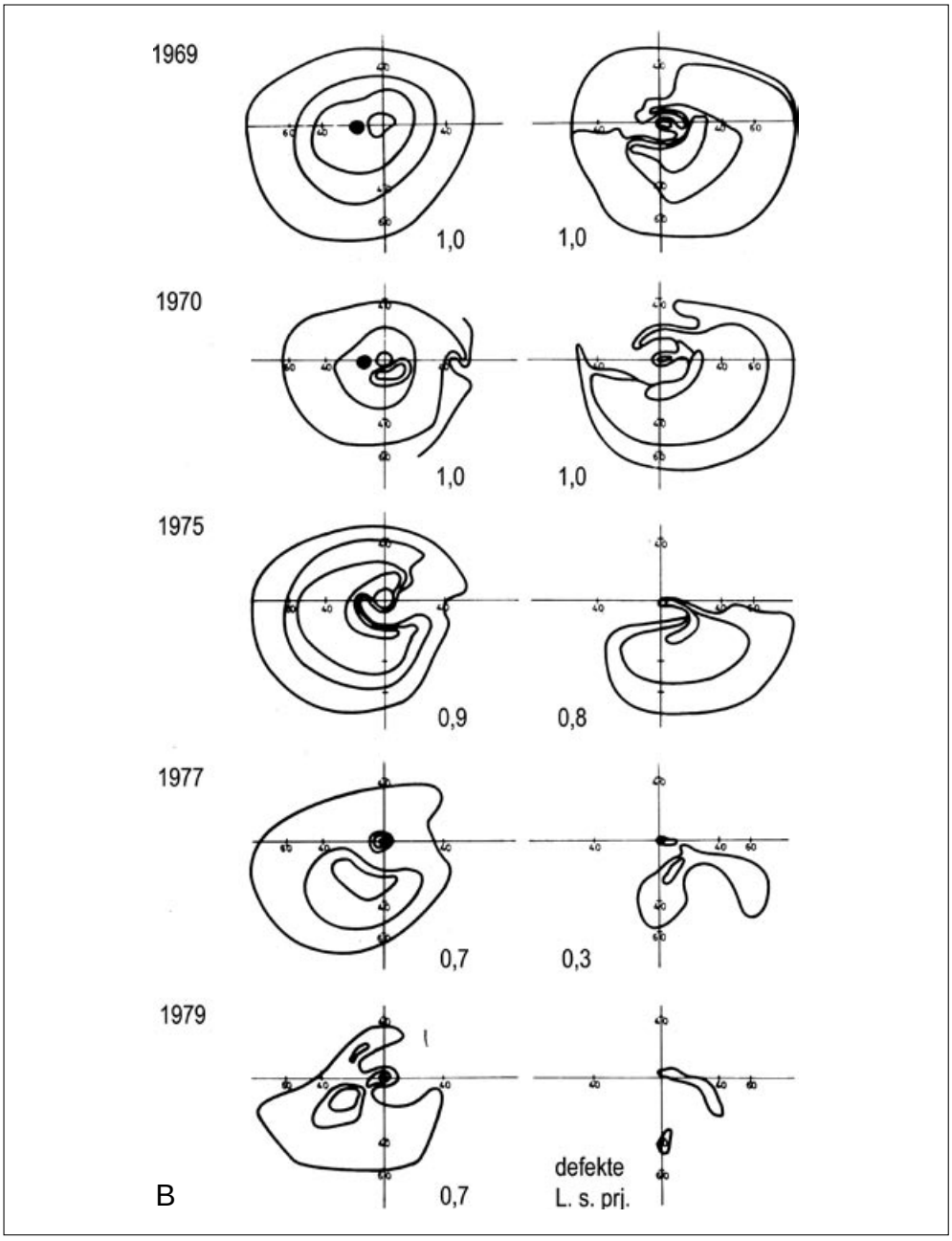


Fig. 5 Visual field stages according to AULHORN (*A*). Follow up of progressing visual field damage in an individual patient (*B*). (From GREHN and MACKENSEN 1993)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or at a low intraocular pressure, whether optic nerve damage and visual field damage are moderate or advanced, and how long the individual life expectancy of the patient is. Consequently, younger patients with relatively moderate visual field damage (< 50 years) are nevertheless at higher risk to advance to blindness than very old patients with a more advanced visual field damage in one eye but a shorter period to live.

Beyond this general approach of intraocular pressure reduction, the individual situation of the patient plays a major role in planning and conducting therapy. A major issue is compliance, as many patients are not able to administer eye drops correctly and do not comply with the follow up visits.

In general, the individual course of the visual field of a patient is the basis on which to establish a therapeutic plan, be it medical or surgical (Fig. 5). Today, the trend analysis of visual field damage by regression analysis of several visual fields using a modern automated threshold perimeter is mandatory. Six to nine visual fields obtained in 2–3 years can give sufficient statistical significance to rule out biological scatter and variation in performance.

The concept of target pressure with a long term analysis of functional parameters as well as morphological measurements of the optic disc will allow the establishment of therapeutic concepts that can slow or hold the progression of glaucoma and can avoid blindness in most patients. Nevertheless, early diagnosis of undetected cases has to be improved all over the world. As of now, glaucoma is still the second-leading cause of eye diseases with avoidable blindness.

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Telemetric Intraocular Pressure Measurements – from Bench to Bedside

Bernhard Heck (Hennigsdorf)

With 9 Figures

Abstract

Patient monitoring providing remote access to the actual data using telemetric recording systems is getting more and more important. Highly reliable sensors that measure the vital parameters and transmit them to the outer world are of essential importance. One of the most widespread causes of blindness is glaucoma. Glaucoma is often associated with elevated pressure inside the eye (intraocular pressure, IOP). The mainstay of glaucoma treatment is to reduce intraocular pressure by medication or implants. At present, continuous measurement of IOP is difficult, and patients typically have periodic IOP measurements every 6 to 12 weeks. It would be highly appreciated to continuously monitor the short and long term efficiency of treatments aimed to reduce the intraocular pressure. Also a pressure deviation from target value may be used as a trigger for the intake of a drug. The following paper describes the physical properties of a pressure sensing device which can be implanted as part of an intraocular lens in cataract patients. Using modern transponder technology, the system will provide information on short and long term behavior of the intraocular pressure. As it will be a permanent implant in the human eye, particular focus is placed on the biocompatibility and influences of the coating.

Zusammenfassung

Telemetrisches Patientenmonitoring mittels Implantaten gewinnt in der Medizintechnik zunehmend an Bedeutung. Funktionell geht es hierbei um die sensorische Erfassung von Vitalparametern im Körperinneren sowie deren Übertragung an die Außenwelt mit modernster Transpondertechnologie. Eine der häufigsten Ursachen für die Erblindung ist die Erkrankung an Glaukom. Diese Erkrankung geht oft einher mit einer Zunahme des Augeninnendrucks. Als eine wichtige therapeutische Maßnahme gilt das Absenken des Augeninnendrucks und die möglichst kontinuierliche Überwachung desselben. Bisher sind kaum kontinuierliche Messungen des Augeninnendrucks möglich, und bei erkrankten Patienten erfolgen die Druckmessungen meist in Intervallen von 6 bis 12 Wochen, die aus unterschiedlichen Gründen starken Schwankungen unterliegen. Um objektive Informationen über die pathologische Drucksituation beim einzelnen Patienten zu erhalten, müsste eine kontinuierliche Druckmessung über eine längere Zeit durchgeführt werden, auf deren Messdaten dann eine geeignete Therapie eingeleitet wird. Zu diesem Zweck wird auf Basis früherer Erkenntnisse ein Messsystem entwickelt, das eine kontinuierliche Messung, Auswertung und Speicherung des intraokularen Drucks erlaubt. Ein Interface zu telemedizinischen Anwendungen ist vorgesehen. Mit diesem Implantat wird es möglich sein, Kataraktpatienten mit einer regulären intraokularen Linse zu versorgen und gleichzeitig eine kontinuierliche Druckmessung durchzuführen. Damit steht zukünftig ein Implantat zur Verfügung, das kurativ und gleichzeitig diagnostisch wirkt. Eine Variante, die ausschließlich zur Druckmessung dient, kann einfach abgeleitet werden.

1. Electronic and Physical Aspects of the Design

The basic principle of this system is to incorporate electrically active elements into an ophthalmic implant. These active elements will measure the intraocular pressure (IOP) and transmit the results using modern transponder technology. The basic principle is shown in Figure 1. A transmitter coil located outside the eye supplies by high frequency electrical energy to the receiver coil of the device. This energy is used to feed the electronic components of the device. The communication between the external control unit and the microchip system of the implant can now be established. The device will measure the IOP and transmit the data to the reader unit. Once data transfer has been completed, the reader and control unit will be removed to interrupt the energy supply. The electronics of the device will switch off and turn to a powerless standby mode. The reader and control unit is able to save the pressure data, which can be used for remote patient monitoring.

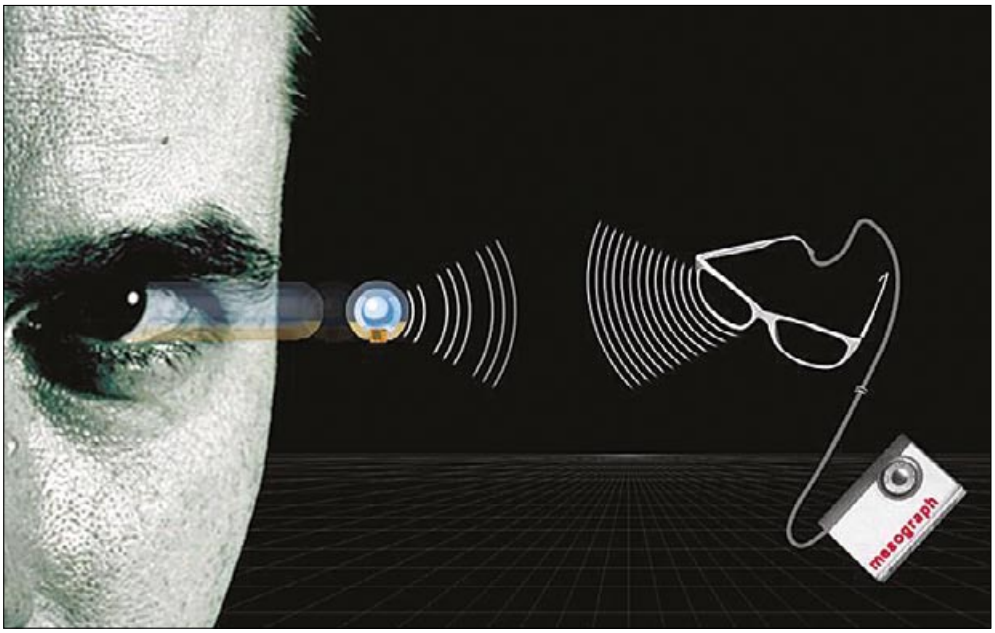

Fig. 1 Basic principle using a transponder technology

Figure 2 shows an example embodiment of the transponder. The implant is encapsulated within a biocompatible material. The lens to replace the cataractous lens of the patient is located in the center of the device, and a circular coil surrounds the device. The upper part of the device shows the backside of the electronics with the contacts. To illustrate the complexity of the connections, Figure 3 shows that part of the implant where electronics and gold coil are connected with each other. This part is exposed to considerable stress during surgical manipulation. Therefore, central focus needs to be placed on sufficient stability and stress resistance of the device.

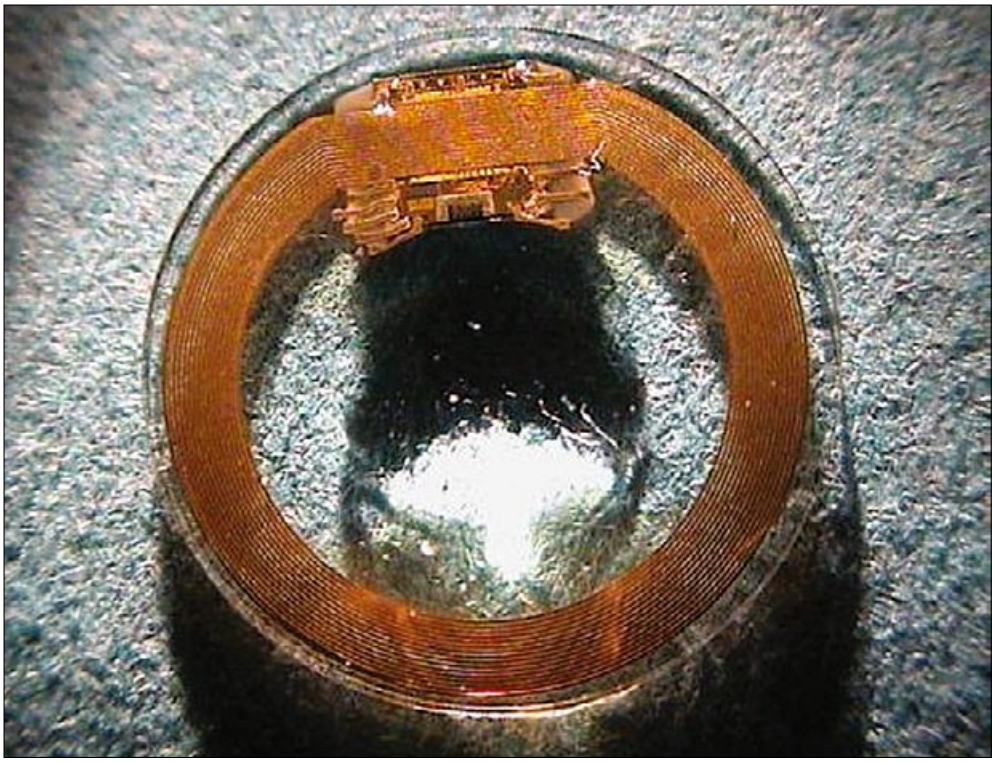

Fig. 2 Embodiment of the transponder

1.1 Chip-Coil System

The application-specific integrated circuit (ASIC) (which has been specifically designed for this purpose), the miniature pressure sensor, and the coil are the key elements of the electronic system of the device. Two competing systems were constructed and analyzed in the process of further development. The main difference is the single-/two-component design of the ASIC and the pressure sensor. A space saving design of the electronics is desirable to leave sufficient space in the center of the device so that the diameter of the lens optic which is necessary for cataract patients can be at least 5 mm. At this point, the monolithic structure of ASIC and pressure sensor (2.7 mm × 4.5 mm) clearly falls behind the separate construction of ASIC (2.7 mm × 2.7 mm) and pressure sensor (1.7 mm × 1.7 mm), allowing for more flexible design options. However, both systems use a similar coil.

1.2 The Pressure Sensors

The operating principles of the integrated pressure sensors are shown in Figure 4. The first option utilizes the effect that the capacity of a condenser changes with pressure, whereas the second option utilizes the changes in electric resistance. These two operating principles require individual compensation to eliminate undesirable effects such as changes in ambient temperature or differences in the energy consumption of the coil due to a change in the

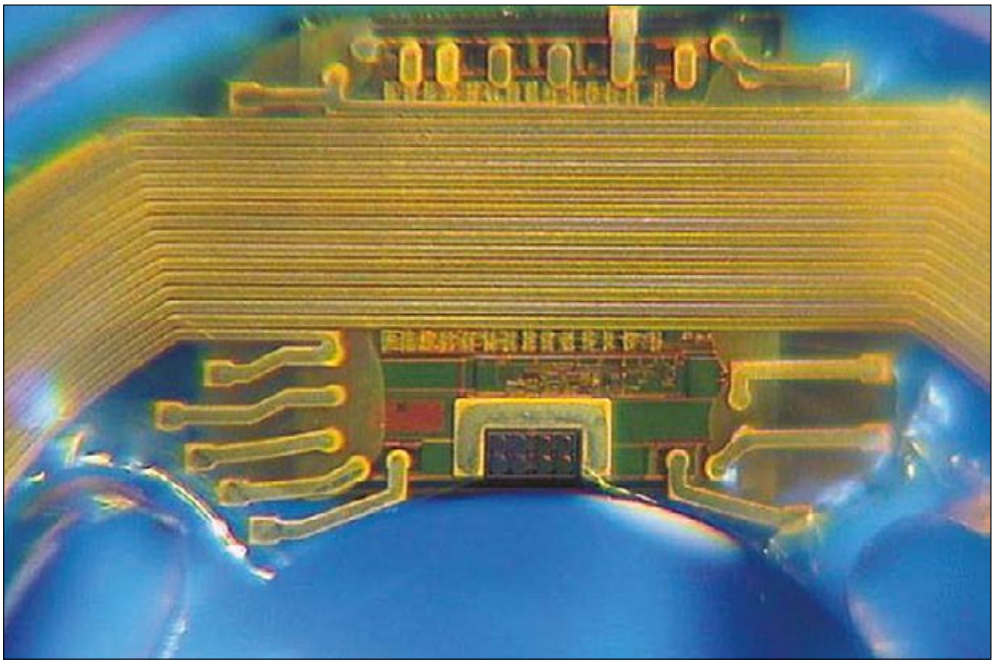

Fig. 3 Electronic connections of the chip-coil system

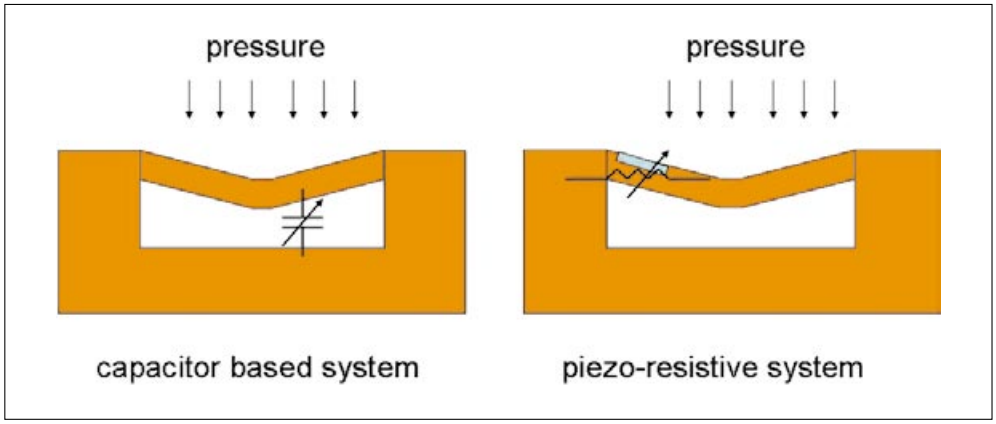

Fig. 4 Operating principles of pressure measurements

distance to the transmitter. The extremely small design of the electronic parts has led to development of new approaches to joining techniques. As a result of constant development, two prototypes are now available. Their functional performance was examined in detail.

The two systems are shown in Figure 5. The system on the left uses a capacitor based pressure sensor which is connected with the ASIC to form a 2.7 mm × 4.5 mm monolithic structure. The system on the right uses a piezo-resistive pressure sensor that is separate from the ASIC.

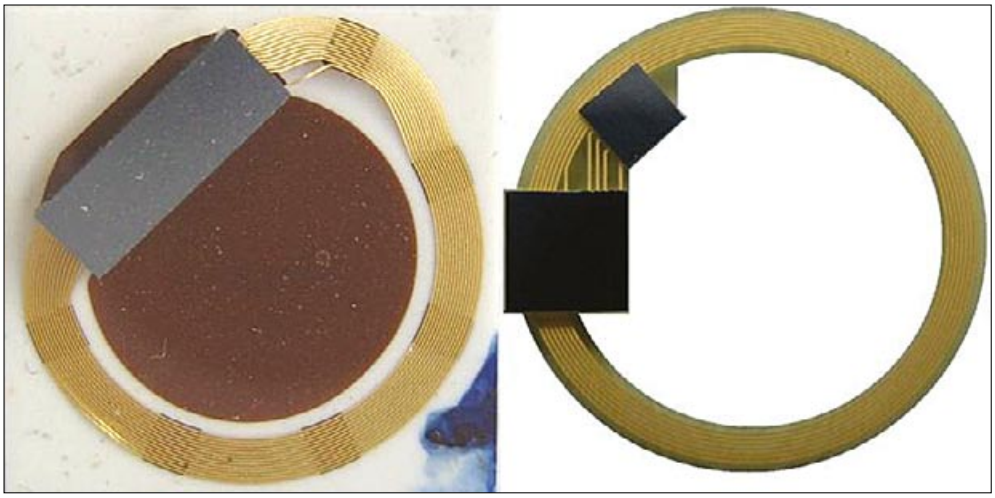

Fig. 5 Pressure sensors (left capacitor based, right piezo-resistive based)

1.3 Reproducibility and Accuracy of Pressure Measurement

Reproducibility is an essential requirement for systems that are designed to provide continuous measurements. Several series of measurements were carried out to compare the two systems. The pressure was increased from 900 mbar to 1150 mbar and then decreased to 900 mbar to detect possible hysteresis effects and to investigate the variations among simi-

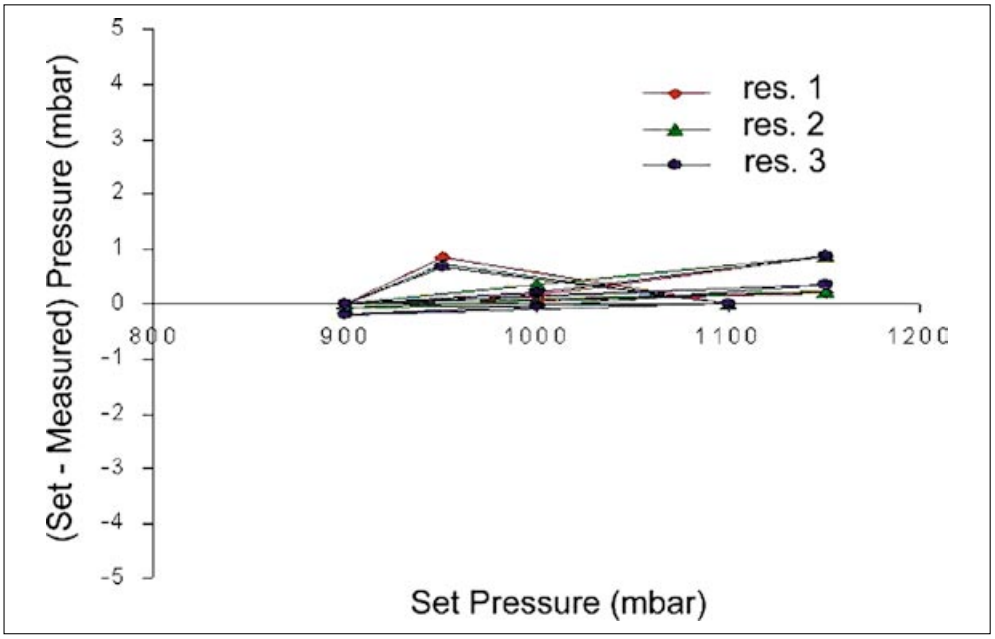

Fig. 6 Difference of set pressure minus measured pressure for capacitor based system

lar systems. Figure 6 shows the results for systems with piezo-resistive sensors. Figure 7 shows the results obtained with systems using capacitor based sensors. For systems with piezo-resistive sensors, the deviations between the fit and the measured pressure are less than 1 mbar, which fully satisfies the required accuracy, whereas with 2 mbar, the deviations found in systems with capacitor based sensors were much higher, and in one system there was no reproducibility in the results.

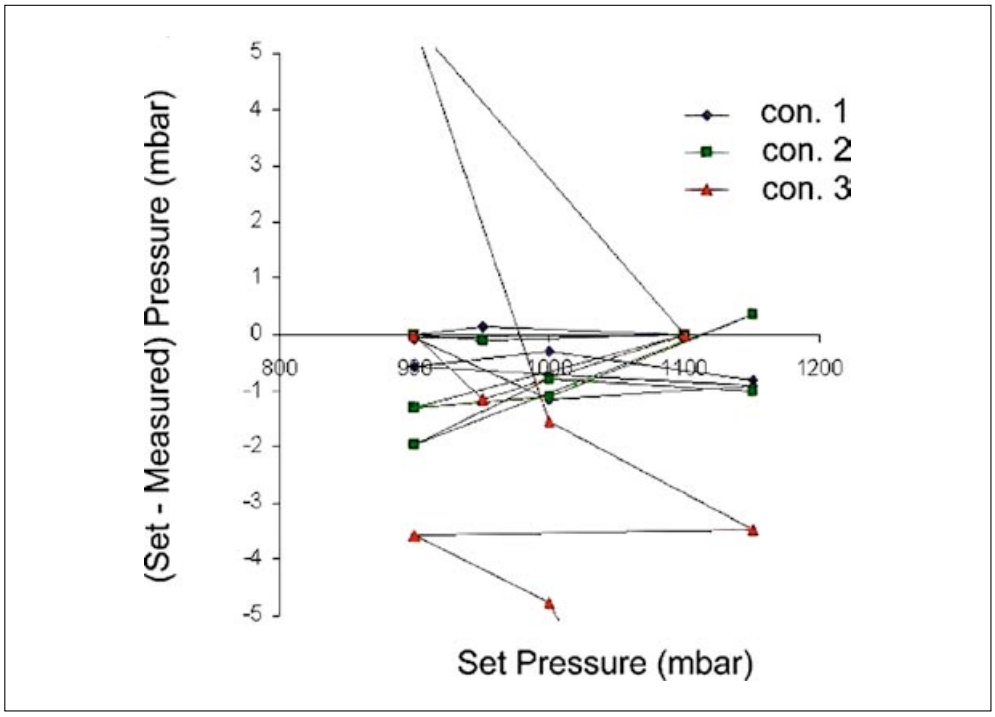

Fig. 7 Difference of set pressure minus measured pressure for piezo-resitive based system

1.4 Relations Between the Results and the Power Supply

The distance between transmitter and receiver plays an important role in electric power transmission via electromagnetic fields. To begin with, one cannot expect that patients will hold the reader unit always at the same distance from the eye. Therefore it must be ensured that the results will not be biased by differences in the positioning distance. As an example, we optimized the transmission power in a system with capacitor based sensor for a distance of 32 mm. The closer the reader unit comes to the sensor system, the higher is the measured pressure. This is shown in Figure 8. The displayed pressure at 32 mm is 8 mbar, whereas at 4 mm the displayed pressure is 38 mbar at constant transmission power. This finding suggests that it is crucial to have transmission power control.

The measurements suggest that we have two mature prototypes with different performance characteristics. These characteristics, together with the geometric boundary conditions, will be the basis for selecting the final design.

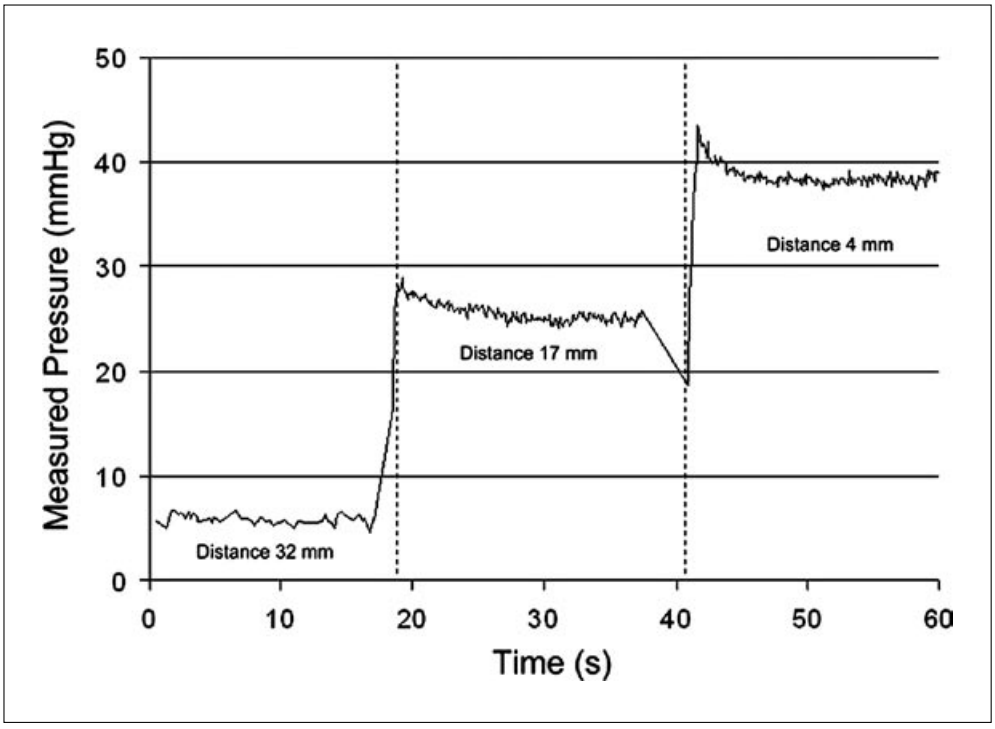

Fig. 8 Influence of constant transmission power on pressure readings at different distances

2. Biocompatibility of the Device

Biocompatibility is a primary requirement for medical implants. It is obvious that active electronic components do not satisfy this requirement without modifications. Moreover, due to the high concentration of electrolytes in the aqueous humor, the inside of the eye remains a particular challenge for electronic circuits. A main focus needs to be placed on preventing certain electrochemical processes, such as electrolysis and corrosion, and on eliminating any risk arising from electric potentials and waste heat. Therefore, applied DC voltages are kept below the threshold of electrolysis, and waste heat temperatures are dimensioned such that the induced temperature increase in the eye during operation remains far below 1 °C. Further, high frequency supply is regulated such that there should be no significant temperature increase in the relevant areas.

Figure 2 shows a coated system. This system is coated with a biocompatible silicone material. The silicone material forms an intraocular lens in the center of the coil. This IOL meets all the requirements of DIN EN ISO 11 979.

However, before choosing one of the designs it must be ensured that the biocompatible coating does not change the electronic and measurement properties of the device. Several systems were set up to investigate the electronic characteristics, such as sensitivity and zero offset. All systems were then coated with a biocompatible silicone material and the

measurements were repeated. Figure 9 shows that the differences between the uncoated and the coated systems are marginal, and much smaller than the differences between the two designs. The differences can be eliminated by individual calibration.

Further, the suitability of the coating has been demonstrated in animal experiments.

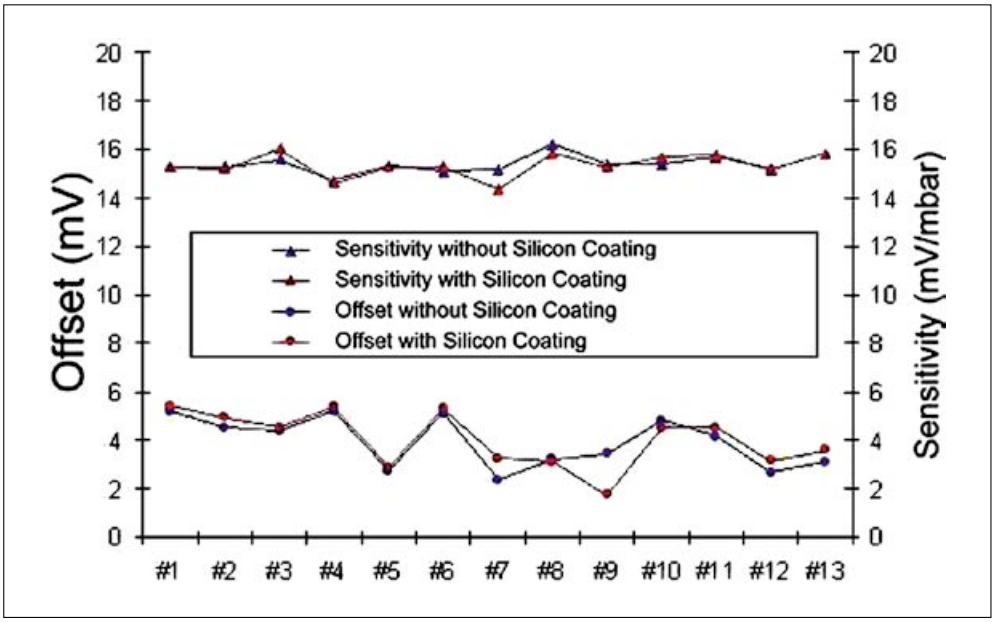

Fig. 9 Influence of a silicon coating on sensitivity and offset of several piezo-resitive based systems

3. Outlook

Two basic designs are now available as a result of these development efforts. The ideal system can now be defined on the basis of the performance characteristics. Next, the manufacturing processes need to be stabilized to ensure reproducibility of the required performance characteristics. Certainly, this will be an enormous challenge because the electronic components must fit into very small space and need to be coated with a biocompatible material. Finally, the implant needs to be resistant to mechanical stress during surgical manipulation.

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Anatomical Considerations in Glaucoma Implant Surgery

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With 3 Figures

Abstract

The main risk factor for glaucoma is an elevated intraocular pressure (IOP), caused by an accumulation of extracellular material in the trabecular meshwork (TM). Outflow facility may be improved by surgical approaches, removing or bypassing the site of increased outflow resistance. We describe here the anatomical structures that have to be taken into consideration, if new surgical procedures decreasing IOP shall be introduced. Reactive changes in the TM depend less on the type of operation than on the kind of injury during surgery. Damage to TM and SC induces slow and incomplete regeneration. However, damage to the scleral side is more critical and can include injury of blood vessels belonging to the episcleral venous system, which is discussed as playing a role in controlling IOP beyond SC. From blood clots, granulation tissue develops and induces scar formation. If blood enters the anterior chamber, blood derived factors may stimulate scaring.

Zusammenfassung

Der wichtigste Risikofaktor für die Glaukomerkrankung ist ein erhöhter intraokulärer Druck, der durch eine Vermehrung von extrazellulärer Matrix im Trabekelwerk (TM) verursacht wird. Der Abfluss von Kammerwasser kann mittels operativer Interventionen verbessert werden, die darauf abzielen, das Gewebe mit erhöhtem Abflusswiderstand zu entfernen oder zu umgehen. In diesem Beitrag beschreiben wir die anatomischen Strukturen, die beachtet werden müssen, wenn neue operative Verfahren zur Augendrucksenkung eingeführt werden sollen. Die reaktiven Veränderungen im TM hängen weniger von der Art der Operation als vielmehr davon ab, welche Verletzungen durch die Operation verursacht wurden. Schäden im TM oder dem Sklerasporn verursachen langsame und unvollständige Regenerationsvorgänge. Hingegen sind Schäden auf der skleralen Seite problematischer und können auch Verletzungen von Blutgefäßen einschließen. Diese Gefäße haben Verbindungen zu den episkleralen Venen, denen eine Beteiligung an der Regulation des IOP jenseits des SC zugeschrieben wird. Ausgehend von Einblutungen entwickelt sich Granulationsgewebe, das zur Narbenbildung führt. Wenn Blut in die vordere Augenkammer eindringt, können Faktoren aus dem Blut die Narbenbildung stimulieren.

1. Introduction

The main risk factor for primary open glaucoma is chronically elevated intraocular pressure, which is the result of an increase in outflow resistance within the trabecular meshwork (TM). The TM may be divided into three portions, the innermost uveal TM, the corneascleral TM and the outermost cribriform TM (Fig. 1). The corneoscleral TM consists of beams forming a sponge-like filter for the drainage of aqueous humour into Schlemm's canal (SC). The core of the beams is formed by collagen and elastic like fibers, which are

enveloped by TM cells resting on a complex basement membrane. In the outermost, cribriform TM adjacent to SC structured beams are lacking, and instead TM cells form a loosely arranged connective tissue embedding extensions of the elastic-like fibrils, termed connecting fibrils reaching the cell lining of the inner wall of SC.

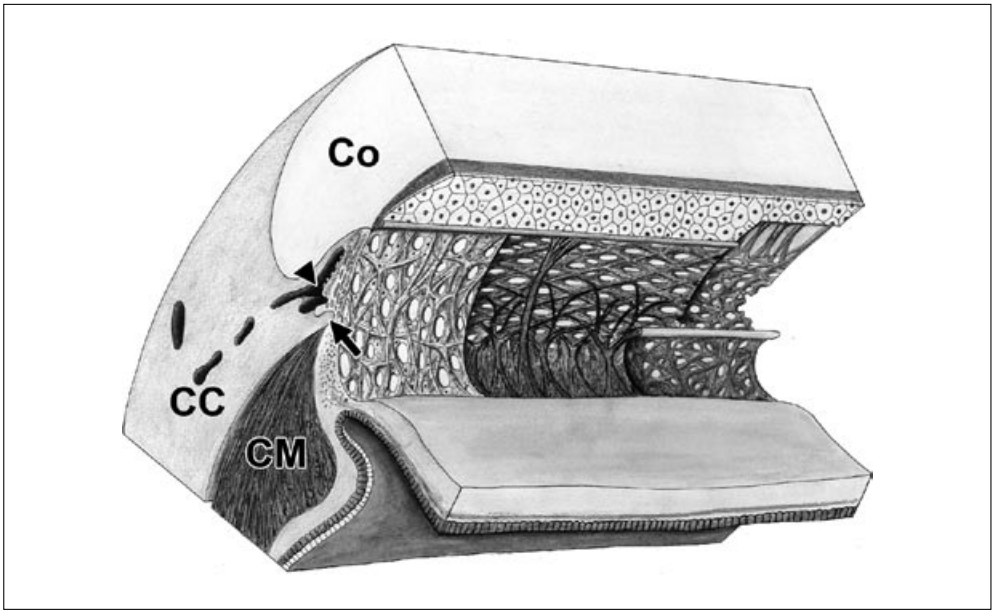

Fig. 1 Schematic drawing of the outflow pathways adopted from tangential sections of the TM. The TM expands from the scleral spur (arrow) to the cornea (Co). The TM consists of three distinct layers shown from left to right. The (innermost) uveal TM, the cornescleral TM and the juxtacanicular or cribriform TM. Note that the tendons of the ciliary muscle (CM) insert in all layers of the TM.
Arrowhead = Schlemm's canal; CC = collector channels

It is well accepted that increased IOP is caused by an accumulation of extracellular material in the TM. More specifically, the sheaths of the elastic like fibers of the trabecular beams are thickened and in the cribriform region, sheaths derived plaques are significantly increased compared to age matched controls (Lütjen-Drecoll et al. 1986). These changes cause an increase of the area occupied by morphologically visible structures and decrease the area of empty spaces in between, which are the preferential pathways for aqueous humour outflow. It was shown that the amount of empty spaces correlates well with outflow facility (Lütjen-Drecoll 1973). The reasons for the increase of extracellular material in the outflow pathways is still not known, although mediators like TGF-beta or the effects of radical oxygen species have been accused of inducing glaucomatous changes in the TM. At present a causative therapy is not yet available. The only two options to reduce IOP are medication or surgery. All the different kinds of glaucoma surgery aim at removing or bypassing the material compromising outflow facility. However, the optimal design of implants, as well as the implementation of suitable surgical procedures, depends on adequate and correct understanding of the anatomical structure, function and interaction of the outflow tissues.

2. Anatomy of the Outflow Region

2.1 Anatomy of the Inner Outflow Region (Trabecular Meshwork and Scleral Spur)

The TM extends from the scleral spur to the peripheral cornea (Fig. 1, 2). In a number of eyes, the scleral spur extends relatively far anteriorly overlaying 1/3 to 1/2 of the length of SC. In these cases the actual filtering area is smaller compared with eyes, in which the scleral spur does not overlay SC. As a consequence, the IOP lowering effect of glaucoma surgery may also be smaller than expected. Since the scleral spur may also contain vessels, an injury of this tissue has to be avoided, or at least minimized, for a second reason. In practice, however, it might be difficult to determine in vivo the exact position of the scleral spur in relation to SC.

In experimental studies applied on human eyes we showed that local dissection of TM by goniotomy or trabeculotomy will open SC. The reactive changes depend less on the type of operation than on the kind of injury during operation. As long as the operation affects only TM and inner wall of SC, the regenerative processes are minor (Lütjen-Drecoll 1972, Lütjen-Drecoll et al. 1972). This little reactivity corresponds nicely with the low metabolic and proliferative capacity of TM cells in general. However, if the outer wall of SC and sclera are damaged, 3–5 days after operation a granulation tissue develops from a blood-fibrin clot, in which blood vessels grow from the scleral side. The low reactivity of TM was also confirmed in a study on the long term effects of trabeculectomy in cynomolugs monkeys up to 15 months after operation (Barany et al. 1972). Although a block of a few milimeters of TM was removed, newly formed trabecular lamellae could not be detected. Typically remaining TM cells generate long cytoplasmic processes covering the wound area.

Dissecting a block of tissue by trabeculectomy also interferes with the biomechanical properties of a ring like structure as SC and TM. After trabeculectomy we observed retraction of TM and even more pronounced of SC, indicating higher elasticity of SC. Surprisingly, in 16 out of 20 cases, the free ends of SC were not only retracted, but also attached to the sclera and their openings closed off (Barany et al. 1972). However, these findings are retrieved from young monkeys. In the eyes of much older human glaucoma patients the elasticity will be substantially reduced. Therefore we assume that retraction and the subsequent closure of the free ends of SC will be less pronounced in glaucoma patients.

Another point is that the glaucomatous changes in the TM are unevenly distributed along the circumference. In the same eye, regions with loosely arranged outflow tissue are followed by regions, where the TM is very dense, filled with great amounts of extracellular material and glaucomatous plaques in the cribriform region. We assume the success of glaucoma surgery will be much better, if diseased parts of the TM are removed and intact parts are left in place. During surgery it may be difficult to identify diseased regions. We would like to recommend using the degree of pigmentation, e. g. the intensity of brown colour of the TM as a marker for intact TM regions. Due to the loosely arranged and therefore transparent TM brown pigment, granules trapped in the TM are much more easily seen. In addition, the flow through intact loosely arranged TM is higher than in glaucomatous dense TM. Therefore the number of pigment granules will be higher in TM with physiological outflow facility compared to TM with decreased outflow facility.

2.2 Anatomy of the Outer Outflow Region (Sclera and Episclera)

In glaucomatous eyes, increased plaque material is not restricted to the cribriform region adjacent to the inner wall of SC, but also occurs in the outer wall of SC and the sclera (Lütjen-Drecoll et al. 1986). In this region the collector channels drain aqueous humour from SC into scleral veins (Fig. 1). It is still a matter of debate, if control of outflow facility, and thereby of IOP, may also occur past SC in the scleral part of the outflow system. In particular the so-called episcleral veins display some special features which make them interesting candidates for a regulatory function. Episcleral veins have numerous arteriovenous anastomoses for control of pressure and flow in these vessels draining aqueous humour. Episcleral veins are rich in smooth muscle α actin similar to arterioles and are surrounded by a dense network of nerve fibers (Fig. 3) expressing a variety of vasoactive transmitters (Selbach et al. 2005) including nitric oxide (Fig. 3), a potent vasodilator. Episcleral veins comprise all morphological prerequisites necessary for controlling blood flow. It is therefore tempting to speculate that episcleral vasculature plays a role in the control of aqueous outflow, and thereby of IOP.

In human eyes the arteriovenous anastomoses are located deeper in the sclera, i. e. closer to SC, than in primates and other animals. In a number of human eyes an artery directly adjacent to the outer wall of SC called Friedenwald artery is present. Glaucoma surgery affecting not only TM and inner wall of SC, but also sclera and outer wall of SC may damage this sophisticated vascular system. Although we do not fully understand the functional significance of the episcleral venous system for the regulation of IOP, we know from experimental studies in human eyes that scaring is significantly higher after trabe-

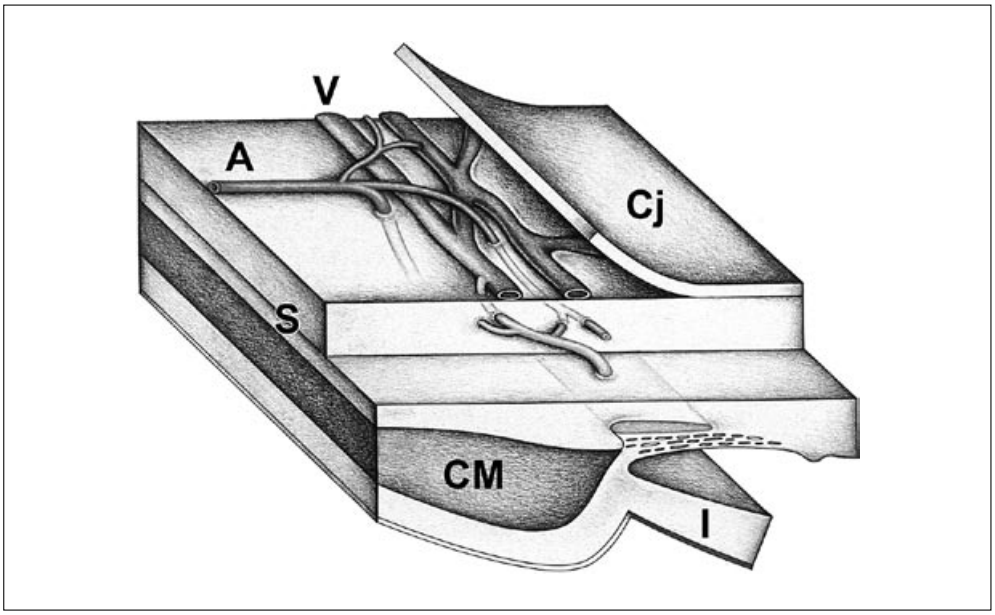

Fig. 2 Schematic drawing of the chamber angle and episcleral vasculature. Note arteriovenous anastomosis between arteries (A) and veins (V). S = Sclera, Cj = Conjunctiva, I = Iris, CM, ciliary muscle

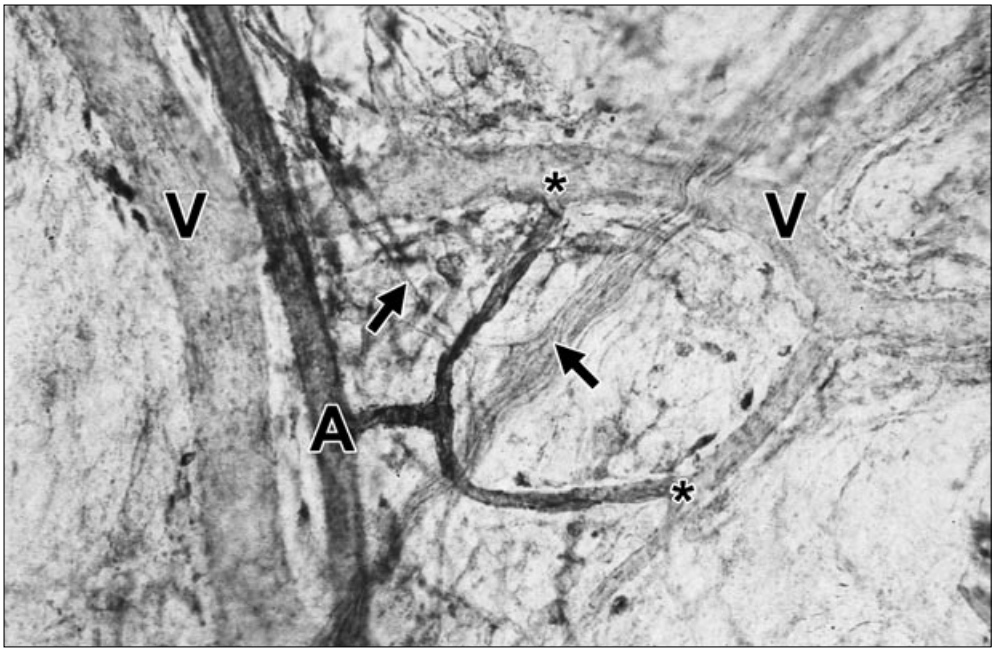

Fig. 3 Whole mount of episcleral region stained for NADPH-diaphorase indicating NO release. Note arteriovenous anastomosis (*) between arteries (A) and veins (B). Arrows indicate nerve fibers stained for NADPH-diaphorase.

culotomy, if the scleral side is affected by the surgical procedure (Lütjen-Drecoll 1972, Lütjen-Drecoll et al. 1972). A possible explanation for this observation is that the risk of bleeding into the anterior chamber is much higher if sclera, episcleral tissue, and vasculature are injured. The entry of blood into the anterior chamber delivers blood derived factors into the anterior chamber, which usually have no access. This blood derived factors might influence the immune privilege of the eye and thereby the process of wound healing and scaring.

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Fluid Dynamic Requirements for Glaucoma Implant Devices

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With 4 Figures

Abstract

In order to develop a microstent with valve function, which normalizes the intraocular pressure (IOP) and drains aqueous humor in the suprachoroidal space, a model is established that predicts the fundamental fluid dynamic requirements for glaucoma implant devices. As a result, typical uveoscleral drainage requires inner diameters of 53 to 68 µm (with IOP in the range from 20 to 60 mmHg) with valve functionality to manage changing IOP conditions. In case of glaucoma (e. g. IOP 30 mmHg) the implant has to drain more than 50 % of total aqueous humor secretion. Technical realization utilizes modern micro-technologies to manufacture such structures. Currently, laser machining using ultra-short pulse lasers supplemented by laser-induced 2-photon polymerization are the favored techniques. Wound healing will be modulated by drug delivery systems in the outflow space to ensure long-term efficacy.

Zusammenfassung

Zur Entwicklung eines Mikrostents mit Ventilfunktion, der den intraokularen Druck (IOP) normalisiert und das Kammerwasser in den suprachoroidalen Raum des Auges drainiert, wurde ein Modell entwickelt, das die wesentlichen fluid-dynamischen Anforderungen an Glaukomimplantate definiert. Im Ergebnis wird gezeigt, dass die typische uveosklerale Drainage Innendurchmesser von 53 bis 68 µm bei einem IOP von 20 bis 60 mmHg und eine Ventilfunktion für wechselnde IOP erfordert. Im Fall eines Glaukoms mit einem IOP von 30 mmHg muss das Implantat mehr als 50 % der gesamten Kammerwassersekretion ableiten. Die technische Realisierung verwendet moderne Mikrotechnologien zur Herstellung derartiger Strukturen. Momentan sind Laserbearbeitungen mittels Ultra-Kurzpulslaser ergänzt durch die laserinduzierte 2-Photonenpolarisation bevorzugte Techniken. Die Wundheilungsmodulation erfolgt im Ausstrombereich durch *Drug-Delivery*-Systeme, um eine Langzeitfunktion zu erreichen.

1. Introduction

In all forms of glaucoma, irrespective of their classification, progressive optic neuropathy can be influenced by lowering intraocular pressure.

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The maintenance of a defined target pressure preoperatively remains a challenge today. This issue can be addressed surgically by creating new intra- or extra-ocular bypass structures using local tissue elements: This approach is still the first choice for the majority of ophthalmologists. Alternatively, or as a procedure for use in otherwise untreatable glaucomatous eyes, a variety of alloplastic implants has been developed and marketed. It is the aim of this study to define some of the fluid mechanical requirements for these devices.

From the early years of the 20th century onwards attempts were made to drain aqueous humor externally through a paracentesis and placement of horse hair or single silk threads (for review, see Lim et al. 1998). Subsequently, metallic platinum devices or even viscoelastic substances were used for drainage to the subconjunctival space to maintain pressure-lowering effects. Unfortunately, these attempts were not as effective as required and were ultimately unsuccessful. More efficient long-term solutions emerged only with the development of draining glaucoma implants, such as that originally proposed by Molteno (1969 a, b). Molteno introduced the concept of a tube and plate system which shunts aqueous fluid through a thin polypropylene tube from the anterior chamber of the eye to a plate below the conjunctiva to drain the fluid. Further developments named after their principal inventors (e. g. Krupin, Baerveldt or Ahmed) utilized the approach embodied in subconjunctival draining implants. All of these devices consist of a thin tube made of silicone or polypropylene and a plate element. The Ahmed device has an additional valve in the plate element to prevent early postoperative hypotony. Other devices have been developed to drain through Schlemm's channel (Eyepass™ and iStent™), or even into the suprachoroidal space (SOLX®). Instructive overviews of current glaucoma implants, construction principles and clinical results are provided by Lim et al. (1998), Dietlein et al. (2008) and Minckler et al. (2008).

Despite all the progress made in this field, none of the devices has demonstrated adequate long-term efficacy and consequently further efforts are required to improve results with new devices.

New technologies for the fabrication of micro-devices and current progress in the application of surface modifications using passive or active drug-eluting concepts encouraged us to develop a microstent for glaucoma therapy which concentrates on pressure-controlled uveoscleral drainage of aqueous humor. In addition to the complex processes at the interface between the implant and the surrounding tissue, a basic understanding of fluid mechanics is required for optimum design of fluid flow within the microstent.

2. Fluid Mechanical Considerations

Our knowledge concerning normal and pathologically altered flow pathways of aqueous humor in glaucoma has been enhanced over the years by the publication of several detailed investigations (e. g. Goldmann 1951, Bill 1966, Nilsson 1997). A gross anatomic view of the main flow routes for aqueous humor is depicted in Figure 1.

Until now, Goldmann's equation has been the basis for most estimates of the fluid mechanics of aqueous humor. It sets out the relationship between aqueous production ($\dot{V}_0$), conventional outflow facility (R_{conv}), intraocular pressure (IOP), episcleral venous pressure (p_{ev}) and uveoscleral outflow ($\dot{V}_{uv}$):

$$\dot{V}_0 = R_{conv}(IOP - p_{ev}) + \dot{V}_{uv} \qquad [1]$$

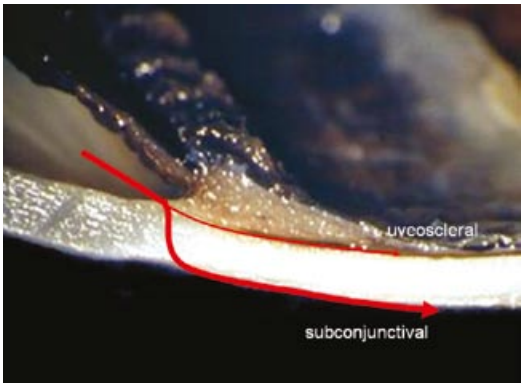

Fig. 1 Anatomy of eye angle, main flow routes of aqueous humor (light microscopy).

This equation suggests that uveoscleral outflow is pressure-independent, although that assumption is now disputed (Becker and Neufeld 2002). Because of the relatively small contribution of uveoscleral outflow in humans compared with conventional outflow (less than 15 %; Nilsson 1997), this detail is perhaps of minor relevance for most approaches. However, when determining the dimensions of pressure-dependent valves draining into the uveoscleral space, uveoscleral pressure and outflow are of fundamental importance and should be considered separately.

Kotliar et al. (2009) recently outlined biofluid mechanical considerations with respect to aqueous outflow after glaucoma filtration surgery. This rather complex model describes fluid mechanical changes following non-penetrating deep sclerectomy or trabeculectomy; however, it still contains simplifying assumptions with regard to pressure dependency and amount of uveoscleral outflow.

When determining the dimensions of a glaucoma drainage device, whatever drainage route is chosen, the central question is: What is the quantitative aqueous humor flow to be achieved with an ideal glaucoma implant under the given intraocular pressure conditions? We have developed a simple model which has proved useful for evaluating existing glaucoma shunts as well as for the design of our new microstent for glaucoma therapy.

2.1 Physiological Situation

The physiological situation in the healthy human eye can be characterized by an intraocular pressure (IOP) of about 15 mmHg. The secretion of aqueous humor is believed to be relatively constant and pressure-independent (which explains the rise in IOP in patients with increased outflow restriction or even obstruction). Physiological experiments have suggested that $\dot{V} \sim 2$ mm³/min (Goldmann 1951), a value that is still generally accepted. All aqueous humor is finally transported into the venous system, i. e. to the episcleral veins which are under lower but almost constant pressure of $p_{ev} = 5$ mmHg.

Under the given circumstances, the outflow resistance of all drainage pathways ($R_{IOP=15}$) is:

$$R_{IOP=15} = \frac{IOP - p_{ev}}{\dot{V}} = 5\frac{mmHg}{\mu l/\min} = R_C \qquad [2]$$

It is important to note that under all conditions (whether IOP is elevated or not) all of the aqueous humor secreted will flow out of the anterior chamber (Fig. 2*A*, *B*). Otherwise there would be no balanced state and IOP would be permanently raised. The calculation does not differentiate between the quantities of outflow through the different known pathways, which can be modeled as parallel circuitry leading ultimately to the venous system.

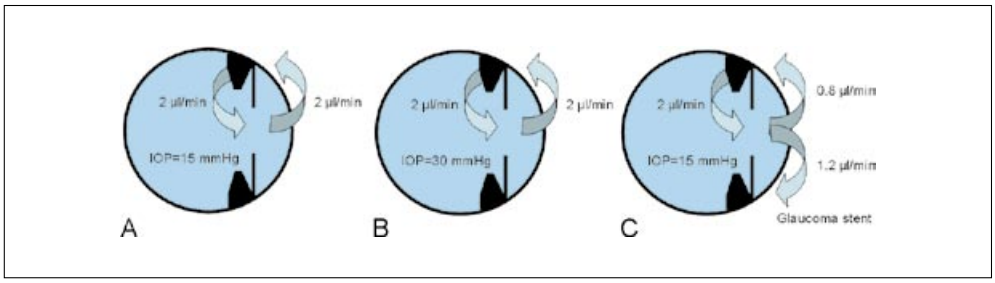

Fig. 2 Physiological situation at normal outflow resistance (*A*), increased outflow resistance at constant volume flow causes increase in IOP (*B*), flow resistance of the additional glaucoma stent adjusts IOP to a normal value (*C*).

2.2 Conditions in Open-Angle Glaucoma

In open-angle glaucoma it is assumed that the outflow resistance of the anterior chamber is increased, resulting in elevated IOP. In our model is chosen as an IOP of 30 mmHg, a value that is within the IOP range typically observed in glaucoma patients (Leydecker 1985). Since the entire volume of aqueous humor generated has to flow out of the anterior chamber, the single – but important – difference compared with the normal physiological situation is the increase in total outflow resistance, resulting in $R_{IOP=30}$:

$$R_{IOP=30} = \frac{IOP - p_{ev}}{\dot{V}} = 12.5 \frac{mmHg}{\mu l / \min} \qquad [3]$$

In other words, the constant secretion rate of aqueous humor at increased IOP produces a greater pressure difference, which drives the aqueous humor against the increased outflow resistance (Fig. 2*B*).

2.3 Solution with a Glaucoma Stent

A glaucoma implant should compensate for increased outflow resistance to re-establish normal pressure conditions. Consequently, the glaucoma stent acts as an additional outflow pathway with its specific flow resistance R_{stent}. It is connected in parallel to the other pathways represented by $R_{IOP=30}$ in our model for open-angle glaucoma.

$$\frac{1}{R_0} = \frac{1}{R_{IOP=30}} + \frac{1}{R_{Stent}} \qquad [4]$$

The required flow resistance can be calculated by transforming equation [4] and using the values determined above for R_0 and $R_{IOP=30}$:

$$R_{Stent} = 8.33 \frac{mmHg}{\mu l / \min} \qquad [5]$$

The resulting R_{Stent} value is an intermediate result that can be used to calculate the flow which has to be driven through the glaucoma stent under particular conditions. In our example this flow is:

$$\dot{V} = \frac{IOP - p_{ev}}{R_{Stent}} = 1.2 \mu l / \min \qquad [6]$$

It is remarkable that more than 50 % of aqueous outflow has to be handled by the implant to reduce the IOP from 30 mmHg to normal conditions (Fig. 2*C*). This functional relationship is dependent on IOP, as illustrated in Figure 3 for different IOP values. It is furthermore concluded that at normal IOP no flow should pass the glaucoma stent. This requires pressure-controlled flow resistance, i. e. valve functionality.

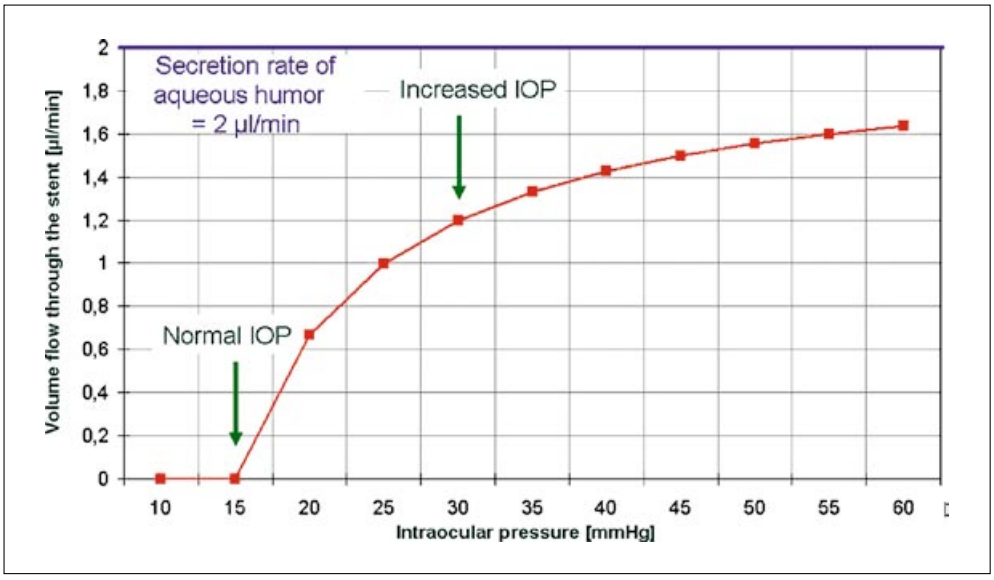

Fig. 3 Volume flow through an ideal glaucoma stent at increasing IOP.

It should be noted that the calculated R_{Stent} value does not necessarily represent the flow resistance of an actual stent because the dimensions depend on the individual pressure conditions at the drainage sites.

3. Conclusions

The results obtained can be used to calculate the dimensions of glaucoma shunts or stents. The optimum dimensions for tubular implants can be derived by taking into account

the fluid mechanical properties of aqueous humor represented by dynamic viscosity η (0.72 mPas), implant length l (depending on anatomy and surgical procedure), and the pressure difference Δp between anterior chamber and stent outflow site. Reference values for Δp for most of the common sites and drainage routes are available from the literature: subconjunctival: 15 mmHg (Hille et al. 2002); via Schlemm's channel: 3 mmHg (Sears 1966); and suprachoroidal: 1 mmHg (anterior) to 3 mmHg (posterior) (Emi et al. 1989). Using Hagen-Poiseuille's law of laminar flow, the required inner diameter of a glaucoma stent is [7].

$$d = \sqrt[4]{\frac{\dot{V} \cdot 128 \cdot \eta \cdot l}{\pi \cdot \Delta p}} \qquad [7]$$

The volume flow $\dot{V}$ through the implant is defined as calculated from [6]. As a result, typical subconjunctival devices should have inner diameters of 40 to 50 µm at a length of 10 mm whereas uveoscleral drainage requires inner diameters of 53 to 68 µm (with IOP in the range from 20 to 60 mmHg). The differences result from the different pressure conditions at the two implantation sites.

Most conventional and commercially available glaucoma shunts have tubing with far larger inner diameters (300 µm and more). More structured inflow and outflow systems incorporating plate elements and valves require more complex estimates and may be characterized by additional flow restriction. However, the risk of post-operative hypotony is present in most cases even though trabecular or uveoscleral bridging implants indeed have smaller cross-sections.

A more precise estimate of actual flow conditions – in particular, when modeling the reaction of the valve construction of a glaucoma stent to the surrounding pressure and flow of aqueous humor – requires highly sophisticated numerical analysis of fluid-structure interaction (FSI). This work is still in progress.

The authors are aware that implant-tissue interactions play a major role in the long-term success of all kinds of glaucoma surgery, including implant devices. These phenomena will be addressed by surface modifications and local drug delivery concepts and are beyond the scope of this publication.

4. Outlook

There are plans to optimize a new glaucoma microstent to prevent hypotony by adjusting cross-sections to an approximate diameter of 50 µm. In addition, the device will incorporate a pressure-dependent valve functionality. Thus, at a defined increase of IOP, the valve will provide a cross-section for outflow in addition to the minimum of 50 µm or less. In this way IOP will be regulated in a pressure-dependent manner. Technical realization requires modern micro-technologies to manufacture such structures. Currently, laser machining using ultra-short pulse lasers supplemented by laser-induced 2-photon polymerisation (2PP) are the favored techniques. It has been shown that the two technologies can be combined to provide structures that are accurate to several microns in relatively large devices of several millimeters in length (Fig. 4).

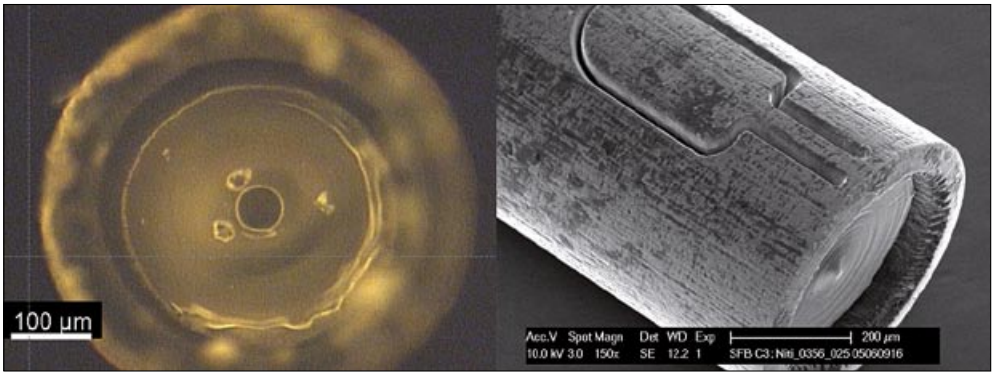

Fig. 4 Combination of an Ormocomp aperture (50 µm, 2PP) with an fs-laser cut tube valve made of Nitinol.

The concept is based on placing the valve in the inflow region of the stent (i. e. the anterior chamber), which is believed to enjoy greater protection from encapsulation by fibroblast activity. Wound healing will be modulated by drug delivery systems in the outflow space to ensure long-term efficacy. The preferred drainage pathway into the suprachoroidal space pursues the same goal. Fibroblast activity is also thought to be reduced in the suprachoroidal space; even there, however, scarring and fibrotic encapsulation may compromise long-term success (Dietlein et al. 2008, Jordan et al. 2006).

The IR laser offers a very promising approach that allows re-adjustment of basic cross-sections. Laser radiation is directed at nanorods embedded in a thin polymer matrix within the microstent. The polymer layer is selectively heated, shrinks and thus changes the active fluid mechanical cross-section of the microstent. Preliminary studies have been conducted to investigate the interaction between incorporated nanorods and laser radiation.

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State of the Art Glaucoma Implant Surgery

Keith BARTON (London, UK)

With 6 Figures

Abstract

Randomized controlled trials have demonstrated that medical and laser treatments are less invasive than surgery in controlling the intraocular pressure (IOP) in patients with glaucoma. Conventional glaucoma surgery does not involve the use of implants but often fails to control the pressure and results in some morbidity even in those who achieve successful control. There is increasing evidence from randomized clinical trials that implants are of comparable efficacy in controlling IOP. In this review, implants are compared in general terms from a functional perspective, with some more detailed discussion of the implants that have been investigated in the greatest depth. Their shortcomings are highlighted, as well as the areas that are likely to prove most fruitful for future implant development.

Zusammenfassung

Randomisierte kontrollierte Studien haben gezeigt, dass zur Kontrolle des Augeninnendrucks bei Patienten mit Glaukom sowohl medizinische als auch Laserbehandlungen weniger invasiv sind als Operationen. Bei der konventionellen Glaukomoperation werden zwar keine Implantate verwendet, aber sie verfehlt öfter die Druckkontrolle und führt sogar dazu, dass Patienten erkranken, bei denen eine erfolgreiche Kontrolle erreicht war. Randomisierte klinische Studien beweisen, dass Implantate bei der Kontrolle des Augeninnendrucks eine vergleichbare Wirksamkeit haben. In diesem Übersichtsartikel werden Implantate im Allgemeinen unter funktionaler Perspektive in eingehender Weise mit Implantaten, die gründlicher untersucht worden sind, verglichen. Ihre Schwachstellen werden ebenso herausgearbeitet wie jene Bereiche, die sich für die zukünftige Entwicklung von Implantaten wahrscheinlich am fruchtbarsten erweisen werden.

1. Why Do We Need Implants?

1.1 Lack of Efficacy of Conventional Filtration

Intraocular pressure (IOP) is only one of several risk factors for glaucoma, but at present this is the only modifiable factor in which clinical trials have shown evidence of benefit. The IOP may be controlled medically or with laser. Both are less invasive than surgery, but fail to achieve the desired level of control in a proportion of patients. These patients then require surgery. Since the 1970s the most common surgical procedure has been the trabeculectomy, an operation that drains aqueous through a small guarded fistula in the scleral wall of the peripheral anterior chamber to a blister or *bleb* on the eye surface close to the corneo-scleral limbus (Fig. 1). Although this has traditionally been the most effective method of controlling the IOP in primary glaucomas, it is much less effective in many

types of secondary glaucoma, including aphakic glaucoma, glaucoma after retinal surgery, and glaucoma with intraocular proliferative conditions such as iris neovascularisation and irido-corneal endothelial syndrome. It is also relatively ineffective in eyes with primary glaucoma that have had previous conjunctival surgery or eyes that have had prolonged exposure to certain types of glaucoma medication.

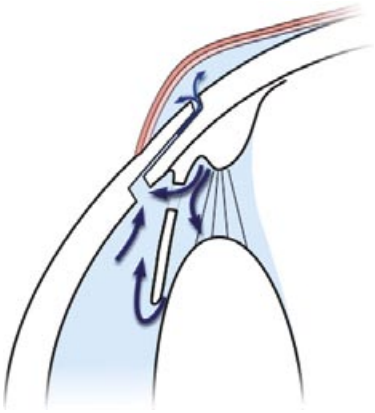

Fig. 1 Aqueous drainage bleb at the limbus following a trabeculectomy procedure

Furthermore, in eyes with successful trabeculectomy, the mean IOP level achieved after surgery is often in the mid-normal range, a level that until the late 1990s was considered satisfactory for most patients with glaucoma. It is now clear that a proportion of patients who have advanced glaucomatous optic neuropathy continue to deteriorate, albeit more slowly, unless the IOP levels can be maintained at the lower end of the normal range. Finally, the filtration procedure has a finite functional lifespan in a proportion of patients.

1.2 Morbidity after Conventional Filtration

One particular concern with the trabeculectomy procedure is a significant risk of subsequent morbidity in otherwise successful and uncomplicated cases. For example, trabeculectomy patients have a higher rate of later cataract surgery than those treated medically for glaucoma. Additionally an aqueous filtration bleb close to the limbus is uncomfortable for many patients (bleb dysaesthesia) (Budenz et al. 2001) and there is a small but finite risk of infection within the bleb (blebitis) and within the eye (endophthalmitis).

2. Implants in Glaucoma Surgery

2.1 Historical Perspective

The first attempts to drain aqueous using an implant date from the early part of the 20th century (Rollett and Moreau 1907, Zorab 1912) but little progress was made until the development of the Molteno implant in the late 1960s (Molteno 1969a) the design of

which consisted of a segment of silicone tubing approximately 600 µm in external diameter, with a luminal diameter of 300 µm. The Molteno implant was constructed not only to shunt aqueous out through a permanent sclerostomy, but also to divert it away from the traditional trabeculectomy drainage area at the superior limbus, to the equatorial subconjunctival space. An end-plate was attached to the distal end of the tube in order to prevent fibrous ingrowth from obstructing the tube orifice (Fig. 2). This basic design was not dissimilar in function from the Schocket or anterior chamber tube shunt to encircling band (ACTSEB) in which a tube without a fixed end-plate was inserted under an encircling band. However, the Schocket-type arrangement was less effective in achieving IOP control than fixed one-piece implants (Fig. 3; LAVIN et al. 1992, SMITH et al. 1992, WILSON et al. 1992).

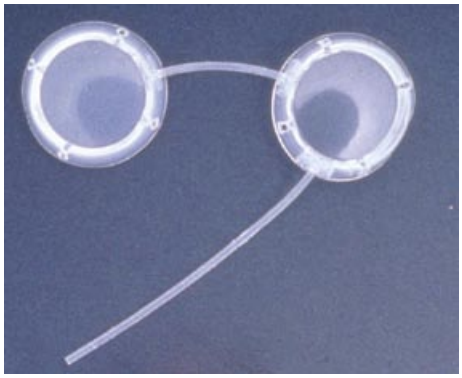

Fig. 2 Double plate Molteno implant

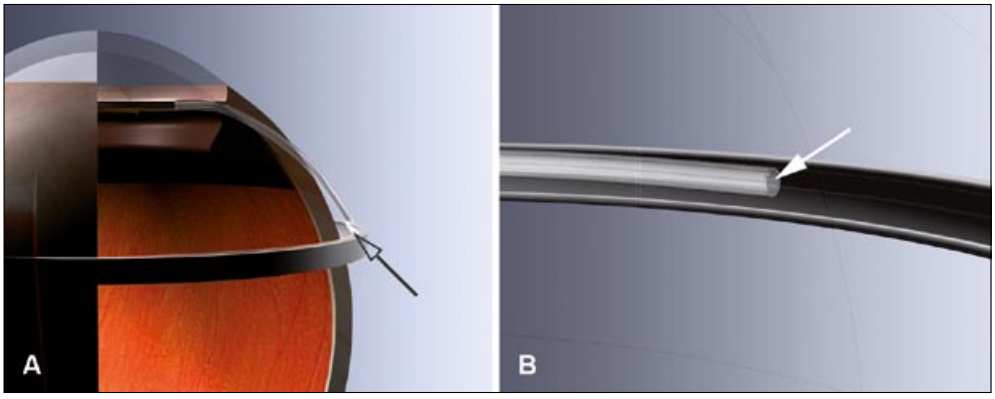

Fig. 3 (*A*) Shocket implant (anterior chamber tube shunt to encircling band). The arrows indicate the positioning of the tube underneath a silicone band that is secured to sclera (*A*, *B*). Aqueous exits the tube into a space between sclera and silicone band.

2.2 Potential Advantages of Implants over Conventional Filtration Procedures

Aqueous shunts have two potential advantages over conventional filtration. Firstly, implants have greater potential versatility in the destination of shunted aqueous e. g. to the equatorial sub-conjunctival space, straight into Schlemm's canal or into supra-choroidal space. Whereas conventional filtration e. g. Trabeculectomy has the limitation that it must utilize the limbal sub-conjunctival space for aqueous collection and absorption. Secondly, any attempted regulation of flow with conventional filtration surgery (e. g. releasable or adjustable sutures, needling procedures, or even goniopuncture after deep sclerectomy) is crude and flow is poorly titratable. Furthermore, the degree of long-term IOP-lowering achieved by these procedures depends largely on the combined influences of the patient's own healing response and the response to any anti-fibrotic agents used to augment the surgery. In theory, use of a mechanical device offers the potential for greater flow regulation than is possible with non-implant filtration procedures.

2.3 Nomenclature

Shunts have been called by many names. A popular term has been *seton*, though strictly speaking this is incorrect as the term *seton* refers to *non-lumened* devices whereas all of the devices in current use have a lumen.

The term *valve* is also popularly used, although some have flow restrictors, none truly contain valves. Likewise, glaucoma drainage device is a popular but slightly inaccurate term as these devices drain aqueous rather than glaucoma.

The ANSI (American National Standards Institute)-approved term is currently *Aqueous Shunt.*

3. Assessing New Implants

There has been an increase in the development of new devices in the last 2 to 3 years. These implants have one feature in common, that they all shunt aqueous. However, they vary in the destination of the shunted aqueous and factors that contribute resistance to aqueous outflow resistance, both within the shunt and distal to the shunt.

In the absence of prospective randomised clinical trials, one can estimate the probable degree of IOP-lowering that might be achieved with some of the new shunts by considering the destination of shunted aqueous and the points of resistance that remain after the device is implanted as well as any extra points of resistance introduced by the device. Finally, it is worth considering if the presence of the implant itself is likely to cause any harm.

3.1 Destination of Shunted Aqueous

Shunts may divert aqueous to another destination within the eye, e. g. the supra-choroidal space or Schlemm's canal. Alternatively, they may divert aqueous externally to either the limbal or equatorial sub-conjunctival space.

Shunts that divert aqueous to the limbal sub-conjunctival space, such as the *Express*™ implant (Optonol Inc), are still bound by the same limitations of limbal drainage that limit the potential development of trabeculectomy and other limbal drainage procedures such as

deep sclerectomy. The limbal subconjunctival drainage offers less versatility for future implant development than other areas.

Most external shunts (Ahmed Glaucoma Valve, Baerveldt Glaucoma Implant, Molteno Implant) consist of an end-plate connected to which is a long tube. The end-plate can be positioned in the equatorial sub-conjunctival space and aqueous routed there by the tube portion positioned in the anterior chamber. The limbal sub-conjunctival space is therefore bypassed (Fig. 2). The efficacy of implants using this mode of drainage has been documented by a number of randomized clinical trials and these will be discussed in more detail below.

Internal shunts have the potential advantage that they result in no external drainage and therefore no drainage bleb. Internal shunts that are currently available function by shunting aqueous either into Shlemm's canal, or into the supra-choroidal space. Shunting into Schlemm's canal bypasses the area believed to be the major point of outflow resistance i. e. the juxta-canalicular trabecular meshwork. In theory, shunting to Schlemm's canal should remove most outflow resistance, permitting IOP to drop to episcleral venous pressure level (Johnson and Johnson 2002). In practice, surgical procedures that perform this function, such as trabeculotomy and excimer laser trabeculotomy, historically have not been able to achieve the low normal pressures that we desire after glaucoma surgery, partly because of the healing response they induce. However, this destination may be limited by other points of resistance to aqueous outflow that remain distal to the shunt (see below).

The supra-choroidal space offers an important potential destination for shunted aqueous as it has the potential to achieve low IOP levels. This has been investigated in the past, and is currently being revisited by a number of device manufacturers. It seems clear from other presenters in this symposium that the only commercially available device, at the time of writing, may induce encapsulation in the supra-choroidal space. However, the supra-choroidal space can be breached without encapsulation in some eyes. We know this from some patients who have develop traumatic cyclodialysis clefts. When a communication is established between the supra-choroidal space and anterior chamber after trauma, a proportion of patients develop very low long-term IOP levels, to the extent that surgery is required to close the cleft. This occurs when the ciliary body band, that is normally tightly adherent to the inside of the scleral wall of the eye, becomes detached creating a pathway through which aqueous flows from the anterior chamber of the eye down a pressure gradient into the suprachoroidal space. This results in fluid

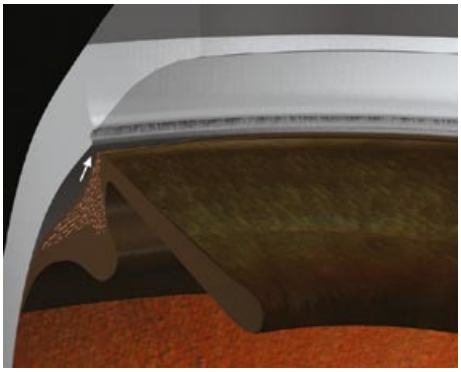

Fig. 4 Cyclodialysis cleft. Arrow indicates the separation of ciliary body band from sclera allowing anterior chamber aqueous to enter the supra-choroidal space.

accumulation in the supra-choroidal space (Fig. 4). The pathophysiology of the hypotony that develops in eyes with supra-choroidal fluid is not well-understood, but therapeutic attempts to induce supra-choroidal drainage via iatrogenic cyclodialysis cleft induction are not new. The limiting factors appear to be unpredictability if an implant device is not used, and fibrosis around the supra-choroidal portion of the device obstructing outflow if an implant is used.

3.2 Factors Contributing to Aqueous Outflow Resistance after the Shunt is in Place

Shunts that drain to the equatorial sub-conjunctival space such as the Ahmed Glaucoma Valve, Baerveldt Glaucoma Implant and Molteno implant remove all of the resistance in the normal aqueous outflow pathway and appear not to be dependent on episcleral venous pressure. With all three devices, a fibrous capsule develops around the end-plate, the permeability of which is the main determinant of aqueous outflow resistance in the longer term. The Ahmed Valve has, in addition, a flow-resistor within the device that adds further resistance, its main function being to avoid early hypotony.

In theory the supra-choroidal space produces very low resistance to outflow, but in practice it does produce fibrosis around the end of devices that are implanted in this space and the resistance to outflow will largely be determined by this fibrosis. Ideally, if fibrosis within the suprachoroidal space can be avoided, the resistance to outflow could be pre-determined exclusively by the design of the implant.

Shunts that divert aqueous to Schlemm's canal are analogous to trabeculotomy-type procedures which are used largely in children and infants to control the IOP. In these procedures the trabecular meshwork and wall of Schlemm's canal are removed so that the latter is open into the anterior chamber. Unlike external filtration or supra-choroidal drainage, these types of procedure are limited by the level of episcleral venous pressure as well as any resistance that develops distal to Schlemm's canal. The effectiveness of these procedures in children supports the widely-held belief that the juxtra-canalicular trabecular meshwork provides the majority of outflow resistance (Johnson and Johnson 2002). Their lower efficacy in adults with glaucoma might indicate that with age further outflow resistance may develop distal to Schlemm's canal or simply that episcleral venous pressure is higher, limiting their usefulness. As the IOP-lowering efficacy of trabecular meshwork bypass stents is limited by episcleral venous pressure, it is unlikely that this type of device will lower the IOP sufficiently to achieve the low normal or high sub-normal IOP levels that are currently believed to be required to stabilize patients with glaucoma who require surgery. From our knowledge of previous procedures that utilize this route, one might speculate that these types of device may be satisfactory for use in mild glaucoma, perhaps as implants to be inserted in patients with glaucoma already undergoing cataract surgery. However, it is likely that a surgical device with an IOP-lowering efficacy that may prove comparable to less invasive modalities such as laser trabeculecoplasty would not be widely adopted.

3.3 Safety

While unpredictable IOP levels in the early post-operative period has been the main safety concern with shunt, long-term safety may increase in importance as shunts are used more frequently, and the concept of a shunt as the primary surgical treatment for primary glau-

coma becomes more realistic. Especially as the predictability of IOP control will probably improve as shunts continue to evolve, and as implantation techniques become more finely-tuned, there will be more focus on the long-term influence of the shunt on the cornea. This has been the subject of some debate (Topouzis et al. 1999, Al Torbak 2003, Alvarenga et al. 2004, Arroyave et al. 2001, Ayyala 2000, Kwon et al. 2001, Sherwood et al. 1993). Concerns about the long-term effect on corneal endothelium are the likely remaining barrier to shunt implantation, as a primary surgical procedure for the treatment of primary glaucomas until there is adequate evidence with which to quantify the risk.

Most shunts involve a portion in the anterior chamber. Usually this emerges in the drainage angle, close to Schwalbe's line, that delimits the periphery of corneal endothelium. Mechanical damage to corneal endothelium from the tube portion of the shunt is a likely cause of corneal endothelial damage. Although Kirkness hypothesized a further potential cause: i. e. that aqueous shunts might elevate the risk of corneal graft failure because they permit a tidal flow of inflammatory cells from the bleb in and out of the eye, thereby compromising immune privilege (Kirkness et al. 1988), it seems that the influence of mechanical factors have not been studied sufficiently to be able to exclude these as a cause, nor the influence of case selection fully accounted for. While the presence of tube-corneal contact is often documented (Topouzis et al. 1999) and in one study, by Al Torbak (2003), physical contact between shunt and endothelium was documented as a significant cause of graft failure, studies reporting endothelial cell counts after aqueous shunts are rare (McDermott et al. 1993). It may not be necessary to have contact between the tip of the tube and the corneal endothelium to induce mechanical damage. The external diameter of the tube portions of the Ahmed, Baerveldt and Molteno implants, at around 600 µm, are large enough to occupy most of the diameter of the angle at the point of insertion. Less than perfect positioning will leave the implant in contact with corneal endothelium at the entry site. The express implant, with a much smaller diameter, may be more easily positioned without corneal contact, as long as the surgeon is aware of the importance of peripheral positioning.

The answer to the question, as to whether aqueous shunt implantation in an eye with healthy corneal endothelium, or a healthy penetrating keratoplasty, and positioned so that there is no possibility of endothelial contact, does or does not compromise the corneal endothelium in the longer-term, has not been adequately investigated.

It therefore remains to be proven whether aqueous shunts can reliably be placed in the anterior chamber in a position that can be guaranteed not to compromise corneal endothelium, e. g. behind Schwalbe's line. However, the intraocular course of a shunt can now be visualized in such cases with anterior segment optical coherence tomography (AS-OCT) (Sarodia et al. 2007). It is likely that with better imaging equipment, such as AS-OCT, and non-contact specular microscopy, the mechanical contribution to the influence of shunts on corneal endothelium will eventually be resolved.

4. Current Shunts and Factors Affecting their Function

At present, the most-widely researched shunts in terms of clinical trials are the Baerveldt Glaucoma Implant (Advanced Medical Optics, Irvine, California, USA), Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, California, USA) and the Molteno

Implant. More recently the Molteno implant has been replaced by the Molteno 3 (Molteno Ophthalmics Limited, Dunedin, New Zealand). However, the design of all of these is still based on Molteno's original implant (Fig. 2).

Extensive experience with the Molteno implant also highlighted two impediments to achieving safe, predictable, physiological, long-term IOP levels. The first is difficulty in producing a physiological IOP in the early postoperative period, and the second is controlling long-term encapsulation. Of the two more popular shunts at the time of writing, the Baerveldt Glaucoma Implant and the Ahmed Glaucoma Valve, the Ahmed has gone some way to address the former problem and the Baerveldt, the latter. Although these implants have a similar luminal diameter and length after implantation and hence a similarly low natural resistance to aqueous flow, the Ahmed Glaucoma Valve (see below) contains an additional flow resistor, designed to reduce the incidence of early hypotony.

The main determinant of longer-term shunt function is the degree to which the plate encapsulates. All shunt end-plates develop a surrounding capsule to some degree (Lloyd et al. 1996, Molteno 1969 a, b). In non-valved shunts, this is the main point of resistance to aqueous flow and therefore the major determinant of IOP in the longer-term.

The factors influencing the degree of encapsulation are not well-defined but include plate surface area, material, surface profile, flexibility and the presence or absence of a flow-resistor.

4.1 Surface Area

Although the surface area of the external plate is only one variable that might influence encapsulation, and hence the major determinant of long-term IOP control, the importance of plate surface area has been well demonstrated in two randomized controlled trials (Britt et al. 1999, Heuer et al. 1992). These, in addition to other non-randomized clinical series (Molteno 1981, Seah et al. 2003) suggest that an optimum plate size exists somewhere between 250 and 350 mm^2.

It seems that shunt size represents a trade-off between smaller plate size and higher long-term pressures, or large plate size, better long-term IOP control, but a higher risk of sequelae from hypotony.

Despite this, plate surface-area is only one of a number of implant-related factors that may influence long-term IOP control, although it is one of the easiest to modify given that there are implants of several different sizes on the market.

4.2 Plate Material

Shunt end-plate material may also influence the degree of reaction around the implant and hence the degree of encapsulation. Polypropylene devices implanted sub-conjunctivally in rabbits induce more inflammation than similar devices made from silicone. Likewise, rigid plates exhibited more inflammatory potential than flexible ones (Ayyala et al. 1999, Ayyala 2000). However, as these plates differ in other factors such as shape, profile, surface texture, contact area with adjacent tissues, flexibility, and micro-motion, all of which might influence the degree of encapsulation, the observed effect may not be exclusively due to the type of plate material or surface area alone (Lim et al. 1998).

4.3 Commercially-Available Devices

A discussion of all the commercially-available shunts would be outside the scope of this review and hence they have been discussed only in general functional terms above (destination of shunted aqueous etc.). The shunts that have been available for longest, and hence studied most, are the Ahmed, Baerveldt, Molteno.

(*i*) The Ahmed Glaucoma Valve (Fig. 5) is manufactured with a flexible silicone plate (FP7) or a rigid polypropylene plate (S2) of similar surface area (184 mm^2). The tube portions are identical and approximately 600 µm in external diameter. Versions with smaller plates designed for pediatric eyes are also available.

(*ii*) The Baerveldt Glaucoma Implant (Fig. 5) features a large (250 or 350 mm^2) flexible silicone plate that is noticeably different from the Ahmed in that it is thinner, broader and barium impregnated to make it radio-opaque.

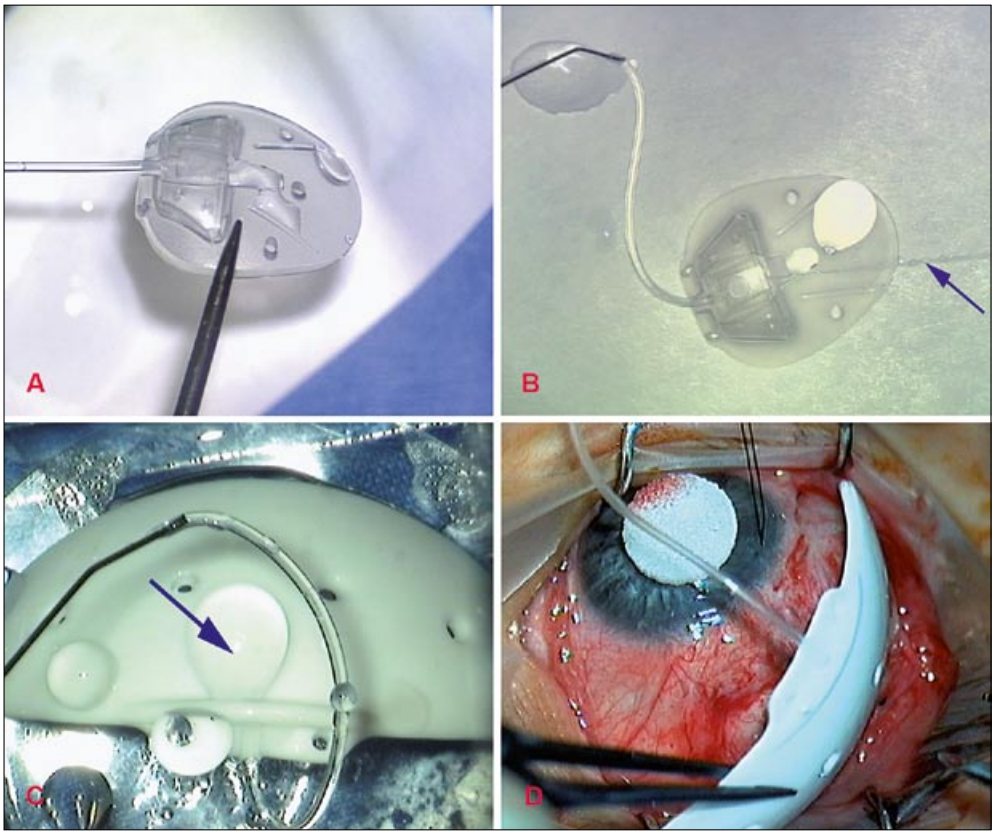

Fig. 5 The Ahmed glaucoma valve (*A*, *B*) contains a flow-restrictor that must be primed (*B*, arrow). The Baerveldt glaucoma implant (*C*, *D*) has virtually no natural flow resistance and therefore fluid exits freely when infused. Through the tube portion (*C*, arrow).

(*iii*) The Molteno Implant. The classical Molteno implant is available as a single polypropylene plate (135 mm^2), and a double plated version in which the two plates are connected to by a tube, similar in manufacture to the anterior chamber tube portion of the implant. The implant is designed so that the two plates sit in the supero-nasal and supero-temporal quadrants (or infero-nasal and infero-temporal) respectively and the interconnecting tube courses under the superior (or inferior) rectus muscle. The Molteno 3 implant is a flexible larger single plate implant that has recently been released. There are two plate sizes 175 mm^2 and 230 mm^2.

4.4 Comparative Studies

At the time of writing, non-randomized retrospective studies provide the majority of comparative data between the Baerveldt Implant and Ahmed Glaucoma Valve (Tsai et al. 2006, Wang et al. 2004, Syed et al. 2004) though the Ahmed versus Baerveldt Comparative (ABC). Study, a randomized prospective controlled trial, has recently completed recruitment. In Tsai et al. (2006) the types and causes of failure differed in the two groups in that the Baerveldt group implants were more likely to fail from hypotony-related complications, and the Ahmed group implants were more likely to require additional glaucoma medications. However, the authors of that report also acknowledge that the two groups were not directly comparable as the Ahmed group included significantly more eyes with inflammatory glaucoma as the indication for surgery.

It has been suggested that sub-conjunctival tissue exposure to aqueous humor in the early postoperative period, is detrimental to the long-term success of the shunt as it might expose subconjunctival tissues to greater levels of inflammatory cytokines than is the case with ligated shunts, where aqueous flow does not occur until 5–6 weeks after surgery. The only evidence in support of this is circumstantial, i. e. high levels of TGF-β have been reported in eyes with elevated IOP and sub-conjunctival exposure to TGF-β is likely to increase fibrosis within the bleb capsule.

The most widely perceived benefit of the Ahmed implant is probably its ability to reduce the risk of early hypotony, and for the Baerveldt it is an ability to achieve low pressure levels in the longer-term. It is easier to achieve satisfactory pressure levels early with the Ahmed, whereas Baerveldt implantation is more complicated requiring ligation of the tube portion with an absorbable suture at the time of surgery to prevent flow for about 5 weeks. During this period of time the IOP often remains high before dropping suddenly when the ligature absorbs. This difficulty in achieving a satisfactory IOP early in the postoperative course without a sudden drop at an unexpected moment is something that is of particular interest to the author. A technique that I have used successfully with the Baerveldt implant is to introduce Sherwood's 3/0 nylon Supramid stent suture (Sherwood and Smith 1993) along the entire length of the tube. When the tube plus stent are introduced into the anterior chamber via an entry site in the sclera that is tighter than normal (25 gauge rather than 23), the tube is squeezed where it passes through the sclera. Squeezing the tube around the outside of the stent suture increases the resistance to aqueous flow through the tube, to a sufficient degree to prevent early hypotony in most cases without the need to ligate the tube. With careful adjustment at the time of surgery, it is possible to achieve IOP levels that are less elevated than after ligation, but have the benefit that there is no sudden drop after 5 weeks.

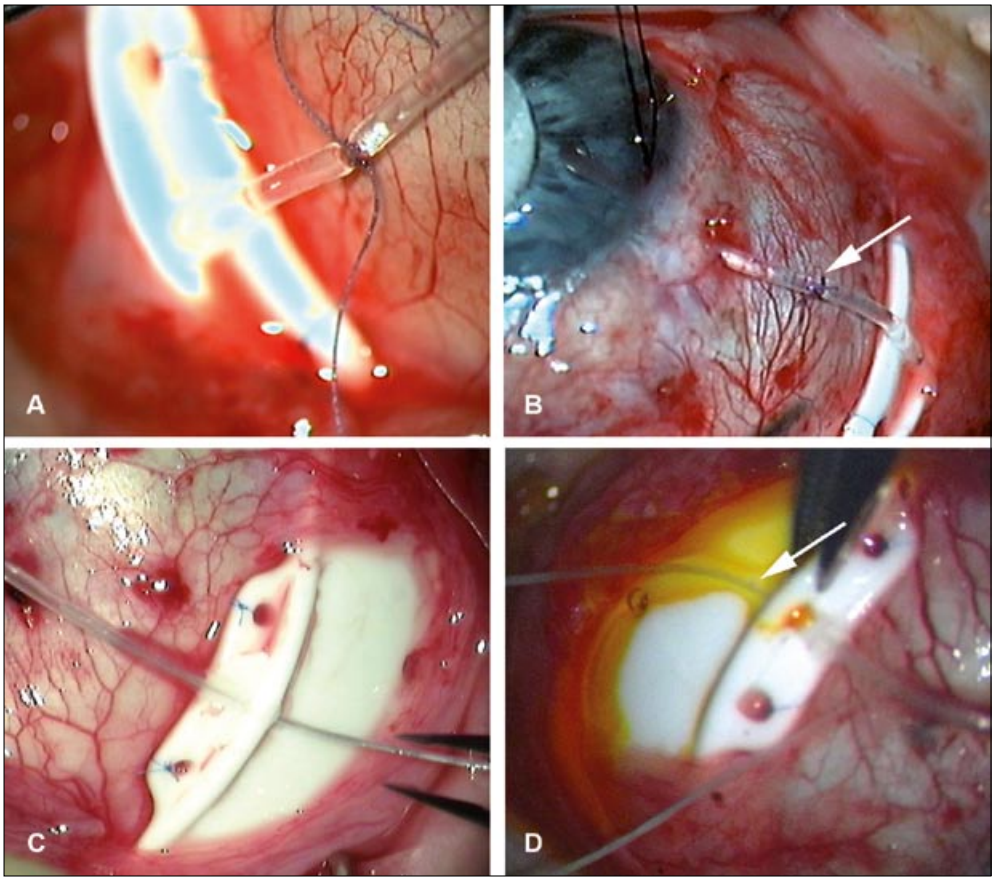

Fig. 6 Conventionally the Baerveldt implant is ligated to prevent early flow (*A*; *B*, arrow). A stenting technique developed by the author (*C*, *D*) can be used to reduce the aqueous flow seen (*D*, arrow), to such a low level that a physiological IOP can be achieved in the early postoperative period in a proportion of patients.

5. Purpose in Developing Implants

In developing a new implant one would look for the following attributes. Firstly, the ability to achieve low target IOP levels in patients with advanced glaucoma. Secondly, shunted aqueous should be diverted to avoid limbal drainage. Thirdly, any benefit must be long-lasting, at least 10–20 years.

It goes without saying that the device should be safely implantable and should not expose the patient to a significant additional risk of visual loss.

6. Future Challenges

Until recently, aqueous shunts have been reserved for complicated glaucomas that are unresponsive to both medical and other forms of surgical therapy. In such cases, the potential benefits in terms of IOP control have outweighed the risks in terms of unpredictability of

early IOP control. However, improving surgical outcomes from aqueous shunts, as demonstrated in the tube *versus* trabeculectomy study (TVT) (Gedde et al. 2005, 2007 a, b) in combination with persistent concern over the morbidity associated even with successful trabeculectomy, have resulted in renewed interest in the use of aqueous shunts as the primary surgical intervention in primary open angle glaucoma.

While there is some evidence of comparability in terms of safety and efficacy with trabeculectomy, (Gedde et al. 2005, 2007 a, b) and also some evidence that shunts may even be relatively safe when used as primary surgery for primary glaucoma (Wilson et al. 2003), there are some additional concerns that should be addressed if aqueous shunts are to be used as a primary alternative to trabeculectomy for primary glaucomas.

Overall, the main limitation in shunt development is a lack of financial investment, as most of the barriers to development of the ideal shunt do not appear to be insurmountable. The external equatorial shunts that are available today are still relatively crude. I have highlighted some of their shortcomings. The supra-choroidal space has not proven to be a predictable route in the past but is worthy of re-investigation. Randomized clinical trials of the existing shunts such as the TVT, ABC, and in the future the primary TVT study, are likely to result in increasing adoption of shunts in preference to trabeculectomy. With a growing marketplace, perhaps the manufacturers can be encouraged to invest more in shunt design.

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Medicine at the Interface between Science and Ethics

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Naturwissenschaft und Theologie/Ethik versuchen mit unterschiedlichen Konzepten, ein Weltbild zu erfassen, das die *conditio humana* besser zu verstehen erlaubt. Die Fragen sind weit gefasst; endgültige Antworten wird man nicht leicht finden. Gemeinsame Diskussionen über diese Probleme könnten beiden Gebieten Anregungen geben und der Biomedizin im Umgang mit der sehr kritischen Öffentlichkeit helfen. Voraussetzung ist Offenheit gegenüber der anderen Denkweise. Der vorliegende Band behandelt daher aus der Perspektive von Naturwissenschaftlern und Ethikern so verschiedene Themen wie die neuen Herausforderungen an Moral- und Ethikdiskurse durch die jüngsten Fortschritte der Biowissenschaften, die Grenzen der ethischen Reflexion bei den neueren Entwicklungen der Molekularbiologie, die Geschichte der Auffassungen vom „Gen“ und seiner Bedeutung in der Humanbiologie, aber auch die Missverständnisse zwischen den beiden Kulturen der Naturwissenschaften und der Geisteswissenschaften in der Forschung über Lebensprozesse. Dazu kommen Beiträge zur Stammzellproblematik, der Verwendung von Tiermodellen in der Translationsmedizin, über Würde von Zellen in Kultur, Fragen der Pluripotenz von Zellen und der Reprogrammierung von Zellkernen sowie der Bedeutung von Methylierungsmustern für die Epigenetik. Die Beiträge sind in englischer oder deutscher Sprache verfasst.

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Glaucoma Implants – Principles, Concepts, and Clinical Aspects

Thomas S. Dietlein and Walter Konen (Köln)

Abstract

Different concepts of antiglaucomatous implant surgery have been studied during the last years. Their target is the establishing or the improvement of an artificial filtration, but also the enhancement of existing outflow pathways, i. e. the uveoscleral and transtrabecular outflow, using special new devices. Recent data reflects significant intraocular pressure reduction using these new devices, but the achievable range of postoperative intraocular pressure does not seem to be as low as following filtering surgery.

Zusammenfassung

Mehrere konzeptionell unterschiedliche Ansätze der antiglaukomatösen Implantatchirurgie sind in den letzten Jahren in der klinischen Erprobung. Diese sind nicht nur darauf gerichtet, eine neue (unphysiologische) Filtration in den subkonjunktivalen Raum zu ermöglichen bzw. zu erleichtern, sondern auch bereits bestehende Abflusswege wie den uveoskleralen bzw. den transtrabekulären durch spezielle neue Implantate zu verbessern. Die bisherigen Daten zeigen, dass hierdurch eine eine signifikante Augendrucksenkung möglich ist, allerdings bisher nicht in dem Ausmaß, dass diese Verfahren mit der transskleralen Filtration klinisch konkurrieren könnten.

1. Introduction

Common target of all glaucoma implants or glaucoma drainage devices is the surgical enhancement of the aqueous outflow from the anterior chamber (Freedman 2006, Lim et al. 1998, Minckler 2001). The history of glaucoma implant surgery started in the early 20th century using very heterogeneous materials to improve transscleral filtration, i. e. horse hairs. The most well-known glaucoma drainage devices in the world are the devices introduced by Molteno, Krupin, Ahmed and Baerveldt.

In this short review we propose a subdivision of the implants according to their functional concept (Dietlein et al. 2008):

- Drainage into Schlemm's canal;
- Drainage into the subchoroidal space;
- Intrascleral implants aiming to improve intra-/transscleral filtration;
- Episcleral implants aiming to improve transscleral filtration;
- Transscleral Drainage to the conjunctiva near to the limbus;
- Transscleral Drainage to the equatorial/retroequatorial conjunctiva.

2. Drainage into Schlemm's Canal

Morphologic and functional studies on human donor eyes have demonstrated the crucial role of the trabecular meshwork for the increased outflow resistance in primary open-angle glaucoma and other subtypes of chronic open-angle glaucoma, i. e. exfoliative glaucoma or pigment dispersion glaucoma. From a theoretical point of view, a trabecular opening of 10–20 µm would re-establish a physiologic outflow facility in a glaucomatous eye. Bypassing the trabecular meshwork is the concept of the i-stent, a microstent made of stainless steel for the *ab-interno* implantation in Schlemm's canal, and of the Eyepass, a very small silicone double-tube that is inserted *ab-externo* following scleral flap dissection (Dietlein et al. 2008, Spiegel et al. 2007, Spiegel und Kobuch 2001). In contrast to the Eyepass, the i-stent is commercially available. Implantation of both devices requires surgical training and skill, but their postoperative safety is not a matter of concern, especially owing to the low risk of postoperative hypotony. As no transscleral filtration develops, the postoperative IOP level is not as low as following trabeculectomy. Consequently, this approach is not recommended in glaucomatous eyes requiring a low target pressure.

The future role of trabecular stents (i. e., i-stent, Eyepass) still has to be determined, but in clinical practice there is an obvious trend to use these devices (and other types of trabecular surgery – i. e. trabectome) in combined glaucoma-cataract surgery, as this concept avoids the risk of postoperative overfiltration and instability of the anterior chamber.

3. Drainage into the Subchoroidal Space

The basis of this concept is the enhancement of the uveoscleral outflow replacing mechanical cyclodialysis with a bypass system. The main problems of cyclodialysis have been early hypotony and late scarring of the uveoscleral cleft. Scarring around the suprachoroidal end of an uveoscleral implant has also been demonstrated (Heine 1905, Jordan et al. 2007). Risk of ocular hypotony with these implants seems to be minor, but there is a tendancy for extrusion if the implants are not sutured in a fixed position (Jordan et al. 2006, Ozdamar et al. 2003, Yablonski 2005). The theoretical advantage of this non-filtering approach is the eligibility of the surgical area even in the lower quadrants of the eye. The devices used for this approach show a tremendous heterogeneity concerning the design and the material reflecting the experimental character of these devices.

4. Intrascleral Implants Aiming to Improve Intra-/Transscleral Filtration

Intrascleral implants aiming to improve intra- and transscleral filtration have been implanted and investigated for many years worldwide (Ates et al. 2003, Sourdille et al. 1999, Wiermann et al. 2007). The supposed concept is an improvement of transscleral flow and the creation of an intrascleral lake with a possible drainage to the intrascleral vessels and the uveoscleral space. However, this hypothesis is not yet strongly supported by morphologic studies. Several materials (i. e., collagen, acrylate etc.) have been used for these implants. Several prospective and retrospective studies focus on the question of whether

these implants enhance the surgical outcome in deep sclerectomy, but these studies are quite contradictory (Devloo et al. 2005, Lüke et al. 2003, Ravinet et al. 2004, Sanchez et al. 1996/1997, Shaarawy et al. 2004).

5. Episcleral Implants Aiming to Improve Transscleral Filtration

The current "gold standard" of glaucoma surgery, filtration surgery with antimetabolites, is burdened by the complications of the filtering bleb including leakage of the conjunctiva, blebitis, endophthalmitis and visual loss. Bioresorbable subconjunctival implants modifying wound healing may be a potential concept to replace the antimetabolites and to reduce the antimetabolite-associated complications. Animal studies have demonstrated that implants made of collagen-glycosaminoglycan-polymeres can signiaficantly reduce the wound contraction of the conjunctiva (Hsu et al. 2000) and prolong the function of a filtering bleb (Chen et al. 2006). At the moment, several prospective studies investigate the safety and efficacy of these implants in combination with conventional trabeculectomy.

6. Transscleral Drainage to the Conjunctiva Near to the Limbus

Implantation of a stent at the limbus in order to directly connect the anterior chamber with the subconjunctival space is a very quick procedure with a lot of risks. Even if hypotony can be avoided by the micro-design of the inner openings there is a considerable risk of implant erosion owing the limbal positioning. Although the ExPress-shunt achieved remarkable results in combined cataract-glaucoma surgery (Traverso et al. 2005, Rivier et al. 2007), nearly all surgeons changed the subconjunctival implantation technique to a scleral-guarded procedure in order to reduce the risk of conjunctival erosion (Stewart et al. 2005, Tavolato et al. 2006). Thus, this implant does not offer a really new concept, but simplifies a standard opening of the anterior chamber during conventional filtering surgery (Dahan und Carmichael 2005, Maris et al. 2007).

7. Transscleral Drainage to the Equatorial/Retroequatorial Conjunctiva

The most well-known glaucoma drainage devices are the "Molteno" (Molteno 1969), the "Krupin", the "Ahmed", und the "Baerveldt" device (Lim et al. 1998, Minckler 2001, Siegner et al. 1995). The common concept is the aqueous drainage from the anterior chamber via a silicone tube (inner diameter 300 µm) to a more or less flexible foot-plate in the equatorial or retroequatorial region. During the first weeks following surgery a fibrotic capsule develops around the foot-plate, but the capsule possesses a certain capacity of aqueous diffusion resulting in an intraocular pressure decrease (Molteno et al. 1999, Nouri-Mahdavi und Caprioli 2003). An important factor for the functional outcome seems to be the size of the foot-plate (Britt et al. 1999, Heuer et al. 1992), but also individual features, similar to filtering surgery. Whether valved implants or certain materials should be prefered has still to be answered by prospective studies (Prata et al. 1995, Ishida et al. 2006).

Pressure-reducing results of the glaucoma drainage devices seem to be comparable to standard filtering surgery. However, the frequency of complications and of additional antiglaucomatous topical medication following surgery seems to be higher for the implant surgery (Gedde et al. 2007b, Stein et al. 2008). Long term analysis of medicare beneficiaries suggests that corneal decompensation is a massive problem (~25 %) in glaucoma drainage devices after 6 years (Stein et al. 2008). By improving the surgical technique the risk of tremendous early ocular hypotony following implantation of a glaucoma drainage device has fallen significantly demonstrated by the early postoperative intraocular pressure values of the TVT study (Gedde et al. 2007a).

As yet there is no clear evidence whether the Ahmed or the Baerveldt glaucoma drainage device is superior concerning efficacy and safety (Coleman et al. 1995, Syed et al. 2004). An ongoing prospective randomized multi-center study now focuses on this topic.

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Surface Coating of Glaucoma Drainage Devices – a Possibility to Enhance Success Rates?

Hagen Thieme (Mainz)

With 3 Figures

Abstract

Glaucoma drainage devices used to treat glaucoma have a firm position in the repertoire of ophthalmic-surgeons. The indication for using these glaucoma drainage devices needs a critical evaluation, since the public has recently received the impression that these devices are competing against common operative procedures, such as filtering or non-filtering glaucoma surgery. The idea to implant an artificial shunt in order to drain aqueous humor has existed for a long time. During the mid-18th century, horse hair and gold thread was used. But since the mid-20th century, surgeons have been using plastic and silicone materials which promoted the development of glaucoma drainage devices. In 1970, Molteno developed the first glaucoma drainage devices consisting of silicone. Thus, he designed the basic type of the episcleral systems that are common today and which connect a small silicone tube with a base plate. This tube ensures communication between the anterior chamber and a filtering bleb formed above the basic plate. Shape and size vary from model to model. The material of which the basic plate consists is different as well. Similar to trabeculectomy, the cicatrization of the filtering bleb limits the efficacy of the glaucoma drainage devices. The data regarding the anterior chamber angle-supported systems vary considerably.

Zusammenfassung

Drainagesysteme zur Behandlung des Glaukoms finden zunehmende Verbreitung im Repertoire des Ophthalmochirurgen. Die Indikationsstellung für diese Systeme bedarf einer kritischen Bewertung, da durch Publikationen der letzten Zeit der Eindruck entstanden ist, dass sie mit den gängigen operativen Verfahren, wie den fistulierenden und nicht-fistulierenden Eingriffen, konkurrieren. Die Idee, einen künstlichen Shunt zu legen, um das Kammerwasser abzuleiten, ist schon sehr alt. Während in der Mitte des 18. Jahrhundert Pferdehaare und Goldfäden zum Einsatz kamen, sind es seit der Mitte des 20. Jahrhunderts Plastik- und Silikonmaterialien, die die Entwicklung der Drainagesysteme voranbrachten. 1970 entwickelte Molteno das erste aus Silikon bestehende System. Er entwarf damit den Grundtyp der heute gängigen episkleralen Systeme, bei denen ein kleiner Silikonschlauch mit einer Basisplatte verbunden wird. Dieser Schlauch stellt die Kommunikation zwischen der Vorderkammer und einem sich über der Basisplatte ausbildenden „Sickerkissen“ her. Die Form und Größe variiert von Modell zu Modell, und auch das Material, aus dem diese Basisplatte besteht, ist verschieden. Ähnlich wie bei der Trabekulektomie ist es auch die Vernarbung des Sickerkissens, die den Erfolg der Drainagesysteme limitiert. Die Datenlage zu den kammerwinkelgestützten Systemen ist uneinheitlich.

Glaucoma drainage devices have a firm position in the repertoire of the glaucoma surgeon. Their use is more accepted in the US even in early stages of surgical intervention, whereas in Europe their indication is reserved for the more difficult glaucoma cases. Here the eyes receiving a glaucoma drainage device usually have had numerous pre-operations which often had not been successful. The much respected TVT study (“tube versus trabeculectomy

study"; GEDDE et al. 2007) showed that after one year, glaucoma drainage devices had better results than standard trabeculectomies. However, the drainage group needed more medical treatment in order to gain lower target intraocular pressure (IOP) than did the other group. Another point of criticism is the relatively short follow up. Side effects from fibrovascular encapsulation usually occur after more than one year. Another late complication is corneal decompensation which is prone to develop in such cases many years after the implantation of the device. As mentioned before, here in Europe often only the worst cases are treated with glaucoma drainage devices making successful results less likely. Prognosis of eyes which had several surgical interventions (including cyclodestructive ones) is poor, especially in juvenile patients.

Foreign body reaction is the principle cause of late failure. As with trabeculectomy, wound healing limits the success of glaucoma drainage devices. Fibro vascular reaction, which can also be observed in cases of buckling, or circling band surgery in cases of retinal detachment (but without involvement of aqueous humor), limits the success of glaucoma drainage devices. Extensive scar tissue formation leads to encapsulation of the devices and again leads to increased IOP levels. The literature gives a cyst development rate of 20–75 % (MINCKLER et al. 2006, SHAARAWY et al. 2009). Once these cysts are punctured with a needle, the aqueous humor gushes out and IOP immediately drops to low levels. One can describe these cysts as an "episcleral anterior chamber" connected to the real an-

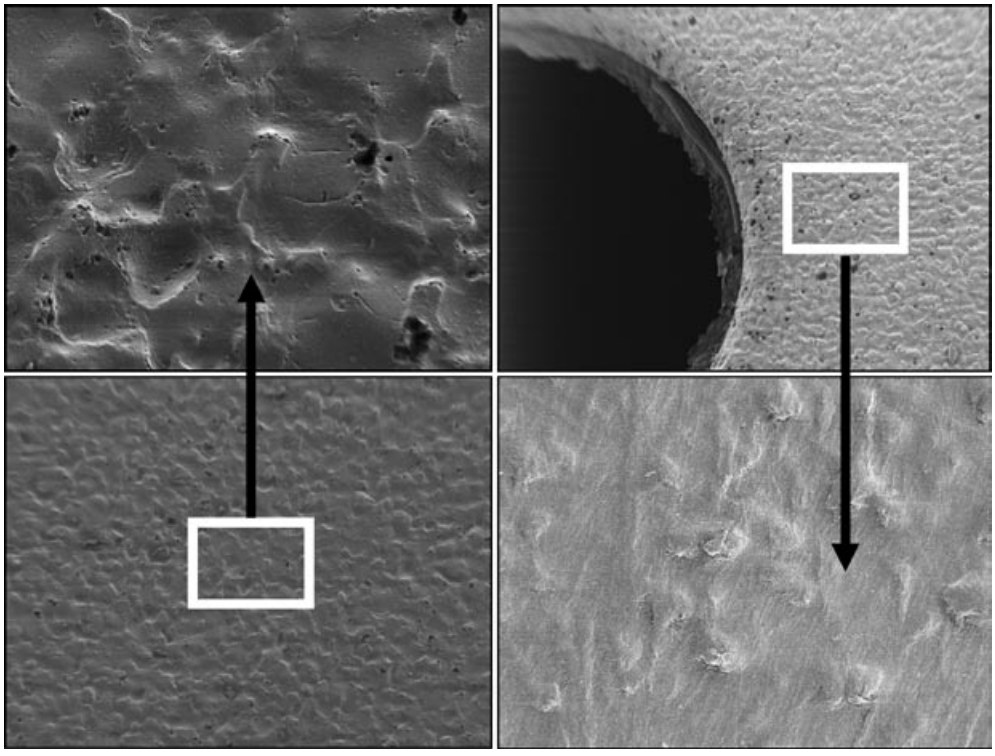

Fig. 1 Ahmed silicone drainage implantat (Type-FP7), confocal microscopy different surface areas of the base plates shown.

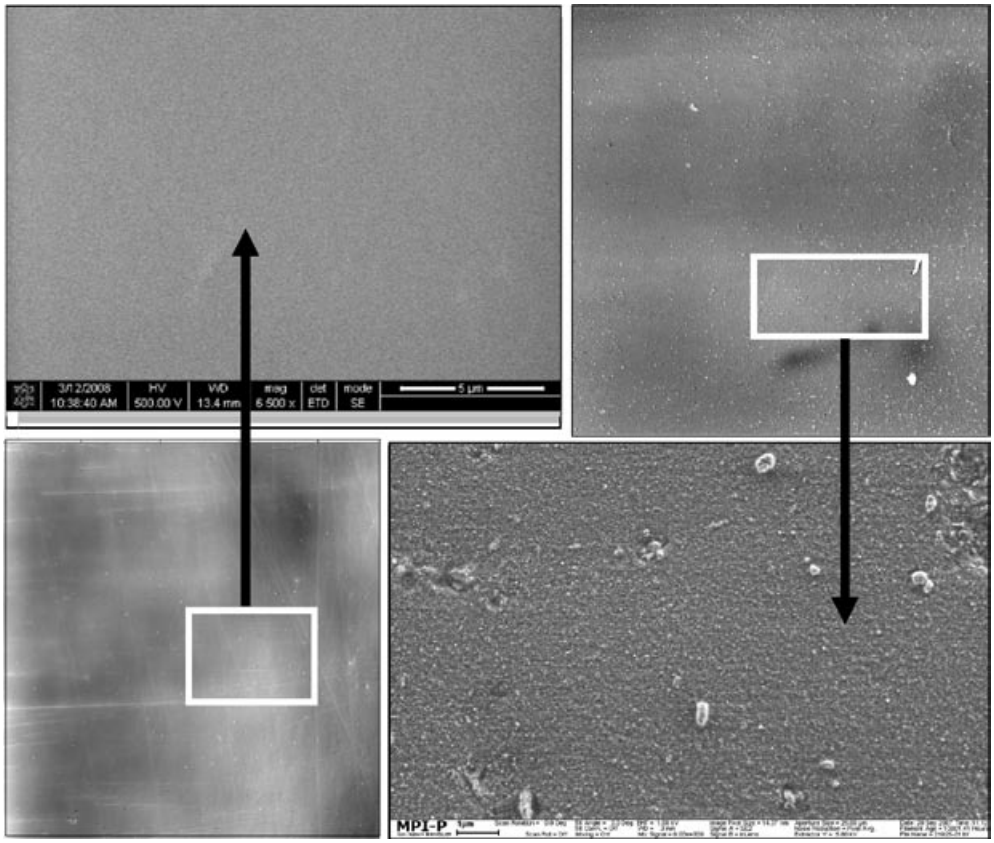

Fig. 2 Molteno implant shown on the left, Baerveldt-implant shown right, confocal microscopy different surface areas of the base plates shown.

terior chamber by the silicone tube of the device but without a proper connection to the blood vessels which could drain the aqueous away from the site. Often surgical removal of these cysts is needed (Thieme et al. 2010).

There are certainly several factors that influence wound healing. Race and age of the patients, the number of previous operations, condition of the conjunctiva and presences and/or absence of postoperative complications such as bleeding and hypotony all influence wound healing. On the molecular level proliferation of fibroblasts, synthesis of extra cellular matrix, and pre-existing conjunctival cellular activation may contribute to failure. The use of antimetabolites such as Mitomycin C and 5-Fluoruracil (5FU) is currently discussed. Their use in children and juvenile patients in whom success rates are poor is also a subject of debate.

All drainage systems use a base plate of varying size. These are fixed between tenons membrane and sclera; connection to the anterior chamber is accomplished by a silicone tube. Molteno, in the late 1970s, was the first to develop the basic principle which all others followed for their episcleral devices. Later the Ahmed and Baerveldt glaucoma drainage devices were introduced. Those three devices are the market leaders in the field while only the Ahmed device features a valve mechanism, thus preventing early postoperative hypotonies.

Usually polypropylene was used as a base plate material in the early devices. Nowadays silicone material is favored due to greater flexibility and ease of implantation. Additionally clinical success seems to be enhanced when silicone material is used. Surface properties of these base plates were considered unimportant up until now. This seems rather surprising as the surface is indeed the first contact between tenon fibroblasts and the foreign body. This may be of importance for cell differentiation and transforming tenon fibroblasts into myo-fibroblasts which may lead to cyst formation.

Our studies show that vast differences exist between different drainage devices as far as surface properties are concerned (see Figs. 1 and 2). While Ahmed devices (type FP7 and S2) feature relatively rough surfaces (between 11.4 and 5.5 microns), the other two are smoother (Molteno and Baerveldt between 0.41 and 0.90 microns respectively). Rough surfaces could be connected to enhanced cell adhesion in *in vitro* studies. Ahmed base plates showed stronger cell adhesion using human tenon fibroblasts in comparison to smoother surfaces (see Fig. 3; Choritz et al. 2010). Comparing these *in vitro* cell adhesion data with encapsulation rates given in the literature for various glaucoma drainage devices, again the Ahmed device shows an impaired success rate with higher IOP spikes after the implantation.

Can these problems be solved? Surely surface modulation could present a method to enhance success rates. Smooth surfaces coated with anti-proliferative substances could present an elegant "drug-to-site" possibility. Using the base plates for drug delivery is an interesting way of implanting "intelligent base plates". Another point of interest would be base plate thickness with thinner devices being less prone to "stretch activation of wound healing". The first studies to address these questions are currently in progress.

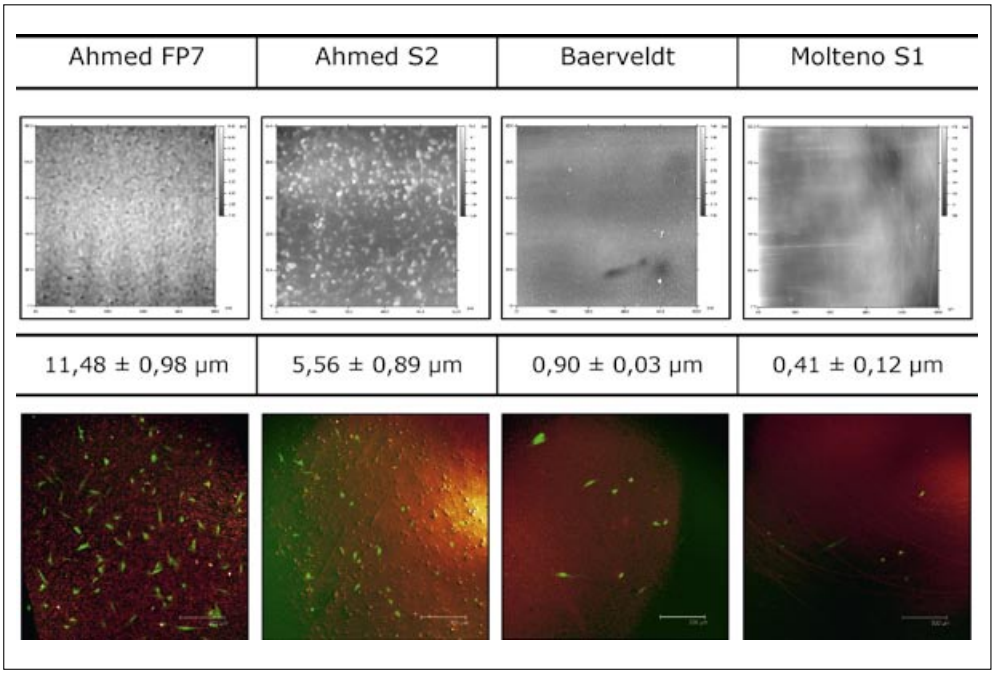

Fig. 3 Images of various drainage implants showing their surface profile and roughness. Clearly visible enhanced cell adhesion on rough surfaces.

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Präkonditionierung und Organprotektion durch Anästhetika

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Patienten, die sich operativen Eingriffen unterziehen müssen, sind entsprechend der demographischen Entwicklung in den Industrieländern zum Zeitpunkt des Eingriffs zunehmend älter und weisen ein immer umfangreicheres Spektrum von Begleiterkrankungen auf. Dem Schutz der Organfunktion und insbesondere der Prävention ischämischer Ereignisse kommt somit im perioperativen Verlauf eine herausragende Bedeutung zu. Daher hat das Verfahren der ischämischen Präkonditionierung in den letzten Jahren sehr großes Interesse hervorgerufen. Unter Präkonditionierung versteht man, dass eine kurz dauernde Ischämie in Zellen Anpassungsprozesse in Gang setzt, die diese Zellen gegen eine nachfolgende, länger dauernde Ischämie widerstandsfähiger machen. Die Beiträge des Bandes zeigen, dass es möglich ist, beispielsweise durch Verabreichung spezifischer Pharmaka, u. a. der sogenannten volatilen Anästhetika, protektive Effekte auf Zell- und Organebene zu erzielen. Mit Blick auf klinische Relevanz und Erarbeitung neuer Therapiestrategien zur Gewebeprotektion ist vor allem die arzneimittelinduzierte Präkonditionierung im Fokus der pharmakologischen Forschung. Molekulare Grundlagen und Anwendungsbereiche des Verfahrens werden diskutiert.

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Wound Healing Peculiarities in Glaucoma Surgery

Günther Schlunck (Würzburg)

Abstract

Scarring is a major problem in glaucoma surgery using either drainage implants or filtering procedures. Frequently, surgically established aqueous drainage pathways are obstructed by cicatrization. TGF-β-induced transdifferentiation of fibroblasts to myofibroblasts is a pivotal step in wound healing and scarring. Biomechanical cues such as tissue elasticity or interstitial fluid flow are additional essential modifiers of scarring processes. New approaches to develop glaucoma drainage devices should therefore consider conjunctival aqueous fluid dynamics as well as mechanisms of cellular mechanotransduction.

Zusammenfassung

Der narbige Verschluss des neu geschaffenen Kammerwasserabflussweges ist ein Hauptproblem der Glaukomchirurgie. Dies gilt sowohl für die Anwendung von Drainageimplantaten als auch für filtrierende Eingriffe. Ein wesentlicher Schritt der Wundheilung und Vernarbung ist die Transdifferenzierung von Fibroblasten zu Myofibroblasten, die durch den Wachstumsfaktor TGF-β-1 (oder -2) ausgelöst wird. Neben TGF-β spielen auch biomechanische Faktoren für den Verlauf von Vernarbungsreaktionen eine Rolle. Hierzu zählen die Elastizität des Gewebes und der interstitielle Flüssigkeitsstrom. Neue Ansätze zur Entwicklung von Drainageimplantaten sollten daher die Hydrodynamik des ausströmenden Kammerwassers im Bereich der Bindehaut und die Mechanismen der zellulären Mechanotransduktion berücksichtigen.

1. The Problem of Excessive Healing

Wound healing processes are essential and desired to avoid infection and to allow for sustained wound closure following any surgical intervention. However, excessive wound healing severely limits the success of glaucoma drainage surgery. Most types of glaucoma drainage surgery aim to shunt aqueous humor from the anterior chamber to the subconjunctival space to allow for aqueous humor resorption by the conjunctival vasculature. Drainage implants are frequently encapsulated by a fibrotic capsule which severely hampers fluid flow and leads to therapeutic failure (Schwartz et al. 2006). In up to 60 % of trabeculectomy patients, fibrotic scarring precludes the attainment of the main goal of surgery, to reach target intraocular pressure (IOP) without a need for additional medication. Intensified postoperative care using sunconjunctival antimetabolite injections may reduce this fraction to 35 % (Marquardt et al. 2004). In contrast, other transconjunctival

procedures such as surgery for strabism or retinal detachment induce only mild fibrotic responses. This raises the question which peculiar aspects of glaucoma drainage surgery enhance the wound healing response.

2. General Aspects of Wound Healing

Tissue trauma elicits an initial inflammatory response which is mediated by platelet aggregation and the release of stimuli such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). Next, polymorphonuclear cells (PMNs) and monocytes enter the wound with lymphocytes to follow. Coagulation, removal of debris and neutralization of infectious agents are the major objectives of this initial phase of wound healing. After 1–3 days the proliferative phase of wound healing begins. Growth factors and altered tissue biomechanics attract fibroblasts, induce their proliferation and further activate them. TGF-β has a major role in this process (Desmouliere et al. 1993). It is expressed in three isoforms, which bind to heteromeric receptor complexes to activate several intracellular signaling pathways. TGF-β1 is released from monocytes and PMNs and is embedded in the extracellular matrix as an inactive storage complex. In a pivotal step, TGF-β1 or -β2 induce the transdifferentiation of fibroblasts to myofibroblasts (Gabbiani 2003). Myofibroblasts express smooth muscle actin, which boosts cell contractility to allow for wound closure. It was shown recently that mechanical tension exerted by myofibroblasts is sufficient to release active TGF-β1 from interstitial stores (Wipff et al. 2007). Furthermore, myofibroblasts generate the foundations of new tissue as they deposit extensive amounts of extracellular matrix. Studies of conjunctival scar tissue in trabeculectomy patients revealed an abundance of activated myofibroblasts with strong TGF-β receptor expression. While myofibroblasts are transiently present in all wounds, persistence of myofibroblasts is associated with cicatrization. In contrast, scarring does not occur in embryonal wound healing which is attributed to a mild embryonal immune response and a lack of TGF-β (Ferguson und O'Kane 2004, Martin et al. 2003).

3. Wound Healing in Glaucoma Drainage Surgery

Primary open angle glaucoma is associated with increased levels of active TGF-β2 in the aqueous humor (Tripathi et al. 1994). Subsequent studies revealed a correlation of aqueous TGF-β2 levels and conjunctival scarring following filtering surgery (Picht et al. 2001). These observations and data from animal studies suggested an essential role for the TGF-β2 isoform in scarring following glaucoma drainage surgery. Accordingly, a neutralizing anti-TGF-β2 antibody appeared beneficial to avoid scarring in subsequent animal experiments and in clinical pilot studies (Cordeiro et al. 1999, Siriwardena et al. 2002). However, two recent randomized multicenter phase III trials failed to detect an advantage of the antibody over placebo (Grehn et al. 2007, Khaw et al. 2007). The specificity of the antibody for the TGF-β2 isoform may have contributed to this result, since PMNs, macrophages and interstitial stores release the TGF-β1 isoform which was not targeted in the trials. It is also unclear if four applications (pre- and postop, as well as one day and within one week after surgery) were sufficient to induce sustained tissue levels. These trial results

notwithstanding, the pivotal role of TGF-β in wound healing and scarring is generally accepted and remains unabated.

Structural tissue changes are also important modulators of wound healing. The ED-A splice variant of fibronectin is induced by TGF-β and has been characterized as an essential contributor to myofibroblast transdifferentiation and a prerequisite for smooth muscle actin expression (Serini et al. 1998). ED-A fibronectin is also strongly expressed in scarred conjunctival tissue following filtering glaucoma surgery (Meyer-ter-Vehn et al. 2008). This may be of particular importance in revision surgery, when failure rate is further increased.

Recent studies in the field of cell biology point towards biomechanical cues as fundamental drivers of diverse cell functions. The intracellular conversion of mechanical stimuli to biochemical signals is termed mechanotransduction. It has become apparent that almost all cell types are able to respond to mechanical stimuli. In general, cell-cell and cell-matrix adhesions transmit mechanical stimuli to intracellular signaling molecule complexes and the cytoskeleton (Ingber 2006). In line with these principles, TGF-β-induced myofibroblast transdifferentiation was blocked by inhibition of cell contractility and the resulting weakening of the actin cytoskeleton and cell-matrix adhesion complexes (Meyer-ter-Vehn et al. 2006). Subsequent studies have confirmed these findings (Honjo et al. 2007, Tura et al. 2007). Tissue elasticity is another important mechanical cue with profound influence on basic cell functions (Discher et al. 2005). Stiff matrices have been shown to enhance myofibroblast transdifferentiation (Grinnell et al. 1999). TGF-β-induced smooth muscle actin expression is stronger on rigid as compared to soft matrices *in vitro*. Longstanding conjunctivitis which often occurs with chronic use of topical medication may alter biomechanical tissue characteristics and may thus influence cell signaling and scarring.

Interstitial fluid flow is one of the most intriguing, yet rarely studied, biomechanical stimuli which may have fundamental implications in glaucoma drainage surgery. It differs from the well characterized vascular blood flow-induced shear force since the interstitial flow rates are much smaller. In a seminal study, Ng, Hinz and Swartz have assessed the effects of slow fluid flow (6.3 μm/s) on fibroblasts *in vitro* (Ng et al. 2005). It became apparent that slow media flow rates induced cell proliferation, cytoskeletal alignment (orthogonal to flow direction) and myofibroblast transdifferentiation. Furthermore, fluid flow was sufficient to induce cell-matrix adhesion-dependent TGF-β1 expression in fibroblasts as a major auto- and paracrine stimulus of myofibroblast transdifferentiation. These data strongly suggest that interstitial fluid flow may suffice to drive a scarring response. The very goal of glaucoma drainage surgery, to induce aqueous flow into the subconjunctival and conjunctival interstitium may thus be detrimental to its own success. Currently no data are available on the flow-dependence of tenon fibroblasts, and further studies are needed to characterize a possible quantitative relationship of flow rates and myofibroblast transdifferentiation. One might assume that lower flow rates induce less scarring. As a result, drainage implants should disperse aqueous outflow over a large area to minimize local flow rates. Clinical observations support this hypothesis: Larger Baerveldt or Molteno implants induced less fibrotic encapsulation than smaller Ahmed valves (Schwartz et al. 2006). The clinical concept to increase outflow gradually when postsurgical inflammation has subsided may not only help to reduce hypotonic complications, it may also make sense with regard to cellular mechanotransduction and its implications on scarring.

In summary, possible scar-promoting effects of altered tissue hydrodynamics should be considered in the design of new drainage implants. When implant surfaces are functionalized to allow for cell adhesion, the effects of substrate elasticity and adhesive strength on cell functions should be taken into account. For the design of drug release systems, pharmacological inhibition of cell contractility or inhibition of TGF-β1 and -β2 signaling may prove beneficial.

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Local Drug Delivery Concepts and Surface Modification in Glaucoma Implant Surgery

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With 8 Figures

Abstract

Glaucoma leads to blindness by damaging the optic nerve. The modern strategies of glaucoma management are to avoid glaucomatous damage and to preserve visual field with negligible side effects. The goal of the present study was to develop a biodegradable drug-eluting coating for a new glaucoma drainage system with a low fibrotic potential. In our investigations poly(L-lactide), poly(3-hydroxybutyrate), and poly(4-hydroxybutyrate) were tested for the manufacture of polymer/drug coatings containing paclitaxel or triamcinolone. The biocompatible poly(4-hydroxybutyrate) exhibits the best ability to act as tubing material due to its mechanical flexibility and as coating material due to its drug release behavior. The applicability of this polymer was also confirmed by *in vivo* studies, which demonstrated a decrease of intraocular pressure in rabbit eyes after implantation of paclitaxel coated poly(4-hydroxybutyrate) tubes.

Zusammenfassung

Das Glaukom ist eine der häufigsten Erkrankungen des Sehnervs. Als Folge kommt es zu charakteristischen Gesichtsfeldausfällen und im Extremfall zur Erblindung des Auges. Diesem Krankheitsverlauf wird heute durch moderne Therapiekonzepte entgegengewirkt, die die Lebensqualität der Patienten erhalten und möglichst geringe Nebenwirkungen für den Patienten bedeuten. Das Ziel unserer Untersuchungen bestand darin, auf der Basis der biodegradierbaren Polymere Poly(L-lactid), Poly(3-hydroxybuttersäure) und Poly(4-hydroxybuttersäure) medikamentenhaltige Beschichtungen zur Verhinderung der Fibrose bei Glaukomimplantaten zu entwickeln. Als Modellpharmaka wurden das antiproliferativ wirkende Zytostatikum Paclitaxel und das Antiphlogistikum Triamcinolon untersucht. Es wurde festgestellt, dass sich die biokompatible Poly(4-hydroxybuttersäure) hinsichtlich ihrer mechanischen Eigenschaften und ihres Wirkstofffreisetzungsverhaltens am besten für diese Anwendung eignet. Dies wurde auch in ersten *In-vivo*-Studien bestätigt, da mit Paclitaxel beschichteten Implantatprototypen eine Erniedrigung des Augeninnendruckes im Kaninchenauge erreicht werden konnte.

1. Introduction

Glaucoma, as a significant public health problem, affects more than 67 million people in the world, and approximately 10 % of them are estimated to be blind (Lim et al. 1998,

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Dietlein et al. 2008). A significant risk factor for glaucoma is a raised intraocular pressure (IOP) of above 22 mmHg. Glaucoma is a disease that affects the optic nerve and involves the loss of retinal ganglion cells.

The modern goals of glaucoma management are to avoid glaucomatous damage and to preserve visual field and quality of life for patients with negligible side effects. These strategies require appropriate diagnostic techniques and individual glaucoma treatments for each patient. The decrease of IOP via various drugs and/or surgical techniques is currently favored for glaucoma treatment.

The IOP can be lowered with medication, usually with eye drops. In addition, several surgical techniques and devices were developed for artificial aqueous drainage in glaucoma. In glaucoma surgery, the scarring of the tissue leads to the development of a fistula which is the limiting factor for long-term IOP control. Only glaucoma implants, such as the open, unobstructed Molteno tube-plate system (Taglia et al. 2002, Deokule et al. 2007) implanted from the anterior chamber to the conjunctiva seems to provide more efficient long-term success. Comparable with the Molteno implant is another open tube, non-valved drainage implant, the Baerveldt implant (Sarkisian 2009). Further developments are the Ahmed and Krupin implants which are designed to have flow-restricting valve mechanisms (Taglia et al. 2002, Lee et al. 2009). The glaucoma drainage devices are based on materials such as silicone, polypropylene, or polytetrafluoroethylene, which may enhance the adherence of fibroblasts and cause inflammation in surrounding tissues. Consequently, there is a strong need for a drainage system that inhibits fibroblast proliferation and inflammatory reactions. In a system comparable to Drug-Eluting Stents, employed in vascular intervention (Bünger et al. 2006, Sternberg et al. 2007) and avoiding systemic toxic side effects a drug-eluting glaucoma drainage system, based on more biocompatible implant materials as well as antiproliferative and anti-inflammatory implant coatings, should be developed.

The goal of the present study was to develop a biodegradable drug-eluting coating for a new glaucoma drainage system by Guthoff et al. (2009) that could prevent the fibrotic reaction by liquid drainage from the anterior chamber into the suprachoroidal space within the eye, with a low fibrotic potential. In our investigations different polymers were tested that could be utilized to manufacture polymer-based drug coatings in terms of the suitability to release drugs in required concentrations and time periods, and in terms of their biocompatibility *in vitro* and *in vivo*.

2. Local Drug Delivery Concepts

In order to avoid systemic toxicity, implant-based local drug delivery via a non-polymer or polymer-based drug coating is an attractive therapeutic approach to control the implant-induced cellular processes. A number of polymers, biodegradable and non-degradable, were tested concerning their potential to act as coating material. Different drug classes are under consideration, such as agents that are anti-inflammatory, antiproliferative or antibiotic agents, drugs which affect cell migration and extracellular matrix production, and drugs for Drug-Eluting Stents that promote vascular healing and re-endothelialization.

Well-established and promising local drug delivery concepts to control implant-induced cellular processes are:

- Drug release from swellable polymer coatings;
- Drug release from biodegradable polymer coatings;
- Drug release from nanoporous coatings;
- Drug loading between drug-free polymer coatings, drug diffusion through drug-free polymer top coating;
- Drug release from cavities;
- Drug-polymer conjugates, drug release by conjugate cleavage;
- Drug release from fully biodegradable implant materials;
- Chemical linkage of drugs to implant or polymer surfaces.

Our work focuses on the implant-based local drug delivery from biodegradable polymer coatings, or fully biodegradable implant materials with the aim to prevent foreign material reactions caused by permanent polymeric matrices and the enhancement of tissue regeneration. In this context, we used biodegradable polymers, such as poly(L-lactide) (PLLA), poly(3-hydroxybutyrate) (P(3HB)), and poly(4-hydroxybutyrate) (P(4HB)). PLLA, one of the most common biodegradable polymers, is used in a wide range of medical applications. These include surgical devices and sutures, urological and vascular stents, as well as drug delivery implants (Makela et al. 2002, Tsuji et al. 2003, Zhu et al. 2003, Saito et al. 2004, Sternberg et al. 2004).

Our study describes in detail the following functional characteristics of antiproliferative and anti-inflammatory coatings for a new glaucoma drainage system: (*i*) *in vitro* degradation profile of the biodegradable polymeric coating materials, (*ii*) *in vitro* biocompatibility of these biodegradable polymers in direct contact with tenon fibroblasts, (*iii*) effects of antiproliferative and anti-inflammatory model drugs on cellular growth and proliferation, (*iv*) *in vitro* drug release behavior of drug coated polymeric tubes, and (*v*) *in vivo* biocompatibility and functionality of polymeric tubes, implanted for liquid drainage from the anterior chamber into the suprachoroidal space.

3. Antiproliferative and Anti-Inflammatory Coatings for a New Glaucoma Drainage System

Polymeric stent coatings were developed based on biodegradable polyesters, such as poly(L-lactide), poly(3-hydroxybutyrate) and poly(4-hydroxybutyrate), containing the antiproliferative drug paclitaxel (PTX) and the anti-inflammatory drug triamcinolone acetonide (TA). PTX is an inhibitor of cell division, due to the ability to stabilize microtubules and to interfere with the normal breakdown of microtubules during mitosis. PTX is an established antiproliferative drug in coronary Drug-Eluting Stents. The synthetic corticosteroid TA is a triamcinolone derivative which has a higher anti-inflammatory potential than triamcinolone.

Small diameter tubes were prepared in an automated dip coating process. A stainless steel core (~ 0.3 mm diameter, 40 mm length) was dipped into the polymer/chloroform solution (~ 0.7 to 1.1 % w/w). With intermittent drying cycles, this process was repeated until a tube with the desired wall thickness of ~ 280 to 320 µm was obtained. The tube was removed from the core and dried *in vacuo* at 40 °C. The polymer drug solutions were applied onto the tube surface by a spray-coating process. The coating quality was evaluated by use of microscopic methods (Fig. 1).

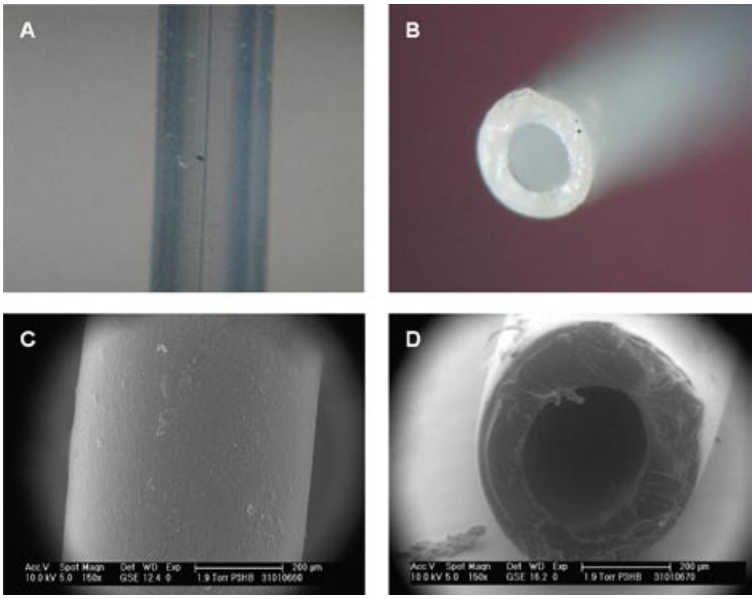

Fig. 1 Surface morphology and cross section of drug-coated polymer minitubes – Light Microscopy, Scanning Electron Microscopy (SEM).

In vitro degradation tests of the polymers PLLA, P(3HB), and P(4HB) were performed. The degradation behavior of natural, isotactic P(3HB), a blend of 70 % (w) natural, isotactic P(3HB) with 30 % (w) atactic P(3HB) as well as P(4HB) is shown in Figure 2. PLLA was used as reference. Molecular weight and polydispersity were determined by means of gel permeation chromatography (GPC). Chloroform was used as a solvent at a flow rate of 1 ml/min, sample concentration was in the range of 0.4 to 1.4 mg/ml, and an injection volume of 0.1 ml was applied. The results were obtained via a universal calibration method with narrow disperse polystyrene standards as a reference.

The *in vitro* degradation tests, carried out in Sørensen buffer, confirmed the slow degradation of pure P(3HB) within the range of PLLA degradation (Fig. 2). The addition of atactic P(3HB) led to an accelerated degradation of natural P(3HB) at 37 °C. P(4HB) possesses the highest degradation rate, because the degradation was nearly complete after 52 weeks.

In order to evaluate the biocompatibility of the used polymers several cytotoxicity tests were performed according to ISO-10 993. Cell lines, as well as human primary cells, were used to assess cytotoxicity. Figure 3 shows the results of cell viability tests with tenon fibroblasts in direct contact with films of degradable polymers P(3HB), a 70/30 % (w/w) blend of natural, isotactic and synthetic, atactic P(3HB) and P(4HB). The tests were carried out with tenon fibroblasts seeded onto the polymer surface and cultured for 48 hours. The cell viability assay (MTS test) determines the activity of mitochondrial and cellular dehydrogenases of viable, metabolic active cells. The yellow color of the MTS-reagent, the tetrazolium salt, changed to a violet brown color of the formazan salt and was quantified with an ELISA reader at a wavelength of 492 nm and a reference wavelength of 690 nm.

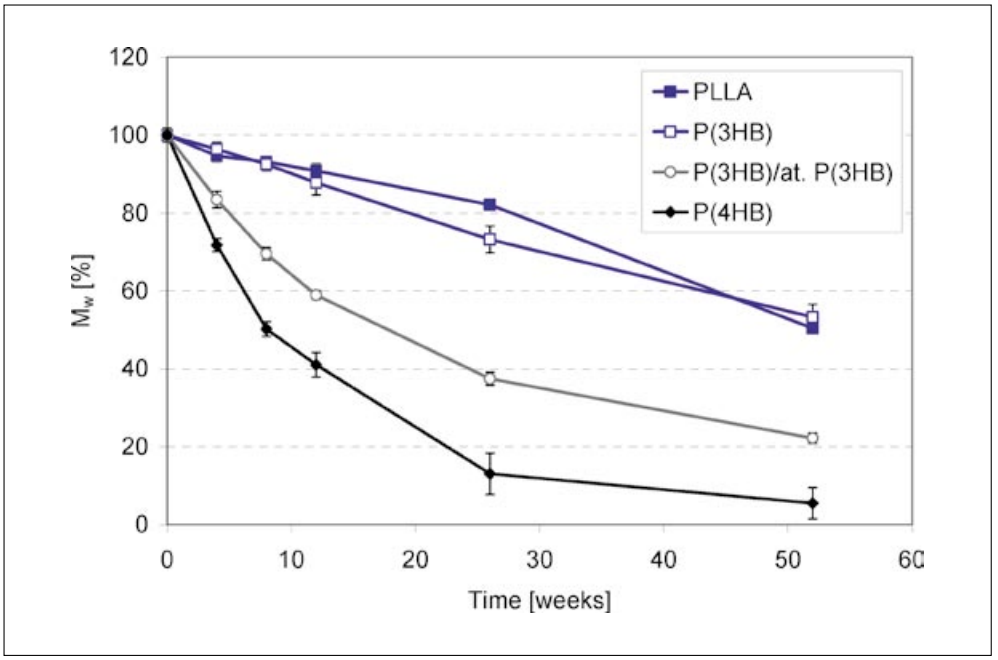

Fig. 2 Polymer degradation in Sørensen buffer (pH 7.4, 37 °C) and determination of molecular weight decrease by means of GPC; PLLA degradation of P(3HB) and P(3HB)/at. P(3HB) according to Freier et al. 2002.

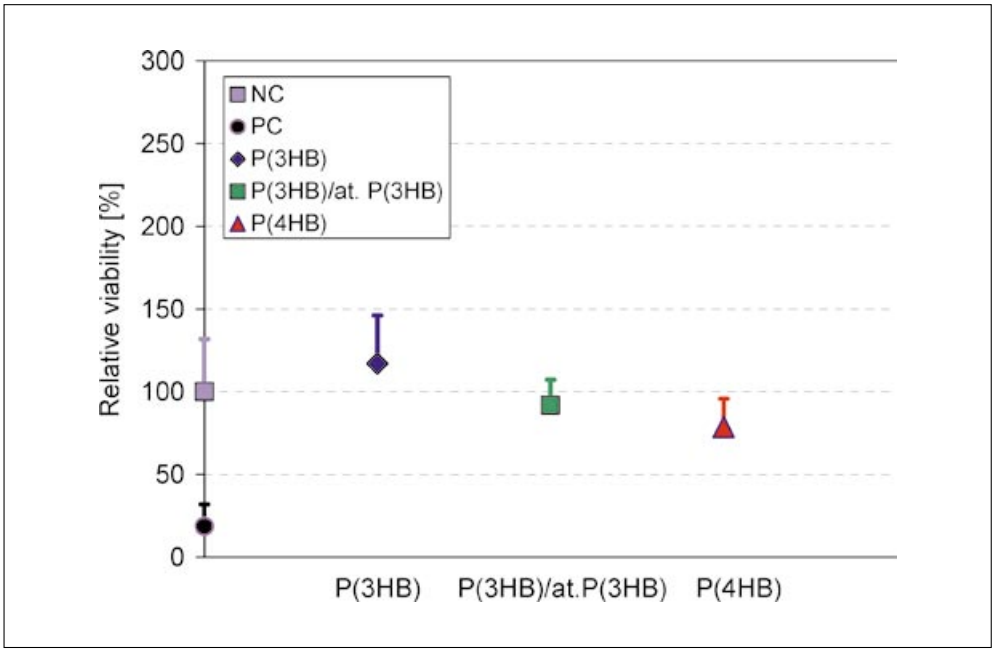

Fig. 3 Relative viability of tenon fibroblasts seeded on the polymer surfaces (cultured for 48 h, each with n = 6).

The *in vitro* results demonstrated that the relative viability of tenon fibroblasts was lower on P(4HB) in comparison to natural P(3HB) and the P(3HB) blend combination.

The drugs PTX and TA were tested for their potential to control tenon fibroblast growth. The seeded tenon fibroblasts as well as the seeded keratocytes with L929 mouse fibroblasts as a reference were incubated in their respective growth medium for one day at 37 °C under 5 % CO_2 and 95 % relative humidity. The growth medium was replaced by the antiproliferative drug PTX in a growth medium within a concentration range of 10^{-2} and 10^{-4} mol/l (M). The cell viability was measured by means of the CellQuanti-Blue assay after 24 h. Cellular reductase activity was quantified by fluorescence measurements (excitation wavelength 544 nm, emission wavelength 590 nm). It was detected that all cell types were inhibited in their growth in a concentration dependent manner. The highest reduction of relative viability up to 80 % was achieved with 10^{-4} M PTX (Fig. 4).

Additionally, the antiproliferative potential of the anti-inflammatory drug TA was investigated in the same concentration range. Our *in vitro* results indicated that tenon fibroblast viability was inhibited in a concentration range of 10^{-8} to 10^{-4} M TA (Fig. 5). An advantage of both drugs was the higher sensitivity of tenon fibroblasts to PTX and TA, compared to keratocytes (Figs. 4 and 5).

The time course of drug release from coated tubes was determined at 37 °C in isotonic (0.9 %) sodium chloride solution by means of HPLC. The release behavior of PTX or TA embedded in P(3HB) or P(4HB) coatings in a polymer/drug ratio of 70/30 % (w/w) is shown in Figure 6. It was assessed that the drug release is faster mainly in the initial phase if the drug was embedded in P(4HB). However, with all coated tubes relevant drug concentrations of 2.0–3.2 × 10^{-5} M PTX/d (initial) and 3.5–5.6 × 10^{-7} M PTX/d as well as 1.0 × 10^{-4} M TA/d (initial) and 6.2 × 10^{-6} M TA/d were obtained.

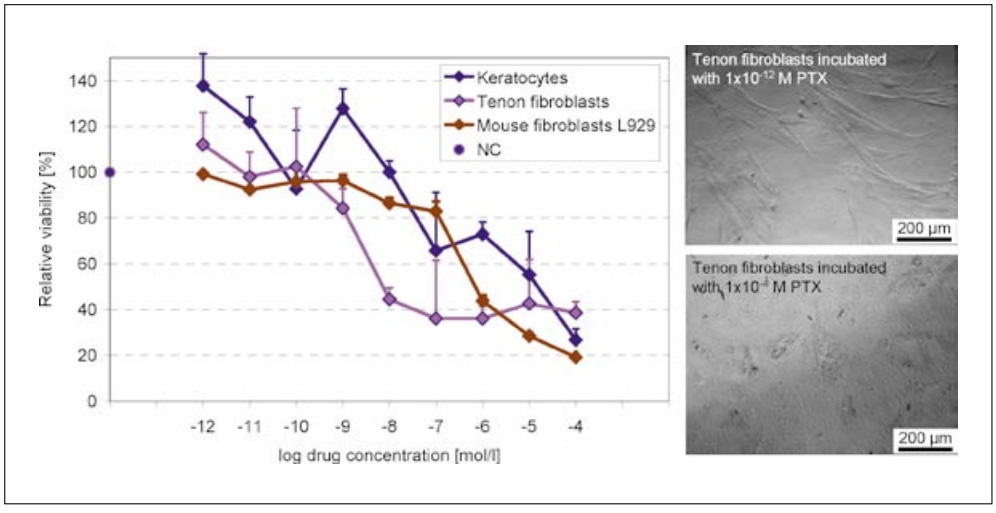

Fig. 4 Relative cell viability after 24 h-incubation with PTX solutions of different concentrations (each with n = 6).

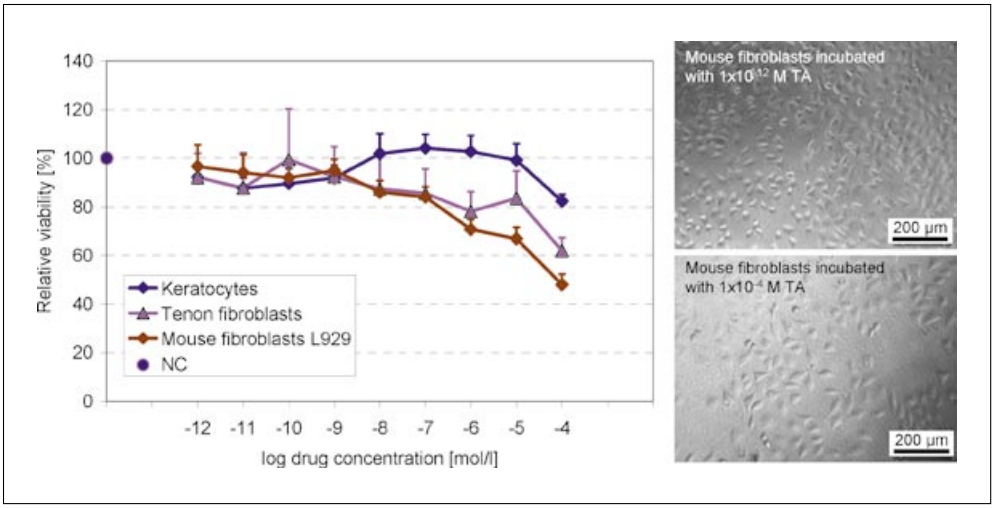

Fig. 5 Relative cell viability after 24 h-incubation with TA solutions of different concentrations (each with n = 6).

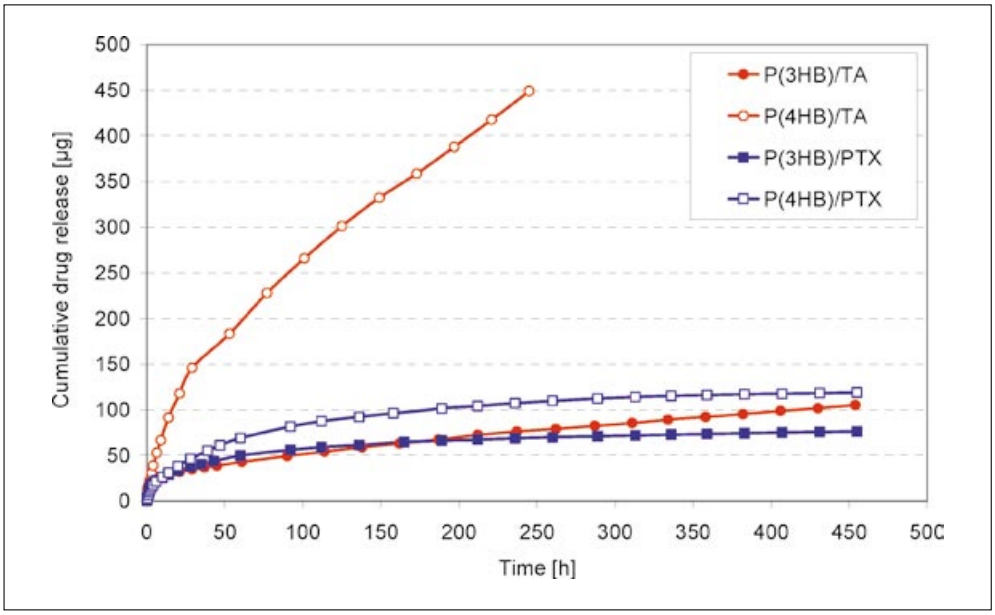

Fig. 6 Cumulative absolute drug release [µg] of P(3HB) or P(4HB)/drug coatings in isotonic NaCl solution at 37 °C.

Furthermore, the *in vivo* biocompatibility and functionality of PTX coated P(4HB) tubes implanted to drain liquid from the anterior chamber into the suprachoroidal space of White New Zealand rabbits were studied. One hundred days postoperatively a moderate vascularization in the cornea and conjunctiva was found and an open stent lumen within the anterior chamber (Fig. 7).

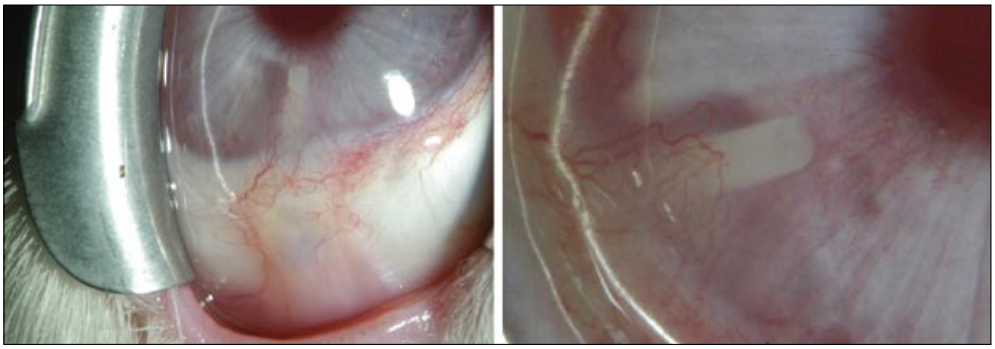

Fig. 7 White New Zealand rabbit eye (100 days postoperatively).

The success of the treatment was confirmed by IOP measurements. For this purpose IOP was measured non-invasively with an iCare tonometer. Calibration was performed by systemic measurements on *ex vivo* rabbit eyes, comparing results to invasive pressure data. The results, illustrated in Figure 8, represent that the IOP is lower in the left eye supplied with a P(4HB)/PTX tube than in the untreated right eye. A tube closure due to fibrosis or scarring was not observed.

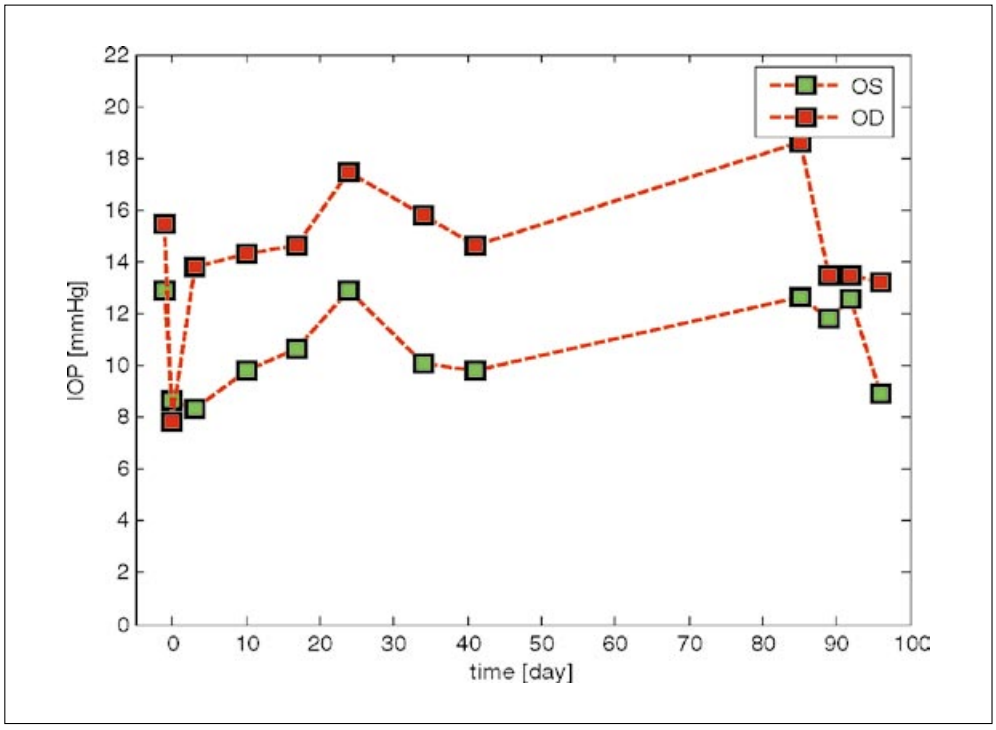

Fig. 8 Results of IOP measurements in White New Zealand rabbit eyes (100 days postoperatively); right eye (OD): untreated, without tube implantation, left eye (OS): with P(4HB)/PTX tube implantation (suprachoroidal drainage).

4. Conclusions

Glaucoma is characterized by a long term increase of mean IOP and hence bears the risk of irreversible damage to the optical nerve leading to blindness. In order to reduce the IOP and inhibit fibrotic and inflammatory processes caused by conventional implants, biodegradable drug-loaded polymeric coatings for a new glaucoma drainage system, which is currently under development by Guthoff et al. (2009), were analyzed. In this respect, polymer tubes, based on P(3HB) and P(4HB), were used as carrier and were coated with the model drugs PTX and TA. From our *in vitro* investigations it can be stated that the biocompatible P(4HB) exhibits the best ability to act as tube material due to its mechanical flexibility and as coating material due to its drug release behavior.

The applicability of P(4HB) was also confirmed in first *in vivo* studies, which demonstrated a decrease of IOP after suprachoroidal implantation of P(4HB)/PTX tubes in rabbit eyes (OS) (100 days postoperatively) in comparison to the untreated eyes (OD).

5. Outlook

Further investigations are necessary to develop a suitable glaucoma drainage system and to elucidate the exact physiologic mechanisms underlying the draining, the capacity and duration of the draining effect.

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Accommodation – Young Eyes for Elderly People

Nova Acta Leopoldina NF *111*, Nr. 379, 107–114 (2010)

Surgical Restoration of Accommodation: Fact or Fiction?

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With 4 Figures

Abstract

There is considerable and growing interest in understanding if it is possible to restore accommodation to the presbyopic eye. If accommodation is to be restored to the presbyopic eye, it requires a sound understanding of the accommodative anatomy, the accommodative mechanism, the causes of presbyopia, and an understanding of how to measure accommodation. It is necessary to do objective measurements of accommodation to evaluate accommodation restoration concepts. Accommodation could be restored to the presbyopic eye with so-called accommodative intraocular lenses that are designed to undergo a movement in the eye to increase the optical power of the lens and the eye. Although accommodation restoration concepts have been disappointing thus far, several different kinds of accommodative IOLs are currently under investigation that may hold promise for the future.

Zusammenfassung

Es gibt ein deutlich steigendes Interesse für ein Verständnis der Möglichkeiten, die Akkomodation im presbyopen Auge wiederherzustellen. Zur Wiederherstellung der Akkomodation im presbyopen Auge ist eine gründliche Kenntnis der entsprechenden Anatomie, des Akkomodationsmechanismus, der Ursachen der Alterssichtigkeit und der Akkomodationsmessungen erforderlich. Objektive Messungen der Akkomodation sind notwendig, um Konzepte zur Wiederherstellung der Anpassung zu bewerten. Die Akkomodation im presbyopen Auge könnte mit Hilfe sogenannter akkomodativer Intraokularlinsen wiederhergestellt werden, die so konstruiert sind, dass sie sich im Auge bewegen, um die optische Leistung der Linsen und des Auges zu erhöhen. Obwohl Konzepte zur Wiederherstellung der Anpassung bisher enttäuschend waren, werden zurzeit verschiedene akkomodative Intraokularlinsen getestet, die vielleicht Hoffnung für die Zukunft geben.

1. Introduction

Accommodation is a dioptric (i. e., optical) change in power of the eye to focus at near distances due to an increase in optical power of the lens with ciliary muscle contraction. Presbyopia is the age-related loss of accommodation. Accommodation is essentially completely lost by about the age of 55 and is primarily due to an increase in stiffness of the lens. There is considerable and growing interest in understanding if it is possible to restore active and dynamic accommodation to the presbyopic eye (GLASSER 2008). This effort is aimed at not simply alleviating the symptoms of presbyopia, but at actually restoring true, dynamic accommodation to the presbyopic eye. To understand if it is possible to restore accommoda-

tion to the presbyopic eye, it is necessary to understand the accommodative anatomy, the mechanism of accommodation, the causes of presbyopia and the accommodation restoration concepts that are being investigated.

2. The Accommodative Triad

Three events occur when an effort is made to focus at a near distance. The eyes undergo a convergence response to achieve single vision on a near object, the pupils constrict, and the ciliary muscles contract to produce the accommodative increase in optical power of the eye. Accommodation, convergence, and pupil constriction are coupled in the brain. These three events are referred to as the accommodative triad. The act of convergence also results in accommodation and constriction of the pupils. Therefore, every effort to focus on a near object probably results in a contraction of the ciliary muscle, even in the presbyopic eye. Evidence shows that the ciliary muscle continues to contract with an accommodative effort even in presbyopes (Stachs et al. 2002, Strenk et al. 1999).

3. The Optics of Accommodation

To focus on a distant object, an emmetropic eye (i. e., an eye without a refractive error) is unaccommodated. A distant object subtends parallel rays at the cornea. These parallel rays enter the eye and are refracted by the cornea and lens to cause the rays to converge to a point image on the retina. A near object subtends divergent rays at the cornea. When these divergent rays are refracted by the cornea and the unaccommodated lens, the overall optical power of the eye is insufficient for the rays to be brought to a sharp focus on the retina. The result is a blur circle on the retina and an out of focus image. When the eye accommodates to the near object, the optical power of the lens increases and the increased optical power of the eye then allows the rays diverging from the near object to be focused on the retina to form an in focus image. It is this increase in optical power of the lens and the eye that characterizes accommodation.

4. The Accommodative Anatomy

The ciliary muscle resides beneath the anterior sclera of the eye just posterior to the limbus. The ciliary muscle is the engine that drives accommodation. The ciliary muscle is surrounded by the ciliary body, a highly vascularized tissue that supplies nutrients and oxygen to the ciliary muscle. The anterior zonular fibers extend all along the base of the ciliary body to cross the circumlental space and insert into the lens capsule all around the lens equator. The lens capsule is a thin elastic membrane that surrounds the lens. There is a secondary group of zonular fibers, posterior zonular fibers, which extend from the apex of the ciliary process posteriorly towards the posterior attachment of the ciliary muscle.

5. The Accommodative Mechanism

At rest, when the emmetropic eye is focused for distance, the ciliary muscle is relaxed and resting tension on the zonular fibers spanning the circumlental space and inserting into the lens capsule around the lens equator hold the lens in a flattened and unaccommodated state. To focus on nearby objects, the ciliary muscle contracts and the apex of the ciliary muscle moves anteriorly-inward in the eye. This results in a release in the zonular tension at the lens equator and allows the elastic lens capsule surrounding the lens to mold the young, soft lens into a more spherical and accommodated form. This results in a decrease in lens diameter, an increase in lens thickness, but most importantly for the accommodative increase in optical power of the lens, it results in an increase in the lens anterior and posterior surface curvatures. This mechanism of accommodation is largely in accordance with the accommodative mechanism originally described by HELMHOLTZ (VON HELMHOLTZ 1855) (Fig. 1).

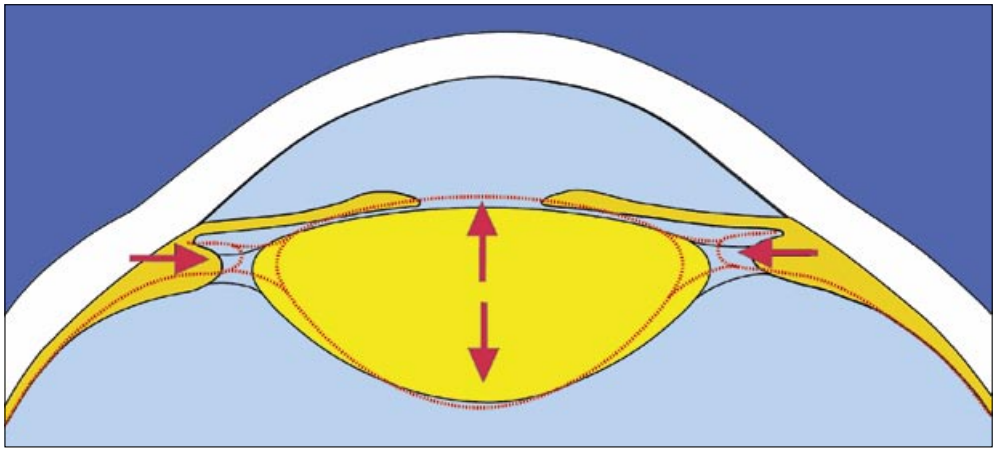

Fig. 1 The mechanism of accommodation similar to that originally described by HELMHOLTZ. The accommodated structures are shown in red. During accommodation, lens diameter decreases, lens thickness increases and the lens anterior and posterior lens surface curvatures increase.

6. Presbyopia

With increasing age, the human eye gradually and progressively loses the ability to focus on near objects. This progressive loss of accommodation actually begins early in life with a progressive loss of accommodative ability from about age 10. DUANE measured that accommodative response in some 1500 subjects ranging in age from 8 to 72 using a subjective push-up technique (DUANE 1912) (Fig. 2). His results show that young subjects have between 12 to 16 D of accommodation. With increasing age, this declines to about 1 D after about 50 years of age. This 1 D that remains after the age of 50 is an artifact due to the subjective measurement of accommodation and is due to the depth of field of the eye. More recent experiments with negative lens induced stimulus to accommodate suggests that the accommodative response amplitude is more constant up to the age of about 20 and then declines with increasing age and that this relationship is best described as a sigmoidal change with age (ANDERSON et al. 2008).

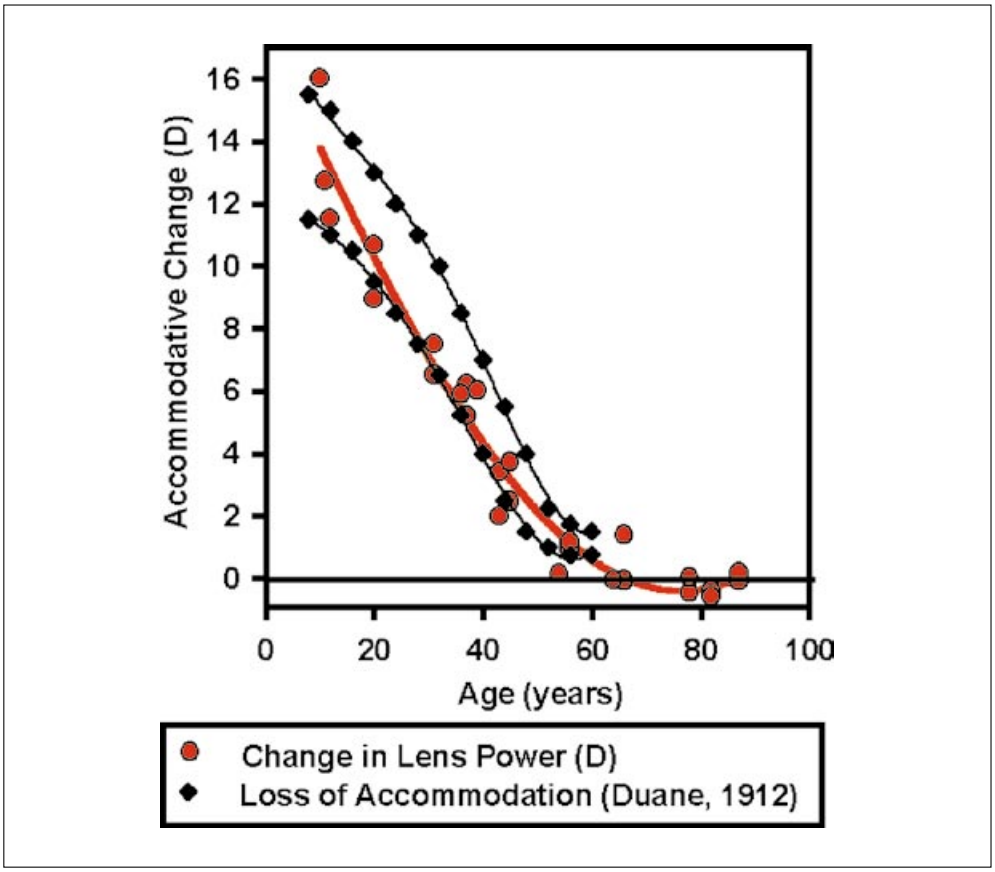

Fig. 2 Mechanical stretching experiments (red symbols) show that young human lenses undergo 12–16 D of accommodative change and that by 60 years of age, the same degree of mechanical stretching fails to produce any accommodative optical change in the older lenses. The data from human lenses is shown together with the subjective measurements in some 1500 subjects (black symbols) from DUANE (1912). (Reproduced with permission from GLASSER and CAMPBELL 1998, p. 219)

Experiments to understand the causes of presbyopia have been undertaken with human eye-bank eyes in which the eyes are dissected and the anterior segment tissues glued to a mechanical stretching device (GLASSER and CAMPBELL 1998). An optical ray-tracing method was then used to measure the accommodative optical changes in the lenses as a function of the applied stretching. This system relies on the capsule molding the young lens into an accommodated state when the stretching tension is released. Stretched lenses are therefore in an unaccommodated state and the unstretched lenses are in a maximally accommodated state. The experiments were undertaken on 19 human lenses ranging in age from 10 to 86. These mechanical stretching studies show that young human lenses undergo about 12–16 D of accommodative change in optical power, but that this accommodative ability is progressively lost such that at about 60 years of age, the same amount of mechanical stretching as is applied to the young

lenses results in no change in optical power of the older lenses. These experiments show that the human lens gradually and progressively loses the ability to undergo accommodative optical changes. These results strongly support the notion that at its endpoint, presbyopia is characterized by a complete loss of accommodative ability of the lens (GLASSER and CAMPBELL 1998).

7. Subjective and Objective Measurement of Accommodation

Clinically, accommodation is most commonly measured subjectively. Perhaps the most common clinical technique used is the subjective push-up technique (WIN-HALL et al. 2007, WIN-HALL and GLASSER 2008, 2009). This is actually not a reliable measure of accommodation, but is better described as a test of near reading distance. In this test the distance corrected subject is asked to bring a reading text closer to the eyes until the subject can no longer sustain clear focus on the near letters. The reciprocal of the distance between the letters and the eyes in units of meters is then expressed as the accommodative amplitude in diopters. This test is easy to administer and does not require any specialized instrumentation. However, this test does not simply measure the accommodative increase in optical power of the eye, but rather it measures some complex combination of factors that includes the optical change in the eyes, but also includes the depth of field as well as subjective and perceptual factors that contribute to functional near vision.

To understand if it is possible to restore accommodation to the presbyopic eye, it is necessary that objective means be used to measure accommodation. This requires the objective measurement of the optical change in power of the eyes that occurs as the subject makes an effort to focus on near. Objective autorefractors, refractometers, or aberrometers can be used to do such objective measurements of accommodation (WIN-HALL et al. 2007, WIN-HALL and GLASSER 2008, 2009). These instruments can be used to measure the refraction of the eye as the subject focuses on a distant target and then the refraction of the eye as the subject focuses on a near target. The change in refraction that occurs between the distant and the near target is the accommodative response. If the response is measured as a function of an increasing near stimulus presentation, a stimulus-response function can be generated. The accommodative response amplitude can then be ascertained from the maximum value of the stimulus-response function. Such objective measurement of the accommodative change in optical power of the eye is the appropriate method to measure the true accommodative ability of the eye. Objective accommodation measurements with an autorefractor and an aberrometer show these instruments to be reliable, comparable, and suitable for objective measurements of accommodation in young phakic eyes (WIN-HALL et al. 2007), older phakic eyes with lower accommodative response amplitudes (WIN-HALL and GLASSER 2008) and in pseudophakic eyes (WIN-HALL and GLASSER 2009). When the objectively measured, accommodative response is compared with the subjective push-up measurement of near reading distance, the subjective measurement can overestimate the objective measurement by more than 2 D (Fig. 3, 4). This overestimate is even more pronounced in non-accommodative, standard monofocal pseudophakic eyes which have no objectively measurable accommodation, but have as much as 3–4 D when measured subjectively.

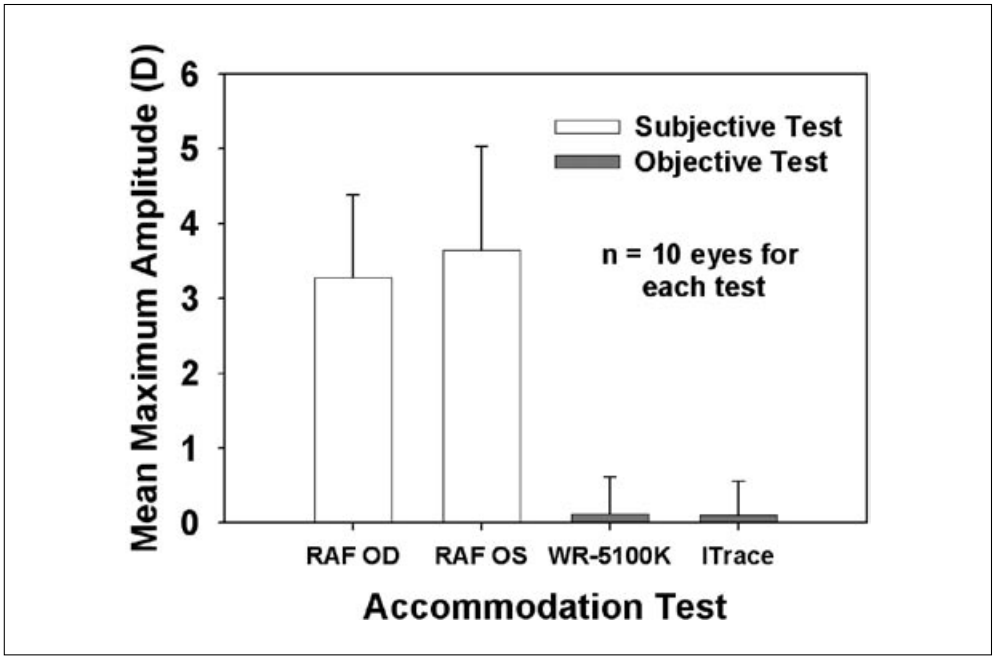

Fig. 3 Comparison of subjectively and objectively measured accommodative amplitudes from 10 pseudophakic subjects. These are subjects with standard, monofocal, non-accommodative intraocular lenses and so no accommodation is expected of them. The subjective responses were measured with the push-up test using the Royal Air Force (RAF) Rule in the left (OS) and right (OD) eyes. The objective responses were measured using the Grand-Seiko autorefractor (WR-5100K) and the Tracey Technologies aberrometer (iTrace). (Reproduced with permission from WIN-HALL and GLASSER 2009, p. 287.)

8. Surgical Restoration of Accommodation

Several different approaches are being investigated to restore accommodation to the presbyopic eye. These include scleral expansion procedures in which PMMA segments are inserted in scleral tunnel incisions in the sclera overlying the ciliary body. This procedure is based on revisionist and unsubstantiated ideas of how the eye accommodates and the causes of presbyopia (OSTRIN et al. 2004). Given that the predominant cause of presbyopia is a stiffening of the lens and a loss in the ability of the aging lens to undergo accommodative changes, surgical treatments of the sclera cannot restore the accommodative capacity to the lens.

Other approaches that might be considered more viable include a variety of different kinds of so-called accommodative intraocular lenses (IOLs). These are IOLs that are designed to be surgically implanted in the eye during cataract surgery to replace the natural lens. They are designed to undergo a movement or a physical change in the eye in response to ciliary muscle contraction. A forward shift of an optic in the eye would impart an increase in optical power to the eye. However, theoretical calculations show that a forward shift of about 1 mm would be required to achieve about 1 D of accommodation. Given that the natural lens does not undergo a forward shift during accommodation

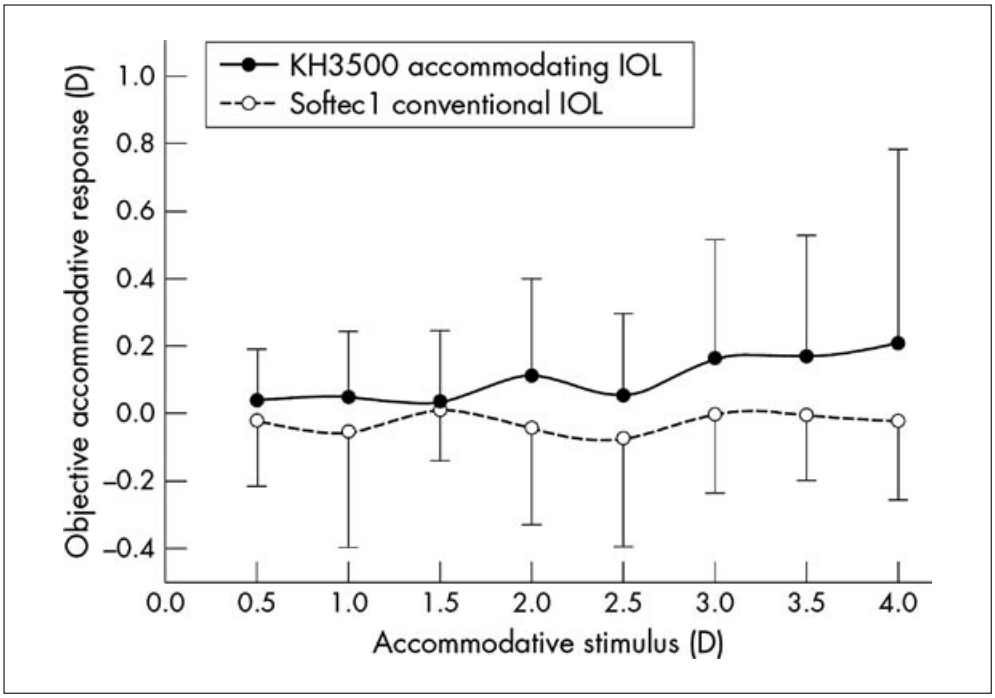

Fig. 4 Objective measurements of accommodation in one so-called accommodative intraocular lens (the KH3500 IOL from Lenstec) compared to a non-accommodative, monofocal IOL (Softec 1). The objective measurements show that no more than about 0.25 D of accommodation is restored on average. (Reproduced with permission from WOLFFSOHN et al. 2006)

and that the natural lens is only 3–4 mm thick, a 1 mm forward movement would be considered as a large amount of movement. Inducing an accommodative optical change with a forward shift is a relatively inefficient method to produce accommodation. Dual optic IOLs are also being investigated. These are IOLs that have two optics that are designed to move apart from each other with a contraction of the ciliary muscle. Such IOLs might produce up to 3 D of accommodation with an increase in separation of the IOLs by as little as 3 mm. This is a more efficient optical process for producing accommodation, but 0.5 mm increase in separation between two IOLs is still a relatively large movement required. Other optical designs can achieve an increase in optical power by virtue of a lateral shift of the two optics. Such systems may be able to produce 5–6 D with as little as 60 mircons of lateral shift of the optics. These are even more efficient optical designs. Finally, IOLs are being investigated that provide an accommodative increase in optical power by virtue of a change in lens surface curvatures. This is perhaps the most efficient method to produce an accommodative optical change in power of a lens since relatively small changes in curvature can produce relatively large changes in optical power. Several such curvature change IOLs are under investigation including IOLs in which fluid shifts from a ballast chamber to within the lens during accommodation to increase the lens anterior surface curvature or in which a soft polymer is forced through a rigid aperture with a rigid piston.

9. Conclusions

While efforts aimed at surgical restoration of accommodation have been disappointing thus far, several possible approaches are being investigated that may hold promise for the future. Certainly, if these approaches are to achieve what is expected of them, namely, restoration of the true accommodative optical change in power of the presbyopic eye, they must be based on a sound understanding of the accommodative anatomy, the accommodative mechanism, and the causes of presbyopia. Objective accommodation measurements are necessary to evaluate the outcomes of these procedures to establish if they do actually restore accommodation.

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High Precision Measurements of IOL Position

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With 8 Figures and 2 Tables

Abstract

The Zeiss ACMaster, an optical biometry instrument based on partial coherence interferometry, is well suited to measure distance variations in the anterior ocular segment with reproducibilities smaller than ≈ 6 µm. With accuracy below the range of physiological fluctuations, such processes themselves can be studied with this instrument. Applied to a group of 59 eyes supplied with a focus-shift IOL, no evidence for lens movements larger than 227 µm due to an optical accommodation stimulus were found with a mean value below 50 µm. Pilocarpine stimulation caused slightly larger displacements with a singular, maximum value of 600 µm. Subjectively determined accommodation amplitudes were higher in all patients and could not be explained by the objectively measured lens displacements. For an explanation, effects of pseudo accommodation have to be considered.

Zusammenfassung

Der Zeiss ACMaster, ein optisches Biometriegerät nach dem Laserinterferenzprinzip, ist mit Reproduzierbarkeiten kleiner ≈ 6 µm für Messungen von Distanzänderungen im okularen Vorderabschnitt gut geeignet. Bei einer Genauigkeit unterhalb der Schwelle physiologischer Fluktuationen können diese Prozesse selbst Gegenstand der Messung mit diesem Gerät sein. Bei 59 Augen mit einer IOL nach dem ‚focus-shift'-Prinzip konnten keine Beweise für Linsenbewegungen größer als 227 µm infolge eines optischen Akkommodationsreizes erbracht werden. Die mittlere Linsenverschiebung lag unterhalb von 50 µm. Pilocarpin-Reize führten zu geringfügig höheren Verschiebungen mit einem einzelnen Maximalwert von 600 µm. Die subjektiv bestimmten Akkommodationsamplituden waren bei allen Patienten deutlich höher und konnten durch die objektiv gemessenen Linsenverschiebungen nicht erklärt werden. Für eine Erklärung müssen Effekte der Pseudoakkommodation mit herangezogen werden.

1. Introduction

Since 1956, when Mundt and Hughes (1956) performed the first echographic axial length measurement, ultrasound has been the method of choice to determine ocular distances. In 1986, Fercher and Roth introduced the principle of laser interference biometry (Fercher and Roth 1986), which became clinically available as a measuring instrument in the Zeiss IOLMaster in 1999. Since then optical biometry has been well accepted in the ophthalmic community and has become an essential tool in cataract and refractive surgery. In fact, modern intraocular lenses (IOL) like multifocal or accommodative lenses are dependent on the exactness of optical distance measurements in order to fully develop the advantages of these new IOL technologies.

In the following, clinical applications of optical biometry will be described with special consideration given to potentially accommodative intraocular lenses following the 'optic-shift' principle.

2. Laser Interference Biometry

2.1 Optical Biometry Instruments

Although the IOLMaster uses the principle of laser interference biometry (also known as partial coherence interferometry PCI) to measure axial length with a reproducibility of 22 µm (Haigis 2002), PCI is not applied in the instrument's anterior chamber depth measuring module which instead makes use of the classic slit image technology. This is due to the IOLMaster's measuring direction being along the visual axis of the eye which accounts for an essential advantage of this instrument in the biometry of high myopes (Haigis 2002). To collect enough energy sent back from the interfaces in the anterior ocular segment, it is necessary for them to be met by the light at right angles. A segmental axial length measurement by PCI can thus be obtained by measuring along the eye's optical axis, as in ultrasound, or by a combination of measurements along the optical and the visual axes (Drexler et al. 1997).

To measure along the optical axis, a separately adjustable fixation target independent of the measuring light beam can be applied. An example of such a measurement is shown in Figure 1, obtained from a pseudophakic eye by a modified IOLMaster at a wavelength of $\lambda = 850$ nm. Here, an external light emitting diode (LED) was used as a fixation target causing the eye's optical axis to be presented coaxial with the IOLMaster's measurement axis.

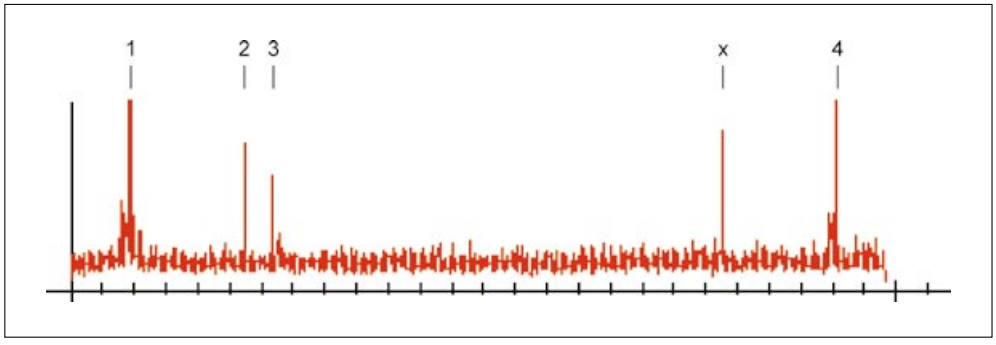

Fig. 1 Optical A-scan of a pseudophakic eye, obtained from one measurement along the optical axis with a modified Zeiss IOLMaster at a wavelength of $\lambda = 850$ nm. Legend: 1: anterior corneal surface; 2, 3: anterior, posterior surfaces of IOL; 4: retinal pigment epithelium; x: artefact.

A similar principle (separate axes for fixation and length measurement) is implemented in the Zeiss ACMaster, another member of the Zeiss PCI family. Both instruments apply PCI technology, yet from different radiation sources: a multimode laser diode at $\lambda = 780$ nm in the IOLMaster, and a superluminescent diode at $\lambda = 850$ nm in the ACMaster. The latter instrument allows optical pachymetry, measurements of anterior chamber depth and lens

thickness in phakic and pseudophakic eyes, and the determination of changes in all anterior segment dimensions under different accommodative stimuli. Such accommodation related variations are of special interest in the clinical evaluation of potentially accommodative intraocular lenses.

2.2 Biometry of the Anterior Ocular Segment

In our laboratory, which is involved in the development and clinical introduction of PCI biometry (Haigis 2004a, b, Haigis and Lege 2004, Haigis et al. 2006a, Hasche and Haigis 2004, Much and Haigis 2006), several prototypes of the ACMaster were used for highly precise measurements in the anterior segment. Figure 2 shows a typical interferogam of the axial length of a 73 year old female patient with a conventional lens (HumanOptics MP2125, 22.5 D) measured with this instrument. The figure also contains 3 artefacts (marked 'x') appearing as 'unwanted' interferences: the signal right to the posterior corneal surface represents the lens thickness, while the peaks left to the respective IOL surfaces are linked to the corneal thickness. The origin of these artefacts lies in the PCI measurement principle itself (Haigis 2005).

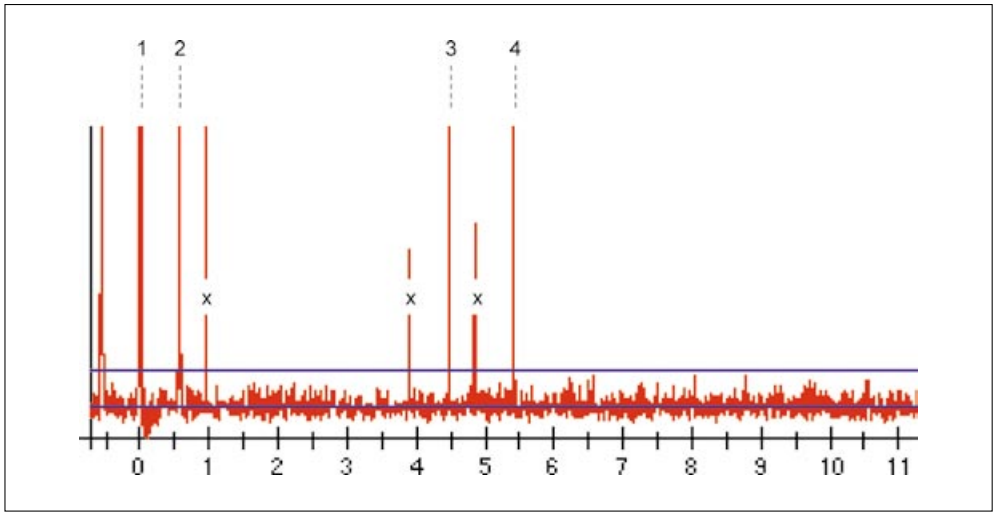

Fig. 2 Optical A-scan of the anterior ocular segment of a patient with a conventional PMMA lens (HumanOptics MP2125, 22.5 D), measured with the Zeiss ACMaster. Legend: 1, 2: anterior, posterior corneal surfaces; 3 : 4: anterior, posterior surfaces of IOL; x: artefact. Measurement results: corneal thickness: 561 ± 1.6 µm; anterior chamber depth: 4,539 ± 2.2 µm; IOL center thickness: 924 ± 1.8 µm.

It should be borne in mind that neither ultrasound nor PCI measure true 'distances': while the primary measurement parameter in ultrasound is 'time of flight', it is 'optical path length (OPL)' for PCI. Geometrical path length (GPL) and OPL are linked by the group refractive index n of the propagated medium via the relation $OPL = n \cdot GPL$.

Not much information concerning group refractive indices of ocular media and IOL materials at the wavelengths of interest is available in the literature. Therefore, it is neces-

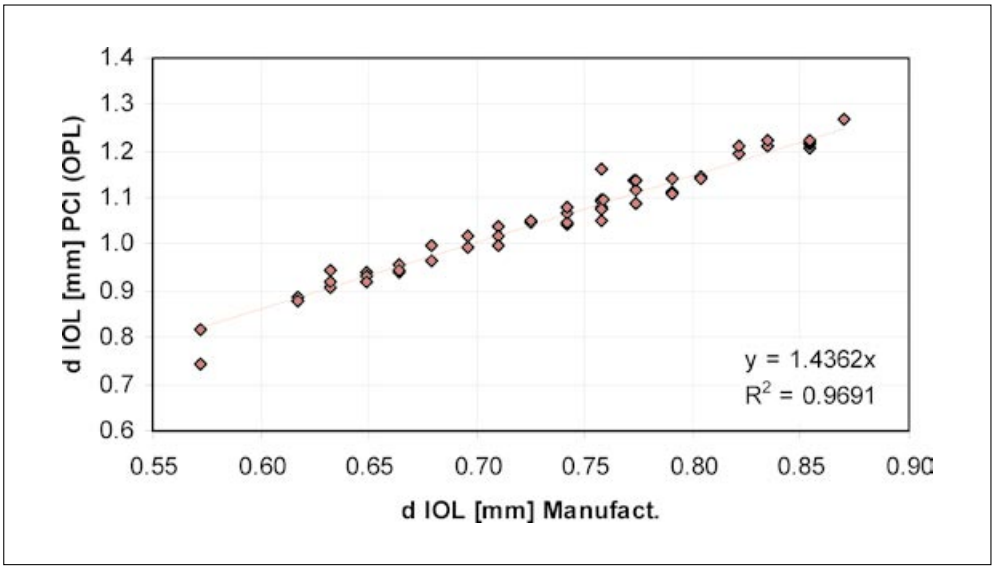

Fig. 3 Optical path length of the center thickness of the HumanOptics 1CU lens vs geometrical center thickness as given by the manufacturer. The slope of the line gives the group refractive index of the IOL material (1.4362 ± 0.0037).

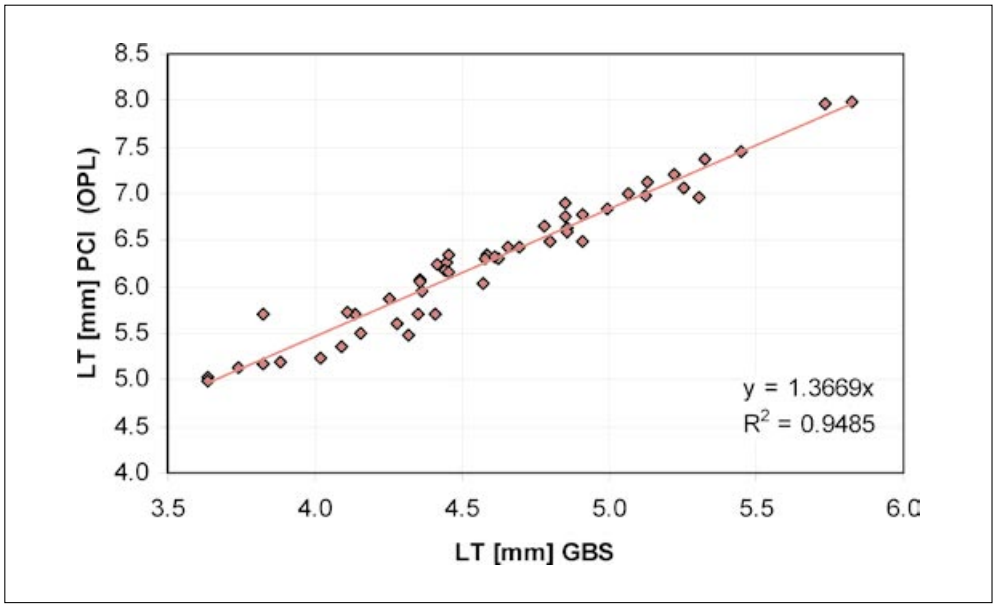

Fig. 4 Optical path length of the thickness of the crystalline lens as measured with the Zeiss ACMaster vs geometrical lens thickness measured by immersion ultrasound with the Grieshaber Biometric System GBS. The slope of the line gives the group refractive index of the crystalline lens (1.3669 ± 0.0051).

sary to measure optical path lengths of different ocular media and biomaterials and compare them to their true geometrical dimensions. Figures 3 and 4 show examples. In Figure 3 the optical path length – acquired by the ACMaster – of the center thickness of the HumanOptics 1CU lens is plotted *versus* the geometrical center thickness as given by the manufacturer. The slope of the regression line gives the group refractive index of the IOL material (1.4362 ± 0.0037, n = 59). Figure 4 shows the same type of plot for the optical thickness of the crystalline lens compared to the geometrical lens thickness measured by immersion ultrasound with the Grieshaber Biometric System (Haigis et al. 2006b). The group refractive index of the crystalline lens (1.3669 ± 0.0051, n = 50) is again derived from the slope of the regression line.

Table 1 gives an overview on group refractive indices at λ = 850 nm for the anterior ocular segment. For the measurements of corneal (CT) and lenticular thicknesses (LT), anterior chamber depth (ACD) and the position of the posterior lenticular surface (PLS), the following reproducibilities were determined: CT: 1–2 µm; ACD: 4–5 µm, phakic LT: 5–6 µm, pseudophakic LT: 1–2 µm (Haigis 2004a, b, Haigis and Lege 2004).

Tab. 1 Group refractive indices at λ = 850 nm for the anterior ocular segment from comparative measurements between PCI biometry (Zeiss ACMaster) and immersion ultrasound (Grieshaber Biometric System GBS, Ultrasound Biomicroscope Zeiss Humphrey UBM 840). Anterior chamber depth = distance from anterior corneal vertex to anterior lenticular vertex. R: correlation coefficient between optical and acoustical measurements. [1]: from Drexler et al. 1998 at λ = 855 nm. [2]: Drexler et al. 1998; [3]: Haigis et al. 2004; [4]: valid for the endo-ACD = distance from the corneal endothelium to the anterior lenticular vertex.

	Cornea	Anterior chamber depth		Crystalline lens
		Compared to GBS	Compared to UBM	
$n^{[1]}$	1.3817 ± 0.0021			1.4055 ± 0.0002
$n^{[2]}$	1.3851	1.3454[4]		1.4065
$n^{[3]}$	1.3616 ± 0.0015	1.3718 ± 0.0036	1.3802 ± 0.0049	1.3669 ± 0.0051
R [%]	98.5	98.4	99.5	97.4

2.3 Measurement Limits

From the above reproducibilities of ACMaster measurements it becomes clear that the accuracy of PCI measurements in the anterior segment is not limited by hardware-related features but rather by physiological fluctuations. This can be seen from Figure 5, which documents changes of anterior chamber depth with time for a female volunteer over a period of 258 days. For easier visualization of the distance variations, the optical path length is plotted. From the slope of the regression line, a decrease of the anterior chamber depth of 68 nm/day ≈ 25 µm/yr in true dimensions (geometrical path length) is derived.

Each data point represents the average of up to 60 single measurements. From the standard deviations in Figure 5 it can be seen that the measured eye obviously was met in varying physiological conditions, e. g. different accommodative states, possibly with different biological rhythms superimposed.

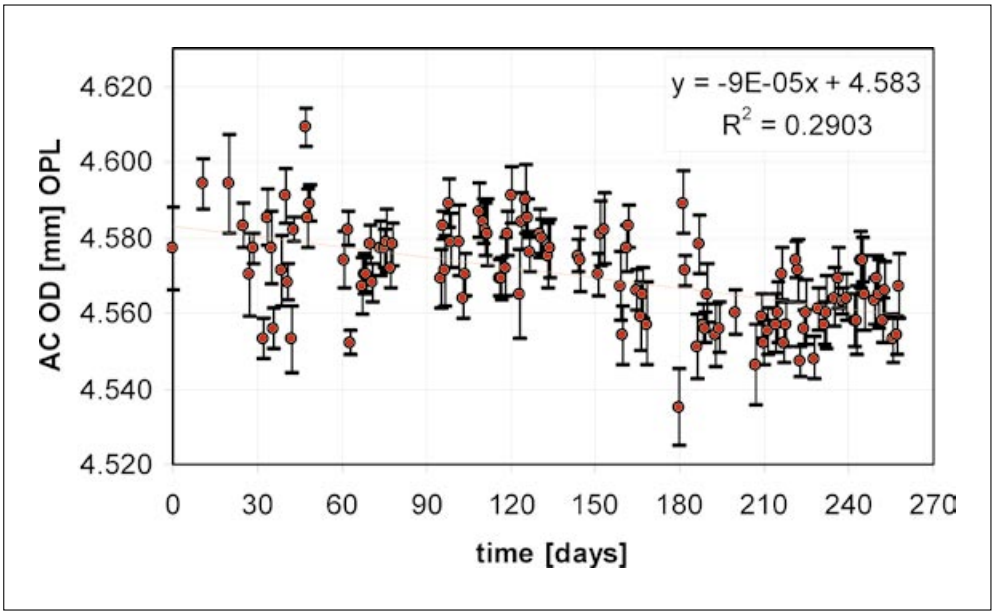

Fig. 5 Change of anterior chamber depth AC (optical path length) with time for the right eye of a female volunteer.

3. Measurements on Potentially Accommodative IOLs

Presbyopia causes the continuous loss of accommodation. Up to now, there is no artificial lens which truly restores accommodation, although there are several IOL models in the market claiming to effect this – at least in part. Of special interest are lenses based on the 'optic-shift-principle' by which an anterior displacement of a suitably designed optic under accommodation causes a decrease in the total focal length of the eye's optical system thus providing clear near vision. For a recent overview on the current status of accommodative lenses, the reader is referred to Buznego and Trattler (2009).

The high precision and the availability of an internal optical stimulus adjustable from –6 to +6 D in 0.25 D steps make the ACMaster an ideal instrument to measure possible variations in the position of the crystalline or a potentially accommodative IOL evoked by suitable stimulations.

3.1 Individual Measurement Results

Figure 6 shows typical results of such measurements on 2 different IOLs (top, Uthoff et al. 2009: potentially accommodative IOL type HumanOptics 1CU102 [22.5 D]; bottom: conventional spherical IOL type HumanOptics MC TE [16.0 D]).

The measurements were carried out in 3 stages (A, B, C): In stage A, the baseline IOL position was measured with a fixation target in the ACMaster set to the patient's best distance correction. In stage B, the fixation target was defocused individually such as to evoke

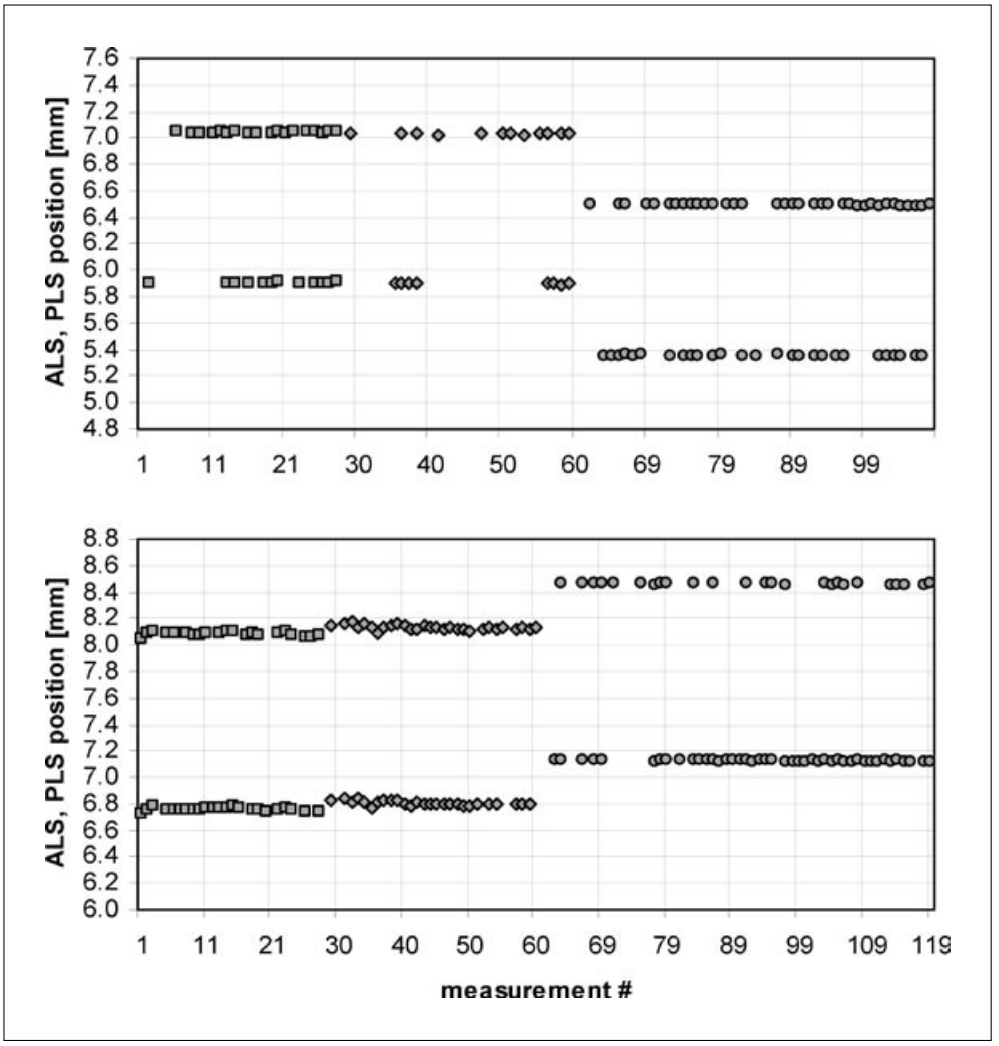

Fig. 6 Measurement series of the positions of the anterior (ALS) and posterior (PLS) lens surfaces for 2 different intraocular lens types and different conditions: top: IOL: HumanOptics 1CU102 (22.5 D); A: measurement #1–#28: baseline (0 D); B: #29–#60: optical stimulation (–2.5 D); C: #61–#108: pilocarpine stimulation (–1.0 D); bottom: IOL: HumanOptics MC TE IOL (16.0 D); A: #1–#28: baseline (–1.5 D); B: #29–#60: optical stimulation (–2.5 D); C: #61–#119: pilocarpine stimulation (0.0 D). The different stages A, B, C are characterized by different symbols (square, diamond, circle). Distances are optical path lengths (OPL); geometrical distances are ≈ 75 % of OPL. The zero-point corresponds to the anterior corneal surface.

the patient's near accommodation. Subsequently, 2 % pilocarpine was applied to the measured eye. Half an hour later, in phase C, the anterior segment distances were measured once more.

In the Figure 6, the positions of the anterior (ALS) and posterior (PLS) lenticular surfaces are plotted in optical path lengths instead of geometrical distances to allow for easier identification of lens movements. The origin of the vertical axes corresponds to the an-

terior corneal vertex. The different stages A, B, C are characterized by different symbols (square, diamond, circle).

While under optical stimulation, hardly any movement (7 ± 3 µm) can be seen for the potentially accommodative IOL (Fig. 6, top), the pilocarpine-induced shift (ΔAC) is 402 ± 4 µm, which would account for a refractive change ΔRx of some 0.6 D. For this calculation the rule of thumb $\Delta Rx \approx 1.5\ \Delta AC$ has been used.

The conventional IOL in the bottom of Figure 6 shows an opposite behavior. The acrylic MCTE lens in a male patient aged 63 has a 10° angulation backwards and can be seen to move posteriorly both under optical and pharmacological stimulation, as would be expected from a radial force acting on the lens haptic. Here, optical stimulation caused an excursion of –35 ± 16 µm, pilocarpine –269 ± 10 µm ('–' sign indicates backward movement).

3.2 Results of Group Measurements

In several studies with different working groups in Erlangen (Haigis et al. 2004, 2006b), Kiel (Uthoff et al. 2009) and Heidelberg (Haigis et al. 2005), a total of 59 eyes implanted with a 1CU lens was examined. Results for all patients are compiled in Table 2.

Tab. 2 Demographic data and measurement results for all patients supplied with a potentially accommodative IOL type HumanOptics 1CU. Axial length measured with the Zeiss IOLMaster, accommodation amplitude measured subjectively with an accommodometer. IOL displacements due to optical or pharmacological stimuli measured with the Zeiss ACMaster.

Group	Erlangen	Heidelberg	Kiel
Patients	16 eyes 9 patients: 5 m, 4 f	28 eyes 20 patients: 12 m, 8 f	24 eyes 14 patients: 2 m, 12 f
IOLs	16 × 1 CU	28 × 1 CU	13 × 1 CU 2 × 1 CU102 9 × other
Age [years]	58.3 ± 13.8 (30.2…71.9)	49.1 ± 11.6 (27.5…68.8)	71.2 ± 5.2 (63.7…79.9)
Axial length [mm]	23.91 ± 0.84 (22.65…24.44)	23.32 ± 0.86 (21.83…24.57)	23.15 ± 0.84 (21.93…24.43)
Accommodation, amplitude [D]	1.9 ± 0.4 (1.2…2.7)		1.7 ± 0.5 (1.0…2.6)
IOL (1CU) displacements [µm] (opt. stimulus)	45 ± 71 (–28…183)	31 ± 48 (–8…+227)	5 ± 14 (–10…+40)
IOL (1CU) displacements [µm] (2% pilocarpine)	132 ± 114 (–75…283)	80 ± 146 (–16…600)	93 ± 162 (–321…+402)

It can be seen from the table that the average lens displacements due to an optical accommodation stimulus were below 50 µm in all groups, with an individual maximum value of 227 µm. The respective mean values for pilocarpine-induced displacements were below 140 µm in all groups with a single maximum excursion of 600 µm. A displacement of 600 µm would correspond to a change in refraction of approximately 0.9 D.

The calculated refractions from the measured displacements of the 1CU lens do not in any case explain the clinically determined accommodation amplitudes obtained subjectively with an accommodometer.

Figure 7 shows such a comparison between measured accommodometer values and refractive changes calculated from the individual AC decrease under pilocarpine as measured with the ACMaster for 9 patients (Haigis et al 2006b). The figure shows clearly that the optically derived IOL displacements cannot account for the clinical findings. The reason for this discrepancy is not yet quite clear; pseudoaccommodative effects like increased depth of field, myopic astigmatism and/or refraction, corneal multifocality, aberrations etc. certainly contribute to this effect.

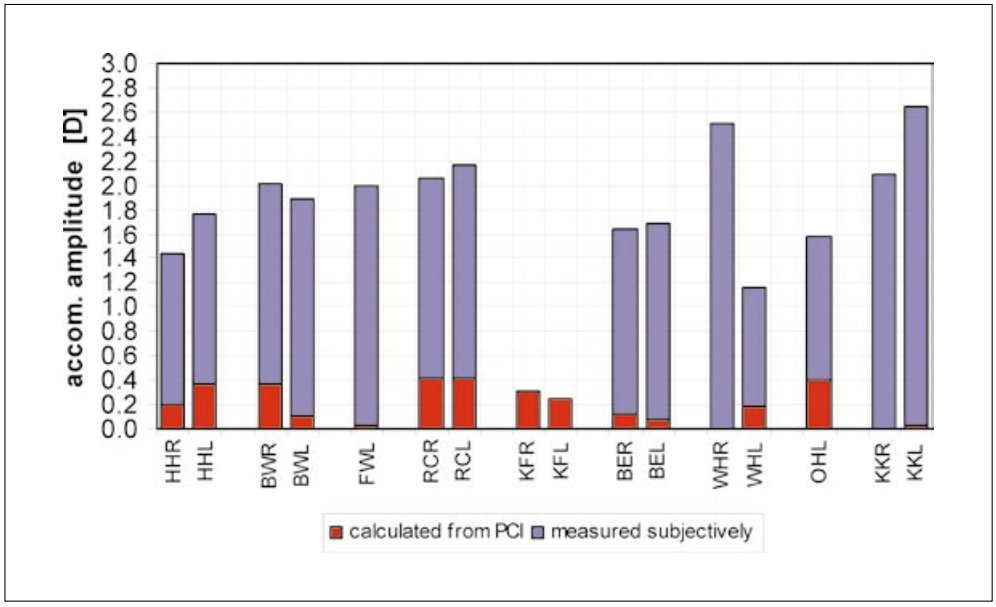

Fig. 7 Accommodation amplitudes measured subjectively with an accommodometer and calculated from PCI measurements for 9 patients using $\Delta Rx \approx 1.5\ \Delta AC$.

We further analyzed our 1CU results with respect to possible correlations with age and axial length. The results of the dependence of the shift ΔALS on axial length is shown in Figure 8 for optical as well as pharmacological stimulation. A correlation with axial length was found in neither case.

For the dependence of optically stimulated displacements on age, a weak yet significant correlation ($p = 0.001$) with a correlation coefficient of 0.45 was observed (regression line: $\Delta ALS = -1.583 \cdot age + 115.372$). From this it follows that younger age will cause larger IOL movements due to optical stimulation than older age – a finding, which was to be expected.

Our results are in agreement with the literature. In a recent paper, Nemeth et al. (2008) reported a mean change in IOL position of 26 ± 134 µm during physiological accommodation for 51 eyes supplied with conventional IOLs (Alcon SA60AT, MA60AC). In clini-

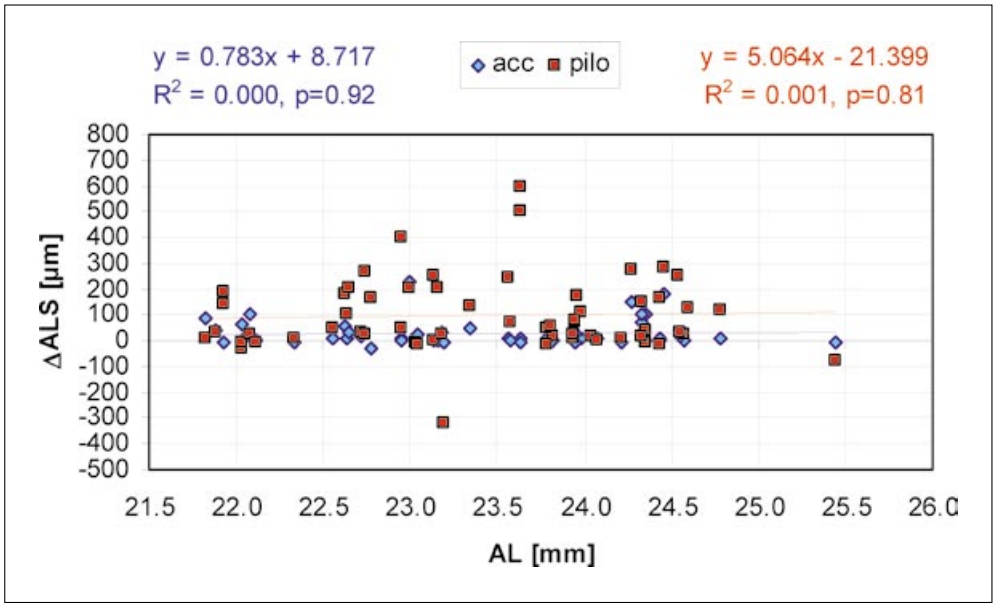

Fig. 8 Accommodative changes ΔALS in anterior lens position of the 1CU lens vs axial length for optical (acc) and pharmacological (pilo) stimulation.

cal studies (e. g. Küchle et al. 2002, Auffarth et al. 2002, Mastropasqua et al. 2003) good functional results were observed after implantation of 1CU lenses. Controversial findings, however, are reported for the relation between measured accommodation amplitudes and observed lens displacements. Similar results were e. g. obtained by Stachs et al. 2005, Findl et al. 2004 and Kriechbaum et al. 2005.

Summarizing the results from objective optic shift measurements in potentially accommodative lenses it turned out that in general there is virtually no movement under optical stimulation and only slight displacement under pharmacological stimulation. Pilocarpine is likely to act as a super stimulus, especially in older eyes.

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New Techniques to Measure Lens Tilt, Decentration and Longitudinal Chromatic Aberration in Phakic and Pseudophakic Eyes

Frank Schaeffel (Tübingen) and Hakan Kaymak (Düsseldorf)

With 7 Figures

Abstract

A new automated technique is presented to measure lens tilt and decentration in phakic and pseudophakic human eyes, along with new data on the variances of these variables in the phakic eye. Our data shows that the natural lens has variable orientation in different subjects and that it is significantly tilted towards the temporal side, relative to the fixation axis. Furthermore, polychromatic eccentric photorefraction is used for the first time to measure chromatic aberration in the eye. Interestingly, no significant chromatic aberration was found, perhaps because the fundal layers show wavelength-dependent reflection in different depths and with different angular distributions. This assumption is supported by the observation that chromatic aberration could be measured in two different artificial eyes with a "mono-layered retina".

Zusammenfassung

Es werden ein neues automatisiertes Verfahren zur Messung der Linsenkrümmung und Dezentrierung in phaken und pseudophaken menschlichen Augen und neue Daten, die die Streuung dieser Variablen im phaken Auge zeigen, vorgestellt. Unsere Daten zeigen, dass natürliche Linsen eine variable Orientierung bei verschiedenen Personen aufweisen und dass sie in Bezug zur Fixationsachse erheblich in Richtung Schläfenseite gekrümmt sind. Außerdem wird die mehrfarbige exzentrische Photorefraktion erstmals zur Messung der chromatischen Aberration im Auge verwendet. Interessanterweise wurde keine signifikante chromatische Aberration gefunden. Das liegt vielleicht daran, dass die Fundusschichten eine wellenlängenabhängigen Reflexion in verschiedenen Tiefen und mit verschiedenen Winkelverteilungen zeigen. Diese Annahme wird durch die Beobachtung gestützt, dass die chromatische Aberration in zwei verschiedenen Kunstaugen mit einer einschichtigen Netzhaut gemessen wurde.

1. Semi-Automated Measurement of Lens Tilt and Decentration by Analysis of the Purkinje Images in Phakic and Pseudophakic Eyes

1.1 Purkinje Images and Kappa

If a light source is positioned in front of the eye of a subject, three virtual images and one real image of this light source can be seen which originate at the refracting surfaces of the optics of the eye. These images have been named "Purkinje images", after the Czech anatomist Jan Evangelista Purkyně (1787–1869) who first made drawings of them in 1823 and recognized that they could permit the determination of lens shape and the distance of the lens center from the iris (Purkinje 1823). As expected from the presence of four major re-

fracting surfaces in the eye, four Purkinje images are recognized, the first originating from the air-cornea interface (P1, upright, sharp and bright), the second from the back side of the cornea (P2, upright, relatively bright but only visible if the light source is located in the periphery of the visual field), the third from the anterior lens surface (P3, upright and large, but diffuse and weak) and the fourth from the backside of the lens (P4, inverted, small, but bright and sharp) (Fig. 1).

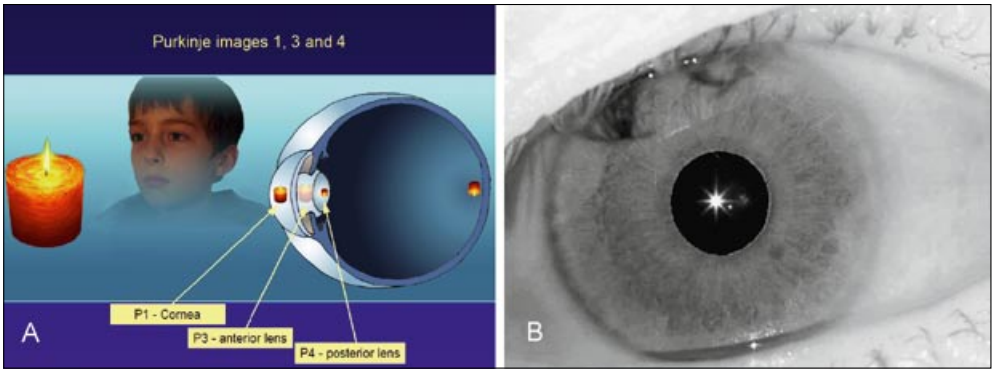

Fig. 1 (*A*): Illustration of Purkinje images 1, 3, and 4, and their orientations. (*B*): Original picture of Purkinje images 1, 4, and 3 (visible in this sequence, from left to right). The second Purkinje image is not shown, since it was not used in the measurement procedure described below.

P3, originating from the anterior lens surface, is difficult to detect, since it has low contrast and is diffuse because the small differences in refractive index between aqueous and lens capsular bag, and also because of the lenticular index gradient (see Fig. 1). Furthermore, it tends to disappear behind the iris already for small angular rotations of the eye since the anterior lens surface is rather flat. However, P3 and P4 need to be detected to permit measurements of the orientation of the lens. In addition, it has to be considered that the axis of fixation and the pupil axis diverge by the angle "kappa" (Fig. 2). The orientation of the fixation axis cannot be determined solely from Purkinje images since the position of the fovea cannot be determined from outside, using pictures, as shown in Figure 1 (*bottom*). It is necessary that the subject fixates a target that is presented under a defined angular position and that the position of the first Purkinje image in the pupil is recorded during fixation. The pupil axis, on the other hand, is defined by the eye position in which the first Purkinje image is centered in the pupil.

1.2 Measurement of Lens Tilt and Decentration Based on the Purkinje Images

Rather than tracking the positions of P1, P3, and P4 in the pupil separately to determine the orientations of the optical surfaces relative to the light source, a simplified procedure was employed. The procedure was first proposed by Tabernero et al. (2006) (a second "Purkinjemeter" was also recently published by Rosales and Marcos 2006). An advantage of the procedure is that nothing needs to be known about the linear regression equations which describe the movements of the Purkinje images as functions of eye position. As light

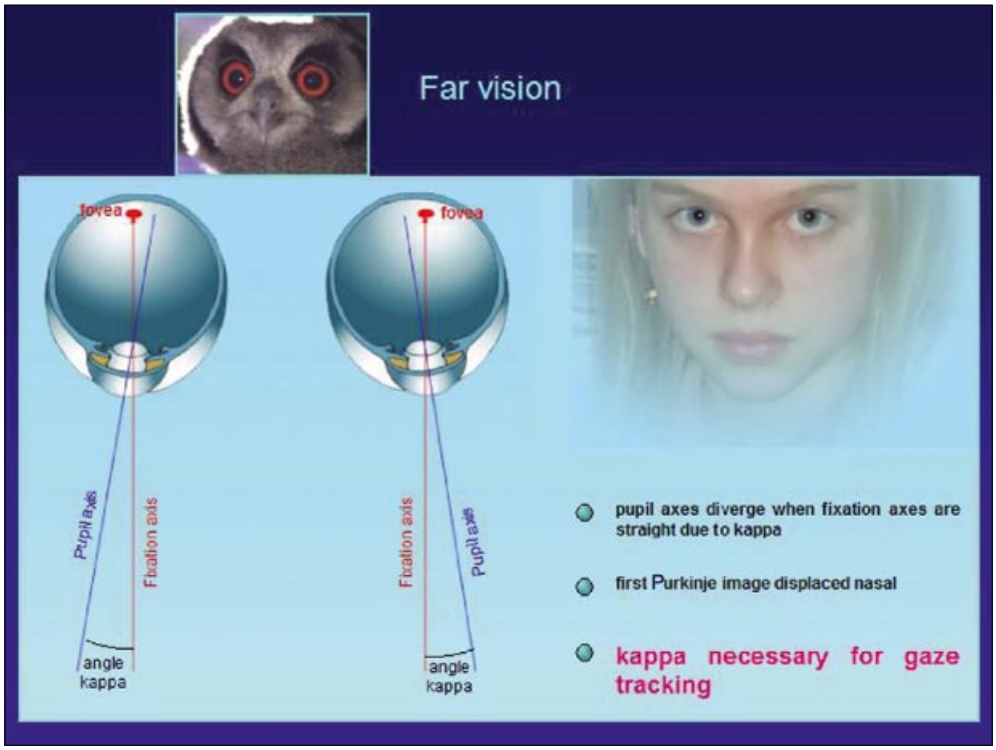

Fig. 2 The first Purkinje image is not centered in the pupil when the subject fixates a distant target behind the observer, presenting the light source, but rather nasally displaced. The displacement results from the fact that the fixation axis (connecting the fovea with the fixation target) emerges from the eye typically nasally from the pupil axis. The angle between both axes is "kappa". It ranges typically between 0 and 11° in humans (e. g. SCHAEFFEL 2002) but may be much larger in other vertebrates (e. g. 30 deg in the owl).

source, an infrared light emitting diode (IR LED) was used which was placed close to the camera aperture. Infrared light has the advantage that it cannot be seen and that the pupil remains large.

To measure the direction of fixation of the subject, kappa needs to be known. To this end, the subject had to fixate a target of known angular position – in this case a little green LED positioned next to the IR LED, just above the aperture of the lens of the video camera. From the position of the first Purkinje image relative to the pupil center, kappa can be determined, given that the "Hirschberg ratio" (HQ) is known. HQ is the angular rotation of the eye that is necessary to move the first Purkinje image in the pupil linearly by 1 mm. Typically, the HQ in humans is close to 12, with a standard deviation of about 8 % (e. g. SCHAEFFEL 2002). If gaze tracking should be very precise, individual measurement of HQ might be worthwhile. In the present case, however, a common value of 12°/mm provides sufficient precision for gaze tracking in all subjects.

Positions of P3 and P4 are now recorded for three different eye positions, separately for horizontal (x) and vertical (y) coordinates. Since the direction of gaze is "known" by the software, based on the position of P1 relative to the pupil center, there is no further need to provide fixation targets in the visual field at defined angular positions. The distance between P3

and P4 is plotted, both in x and y directions, versus angular gaze position. A linear regression through these points provides the eye position for which P3 and P4 would be exactly superimposed. For this gaze position, the crystalline lens is oriented perpendicular to the camera axis and the negative value of the respective gaze position provides lens tilt (TABERNERO et al. 2006, SCHAEFFEL 2008). In the next step, the centration of the lens relative to the pupil center can calculated from the position of the superimposed P3 and P4, relative to the pupil center.

These measurements require that the user marks the Purkinje images in the video frame with the computer mouse since automated detection was too noisy in the case of P3. Software to perform all these steps was developed in Visual C++. Positional data is stored and a regression analysis is automatically performed after the third measurement (Fig. 3, see top right).

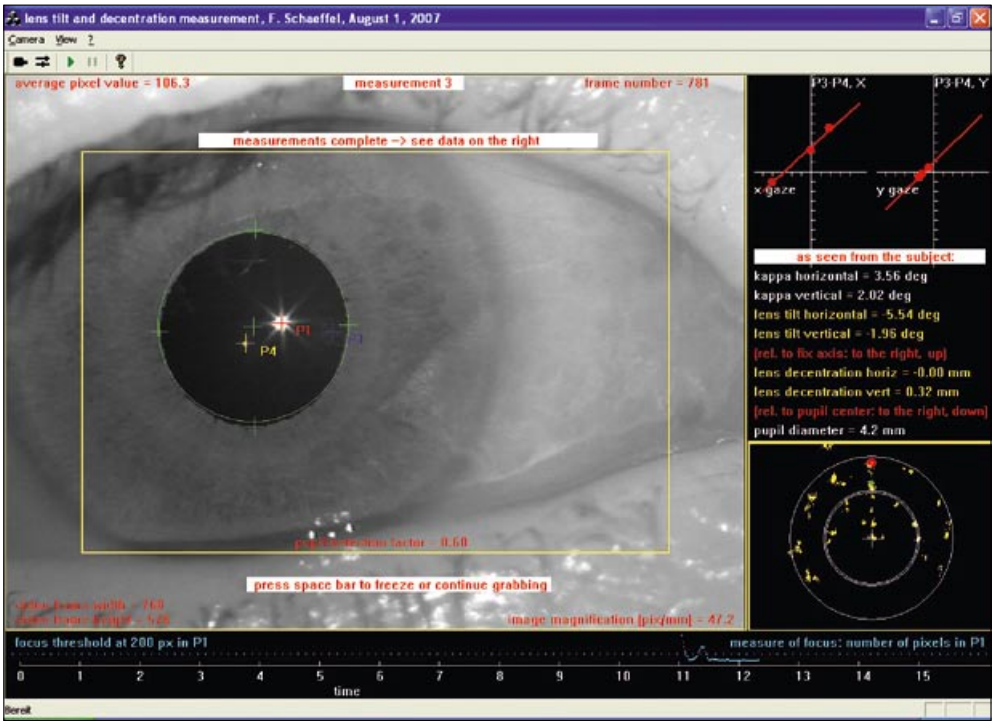

Fig. 3 Software output of the custom-developed program to measure lens tilt and decentration in a phakic subject. In the top, right, the distance between P3 and P4 is plotted as a function of the direction of gaze. A regression analysis is automatically performed to find the direction of gaze for which P3 and P4 would just be superimposed. In this gaze position, the crystalline lens is oriented perpendicular to the camera axis. Decentration of the lens, relative to the pupil center, can be determined from the linear distance of the superimposed P3/P4 from the pupil center (see output data on the right, middle).

1.3 Results of Measurements of Lens Tilt and Decentration in 11 Young Phakic Subjects

In our data set (originating from 11 young co-workers in the lab) both eyes showed a high degree of mirror symmetry regarding horizontal angle kappa and horizontal lens tilt, but not regarding horizontal lens decentration. There was a striking scatter in kappa and lens

tilt across subjects – some had small kappa and little lens tilt, but values of up to 10° were also observed (Fig. 4). Significant degrees of symmetry were also observed in the vertical angle kappa, vertical lens tilt, and decentration.

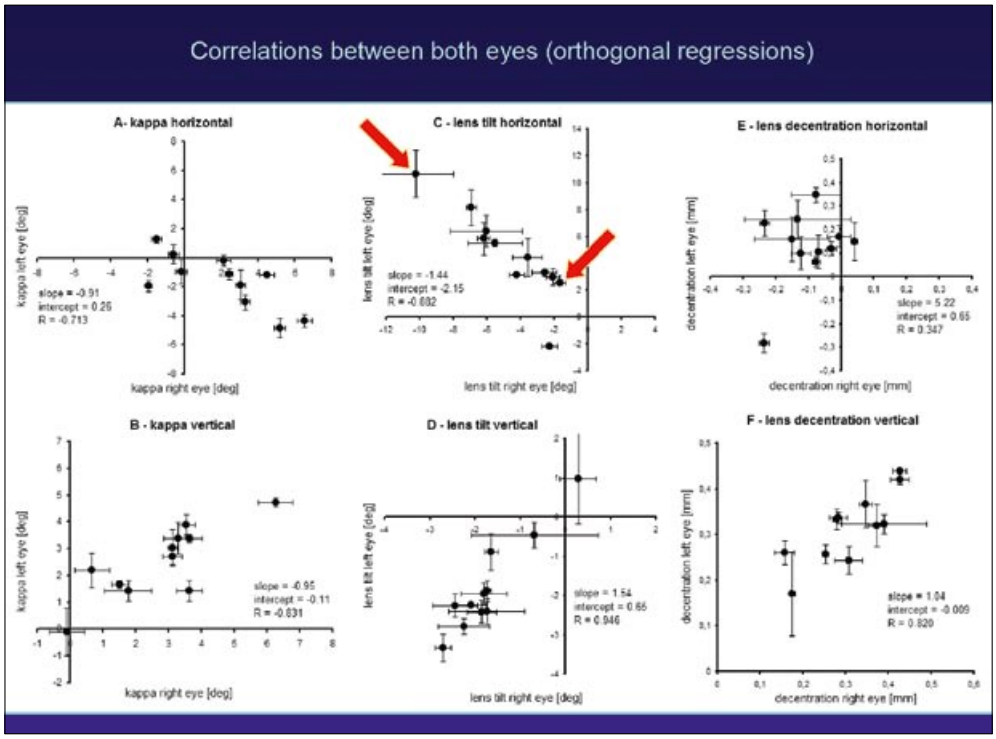

Fig. 4 Correlations of kappa, lens tilt, and lens decentration in both eyes, studied separately for the horizontal and vertical axis. Since a comparison of both eyes does not provide a dependent and an independent variable, orthogonal regression analysis was necessary. There was a surprisingly large variability in lens tilt among the different subjects (see red arrows in Fig. 4*C*). It is also striking that the lenses were tilted towards the temporal side, even if measured relative to the fixation axis (from SCHAEFFEL 2008).

1.4 Summary and Prospects

Apparently, there was little selective pressure in the course of evolution to position the lens exactly perpendicular to the "optical axis" of the eye, or to the "fixation axis". Within the range of scatter of lens tilts it appears possible to maintain a sufficient quality of the retinal image. Exactly the same conclusion was drawn by ARTAL and TABERNERO (2008). The design of the natural crystalline lens seems to leave the optics of the eye with little sensitivity to lens tilt.

In the case of pseudophakic eyes, the condition is changing. In particular, tilt and decentration become critical in the aspherical lenses (PIERS et al. 2007). At least, the proposed device can be nicely used to measure tilt and decentration of implanted artificial lenses (MESTER et al. 2009). In pseudophakic eyes, P3 is easily detected because the difference in refractive index is large between aqueous and the plastic lens material. Furthermore, there is no index gradient in the lens that diffuses the reflection.

2. Measurement of Longitudinal Chromatic Aberration by Polychromatic Eccentric Photorefraction

2.1 Eccentric Photorefraction in Infrared and White Light

Eccentric photorefraction is a technique to measure refractive state from a distance of 0.5 to 5 m in which measurements of the brightness distribution in the pupils can be fully automated, by use of digital video images (Schaeffel et al. 1993). Typically, IR LEDs are used with an emission peak between 850 and 890 nm. Since they are scarcely visible, they do not stimulate a pupil constriction. Measurement are typically done in dim light, and the pupil remains large which reduces the measurement noise during analysis of the brightness distribution in the pupil because it is based on many pixels. The technique also has the advantage that both eyes can be measured simultaneously, and that high temporal sampling

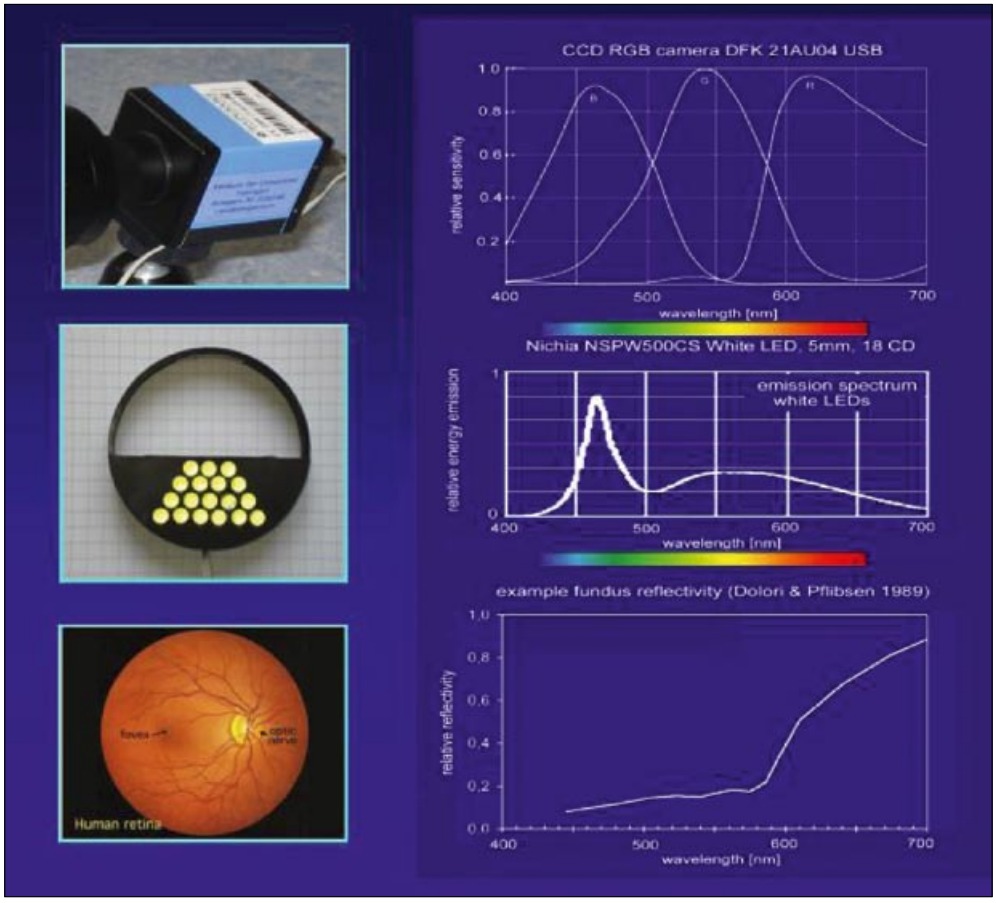

Fig. 5 Spectral human fundus reflectivity (after Dolori and Pflibsen 1998, see curve on the *right, bottom*). The spectral emission of the high power white light LED in the photoretinoscope is shown in the middle. The spectral sensitivity of the single chip RGB CCD camera is shown in the top (available through The Imaging Source, Bremen, Deutschland).

rates can be achieved (depending on the frame rate of the camera). Furthermore, the measurements are not realized by the subjects and largely natural viewing conditions are possible (apart from the dim room illumination). Myopia, astigmatism and anisometropa are reliably detected, while hyperopia in young subjects may be partially masked by accommodation. A further limitation is the inter-individual variability of the calibration of the technique. If trial lenses are placed in front of the eye and the expected change in refractive state is compared to the measured one, deviations of up to 20 % may occur – an error of 0.2 D in the case of a one diopter lens, but already 1 D in the case of 5 D trial lenses. The optical reason for the inter-individual variability is still not understood (Seidemann and Schaeffel 2003).

If white light is used instead of infrared light, and only a short flash is presented rather than a continuous operation of the LEDs, refractions can be measured simultaneously at different wavelengths. Right after the flash, the pupil is still large because of the long latency of the light-induced pupil response. A problem is that the fundus shows low reflectivity in the blue end of the spectrum (Fig. 5) and it is necessary to provide sufficient light energy in the blue. In the current case, high power white light LEDs were used which had an emission peak around 420 nm. This peak overlaps nicely with the "blue channel" of the single chip CCD RGB camera DFK21 AU04 (TheImagingSource, Bremen, Germany).

2.2 Technical Issues in Polychromatic Photorefraction

Commercial video systems providing chromatic information have automatic white balance built in which adjust the gains of the blue (B), green (G) and red (R) channels. In the current case, one would like to measure the absolute brightness values in BGR and all automatic controls had to be switched off. Furthermore, the pixel values in the BGR channels had to be adjusted to provide similar pixel values to minimize the effects of non-linearities during the conversion of object brightness to pixel value. To this end, the gain of the B channel was manually set higher than the G and R channel. Thereafter, calibration curves were determined by taking pictures of a "white" surface with different aperture settings of the camera lens and recording the respective pixel values. The response curves were fit by exponential functions so that each pixel value was assigned a defined object brightness. Software was developed under Visual C++ to flash the white light LEDs through the USB port of the laptop, and to record a video frame during the flash. The software automatically analyzed the slope of the brightness profiles in the vertical pupil meridian in the B, G, and R channel (Fig. 6).

2.3 Calibration and Measurement Noise

The technique was calibrated simultaneously in B, G, and R, by holding various trial lenses in front of the right eye of 6 subjects. Interestingly, no differences were found in the changes of the brightness gradients in the pupil with changing lens powers for the B, G, and R channels. However, the well-known inter-individual variability in the calibration of eccentric photorefraction showed up again – the trial lens induced slightly different changes in the slopes of the brightness profiles in the pupils of different subjects. However, this should not represent a major problem, since the expected longitudinal chromatic ab-

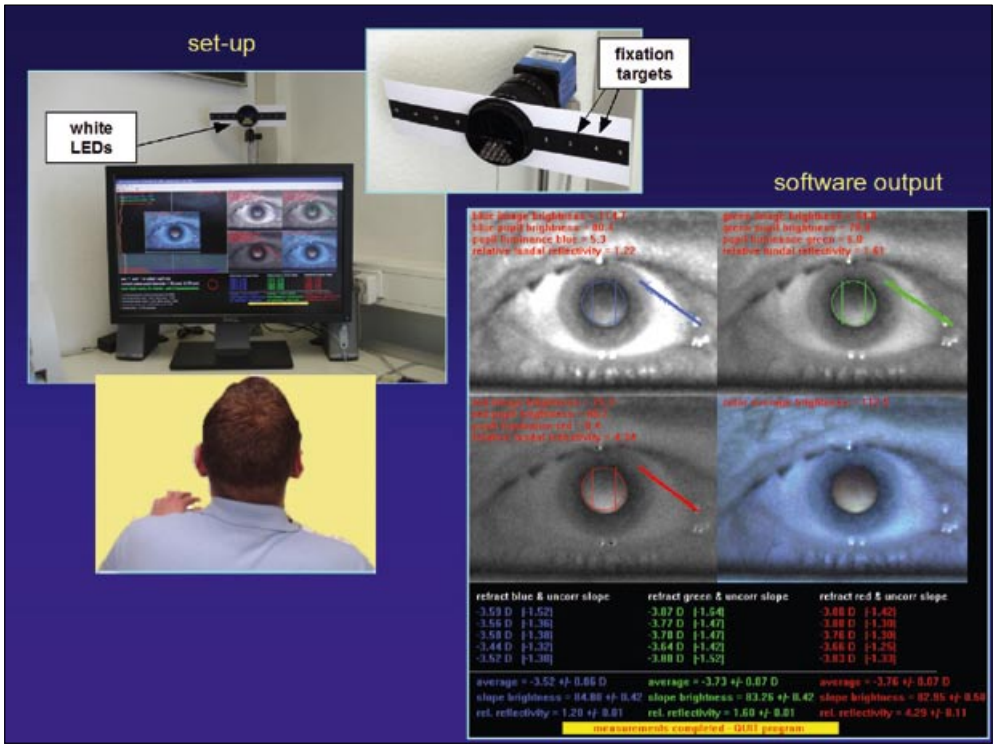

Fig. 6 Measurement set-up (*top left*) with a subject in front of it, USB video camera with white light photoretinoscope and black cardboard with fixation targets at ±1, 2, 3, 4, 5°, seen from 1 m distance (*top, middle*), and frames showing the output of the B, G, and R channel (*right, bottom*). BGR frames appear in black and white here because the output of each channel was loaded into the remaining two other channels before display, to improve contrast and visibility on the screen. *Bottom right* shows the results of five consecutive measurements. Note that the standard deviations of these five measurements were very low, here below 0.1 D.

erration should be in the range of 1 D, much more than variability in the inter-individual calibrations (at the most, about 20%). For an expected difference of 1 D, 20% would only be equivalent of about 0.2 D. Repeated measurements in B, G, and R gave standard deviations of only about 1/10 of a diopter – again, one would not expect that noise could limit the possibility to measure longitudinal chromatic aberration.

2.4 Results

The technique permitted also the evaluation of fundus reflectivity in B, G, and R across the visual field, as well as measurements of the longitudinal chromatic aberration in different angular positions (data not shown here). Foveal refractions of 11 subjects are shown as measured in B, G and R (Fig. 7). Except for two subjects, who showed more myopia in the blue as expected from typical longitudinal chromatic aberration, the refractions remained largely independent from the wavelength in which they were measured.

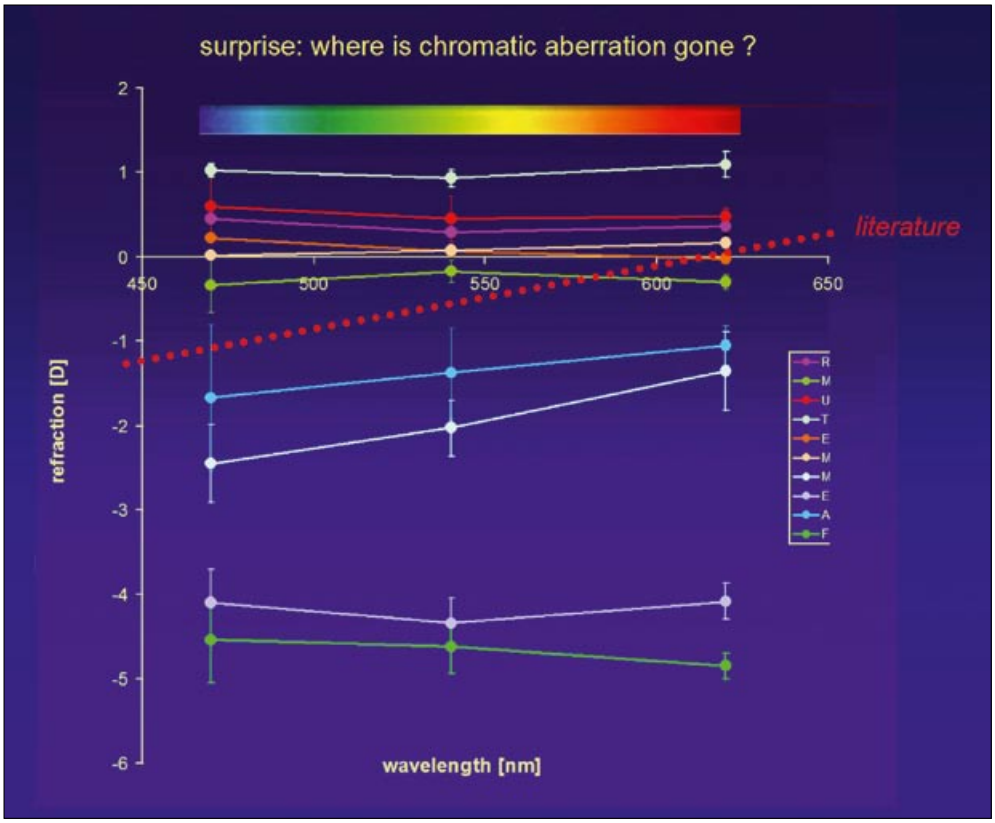

Fig. 7 Refractive states of 11 subjects, measured at 460, 540, and 620 nm. Except for subjects M und A, the refractions remained similar in the blue, green, and red. Literature data on longitudinal chromatic aberration are also shown for comparison as dotted red line.

Polychromatic photorefraction has provided unexpected results – namely the lack of an effect of wavelength on refractive state. The most likely explanation could be that the light in reflected at different layers in the fundus. If red light would penetrate deeper into the fundus, an apparently longer and more myopic eye would be measured. This effect could counter-balance the effect of longitudinal chromatic aberration, originating from dispersion in the ocular media of cornea and lens. In humans, one diopter is equivalent to a longitudinal shift in axial length of about 330 µm – about the thickness of the retina.

Measurements with the device in two different artificial eyes with "single layered fundus" (plastic or cardboard) showed longitudinal chromatic aberration in the expected magnitude (data not shown).

While the mechanism underlying the lack of longitudinal chromatic aberration in our measurements could not be identified with confidence, future measurements with quasi-monochromatic light could help to clarify this issue. Perhaps such studies would also help to finally understand the reasons for the inter-individual variability in the calibration of photorefraction. Of particular interest are the two subjects in which longitudinal chromatic aberration was, in fact, detected since they may show also other difference in calibrations.

Acknowledgements

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Clinical Experience with the Implantation of Accommodative Intraocular Lenses (A-IOL)

Gerd U. AUFFARTH (Heidelberg)

With 4 Figures

Abstract

The demand for surgical techniques to correct presbyopia will increase further in the future; millions of presbyopic patients are waiting for an appropriate and contemporary correction of their age related farsightedness. Today a wide range of intraocular lenses (IOLs) are available for presbyopia surgery. Highly important for a satisfied patient is the correct selection of patients and detailed information on the possible complications of these Premium IOLs. Recently, new developments of accommodative IOLs have overcome some of the initial problems providing independence from glasses with the advantage of less photopic phenomena compared to multifocal IOLs. New accommodative lenses change the curvature of the IOL resulting in higher accommodative dioptric power.

Zusammenfassung

Der Bedarf an operativen Korrekturmöglichkeiten der Presbyopie wird weiterhin ansteigen, denn Millionen von presbyopen Patienten warten auf die Korrektur ihrer Altersweitsichtigkeit. Für die Presbyopiekorrektur mittels Intraokularlinsen (IOLs) gibt es heute eine Vielzahl von Möglichkeiten. Die Patientenselektion und -aufklärung über mögliche Probleme, aber auch realistische Erwartungen sind wichtige Parameter für die postoperative Patientenzufriedenheit. Neue Entwicklungen akkommodativer IOLs habe heute initiale Probleme überwunden und ermöglichen eine weitgehende Brillenunabhängigkeit mit dem Vorteil, dass photopische Phänomene im Vergleich zu multifokalen IOLs geringer auftreten. Neue akkommodative IOLs ändern die Kurvatur der HH-Oberfläche, was zu einem durchaus ausreichendem Anstieg der Akkommodation führt.

1. Introduction

Presbyopia was the first refractive error which was corrected by optical aids. The first efficient bifocal glasses for presbyopes, which corrected near and far vision in one frame, were invented by the American Benjamin FRANKLIN (1706–1790) in 1785 when he was already 79 years old: two lenses were shown each cut in half, the upper part for distance vision, the lower, convex part for close viewing (GERSTE and FRANKLIN 2006).

2. Theories of Accommodation

Accommodation is the ability to change the refractive power of the eye to enable to see sharp pictures on the retina of far as well as close objects (ATCHISON 1995, GILMARTIN 1995). Research on the physiological process of accommodation is still ongoing. The theory of

Herrmann von Helmholtz, dated 1855, seems to be widely approved today (Helmholtz 1855): When focusing near the circular muscle fibers of the ciliary, muscles contract decreasing the equatorial circumlenticular space, which reduces zonular tension and allows the lens to round up and increase in optical power. When viewing a distant object the circular ciliary muscle fibers relax, which increases the equatorial circumlenticular space causing an increase in zonular tension. The increase in zonular tension causes the surfaces of the lens to flatten and the optical power of the lens to decrease. Glasser and Kaufman (1999) did research on accommodation in primates. Accommodation was induced by surgical implantation of a stimulating electrode in the mesencephalon. Furthermore, a muscarine antagonist was applied to achieve non-accommodation by pharmacological means. The equator of the crystalline lens, as well as the movements of the ciliary body, were monitored by ultrasound biomicroscopy and goniovideography during accommodation and, respectively, non-accommodation. In all cases the ciliary body as well as the equator of the crystalline lens moved away from the sclera during accommodation. These findings support the Helmholtz theory and contradict the theory of Schachar (2001) (Croft et al. 2001).

3. First Steps to Accommodative Intraocular Lenses (IOLs)

Modern cataract surgery has shown tremendous development during the past 20 years. Improved surgical techniques, as well as improved materials for implants and advanced designs, have enlarged patient profiles and indications for cataract surgery. This was accompanied by much higher patient expectations. The loss of accommodation is a distinct loss of quality of life for presbyopic and especially young pseudophakic patients. The final step of restoring accommodation is still the challenge for complete visual rehabilitation in pseudophakia (Auffarth and Dick 2001, Auffarth and Apple 2001, Dick 2005).

Scientific research on accommodative IOLs (Dick 2005, Findl and Leydolt 2007, Macsai et al. 2006) started in the 1980s. Creative ideas on bifocal and multifocal design, as well as lens refilling (Nishi et al. 1998) and accommodative IOLs, came up but until the 1990s the vigorous efforts in surgical techniques and materials did not succeed. The request for accommodative IOLs was, and still is, very high: longing for independence from glasses, combined with natural vision which would not be affected by any photopic phenomena, would mean a distinct improvement of quality of life for elderly people.

Recently, new developments of accommodative intraocular lenses (IOL) try to overcome the initial problems of only insufficient presbyopia correction with the advantage of independence from glasses with less photopic phenomena compared to multifocal IOLs. The first generation of accommodative IOLs were supposed to provide a change of focus, for example by anterior-posterior movement in the eye, facilitated by contractions of the ciliary body which lead to a change in focus. To facilitate this process these IOLs have a special haptic design which should enable the required movement in cooperation with the capsular bag.

Different modern IOLs have been introduced and evaluated in the last decade: Among them is the BioComFold Type 43A (Morcher GmbH, Stuttgart, Germany) (Legais et al. 1999) and the 1CU (HumanOptics AG, Erlangen, Germany) (Küchle et al. 2002, Mastropasqua et al. 2007) (Fig. 1*A*) both made from hydrophilic acrylate. The AT-45 CrystaLens (B&L, Aliso Viejo, CA, USA) (Patel et al. 2008, Pepose et al. 2007, Cumming et al.

2006) (Fig. 1*B*) is made from silicone material as well as the dual optic based Synchrony (Visiogen Inc., Irvine, CA, USA) (Ossma et al. 2007, McLeod et al. 2007) (Fig. 1*C*).

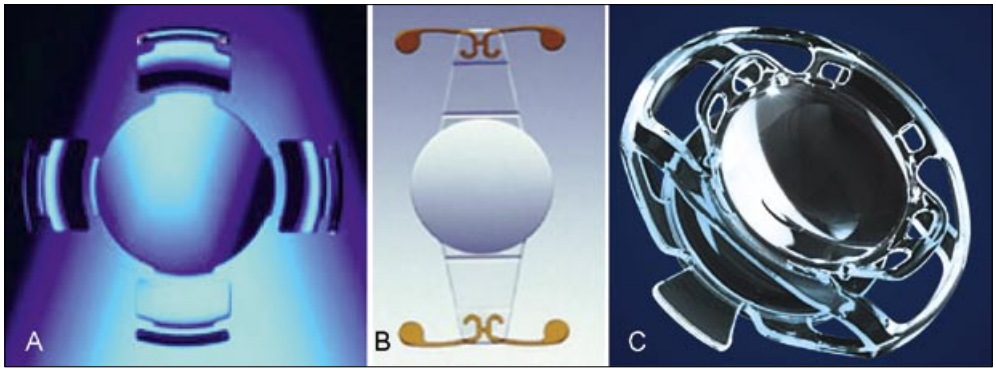

Fig. 1 (*A*) 1CU IOL (CE-marked and approved in Europe), (*B*) CrystaLens IOL (CE-marked and FDA-approved), (*C*) Synchrony dual optic IOL (CE-marked and in FDA-Trials)

The 1CU accommodative IOL (HumanOptics) (Fig. 1*A*) represents accommodative IOLs with a single-optic design. It shows potential accommodative capabilities in laboratory tests as well as in some clinical studies. However long-term evaluation indicated that this IOL type was not able to provide sufficient near correction (Mastropasqua et al. 2007). The extent and strength of accommodative power is difficult to predict individually and is mostly influenced by pseudoaccommodation. Furthermore, the potentiality in diopters is limited due to the optic conditions. For example, for accommodation of +3 diopters a forward movement of circa 2.3 mm is needed with a single optic IOL.

The dual optic system like the Synchrony IOL (Fig. 1*C*), however, only requires approximately 1.4 mm for the same three diopters power change and therefore seems to be a promising idea. Clinical results show good results (Ossma et al. 2007, McLeod et al. 2007).

In 2008 the Crystalens HD (Fig. 1*B*) was approved by the American Food and Drug Administration (FDA) featuring a single optic design with an aspherical optic. Again pseudoaccommodative factors have in some cases been shown to generate quite satisfying near acuity results, but still objective measures proved that this lens is not moving much inside the capsular bag.

4. New Developments

All accommodative lenses based on the anterior shift principle lack the ability to move the required long distance inside the eye to achieve enough dioptric power. The Fluidlens from Powervision (Fig. 2–4) has a totally different approach. Inside the haptics and optic of the lens is a system of channels filled with a special channel system. This system is filled with silicone oil, which is pumped from the haptics into the optics (Fig. 4) thus changing the curvature of the anterior lens capsule (Fig. 3). By this method accommodative amplitudes up to 10 diopters have been measured. So far only blind eye studies have been able to show, that this large lens fit into the eye.

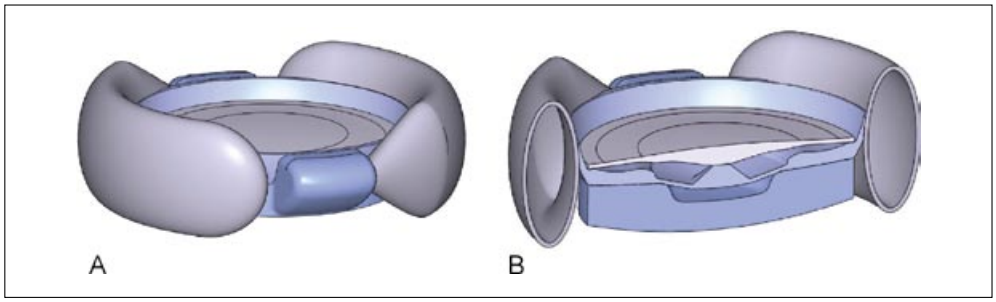

Fig. 2 The Powervision FluidLens. (*A*) Design of the lens. (*B*) Cut through the middle of the IOL showing the fluid channels.

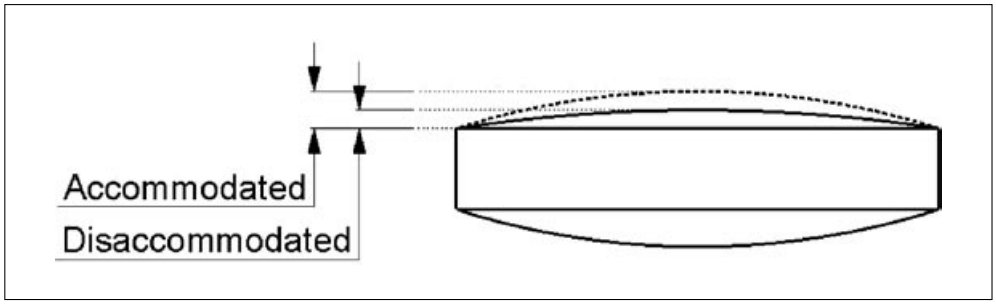

Fig. 3 Change of curvature of the lens optic resulting in increase of radius and dioptric power.

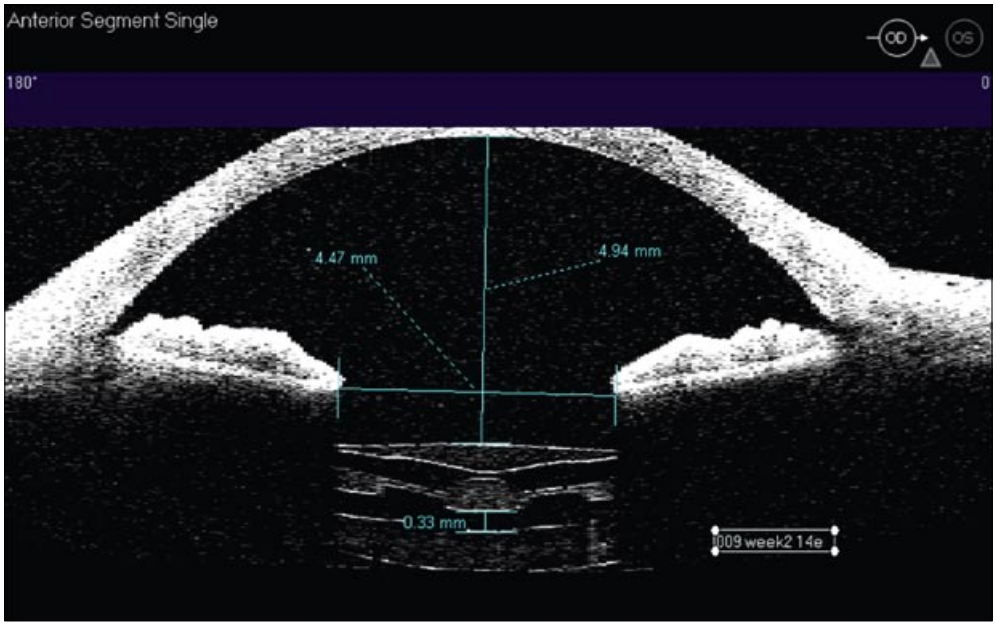

Fig. 4 Picture of a Synchronie IOL in the capsular bag in a blind eye study. Notice the small channels inside the optic, causing a change of curvature representing 8–10 diopters.

5. Conclusions

The optical sense represents the most important sensory perception for humans – between 75 and 80 % of the environmental information is taken up via the eyes. Throughout the history of mankind there have been people with refractive errors.

Today a wide range of intraocular lenses are available for presbyopia surgery. Highly important for a satisfied patient is the proper selection of patients and detailed information on the possible drawbacks of the IOL under consideration. Furthermore, the expectations of the patient have to be considered as well when deciding on an IOL. As is also true for other IOLs, posterior capsular opacification (resp. its prevention) is highly important. Cataracta secundaria is a special drawback with multifocal and accommodating IOLs, as the capsular opacification could facilitate a loss in function of these IOLs.

Ongoing research and numerous inventions in corrective lenses led from the first bifocal glasses to modern multifocal glasses, contact lenses and intraocular lenses, as well as to multifocal patterns in refractive laser surgery and in accommodative IOLs. To offer a differentiation in accommodation and pseudo-accommodation, improved objective and reproducible techniques in measurement of refractive errors are a general aim to enhance visual outcomes especially in presbyopic patients. At the moment intelligent systems such as the dualoptic IOL Synchrony can provide sufficient near addition. However, A-IOLs based on the change of curvature of the anterior lens capsule, such as the Fluidvision IOL are much more promising. Need, demand, as well as the market for surgical techniques to correct presbyopia will increase further in future; millions of presbyopic patients are waiting for an appropriate and contemporary correction of their age related farsightedness.

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Rostock Animal Studies on Restoring Accommodation

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With 5 Figures and 2 Tables

Abstract

The concept of replacing the stiff presbyopic lens with a material imitating the young crystalline lens is not a new one. A variety of pertinent publications are available. Our advanced *ex vivo* investigations and animal studies address two major problems (*i*) preventing posterior capsular opacification (PCO) and (*ii*) lens capsular volume variability.

Zusammenfassung

Das Konzept, die starre presbyopische Linse durch ein Material zu ersetzen, das die junge kristalline Linse nachahmt, ist nicht neu. Eine Vielzahl entsprechender Publikationen ist vorhanden. Unsere weiterführenden Untersuchungen versuchen zwei Hauptprobleme, nämlich (*a*.) die Verhinderung des sekundären Katarakts und (*b*.) die Variabilität des Linsenkapselvolumens, anzugehen.

1. Introduction

Replacing the lens of a human eye by an artificial intraocular lens (IOL), either during cataract surgery or for other medical reasons, restores clear vision. Approximately 14 million IOL units were sold globally in 2005, producing 1.28 billion USD in total revenues. An aging global population, newly developed IOLs, and growing worldwide access to advanced medical technology are expected to produce a very high annual growth rate over the coming years.

Efforts are being made on several fronts to develop even more advanced IOLs that mimic the natural lens, that are injectable through a tiny incison, and restore accommodation. Today, technological developments with regard to phakic, accommodative, multifocal, adjustable and toric IOLs are being pursued along different tracks. The most immediate beneficiaries of new IOL designs are cataract patients seeking improved vision, thus

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eliminating the need to wear glasses. If these future IOLs perform according to expectations, cataract patients will experience significantly improved visual acuity and will be able to live without glasses.

2. Concepts of Restoring Accommodation

During cataract surgery an intraocular lens is implanted in the capsular bag. Despite excellent restoration of visual acuity and biocompatibility no accommodation is detected in pseudophakic eyes, as the IOL optics change neither shape nor position in any way.

To restore accommodation in the human eye, the physiology of the accommodative structures must remain viable. Any residual activity needs to be utilized in order to design an implant to restore the accommodative ability.

Various attempts have been made to solve or bypass this problem:

- Monovision to correct presbyopia;
- Multifocal vision to correct presbyopia (lens-based, corneal);
- Laser treatment of the lens content;
- Scleral expansion procedures;
- Accommodative intraocular lenses;
  - Single optic IOLs with flexible haptic support;
  - Dual optic IOLs;
  - Deformable Accommodating IOLs;
  - Cubic optical elements (Alvarez principle);
- Refilling the empty lens capsule (lens refilling, “Phakoersatz”);
- Mechatronic concepts.

These different approaches have met with varying success. Monovision is not physiological. Optical or mechanical concepts afford limited accommodative ability. Scleral or corneal concepts show doubtful results. Artificial lens material concepts are the most promising strategies, but they are still at a very early experimental stage.

3. Injectable Accommodative Lenses

The concept of replacing the stiff presbyopic lens with a material imitating the young crystalline lens is not a new one. A variety of pertinent publications are available.

In general, although each of the investigators (Tab. 1) successfully elucidated many of the ideal parameters, some major problems still remain:

- Creating a minicapsulorhexis: An injectable gel lens requires a robust capsule and therefore a very small capsulorrhexis (< 2 mm), which necessitates innovative microinstrumentation as well as extensive surgical training.
- Phacoemulsification through minicapsulorhexis: Performing phacoemulsification through such a tiny capsulorrhexis presents a significant challenge. Although bimanual microincision techniques allow increasingly smaller incisions, performing the entire procedure through a hole in the capsule smaller than 1 mm requires an innovative approach.

– Sealing the minicapsulorrhexis: Sealing the microcapsulorrhexis to prevent leakage from the bag is a challenge.
– Polymer biocompatibility: Whatever gel material is selected, its biocompatibility is still essential and must be reliably established. Many of the materials used in current IOL designs have passed years of biocompatibility testing.
– Lens capsular volume variability: Lens capsular volumes vary widely among patients. In theory, only the optimum amount of gel allows the necessary changes in lens curvature. Controlling the injection of a gel with this much precision is a significant challenge.
– Polymer refraction: Achieving the desired refraction is not so easy either. IOL lens power requirements vary widely among patients and determining the optimal amount of gel required to achieve the desired power correction is a challenge.
– Preventing capsule opacification (CO): Finding a way to prevent anterior and posterior CO presents another significant challenge. With conventional IOLs, an Nd:YAG laser pulse can eliminate opacification; however, an injectable gel material would leak from the opening created with a laser.

Tab. 1 Fundamental studies regarding lens refilling procedures

Study	Specimens	Refilling material
Kessler 1975	cadaver and rabbit	immersion oil, silicone fluids, silastics
Agarwal et al. 1967		silicone elastomer
Parel et al. 1986	cadaver, cat, rabbit, monkey	divinylmethylcyclosiloxane
Nishi et al. 1998	rabbit	polymethyldisiloxane liquids
Stachs et al. 2003	rabbit	polymer silicone material
Hettlich et al. 1994	rabbit	monomer mixture (photopolymerization)
Haefliger et al. 1987	monkey	silicone polymer gel
Koopmans et al. 2004	monkey	polymer silicone material
Aliyar et al. 2005	porcine cadaver	polyethylene glycol-based hydrogels; acrylamide and bisacryloylhistamine-based hydrogels
de Groot et al. 2001	*in vitro*	isocyanate-crosslinked hydrogels derived from polyalcohols
Han et al. 2003	*in vitro*, rabbit	poloxamer hydrogel

Our advanced *ex vivo* investigations and animal studies address two major problems (*i*) preventing posterior capsular opacification (PCO) and (*ii*) lens capsular volume variability.

4. Preventing PCO

The major problem seems to be PCO development because of the lens epithelial cells found on the inside of the capsular bag after phacoemulsification.

Opacification of the posterior capsule caused by postoperative proliferation of cells in the capsular bag remains the most frequent complication of cataract-intraocular lens surgery (Apple 2000). In addition to classic posterior capsular opacification (PCO, sec-

ondary cataract, after cataract), postoperative lens epithelial cell proliferation is also involved in the pathogenesis of anterior capsular opacification/fibrosis (ACO) as well as interlenticular opacification (ILO). Secondary cataract has been recognized since the origin of extracapsular cataract surgery and was noted by Ridley in conjunction with his very first IOL implantations. This phenomenon was particularly common and severe in the early days of IOL surgery when the importance of cortical cleanup was less appreciated. Through the 1980 s and early 1990 s the incidence of PCO ranged between 25 % and 50 %. PCO is a major problem in pediatric cataract surgery where it occurs in almost 100 % of all cases.

One of the crowning achievements of modern cataract surgery is the gradual, almost unnoticed decrease of this complication. The literature at present shows that with modern techniques and IOLs, the expected rate of PCO and the subsequent Nd: YAG laser posterior capsulotomy rate is now less than 10 %.

There are a number of surgery-related and IOL-related factors to prevent posterior capsular opacification. Surgical factors include hydrodissection-enhanced cortical cleanup, in-the-bag (capsular) fixation, and the capsulorhexis edge on the IOL surface. Besides, there are basically three IOL-related factors to reduce PCO: IOL biocompatibility, maximum IOL optic-posterior capsular contact, and the barrier effect of the IOL Optic. But none of these techniques are suitable for lens refilling.

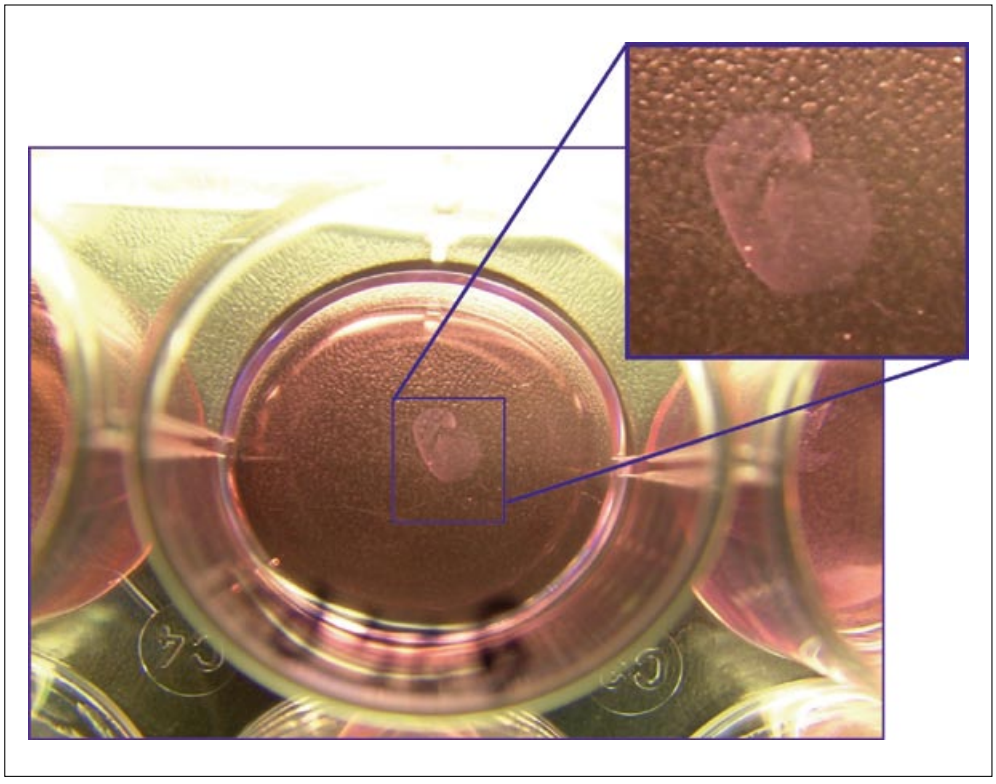

Fig. 1 Utilization of capsular rhexis specimens from standard cataract surgery

Another approach to prevent PCO involves the intraocular application of pharmacological agents (Awasthi 2009). Numerous investigators examined the potential of pharmacological substances in order to successfully prevent LECs from proliferating and migrating in cell culture studies. Pharmacologic agents that have been investigated include cytostatic drugs, such as 5-Fluorouracil, Daunomycin, Colchicine, Doxorubicin, Mitomycin C, Methotrexate, anti-inflammatory substances, such as Dexamethasone and Diclofenacs, calcium-channel blockers, such as Mibefradil, and immunological agents, such as Cyclosporine A. In addition, adhesion inhibitors and osmotic effective solutions were tested. In several studies different drug delivery systems were investigated in order to provide a longer and more effective impact on LECs.

The goal of our studies was to develop an *ex vivo* model by utilizing capsulorhexis specimens obtained during standard cataract surgery that can be tested for the ablation of LECs from the basal membrane. Since capsular rhexis specimens contain a LEC layer on the natural substrate, the basal membrane, an effective cell ablation method established in the *ex vivo* model should also be effective *in vivo*.

Cultured capsular rhexis specimens from standard cataract surgery were used for these experiments (Fig. 1). For the evaluation of the cell inhibitory and detaching potential of drugs the culture medium was replaced by different drug solutions. The specimens were incubated with these solutions for 5 min. The drugs were embedded in the sodium hyaluronate solution.

After drug treatment the total number of residual cells on the surfaces of capsular rhexis specimens was assessed by use of microscopic methods. The residual viable and dead lens epithelial cells were differentiated by use of the live-dead assay. Quantification of the lens epithelial cells was facilitated by staining with Hoechst-dye (Fig. 2).

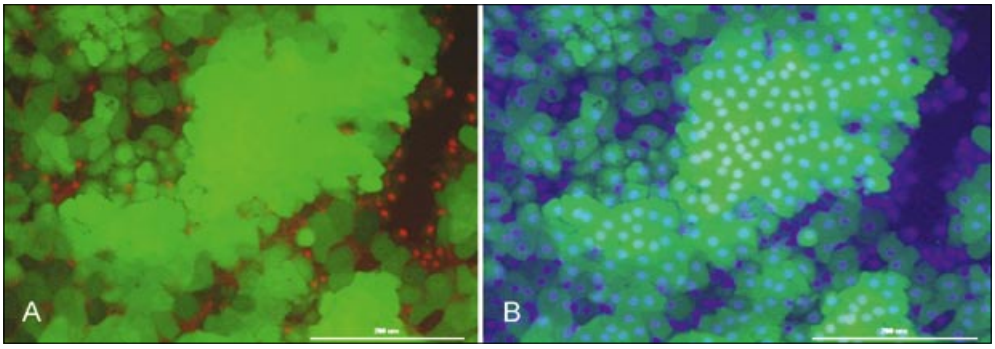

Fig. 2 Epithelial cell staining with LIVE-DEAD assay and cell nucleus staining with Hoechst-dye (*A*: viable LECs – calcein AM, dead LECs – ethidium homodimer-1; *B*: viable LECs – calcein AM, nuclei of all LECs – Hoechst 33342)

In Table 2 specified drugs were tested using the established *ex vivo* cell culture model. There can be found also the number of vital and dead cells for each drug. In conclusion and without discussing all findings in detail for the secondary cataract prevention the pure substances Actinomycin, Paclitaxel, and Tween 20, embedded in HA, were most effective in our *ex vivo* model. Combinations of two or more drugs reduce the efficacy regarding inhibition and ablation of LECs. Tween 20/PTX, Tween 20/ActD, ActD/MTX/CAPE, PTX/MTX/CAPE, and PTX/CAPE were the most effective drug mixtures (Sternberg et al. 2008).

Tab. 2 Drug tested using the established *ex vivo* model and tested using rabbits (grey overlay), drugs embedded in 1 % HA

Treatment	vital cells/mm^2			dead cells/mm^2		
	mean	std. dev.	%	mean	std. dev.	%
untreated	1229	±259	93.32	88	±93	6.7
1 % Healon	1	±2.9	0.08	512	±494	38.9
ActinomycinD (ActD)	0.1	±0.3	0.01	165	±163	12.5
Methotrexat (Mtx)	3.7	±6.9	0.28	246	±268	18.7
Paclitaxel (Ptx)	0.4	±0.5	0.03	264	±187	20.0
CAPE	7.1	±8.4	0.54	609	±505	46.2
Cisplatin	49.5	±78.9	3.76	427	±399	32.4
Carboplatin	34.7	±61	2.63	604	±634	45.9
ActD + CAPE	48.9	±105	3.71	366	336	27.8
ActD + Mtx	3.3	±9.1	0.25	362	±474	27.5
ActD + Mtx + CAPE	1.1	±1.7	0.08	100	±140	7.6
ActD + Ptx + CAPE	31	±47.4	2.35	1241	±141	94.2
Ptx + CAPE	2	±3.3	0.15	466	±263	35.4
Ptx + Mtx + CAPE	1.8	±3.4	0.14	383	±315	29.1
3,4 Dihydroxybenzoic acid ethyl ester	31.6	±45.2	2.40	801	±709	60.8
Minoxidil	9.3	±18.7	0.71	848	±715	64.4
Hexadecylphosphocholine	13.2	±35.1	1.00	853	±305	64.8
Tween 20	0.1	±0.26	0.01	358	±244	27.2
Tween 20 + Ptx	0	±0.0	0.00	1260	±603	95.7
Tween 20 + ActD	0.7	±1.2	0.05	780	±456	59.2

In a next step these discovered effective drug and drug mixtures specified in Table 2 were tested in rabbit experiments. Polymer lens refilling surgery was performed on eyes of New Zealand white rabbits (age 12–15 weeks) with the following steps: (*i*) limbal incisions, (*ii*) minicapsulorhexis (1.5 mm) of the anterior capsule with high frequency diathermy, (*iii*) endocapsular phacoemulsification, infusion through the second paracentesis in the anterior chamber, (*iv*) bimanual capsule polishing, (*v*) injection of the silicon mixture in the capsular bag. To prevent leakage of the liquid silicone the capsule was sealed before polymerization. The wound closure was achieved with 10–0 nylon sutures. In between steps (*iv*) and (*v*) the empty capsular bag was treated with a drug-loaded solution to prevent after cataract development specified later. To protect the corneal endothelium Healon 5 was inserted into the anterior chamber. The drug-loaded viscoelastic solution that is utilized to inflate the capsular bag for LEC treatment was filled into the capsular bag for 5 min. Thereafter the drug-loaded solution and Healon 5 were removed carefully.

Without discussing all findings in detail, a high efficacy to reduce the PCO development with a pharmacological treatment using the combination Actinomycin-D + Methotrexate was found. All eyes treated with the viscoelastic AD + MTX mixture showed no posterior capsule opacification (PCO) at 12-months postop and no-to-low PCO 3 years

postop (Fig. 3) (GUTHOFF et al. 2008). *In vivo* confocal laser scanning microscopic investigations have shown a normal distribution and number of endothelial cells. This shows that a careful capsular bag treatment with closing the capsular rhexis during treatment using Healon 5 is a safe procedure.

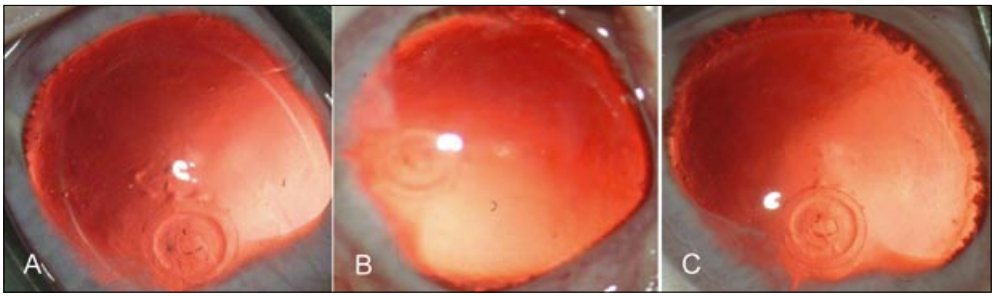

Fig. 3 PCO development with pharmacological treatment using Actinomycin-D + Methotrexate + Sodium-hyaluronate, 15 (*A*), 32 (*B*) and 36 (*C*) month postoperatively

5. Lens Capsular Volume Variability

During further development of the lens refilling procedure, an assessment of the refilled lens shape without anamorphic distortions is necessary. Anterior segment imaging has advanced greatly over the recent years, especially with the ultrasoundbiomicroscopy, Scheimpflug imaging (FINK 2005) and optical coherence tomography. But all these methods have some major limitations in evaluating the entire lens shape after lens refilling surgery. The iris pigment prevents viewing the important structures of the lens equator in all optical methods except UBM. However, UBM comprised distortions based on different sound velocities in different ocular and related media. All acoustic and light detection methods are subject to image distortion by the intervening surfaces and need mathematical remodeling.

Magnetic Resonance Imaging (MRI) is a valuable tool in the field of medical imaging. The eye is an ideal tissue for high field MRI due to the wide variation in water content and especially because of the requirement of high spatial resolution in a small field of view. MRI, by contrast, is only reliant on uniform field strength to give true anatomical proportions. At the present time access to the technology is still limited, especially for human examination, but small animal ultra-high field units open new dimensions in distortion free, high resolution intraocular imaging. The aim is to use this technology to assess the anterior segment in rabbit eyes after lens based refractive surgery. High field MR imaging using a 7.1 T device was used to assess the lens geometry after experimental lens refilling surgery in combination with a pharmacological capsular bag treatment to prevent secondary cataract (STACHS et al. 2008).

The spatial arrangement and the dimensions of refilled lenses were visualized by *in vivo* micro-MRI (Fig. 4) without anamorphic distortions and with a maximal in-plane resolution of 125 × 125 microns 3 years after surgery. In the refilled eyes the capsule and homogenous silicone polymer remain in close contact with no visible interface 3 years postoperatively. Different lens dimensions were found in refilled lenses and crystalline lenses of the contralateral eye (Fig. 5).

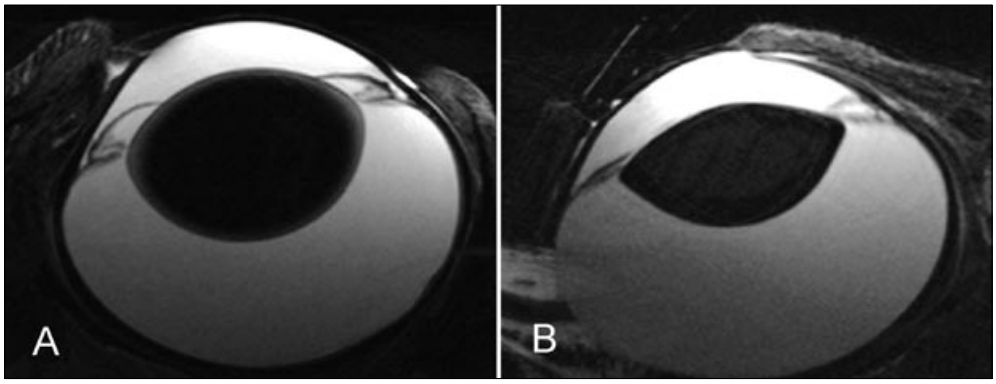

Fig. 4 High field MR imaging in a rabbit with refilling (*B*) and contralateral control (*A*) lens, 36 months postoperatively

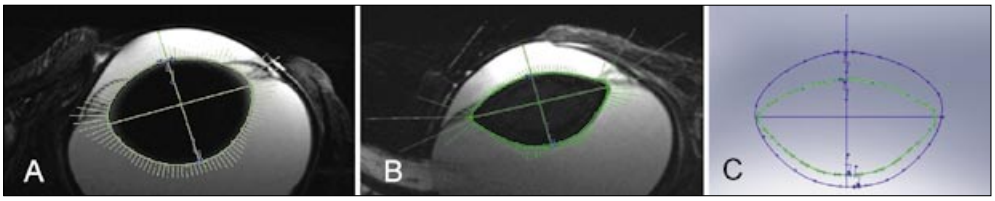

Fig. 5 Lens shape approximation with marked radius of curvature of the crystalline (*A*) and the refilled lens (*B*). The lengths of the green bars represent the local radius of curvature. Lens shape comparison of the crystalline (blue) and the refilled lens (green) of rabbit 40 extracted from (*A*) and (*B*) is shown in (*C*).

It could be seen clearly that the contour length of the capsular bag section of the polymer lenses is less than that of the crystalline control lenses. The cross sectional area of the polymer lenses is smaller in all cases, the lens diameter and the lens thickness is smaller, and the anterior chamber depth is higher than those of native lenses. The polymer lenses are flatter and smaller than the native lenses, which leads to apparently higher curvature radii of the anterior and the posterior surface.

In principle there are two main possibilities to explain the final lens shapes found. (*i*) The empty capsule has a shape with a smaller contour length in comparison to the original crystalline lens. The original lens shape can be obtained only by a refilling procedure using over pressurization. (*ii*) The capsule was not completely filled intraoperatively and the postoperative capsule bag shrinkage generates the final lens shape. In both cases new technologies are necessary to close the capsule during refilling, and the intraoperative refilling procedure needs to be optimized. Additionally the refraction should be controlled intraoperatively during refilling.

6. Conlusions

In conclusion, the lens refilling procedure is feasible in rabbit eyes without alterations in the cornea and anterior segment configuration with a stable situation over 3 years. Without capsular bag treatment rabbit eyes showed a strong PCO development starting directly aft-

er cataract surgery. An active LEC treatment with AD+MTX proved to be a valid method to prevent PCO in rabbits. Despite silicon plug sealing of the minicapsulorhexis natural lens, volumes could not be achieved by refilling. Therefore further effort is necessary to reconstruct the lens geometry intraperatively.

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Natur und Migration

Vorträge anlässlich der Jahresversammlung vom 5. bis 7. Oktober 2007
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„Natur und Migration“ – assoziiert sehr verschiedenartige Phänomene, die sich durch Wanderungsprozesse auszeichnen. In diesem Band wurden besonders interessante Gebiete ausgewählt, u. a. Migration und Seuchen, Reisen und Epidemien in einer globalisierten Welt, der Vogelzug, aber auch die Migration geologischer Fluide, die Elektronenmigration in Halbleitern, die Migration als treibende Kraft in der Organogenese, die Biophysik der Zellbewegungen, die Migration von Tumorzellen, Migration als Phänomen in der Neurobiologie oder die Migration wissenschaftlicher Ideen. Besondere Akzente setzen die Themen „Diversität als neues Paradigma für Integration?“ und „Vorspiel der Globalisierung. Die Emigration deutscher Wissenschaftler 1933 bis 1945“.
Die Beiträge sind von herausragenden Experten der jeweiligen Gebiete, u. a. durch die Leopoldina-Mitglieder Markus AFFOLTER, Lorraine DASTON, Wolfgang FRÜHWALD, Michael FROTSCHER, Jörg HACKER, Hans KEPPLER und Otmar WIESTLER, in anspruchsvoller, aber durchaus gut verständlicher Form verfasst.

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Lens Refilling – The State of the Art

Thom Terwee (Groningen, The Netherlands)

With 9 Figures

Abstract

The accommodative power of the human eye decreases with age. Since this is mainly due to stiffening of the natural crystalline lens, the problem may be remedied by replacing the natural lens material with a polymer material injected into the capsular bag. The polymer is designed to mimic primary properties of the young crystalline lens material, such as the Young's modulus, the refractive index, and the density. Additionally, this material ought to be optically clear as well as biocompatible. A new technique of treating the lens epithelial cells prevents wound healing reactions that might lead to opacification and stiffening of the capsular bag. In addition, a surgical implantation technique was developed. The success of the entire procedure in terms of restoring accommodation was evaluated using rhesus monkey eyes. It is empirically possible to restore a useful level of accommodation. Within the first six months after implantation, however, the newly acquired accommodation amplitude dropped due to other effects in conjunction with the lens epithelial cells, causing the capsular bag to stiffen. This leaves us facing the challenge of finding a method to permanently stabilize the lens epithelial cells.

Zusammenfassung

Die Fähigkeit des menschlichen Auges zur Akkommodation nimmt mit zunehmendem Alter ab. Da dies in erster Linie auf die Versteifung der natürlichen Kristalllinse zurückzuführen ist, lässt sich das Problem durch Austausch des natürlichen Linsenmaterials gegen ein Polymermaterial beheben, das in den Kapselsack injiziert wird. Das Polymer soll die wesentlichen Eigenschaften des Linsenmaterials junger Linsen simulieren, beispielsweise das Elastizitätsmodul, den Brechungsindex und die Dichte. Außerdem sollte dieses Material optisch transparent sowie biokompatibel sein. Ein neues Verfahren zur Behandlung der Linsenepithelzellen bietet Schutz vor Wundreaktionen, die eine Linsentrübung verursachen können, wobei auch der Kapselsack versteifen kann. Zudem wurde ein chirurgisches Implantationsverfahren entwickelt. Der Erfolg des gesamten Verfahrens im Hinblick auf die Wiederherstellung der Akkommodationsfähigkeit wurde an Rhesusaffenaugen überprüft. Empirisch ist es möglich, eine ausreichend hohe Akkommodationsfähigkeit wiederherzustellen. In den ersten 6 Monaten nach der Implantation verringerte sich die chirurgisch erzielte Akkommodationsamplitude jedoch aufgrund anderer Effekte im Zusammenhang mit den Linsenepithelzellen, wodurch der Kapselsack versteifte. Daher müssen wir uns nun der Herausforderung stellen, ein Verfahren zu finden, mit dem sich die Epithelzellen der Linse auf Dauer stabilisieren lassen.

The eye is an important organ; it is our visual gateway to the world. Together, the cornea and the natural crystalline lens create an objective image that is projected onto the retina (Fig. 1) where the image is converted to signals processed by the brain to afford a subjective optical image.

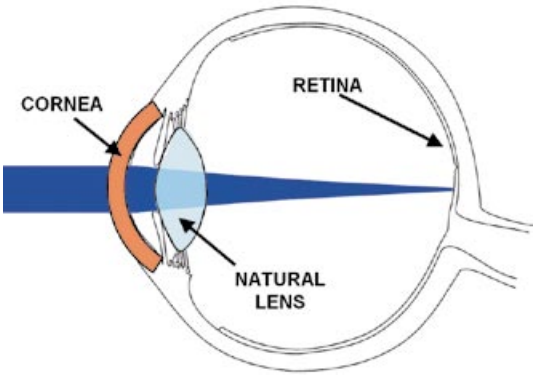

Fig. 1 Schematic drawing of the human eye showing the cornea, the natural crystalline lens, and the retina

The quality of the retinal image depends on the functional quality of the cornea and the lens. While the optical properties of the cornea remain relatively stable with time, this is not true of the natural lens. The lens grows slowly but steadily, accompanied by certain color changes; while being fully transparent at first, the lens later turns yellowish-brown. The clarity decreases and the lens material loses its original flexibility that enables the necessary changes of shape caused by ciliary muscle activity, which is called accommodation.

Presbyopia – loss of accommodation – is a common phenomenon occurring somewhere between 45 and 55 years of age. Even those of us who have never needed any visual aids before will now have to wear glasses. Elderly emmetropes, for instance – those who have good distance vision without glasses – will now have to wear reading glasses in order to clearly see objects close-up.

Natural accommodation has the great advantage that very small shape changes of the natural lens have comparatively large optical effects. In a young natural lens, for instance, a 0.4 mm increase in lens thickness will cause refractive changes of as much as 8 diopters (Dubbelman 2001). These refractive changes, however, decrease with age. According to many researchers (such as Fisher 1969 and Glasser and Campbell 1999), presbyopia is mainly to be attributed to the stiffening of the natural lens material or – in more scientific terms – to the increasing Young's modulus of the natural lens material.

If this presbyopic lens also turns cloudy due to cataract, the associated problems might be solved by replacing the stiff cloudy natural lens material with a clear flexible artificial lens material. This approach was originally suggested by Julius Kessler (1964) who investigated rabbit eyes; the fact that the rabbit eye has no accommodative power, however, made it impossible to measure any degree of accommodation.

The natural lens consists of a very thin, elastic capsular bag containing the crystalline lens material. The primary question is whether the stiffening of the aging lens material is the only cause of presbyopia; it is also conceivable that the decreasing activity of the ciliary body and/or lack of flexibility of the human capsular bag contribute significantly to this process.

A number of studies performed both in Rostock (Bacskulin et al. 2000, Stachs et al. 2002) and in Aarhus (Krag et al. 1997) show that the remaining ciliary body activity, as

well as the remaining elasticity of the capsular bag in the elderly eye, are sufficient to enable a certain degree of accommodation that makes it possible to read and see close-up even without reading glasses.

This means that presbyopia is primarily caused by an age-related increase in the Young's modulus of the natural lens material ("stiffening of the natural lens"). Thus, we may expect that presbyopia, in practice, may be alleviated by replacing the old, stiff, cloudy natural lens material with an artificial flexible polymer material. In order to develop an adequate product that would make for a suitable lens replacement, we must first specify the required properties required for a useful artificial lens material.

Measurements of human donor eye lenses at different ages by Henk Weeber in cooperation with IDM-Ulm (Weeber et al. 2005, 2007) revealed that the human lens modulus depends on the age (Fig. 2).

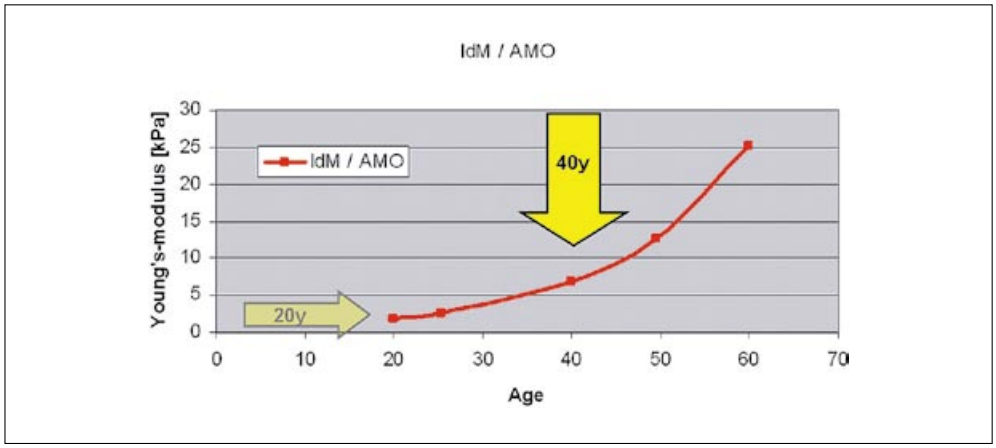

Fig. 2 Lens stiffness of human lenses (courtesy of H. Weeber)

We therefore tried to restore the accommodative ability of a 40-year-old person. To be on the safe side we used an artificial lens material with the Young's modulus of a 20-year-old natural lens – which (as empirically determined) is slightly less than 2 kPa.

Besides, other important properties were also defined: The material must be optically clear, with a refractive index of approximately 1.43 and a density slightly above 1000 kg/m^3 (just higher than water). Also, in order to yield an injectable solution, the material must have a viscosity that allows injection into the eye through a small canula. Polymer scientists have developed such an artificial crystalline lens material (ACL), which is a silicone-based ter-polymer (Fig. 3).

During this type of cataract surgery to restore accommodation, a small incision is made in the cornea and the natural lens material is removed through a mini-capsulorhexis in the lens capsule. After cleaning the capsular bag, the artificial lens material is injected into the capsular bag (Fig. 4). The small opening is then sealed with a plug and the injected material polymerizes at body temperature to afford an artificial crystalline lens within about 45 min (Fig. 5). A number of researchers (Parel et al. 1986, Haefliger and Parel 1994, Hettlich et al. 1997, Nishi et al. 1997) tested this surgical technique in animal experiments.

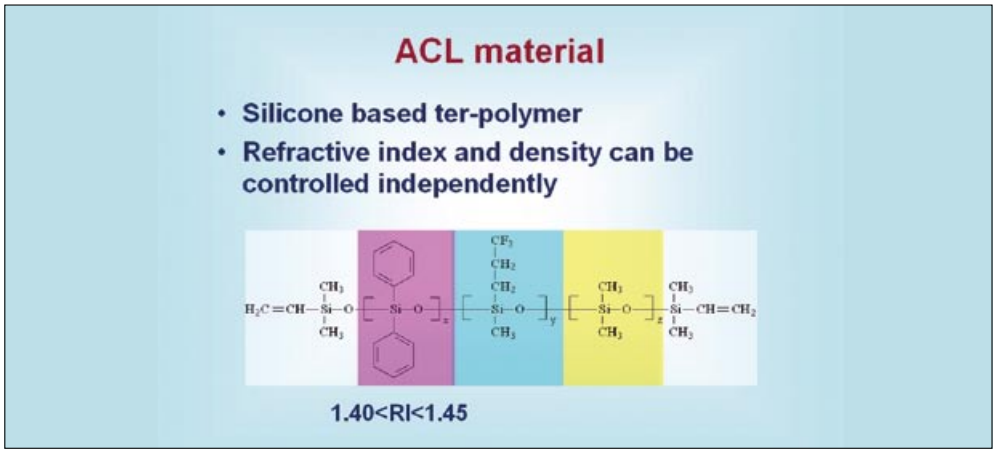

Fig. 3 Basic chemical formula of the ACL material

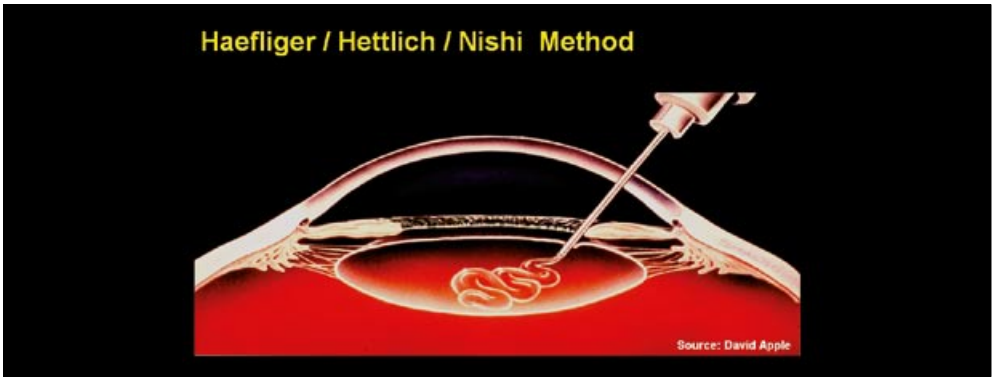

Fig. 4 Lens refilling procedure (courtesy David Apple)

Steven Koopmans (Koopmans et al. 2003) performed a considerable number of experiments involving porcine eyes (from the slaughterhouse), human donor eyes, as well as rabbit eyes and monkey eyes. He improved this technique and developed a stable, reproducible surgical procedure.

Cataract surgery is known to cause wound healing reactions of natural lens epithelial cells (LECs) covering the inside of the capsular bag, leading to opacification and stiffening of the capsular bag, which is referred to as "secondary cataract". For capsule refilling concepts to be successful in the long run, secondary cataract must be prevented. First of all, we tried to prevent the LECs from proliferating by removing them by any means, mechanically as well as pharmaceutically. We developed treatment methods that we tested on human capsulorhexis specimens (the remains of normal cataract surgery). One of our most successful products – a viscous solution of sodiumhyaluronate and Actinomycin D in pure water – was also tested on rabbit eyes; these remained clear for more than three years (Fig. 6). These results were extremely promising, as it is generally considered to be acceptable if a rabbit eye remains clear for more than 6 weeks after standard cataract surgery.

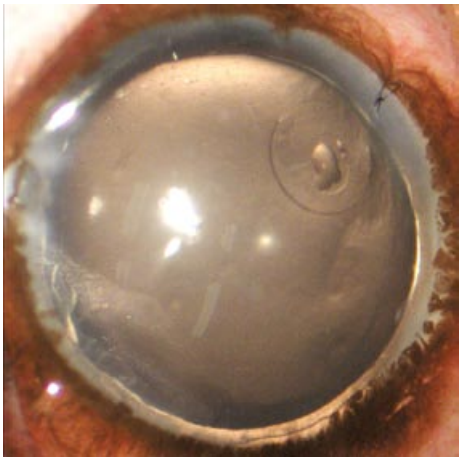

Fig. 5 A refilled monkey lens immediately after surgery. The small capsulorhexis at 2 h is sealed with a simple plug. The eye was iridectomized before surgery so as to enable inspection of the complete lens.

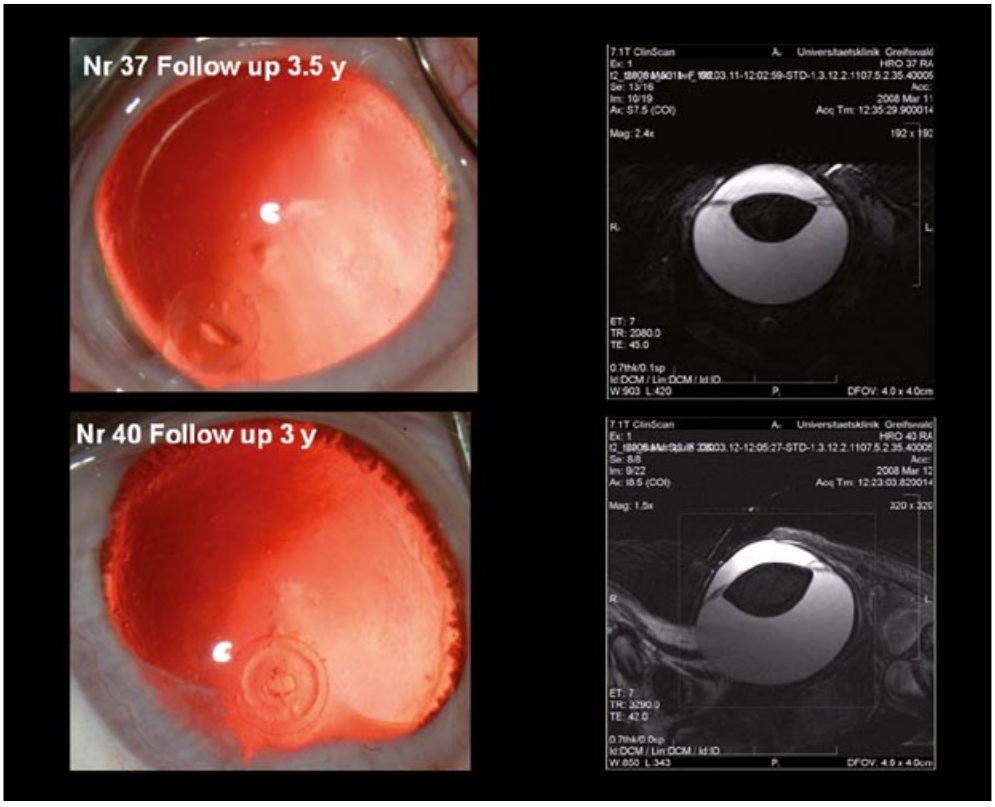

Fig. 6 Rabbit eye with an ACL lens, shown 3 respectively 3.5 years after surgery. Surgical microscope images (*left*) and MRI images (*right*). The pictures on the left show clear lenses; the MRI images reveal how well the lenses are refilled (courtesy of R. Guthoff, H. Schneider, O. Stachs, S. Hadlich, and S. Langner).

Since accommodation cannot be measured in rabbit eyes, we decided to use rhesus monkey eyes instead. Rhesus monkeys, after all, show practically the same kind of accommodation as humans do. After undergoing surgery and receiving our customary post-surgical medication also used in human experiments, the monkeys recovered quickly. During the first 2 months following surgery we measured an accommodation of 6.5 diopters. Subsequently, however, the accommodation amplitude started to decrease, dropping to almost zero within six months after surgery (Fig. 7). Evaluation of the artificial lens revealed a certain opacification of the capsular bag (Fig. 8), apparently caused by a fibrotic reaction of the remaining lens epithelial cells which led to capsular shrinkage and stiffening of the lens equator. The LEC treatment that was so successful in rabbit eyes was not nearly as effective in monkey eyes.

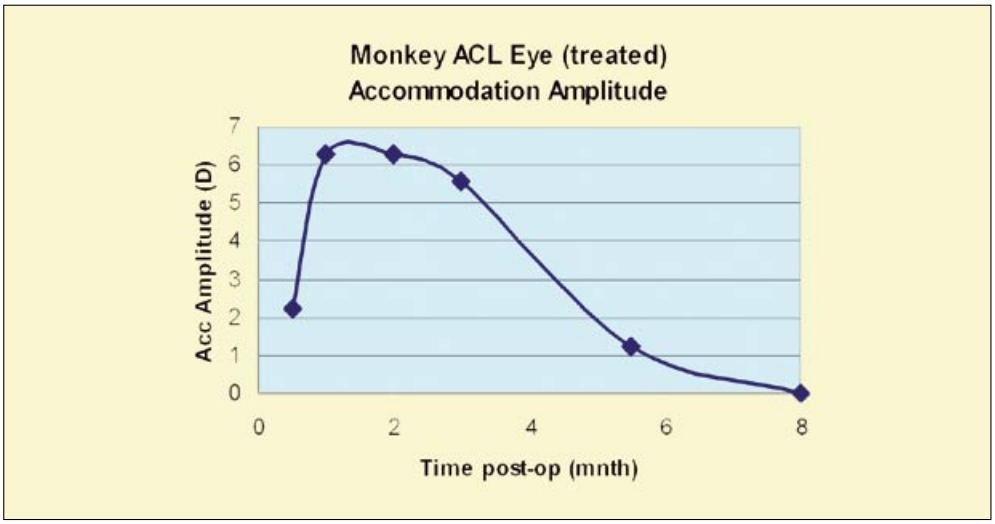

Fig. 7 Accommodation amplitude, calculated from measurements obtained with a Hartinger refractometer (Zeiss) on a 7 years old Rhesus monkey

Although we believe that successful performance in monkey eyes is the best indicator of a functional product for human eyes, this is certainly no guarantee. The final proof is ultimately based on actual human clinical trials.

In another test we filled the monkey capsular bag (first subjected to the usual pharmaceutical pre-treatment) with a pure 1 % sodiumhyaluronate solution. To our great surprise, the capsular bag remained perfectly clear even 3 months after surgery (Fig. 9). While the hyaluronate solution has practically the same refractive index as water, the lens did not have enough refractive power although the lens shape changes under pharmaceutically stimulated accommodation with pilocarpine. After 3 months we replaced the hyaluronate lens with the silicone based ACL lens. This resulted in the same fibrotic LEC reaction as seen previously. The environment enclosing the LECs is obviously highly important.

In conclusion, we showed that refilling the capsular bag basically provides a potential avenue to restoring lost accommodation. The question of how to stabilize the lens epithelial cells and the capsular bag so as to ensure stable long-term accommodation and optical performance remains a challenge.

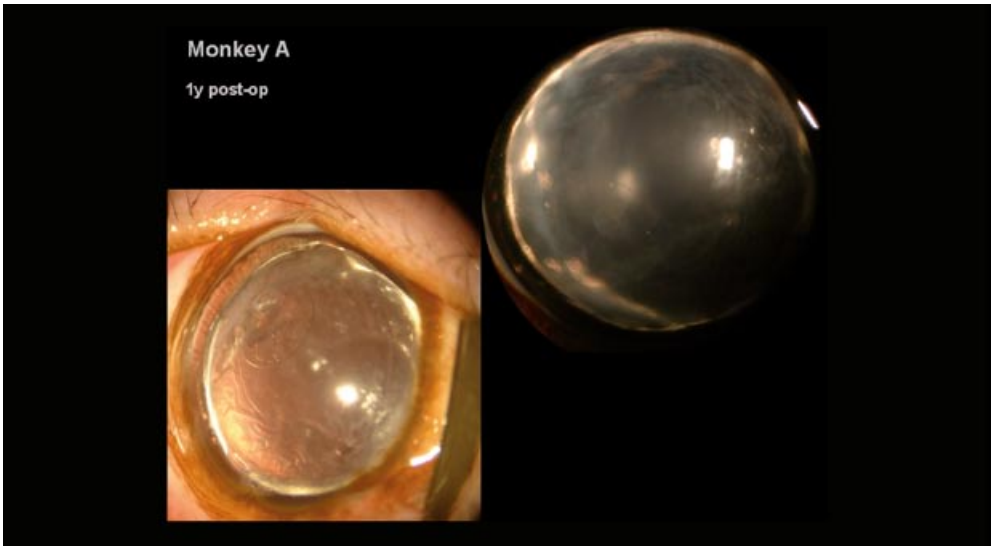

Fig. 8 Rhesus monkey eye (10 years old) with an ACL lens implanted after capsular treatment, 1 year after surgery.

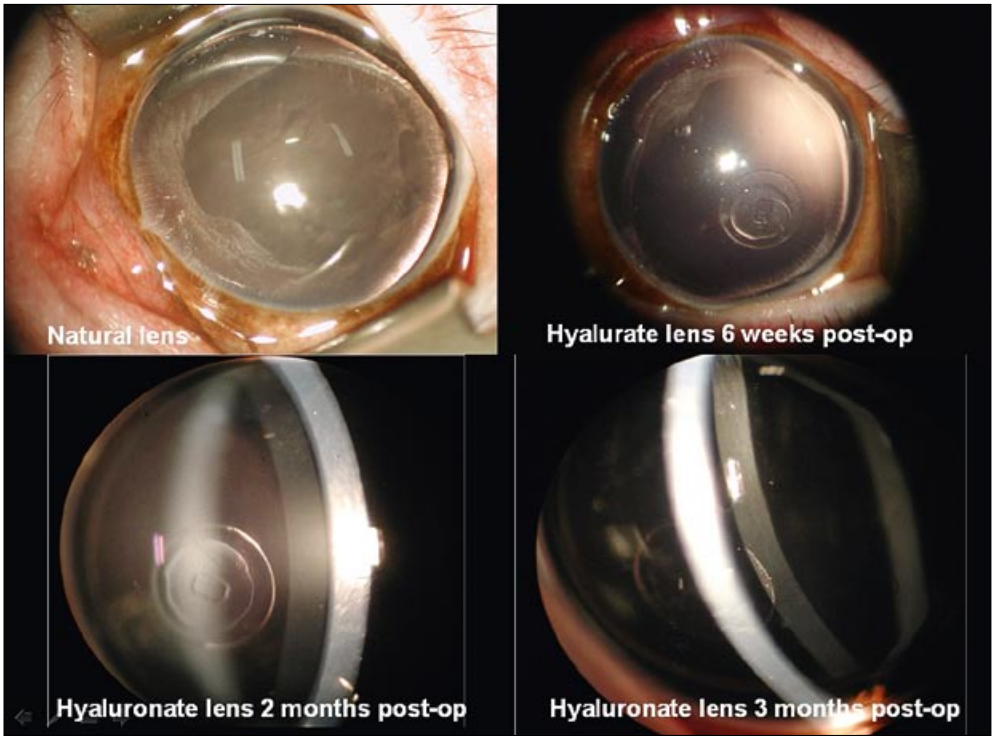

Fig. 9 Rhesus monkey (8 years old). The natural lens and the same lens after refilling the capsular bag with 1 % sodiumhyaluronate: 6 weeks; 2 months and 3 months postoperatively. Regular surgical microscope images (top) and slitlamp images (bottom), respectively.

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Ultrashort Laserpulses and Laser Microscopy in Presbyopia Therapy

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With 4 Figures

Abstract

Purpose: To characterize and evaluate the potential of optical methods, namely confocal scattering microscopy using a diode laser and a femtoscecond (fs) laser for imaging and controlling fs-laser pulse induced microcuts inside the crystalline lens for the treatment of presbyopia.

Method: Lenses removed from porcine eyes were modified *ex vivo* by fs-laser pulses (wavelength 1,040 nm, pulse duration 306 fs, pulse energy 1.0–2.5 µJ, repetition rate 100 kHz) to create defined planes at which lens fibers separate. Lens fiber orientation and fs-laser-induced micro-incisions were examined using a confocal laser scanning microscope (CLSM) based on a Rostock Cornea Module attached to a Heidelberg Retina Tomograph II. Optical sections were analyzed and digitally reconstructed in 3D using AMIRA 4.1.1 software (Mercury Computer Systems, USA). Furthermore, a combined fs-laser multiphoton microscope utilizing backscattered light was built and used to image the corneal structure of enucleated porcine eyes in preliminary experiments.

Results: Normal lens fibers showed a parallel pattern, with diameters between 3 µm and 9 µm, depending on scanning location. Micro-incision visualization revealed different cutting effects depending on fs-laser pulse energy, ranging from altered tissue scattering properties with all fibers intact through to definite fiber separation with a wide gap. Pulse energies that were too high or overlapped too tightly produced an incomplete cutting plane due to extensive micro-bubble generation. Backscattered fs-laser light delivered high resolution images of the anterior part of the eye, enabling a possible online control via the surgical laser itself in future applications.

Conclusions: 3D CLSM permits visualization and analysis of fs-laser pulse induced microincisions inside crystalline lens tissue. To implement a high resolution online imaging control into the fs-laser surgical device, confocal laser microscopy based on scattering can be implemented using a fs-laser beam and may thereby help to optimize fs-laser based procedures in the treatment of presbyopia, especially as the surgical laser can be employed for imaging as well.

Zusammenfassung

Ziel: Charakterisierung und Evaluierung von verschiedenen optischen Methoden, basierend auf der Streulichtbildgebung zur Analyse von fs-Laser induzierten Mikroschnitten innerhalb der kristallinen Linse von Schweineaugen zur Behandlung der Presbyopie.

Methode: Enukleierte Linsen von Schweinen wurden mittels fs-Laserpulsen bei 100 kHz Repetitionsrate, 306 fs Pulsdauer und 1,0–2,5 µJ Pulsenergie bei einer Wellenlänge von 1040 nm behandelt. Durch Setzen von Mikroschnitten wurden Gleitebenen erzeugt, die über konfokale Laser-Streulichtmikroskopie (CLSM), Rostock

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Cornea Modul in Verbindung mit dem Heidelberg Retina Tomograph II, dargestellt wurden. Des Weiteren wurden ein fs-Lasersystem zur Darstellung der Kornea mittels Streulichtmikroskopie realisiert und erste Messungen an der Cornea der enukleierten Schweineaugen durchgeführt.

Ergebnisse: Durch die optische Darstellung konnten die Schnittparameter wie Energie und Spotabstand direkt *in situ* evaluiert und die Auswirkung zu hoher bzw. zu niederiger Energien durch unvollständige Schnittbildung nachgewiesen werden.

Schlussfolgerungen: 3D CLSM erlaubt die Darstellung und Bewertung von fs-Laser induzierten Mikroschnitten im Linsengewebe ohne aufwendiges Präparieren der Proben und ermöglicht dadurch zusätzlich eine Onlinekontrolle des Schnittvorgangs in der klinischen Anwendung. Dabei stellt der Einsatz des Therapielasers als möglicher Imaging-Laser im Rahmen der Streulichtmikroskopie eine sinnvolle Alternative dar.

1. Introduction

Ultrashort laser pulses with pulse durations in the femtosecond regime (100−15 s) enable precise cutting of biological material at micrometer resolution with very few side effects (Stern et al. 1989, Heisterkamp et al. 2002, Vogel et al. 1998). For several years this technology has been successfully used in clinical practice for corneal flap preparation in the LASIK (laser *in situ* keratomileusis) procedure (Juhasz et al. 2000, Liu et al. 1994, Loesel et al. 1994, Lubatschowski et al. 1999). The cutting effects are achieved by creating a microplasma and a optical breakdown by nonlinear absorption in the usually transparent cornea. The separation of tissue is achieved by subsequent relaxation of the microplasma and the formation of a cavitation bubble, which oscillates and finally collapses and leaves a gas bubble behind. Placing several spots in a pattern next to another, a smooth cut within the bulk of biological material can be achieved. Myers and Krueger were the first to use nanosecond laser pulses in the treatment of presbyopia by creating microincisions within the crystalline lens (Krueger et al. 2001). As it is widely accepted that presbyopia is induced by growing sclerosis of the lens tissue while the ciliary body and lens capsule stays intact (Fischer 1998), a regain in elasticity of the lens material would possibly overcome the loss in accommodation during presbyopia. Krueger hypothesized that by structuring the lens tissue by short laser pulses the tissue will soften and the flexibility of the lens tissue will be reestablished. However, the first attempt on human donor lenses using nanosecond laser pulses failed, due to the strong side effects of the procedure at nanosecond pulse durations. With the advent of fs-laser systems in ophthalmology, our group, together with Krueger, demonstrated the increase in flexibility in combination with very low side effects of fs-laser pulses, when applied in human donor lenses (Krueger et al. 2002). Optimization of the microcuts critically depends on the pulse-to-pulse overlap and scanning speed. In order to visualize the cutting effect *in situ* without time consuming tissue preparation, 3D confocal scattering microscopy was employed at the *ex vivo* porcine eyes.

To further study the possible side and wound healing effects, we developed a fs-laser scattering confocal microscope, which employs a fs-laser beam instead of the 670 nm laser diode for imaging and thus allows multiphoton imaging in combination with confocal scattering microscopy. Thereby, online control and post-operative control of the lens tissue by optical imaging could potentially be performed with the very same laser used usually for the surgical procedure. To show the potential of this method, we applied this imaging modality at the anterior part of the eye.

2. Methods

2.1 Laser and Scan System

The ultrashort laser system consisted of a 100 kHz fiber laser system (IMRA Ltd) FCPA Jewel, delivering 400 fs pulses at a central wavelength of 1,041 nm and a maximum pulse energy of 3.6 µJ. The laser energy was controlled by a half-waveplate in combination with a polarization beam splitter.

Delivering the pulses via a computer controlled scanning system (SCHUMACHER et al. 2008) in combination with a contact glass and a suction unit allowed the precise placement of single laser pulses with micrometer accuracy.

2.2 Imaging Systems

2.2.1 3D Scattering Confocal Laser Microscope

The confocal microscope used in this study consisted of an Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering GmbH, Heidelberg, Germany) is a well-established *in-vivo* confocal imaging system widely used in ophthalmology. The HRT uses a 670 µm diode laser and is designed to acquire topographic measurements of the optic nerve head to detect glaucomatous damage. By the addition of a detachable objective system, the Rostock Cornea Module, the HRT has been modified into a high-resolution confocal laser scanning microscope (STAVE et al. 2002).

2.2.2 Fs-Laser Scattering Confocal Laser Microscope

Using a Chameleon Ultra II fs-laser system, wavelength between 700 and 1,040 nm, ultrashort laser pulses were couple into a microscope objective (NA 0.8) via a galvanometer scanning unit, similar to the scanning system used for the surgical procedure. The backscattered fs-laser light was detected using a confocal setup in combination with a photomultiplier (Hamamatsu) and Labview based software.

2.3 Samples

For this study freshly enucleated porcine eyes were collected and treated with different scanning pattern, following SCHUMACHER et al. (2008). In general, a 3D cutting pattern consisting of rings, cylinders, and square planes was applied to each lens (Fig. 1). The rings (top and bottom planes of the structure) had an outer diameter of 2.0 mm and an inner diameter of 0.3 mm. Two cylinders were placed at the rims of the ring at 2.0 mm and 0.3 mm respectively. Additionally, 12 square planes perpendicular to the rings were added to the 3D structure which had a total depth of 240 µm. Pulse energy and spot separation of the laser pulses were varied between 1 µJ and 5 µJ and 5 µm to 7 µm in lateral and 30 µm to 50 µm in axial direction respectively.

For the fs-CLSM the anterior part of the eyes was scanned to a depth of 1 mm and confocal images of the structures were collected.

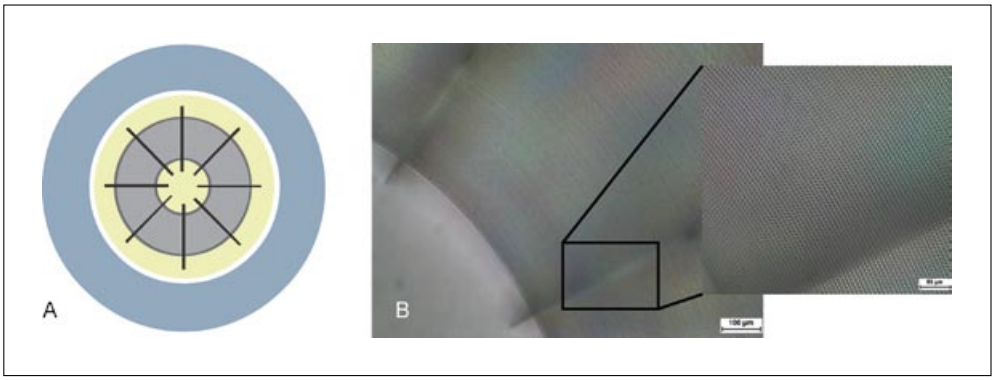

Fig. 1 Steering wheel pattern consisting of annular cuts in several planes and vertical segmental cuts (*left*). Cutting pattern imaged directly after surgical procedure in an *ex-vivo* lens through the surgical microscope (*right*), parameters: 1.3 µJ spot separation in $\Delta x = 6$ µm, $\Delta z = 50$ µm.

3. Results

By tightly focusing femtosecond pulses into the porcine lenses, clear cuts in depth of several millimeter could be achieved (Fig. 1). With 3D CLSM these cuts could be visualized in depth of up to 500 µm. The cutting precision can be visualized and controlled via this method at very high resolution, as shown in Figure 2. At low energies and large spot separation (1.3 µJ and 7 µm spot separation), no clear cut but rather an optical alteration of the lens tissue is visible, see Figure 3. At slightly higher energies of 1.4 µJ and the same spot separation, cutting effects with remaining tissue bridges appear which form a smooth and continuous cut at 1.5 µJ as shown in the middle right image of Figure 3. Even higher energies and smaller spot separations resulted in larger gas bubbles, which lead to a deflection of the fs-laser beam and, thus, no continuous cut.

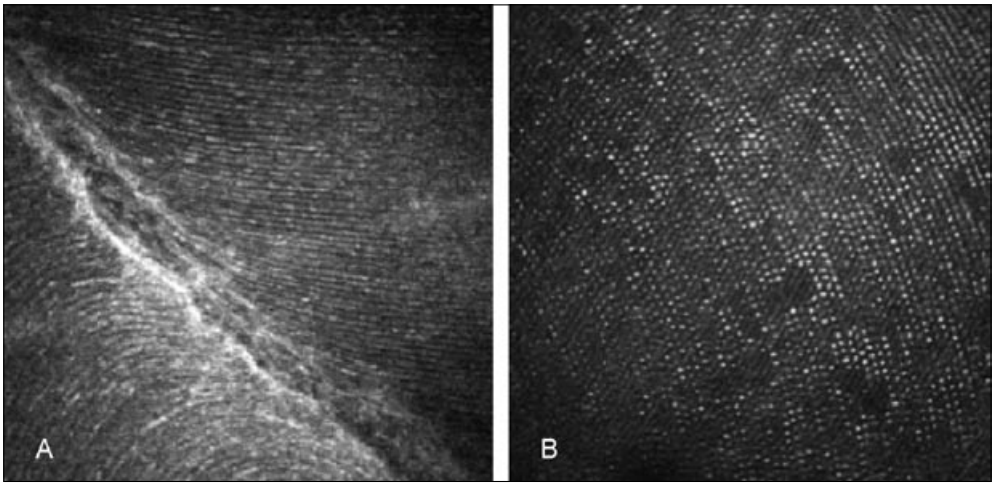

Fig. 2 (*A*) CLSM image of the suture of a porcine lens (field of view 400 × 400 µm), (*B*) cutting plane of fs-laser microincisions imaged by CLSM, single laser spots can easily be identified.

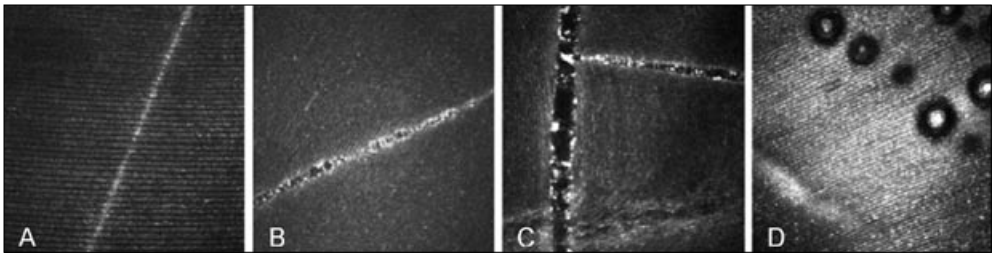

Fig. 3 fs-laser microincision in porcine lenses at rising pulse durations. At low energies only optical alterations are visible, no clear cut (*A*). With higher energies, cut areas appear, interrupted by tissue bridges (*B*). A clear continuous cut develops at optimum energies (*C*), while at too high energies large bubbles form, which deflect following laser pulses and thereby reduce cutting precision (*D*).

Using a custom built multiphoton microscope at wavelengths between 700 and 1,040 nm scanning images of the anterior part of the treated porcine eyes were taken. As shown in Figure 4, high resolution images of several structures within the cornea could be acquired. The epithelial layer and single epithelial cells can easily identified by this imaging method. Moreover, in deeper layers, structures like the sub basal nerve plexus and single keratocytes are visible.

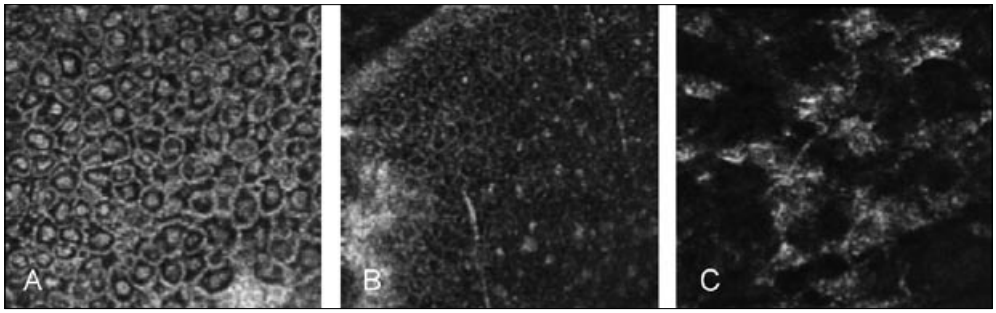

Fig. 4 fs-laser confocal scattering images of the cornea of porcine eyes: The epithelial layer and single epithelial cells are clearly visible (*A*). Below the epithelial layer the sub-basal nerve plexus are visible (*B*). In deeper layers scattering signals originate from single keratocytes (*C*).

4. Discussion

Using ultrashort laser pulses, lens tissue of, in this case, porcine eyes can be cut by microincisions in depths up to several millimeters. However, the control of this procedure, *ex-vivo* for parameter studies as well as *in-vivo* needs high precision imaging, based on non-invasive, non staining methods. Laborious and difficult histological analysis *ex-vivo* did not prove to be suitable for parameter optimization. Moreover, clinical application of this method calls for high precision online control of the cutting process. 3D CLSM proved to be successful in imaging the microincision with porcine lenses in a depth of up to 500 µm. Different parameter sets could be directly evaluated *in situ* using non invasive imaging. For potential integration into clinical systems a setup of fs-laser based confocal scattering microscopy could successfully be applied for imaging the cornea of corneal tis-

sue, resolving cellular structures within the eye tissue with comparable resolution to 3D CLSM. Therefore, further studies applying this technique to treated lenses of porcine eyes are underway.

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Mechatronic Systems to Restore Accommodation

Georg Bretthauer (Karlsruhe), Ulrich Gengenbach (Karlsruhe),
and Rudolf F. Guthoff (Rostock)

With 8 Figures

Abstract

Mechatronic systems are a new approach to restore the accommodative ability of the human eye in case of presbyopia or after cataract surgery. The requirements of such systems, the new concept, and the first results for the different subsystems of an artificial accommodation system are described and discussed.

Zusammenfassung

Mechatronische Systeme sind ein neuer Ansatz, um die Akkomodationsfähigkeit des menschlichen Auges im Falle der Presbyopie oder nach Kataraktchirurgie wiederherzustellen. Die Anforderungen an solche Systeme, das neue Konzept und die ersten Ergebnisse der verschiedenen Teilsysteme eines künstlichen Akkomodationssystems werden beschrieben und diskutiert.

1. Introduction

Accommodation is the capability of the human eye to adjust its refractive power to varying target distances in order to obtain a sharp image on the retina. Unfortunately, the accommodative ability continuously decreases during one's lifetime leading to presbyopia at an age of about 45 to 55 years (Duane 1912). Consequently, visual aids are used. In case of cataract surgery, when the clouded human lens is replaced by an intraocular lens (IOL), the accommodative ability is lost as well. About 7 million IOL are implanted worldwide each year. In both cases there is a loss of accommodation.

Therefore a lot of effort has been made to restore accommodative ability. The existing methods can be subdivided into four groups, namely:

– 1. Different types of IOL's (Ludwig 2003, Stachs 2008, Glasser 2010);
– 2. Ultrashort laser pulses and laser microscopy (Heisterkamp et al. 2010);
– 3. Lens refilling (Terwee 2010);
– 4. Mechatronic systems (Gengenbach 2005, Bergemann et al. 2006, Klink et al. 2006).

In this paper the new mechatronic system, called Artificial Accommodation System (AAS), is described. It is an autonomous, self-sufficient implant in the capsular bag using recent results of micro and nanotechnology for restoring accommodative ability.

The paper is organized as follows. First the different medical and technical requirements of such an implant will be summarized. Then the concept of this new mechatronic system will be described. Subsequently, the different subsystems will be explained, and first results will be given. Some conclusions will finish the paper.

2. Requirements

To realize the vision of an artificial accommodation system several requirements should be fulfilled. They can be summarized into two groups, namely medical and technical requirements.

Medical requirements are the following:

- Size of the implant should be suitable for implantation in the capsular bag;
- Optical properties should be an aperture of 6 mm, an accommodation range of 3 dpt, and a transmission equivalent to the natural lens;
- Unhindered flow of the chamber water;
- Use of biocompatible materials;
- Weight of the implant less than the weight of the natural lens;
- Handling comparable to the implantation of an IOL.

Technical requirements are:

- Lifetime greater than 30 years;
- Safe and permanent energy supply;
- Fail safe modus;
- Reasonable cost of production.

In addition, further restrictions exist for the individual subsystems.

3. Concept

The concept of the artificial accommodation system is shown in Figure 1. Here, from the control point of view the integration of the mechatronic system (technical part, red dotted line) in the human eye (biological part) is represented. The technical part consists of the following subsystems:

- Information acquisition;
- Control unit;
- Optical element and actuator;
- Energy supply,

and the housing.

The information acquisition subsystem determines the accommodation demand. It acquires different signals and uses the information obtained to calculate the accommodation demand. The control unit uses the accommodation demand and calculates the movement of the optical element done by the actuator. In addition, it is responsible for the communi-

cation of all the subsystems. The active optical element guarantees a sharp image on the retina. The change of the refractive power of the optical element to obtain a sharp image is realized by the actuator. The energy supply subsystem provides the energy necessary for the operation of all the subsystems. The housing contains all the subsystems. It has to guarantee biocompatibility and hermeticity for the entire lifetime.

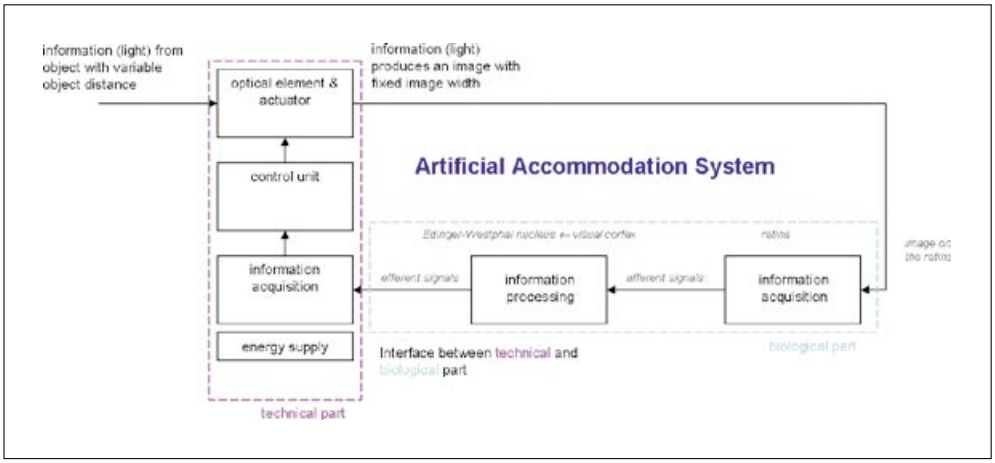

Fig. 1 Concept of the artificial accommodation system

4. Subsystems

4.1 Information Acquisition Subsystem

The information acquisition subsystem is necessary for the calculation of the accommodation demand. Different sensor principles and their applicability for the artificial accommodation system were investigated in KLINK (2007, 2008). As a result of a comprehensive comparison two principles were selected, namely measurement of the

– Pupil near reflex;
– Vergence angle.

The first principle is shown in Figure 2. Here, by means of a sensor array the accommodation demand is determined. It is described in detail in KLINK (2008).

The second principle is given in Figure 3. In this case, the vergence angle is measured by magnetic field sensors, and by a single trigonometric calculation the accommodation demand is obtained.

4.2 Control Unit

The control unit is responsible for controlling and supervising all the subsystems. It uses all the information to guarantee the safe and permanent operation of the implant. The algorithms necessary for the calculation of the accommodation demand, of the movement

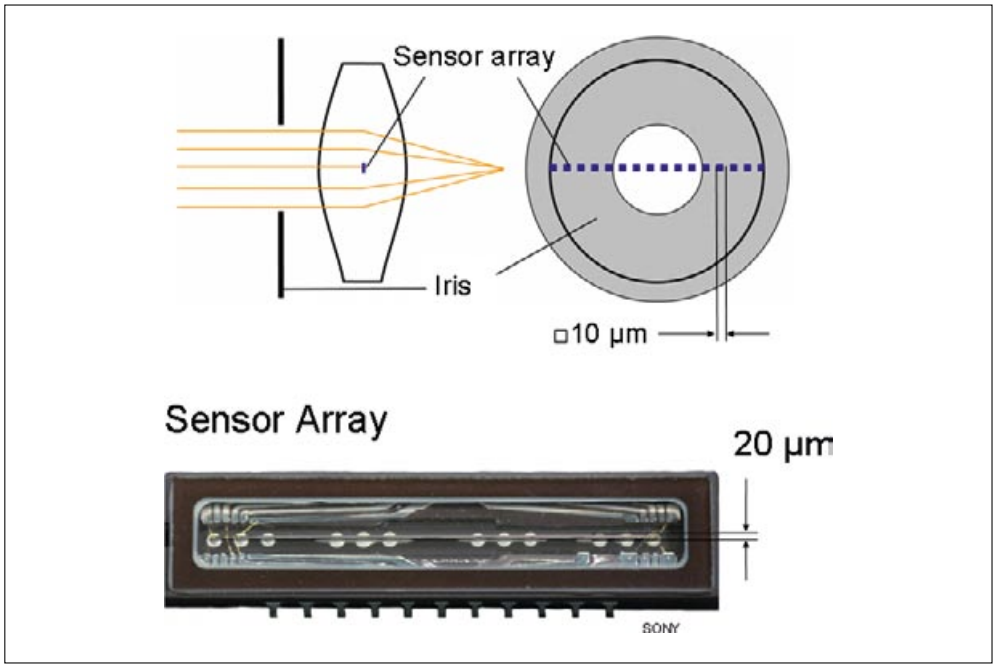

Fig. 2 Principle of the pupil near reflex measurement

of the active optical subsystem, of the energy management, and for the supervision of the correct operation of all the subsystems are implemented here. For this, specific software architecture is required. It is shown in Figure 4.

4.3 Active Optical Subsystem

The active optical subsystem replaces the natural lens. Again, different principles for the adaptation to different focal lengths were examined. The results were given in Bergemann 2007. According to two principles were selected, namely the

– Triple optics;
– Alvarez-Humphrey lens.

The working principle of a triple optics is shown in Figure 5. The subsystem consists of two fixed concave lenses and a movable convex lens which is axially shifted by a microactuator. A movement of about 300 µm is necessary for an accommodation range of 3 dpt.

The Alvarez-Humphrey lens is schematically shown in Figure 6. Alvarez-Humphrey lenses are non-rotational symmetric. In contrast to the triple optics with an axial shift of the spherical surfaces, here a lateral shift of the Alvarez-Humphrey surfaces is done. The minimal lateral stroke is 63 µm for an optical power range of 3 dpt.

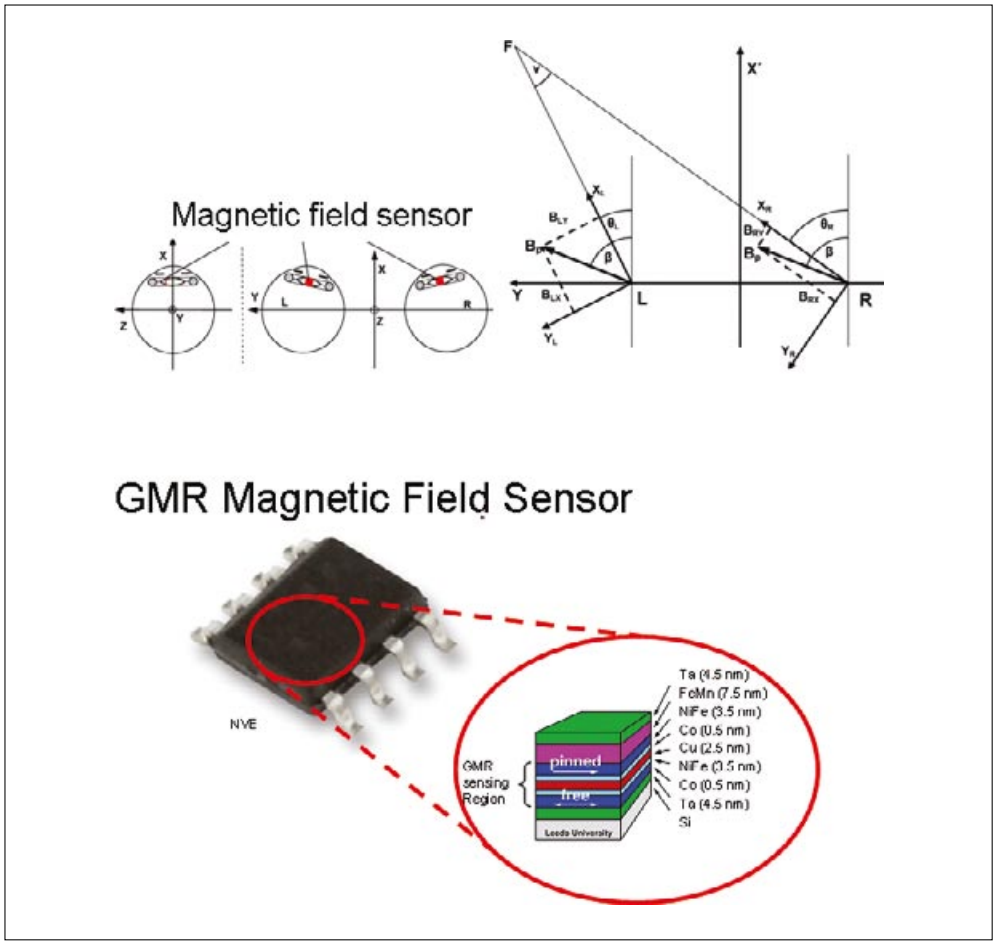

Fig. 3 Vergence angle measurement

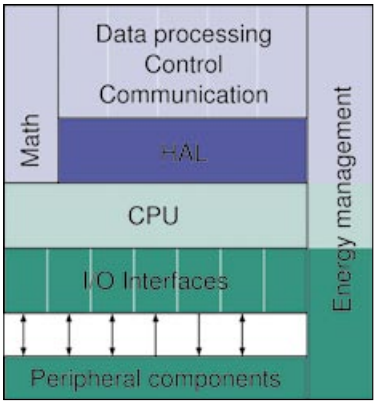

Fig. 4 Software Architecture

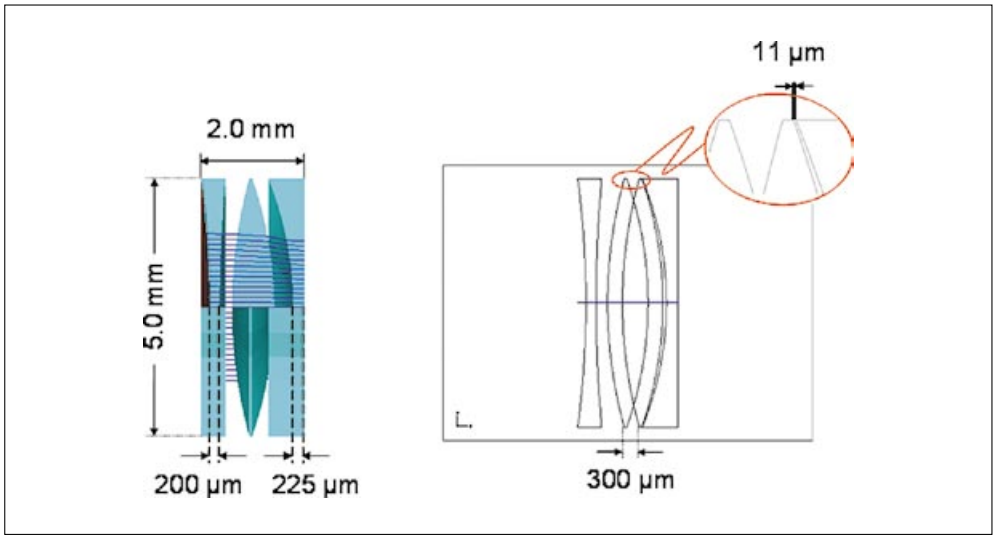

Fig. 5 Triple optics

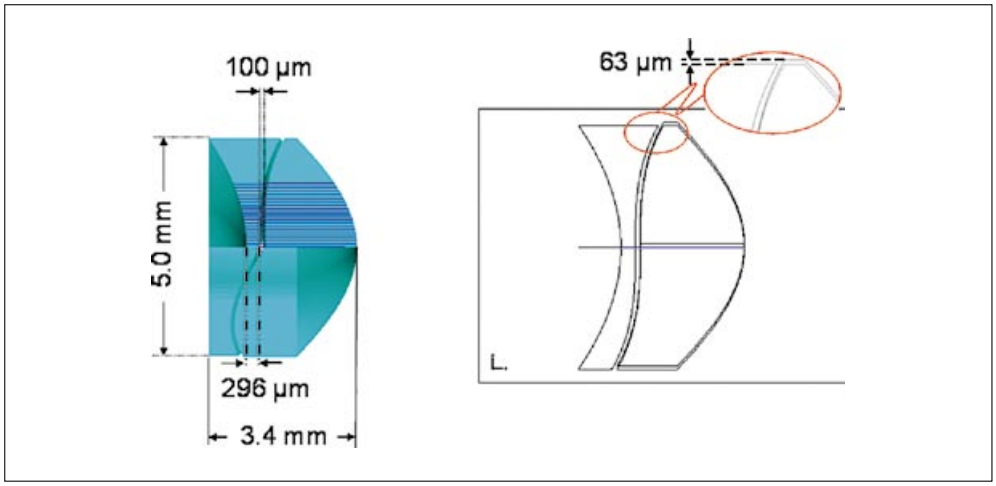

Fig. 6 Alvarez-Humprey lens

The movement of the active optical subsystem is realized by an actuator. For it different working principles have been investigated.

4.4 Energy Supply Subsystem

In normal case, all subsystems of the implant need an energy supply. The energy consumption of the implant should be at most 1 mW and an autonomous operation of 24 h is re-

quired. The lifetime should be at least 30 years. As a consequence of these requirements, the energy consumption of each subsystem should be as low as possible, and an energy management system is necessary. The architecture of the energy management system is given in Figure 7.

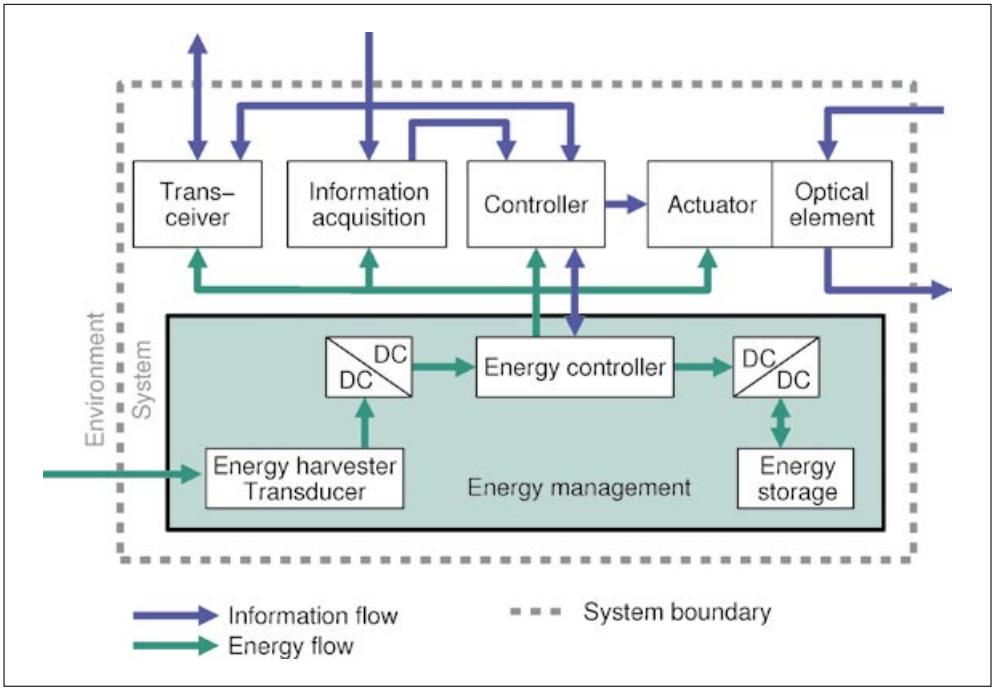

Fig. 7 Energy Management Subsystem

4.5 System Integration

The system integration also comprises the packaging as well as the assembly and interconnection. For packaging the following two functions are necessary:

– Protection of subsystems from body fluids and subsequent corrosion and failure;
– No contact of the human body with substances from the implant's interior.

The requirements are biocompatibility, hermeticity for 30 years, a maximal wall thickness of 300 µm, space constraints of 212 mm³, and no damage of the subsystems during assembly. Possible solutions are a glass housing or a polymer coating as shown schematically in Figure 8.

5. Conclusions

The artificial accommodation system is a new way for restoring a human accommodation. First steps have been done to design and manufacture the single subsystems. However, strong efforts must be undertaken to realize such a complex system in the near future.

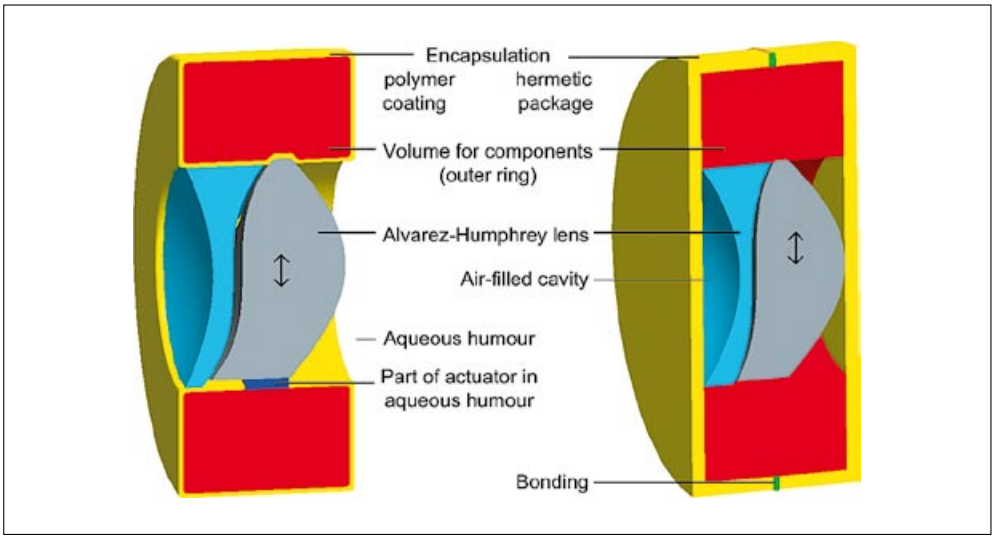

Fig. 8 System integration

Acknowledgement

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Festakt zur Ernennung der Deutschen Akademie der Naturforscher Leopoldina zur Nationalen Akademie der Wissenschaften

Ceremony to Mark the Nomination of the German Academy of Sciences Leopoldina to the National Academy of Sciences

Nova Acta Leopoldina N. F., Bd. *98*, Nr. 362
Herausgegeben vom Präsidium der Deutschen Akademie der Naturforscher Leopoldina
(2009, 76 Seiten, 50 Abbildungen, 21,95 Euro, ISBN: 978-3-8047-2551-5)

Die Deutsche Akademie der Naturforscher Leopoldina wurde am 14. Juli 2008 im Rahmen eines Festaktes in Halle zur Nationalen Akademie der Wissenschaften ernannt. Damit erhielt Deutschland – wie andere europäische Länder oder die USA – eine Institution, die Politik und Gesellschaft wissenschaftsbasiert berät und die deutsche Wissenschaft in internationalen Gremien repräsentiert. Der Band dokumentiert den Festakt mit der Übergabe der Ernennungsurkunde durch die Vorsitzende der Gemeinsamen Wissenschaftskonferenz und Bundesministerin für Bildung und Forschung Annette SCHAVAN. Er enthält die Reden von Bundespräsident Horst KÖHLER, Sachsen-Anhalts Ministerpräsident Wolfgang BÖHMER und Leopoldina-Präsident Volker TER MEULEN sowie den Festvortrag „Rolle und Verantwortung nationaler Akademien der Wissenschaften“ von Jules A. HOFFMANN, Präsident der *Académie des sciences*, Paris. Der Aufbau einer Nationalen Akademie ist ein richtungsweisender Schritt für die deutsche Forschungslandschaft, da für den kontinuierlichen Dialog von Wissenschaft und Politik eine solche Einrichtung erforderlich wurde. Der Publikation ist eine DVD mit dem Mitschnitt der Festveranstaltung beigefügt.

Wissenschaftliche Verlagsgesellschaft mbH Stuttgart

The Retina Implant Project

Nova Acta Leopoldina NF *111*, Nr. 379, 179–180 (2010)

Introduction of the PRO RETINA Deutschland e. V. and their Research Foundation

Franz Badura (Amberg)

The topic of this presentation is the partnership and the interaction between a patient organisation and the professional world of science.

I just want to mention, that there exists an international "umbrella-organisation", which is called Retina-International with more than 40 members worldwide.

The basic tasks of all these organisations are to encourage the interaction between patients and scientists, to promote research into retinal degenerative diseases, to foster mutual support among patients and their families in order to create awareness for RP, AMD, Usher-Syndrome or many other very rare retinal disorders.

1. Who We Are

The German patient organization, "Pro Retina Deutschland e. V.", was founded in 1977 as "Deutsche Retinitis Pigmentosa-Vereinigung" by patients and their relatives with the intention of organizing help for themselves. The three purposes mentioned in the constitution are to actively support research, to offer psychological and social backing (encouragement) for its members, and to inform the public about retinal degeneration.

2. What We Do in Research

The jewel of all this work is the Pro Retina-Foundation for the Prevention of Blindness, which was founded in 1996. From the early beginning we built up a stable network with researchers and ophthalmologists to share information and advice. We support research projects by direct financial funding – since the 'Foundation for the Prevention of Blindness' was established in 1996, more than one and a half million Euro have been donated. We actively initiate research projects and therapy tests and contribute to their implementation. Every year, we award two research prizes, the Retinitis-Pigmentosa Award and the Macula Award. We also finance PhD grants in order to foster research activities and networking between researchers. The main ambition is to secure a long-term support for the large field of research on retinal degeneration, e. g. by granting financial means for the development of new research projects or by financing the initial phase of relevant projects.

For all this work PRO RETINA is consulted by a Scientific and Medical Advisory Board ("Wissenschaftlicher und Medizinischer Beirat", WMB) and a Working Group on Clinical Questions ("Arbeitskreis Klinische Fragen", AKF). In these two councils clinicians and scientists of different medical and other relevant disciplines are taking part.

And last but not least, we organize and support national and international seminars and conferences on relevant topics.

The annual highlight in this context is the organization of the "Potsdam-Meeting", which took place last weekend in the Seminaris Seehotel near the lake Templiner See in Potsdam. This was the 5th international PRO RETINA research colloquium so far, with the special intention to motivate young researchers and to support and improve the dialogue between the various involved disciplines, and of course between the several generations. The meeting resumes the tradition of the earlier meetings and further establishes this series as an integral part of the German and European research community focused on retinal disease and innovative treatment options. In the past, the lectures have mainly addressed the current state of our understanding of the basic mechanisms underlying the retinal disease processes. This year's meeting wanted to go one step further and acknowledge the many recent and most promising advances in the field of translational medicine. The topics were therefore focused on novel treatment options aimed at targeted therapeutic interventions in defined retinal disease entities. Scientists from various disciplines gave a comprehensive and state-of-the-art overview of the current achievements to the point of ongoing preclinical and clinic trials. The program was complemented by lectures specifically addressing the planning, implementation, and experience of clinical trials and was finally intended to further encourage researchers in their efforts to bring basic science to the benefit of the patient.

Research in retinal degenerative diseases can only happen in a good partnership between researchers and affected persons and their family members. The patient organizations therefore try to support you whenever possible. Such a meeting brings researchers and at least two patients together and hopefully will give the opportunity to learn better about the needs of each other.

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Subretinal Implantation of Electronic Chips: Restitution of Visual Function in Blind People

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With 1 Figure

Abstract

Eleven blind patients suffering from retinitis pigmentosa received subretinal electronic implants, powered and controlled via a subdermal cable ending in a thin intraocular foil, placed transsclerally between the retinal pigment epithelium and the neuroretina. The tip of this foil carries two distinct arrays, a Multiphotodiode Array with 1,500 electrodes, each electrode being controlled by an adjacent photodiode and an amplifier within a 3 × 3 × 0.1 mm chip, as well as a second array with 16 electrodes, for direct stimulation. Subretinal multielectrode implants with currents close to recognition threshold (10 to 27 nC/electrode) produce retinotopically correct patterns that allow for the first time recognition of individual letters (8 cm high) even at low luminance levels. Stripe patterns of moderate luminance can be resolved up to 0.35 cycles/deg via the subretinal chip. This clearly supports the feasibility of light sensitive subretinal multi-electrode devices for restoration of useful visual percepts in blind patients.

Zusammenfassung

Elf blinden Probanden mit Retinitis pigmentosa wurde ein subretinales, elektronisches Implantat eingesetzt. Dessen Energieversorgung und Ansteuerung erfolgt über ein subdermales Kabel, das in eine dünne intraokulare Folie mündet, die transskleral zwischen retinalem Pigmentepithel und der Neuroretina platziert wurde. Die Spitze der Folie trägt 2 Elektrodenfelder: ein Mikrophotodioden-Array (3 × 3 × 0.1 mm) mit 1500 Elektroden, von denen jede durch eine lichtempfindliche benachbarte Photodiode über je einen Verstärker angesteuert wird, und ein Direktstimulations(DS)-Array mit 16 Elektroden. Subretinale Multielektroden-Implantate mit elektrischen Reizen nahe der Erkennungsschwelle (10 bis 27 nC/Elektrode) erzeugen retinotop korrekte Muster, die es Blinden erstmals ermöglichten, einzelne Buchstaben (8 cm hoch) sogar bei schwacher Beleuchtung zu erkennen. Streifenmuster mittlerer Leuchtdichte können mit dem subretinalen Chip bis 0,35 Zyklen/Grad aufgelöst werden. Dies zeigt eindeutig die Machbarkeit der Wiederherstellung brauchbarer Seheindrücke bei Blinden durch lichtempfindliche subretinale Multielektrodenfelder.

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4 Department of Ophthalmology, Semmelweis University, Budapest, Hungary.
5 STC Autonomous Nervous System and Safety Studies, Ofterdingen, Germany.
6 NMI Natural and Medical Sciences Institute, Reutlingen, Germany.

1. Introduction

Several concepts have been developed how to restore vision in blind persons by implanting electronic devices to evoke useful visual sensations. Since 1995, our consortium has developed a so-called "active" subretinal microphoto-diode array (MPDA), based on *in vitro* measurements (Stett et al. 2000) and in various animal models (Zrenner et al. 1999, Schwahn et al. 2001). These *in vitro* experiments revealed that:

- Charge injections of about 1 nC per electrode are sufficient to excite post-receptoral retinal neurons;
- Electrode separation distances of 50–150 μm in the outer retina can be resolved in ganglion cell recordings;
- Retinae with completely degenerated photoreceptors (RCS rats, 160 days and older) can be excited sub-retinally in a proper spatially organized manner;
- Surface coating of MPDAs as e. g. with laminins can improve cell adhesion and biocompatibility (Guenther et al. 1999).

In vivo experiments revealed that:

- Inner retinal layers are well preserved in the central retina, as shown by comparative histological studies of human and animal forms of degenerative retinal disorders (Zrenner et al. 1997).
- A safe introduction of the devices via a scleral flap near the limbus through the subretinal space (like in a tunnel) to the back of the eye is possible (Sachs et al. 2005 and ARVO 1999, Shinoda et al. ARVO 2004).
- Inner retinal layers are well preserved after subretinal long term implantation (28 months) in pigs.
- MPDAs remain fixated at stable subretinal positions as investigated in both rabbit and pig.
- Adequate coating has been developed to protect MPDAs from damage tested for 12 months.
- Cortical recordings with multielectrodes and optical recording from the visual cortex of cat revealed a spatial resolution for electrical subretinal stimulation of at least 1 degree (Eckhorn et al. 2006).

Based on these findings a subretinal implant was developed that is suited for implantation into the human eye. Presently, a *clinical study* is ongoing where wire-bound MPDAs are being implanted for four weeks into one eye of 11 blind RP patients. Within a subretinal layer of 1/10 mm there are photodiodes, amplifiers and circuits that adapt the electrical signal to the nerve cell to the strength of the brightness of the object to be seen and its surroundings. This is the first active subretinal chip ever implanted in patients (Zrenner et al. ARVO 2006, 2007, 2008, 2009 and Sachs et al. ARVO 2006, 2007, 2008, 2009 and Gekeler et al. ARVO 2008).

2. Material and Methods

2.1 The Subretinal Implant

The active implant consists of approximately 1,500 light-sensitive cells on a surface of 3 × 3 mm (each cell containing an amplifier and a TiN electrode of 50 × 50 μm, spaced 70 μm) as well as a 4 × 4 array of identical electrodes, spaced 280 μm, for direct stimulation (DS), chronically implanted next to the fovea. MPDA (so-called chip) and DS array are positioned on a small subretinal polyimide foil powered via a subretinal transchoroidal, retroauricular transdermal line that provides power and control signals to the chip and stimulation currents to the DS electrode array. Stimulation parameters for each DS electrode and chip activity and sensitivity can be controlled independently by a software tool that allows to transform the orientation of the visual space to the orientation of the electrode field and to set individual stimulation parameters in the stimulation box via a wireless transmitter. Moreover, all stimulation parameters and patient's "yes" or "no" responses to each parameter are recorded automatically by a particular software (Sailer ARVO 2005). For selection of patients, corneal DTL-electrodes and an alternative forced choice method was used to determine electrical excitability of the retina and of optic nerve transmission in normals and patients with degenerative retinal disease; determination of phosphene threshold with corneal electrodes has turned out to provide an important criterion for the suitability of patients for electrical retinal prostheses (Gekeler et al. 2006).

2.2 Study Design

In the present study, wire-bound MPDAs were implanted for four weeks into one eye of 11 blind RP patients who had no useful vision for more than 5 years and a visual acuity earlier in life >20/200. They were able to perceive corneally elicited electrical phosphenes and had no other serious eye or general diseases.

The implant safely stored in a trocar was guided from a retrauricular skin incision to the region of the upper lid; from there it was fed via a silastic tube into the intraorbital space. After vitrectomy and a small peripheral retinal detachment it was then fed via a flap in the sclera and a trans-choroidal access along a guiding foil into the subretinal space and then gently pushed into a final parafoveal position; radiodiathermy and a specially designed implantation instrument were used to penetrate the choroid without causing bleeding; silicone oil was used as a tamponade (Sachs et al. ARVO 2005, 2006, 2007, 2009). This transchoroidal procedure was applied to all patients without adverse events such as retinal detachment, bleeding, infection etc. (Sachs et al. ARVO 2008).

2.3 Stimulation Procedures

A battery of computerized, standardized tests for patients with visual prostheses was developed to quantify the functional outcome (Zrenner et al. ARVO 2004, Wilke et al. ARVO 2006, 2007). Visual perception of brightness elicited by applying biphasic voltage impulses to DS electrodes from 1 to 2.5 V (t = 0.5 to 6 ms) was assessed using a scale from 5 (very strong) to 0 (none); additionally double impulses with differences up to 0.8 V be-

tween two stimuli (10 s interval) as well as pulse trains were applied. For testing the light sensitive chip, letters were presented to the most recent three patients either by stimulating retinal cells in 10 ms steps via individual electrodes – in a sequence patients had learned to write such letters – or via the light sensitive chip – by individual letters or stripe patterns steadily presented on a screen at 62 cm distance.

3. Results

3.1 Direct Stimulation via the DS-Array

Electrical stimulation of rows, columns and blocks of 4 electrodes allowed some of the first 8 patients to clearly distinguish horizontal from vertical lines and positions, respectively. Under optimal conditions, dot alignment (vertical versus horizontal up to 86 % correct) and direction of dot movement (four-alternative forced-choice [4AFC], up to 91 % correct) was properly recognized, if three or four neighboring electrodes were switched on simultaneously or sequentially at 1 s intervals (Zrenner et al. ARVO 2007).

Brightness perception of spots varied from scale 0 to 5 in a linear manner if voltages between 1.5 and 2.5 were applied (randomly 6 times) to a square of 4 electrodes. This corresponds to a charge increase of approximately 0.23 mC/cm^2 for each of the 5 steps. A difference in brightness between two consecutive pulses was discerned, if a difference in charge of at least 16 µC/cm^2 was applied. If equal charges were applied to both conditions, the second flash was always perceived as slightly dimmer irrespective of the stimulation level. Subjective brightness amplification phenomena were observed at medium stimulation levels with pulse trains and at certain frequencies. The subjective size of spot perception upon stimulation of a square of 4 electrodes increased from 1 to 5 mm at arm's length, if the voltage was increased from 1.5 to 2.5 V. Interestingly at the offset of current, the spot disappeared in a quick sequence of individual, very small pixels.

Recently, a new preoperative planning procedure was implemented to preoperatively define the most appropriate location on the fundus for surgical implantation of the prosthesis (Kusnyerik et al. ARVO 2008).

In the most recent three patients various patterns consisting of 4 × 4 dots were presented, corresponding to letters of approximately 5 cm diameter at 60 cm distance. Patient 1 correctly (20/24) recognized the direction of the letter "U", presented with the opening in four different directions in a 4AFC mode. Patient 2 correctly (12/12) differentiated letters (e. g. C, O, I, L, Z, V) within few seconds, presented via DS-electrodes in random order (4AFC).

3.2 Light Stimulation of the MPDA

Six of eleven patients perceived light projected onto the MPDA. In scanning laser ophthalmoscope (SLO) microperimetry of the MPDA, single light spots down to 100 to 400 µm in diameter were detected. Via the MPDA patients were able to correctly localize a white plate on a black table cloth or a window when freely moving in a room (Zrenner et al. ARVO 2007, 2009). In two of the devices there were problems with cable

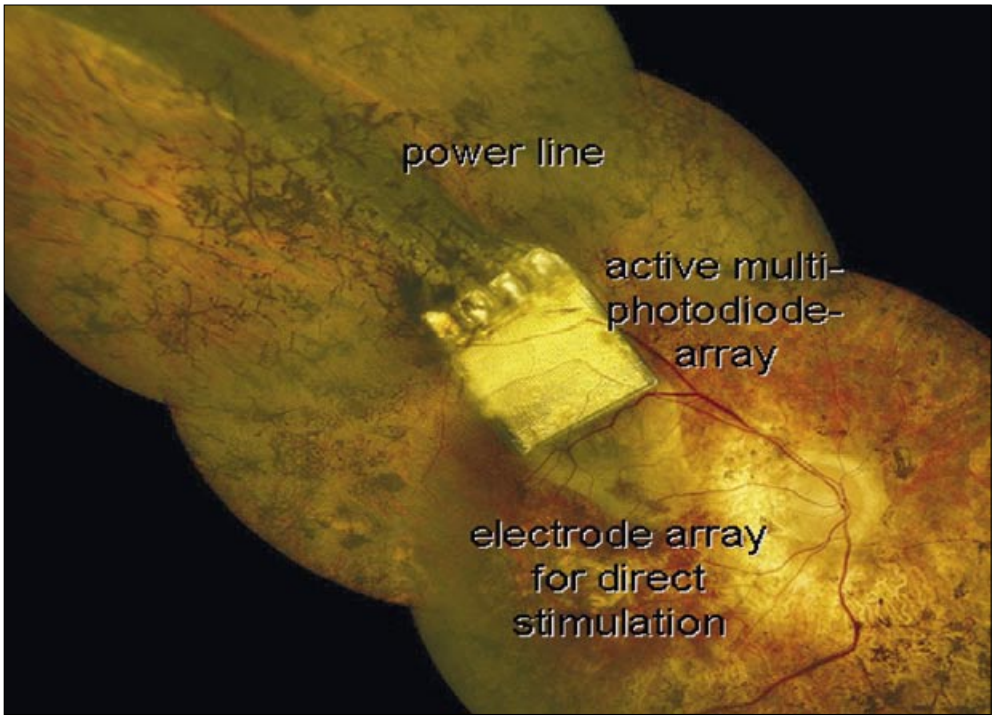

Fig. 1 DS-Array, MPDA and powerline in the subretinal space of a patient suffering from retinitis pigmentosa

contact stability or encapsulation, in two other cases the retina was degenerated too extensively (blindness > 15 years) preventing successful activation of the chip. Of the most recent three patients using the light sensitive subretinal chip, patient 3 correctly (22/24) differentiated without head movements letters (e. g. L, I, T, Z; 8.5 cm high, 1.7 cm line width) steadily presented on a screen at 62 cm distance with a red light (630 nm cutoff) of 3.4 cd/m^2. Patient 3 recognized (15/20 correct, 4AFC) the direction of lines or stripe patterns with the chip, as did Patient 1 (11/14, 2AFC) and Patient 2 (11/12 4AFC) up to 0.35 cycles/deg.

3.3 Life Quality

The brief symptom inventory (BSI) by Derogatis, a validated 53-item questionnaire was used for the assessment of variations in psychological stress of the patients before and during the four week study. The sum score total Global Severity Index (tGSI) was used for evaluation (Peters et al. ARVO 2007). At screening seven out of eight subjects (mean 50.33, SD 12.17) were in the normal range of the tGSI. In addition, we provided regular psychological support and counseling during study participation. The valus mean at the last clinical study visit as compared to screening values (t-test: mean diff 6.17, SD 8.95; $p = 0.08$) showed a tendency to lower values in a sense of better emotional balance at the end of trial participation.

4. Discussion

Active, power driven subretinal implants presented here are able to provide useful visual information; passive elements (Chow et al. 2004) cannot provide sufficient energy for electrical neural stimulation. Subretinal active stimulation always yielded spatially confined retinotopic perceptions in form of round whitish or yellowish dots. Spatial dimensions of percepts elicited by single electrodes could be determined to be approximately one degree of visual angle. The size and brightness of such percepts can be modulated with stimulation strength. However, percepts from multiple-electrode stimulation, although still strictly retinotopic, are somewhat more complex than the mere spatial composite of single electrode stimulation. Several mechanisms leading to this effect will be discussed. Among them, neuronal reorganization (Marc et al. 2003) seems to play a minor role, given the size of retinal area stimulated by individual electrodes and the fact that lateral displacement of neuronal structures rarely exceeds 100 μm (Strettoi, pers. comm.). Temporal characteristics of subretinally elicited percepts depend on numerous factors such as pulse amplitude, characteristics of preceding stimuli, as well as size of retinal area stimulated. These investigations in patients show a window for safety and efficacy of multielectrode stimulation of the retina on the one hand and the necessity of individual adaptation for feasible approaches on the other.

5. Conclusion

Subretinal electrical multielectrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters. Nevertheless, it was shown that active subretinal multielectrode implants with currents close to recognition threshold (10 to 27 nC/electrode) can produce retinotopically correct patterns that allow, for the first time, recognition of individual letters (8 cm high, viewed in appr. 62 cm distance) even at low luminance levels. Stripe patterns of moderate luminance can be resolved up to 0.35 cycles/degree via the subretinal chip. This clearly supports the feasibility of light sensitive subretinal multi-electrode devices for restoration of useful visual percepts in blind patients. Nevertheless, it has to be taken into account that this type of vision is still very limited due to the small area of visual field, limitations in the range of ambient brightness and contrast as well as spatial and temporal resolution. Further developments are needed in order to allow patients to use this technique for free movement in an unknown environment.

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Continents under Climate Change

Konferenz aus Anlass des 200. Gründungsjubiläums der Humboldt-Universität zu Berlin

in Zusammenarbeit mit dem Potsdam-Institut für Klimafolgenforschung (PIK) und der Deutschen Akademie der Naturforscher Leopoldina
Unter der Schirmherrschaft des Auswärtigen Amtes der Bundesrepublik Deutschland

vom 21. bis 23. April 2010 in Berlin

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Der Klimawandel gehört zu den drängendsten globalen Problemen unserer Zeit. Die Menschheit steht vor besonderen Herausforderungen, um insbesondere den CO_2-Ausstoß zu senken. Führende Wissenschaftler aus der Klimaforschung betrachten die Auswirkungen des Klimawandels auf die Kontinente Europa, Asien, Afrika, Amerika und Australien sowie die Polarregionen. Dabei werden neueste Klimadaten unter globalen und regionalen Gesichtspunkten ausgewertet und Simulationsmodelle für zukünftige Entwicklungen diskutiert. Die Ausführungen bieten ein gut fundiertes Bild der Klimaänderungen, die sich weltweit bereits vollziehen bzw. in Zukunft ereignen werden, und untersuchen kritisch die Folgen für Natur, Gesellschaft und Wirtschaft. Der Kongress „Continents under Climate Change“ wurde im Rahmen der 200. Jahrfeier der Humboldt-Universität zu Berlin vom Potsdam-Institut für Klimaforschung und der Deutschen Akademie der Naturforscher Leopoldina – Nationale Akademie der Wissenschaften veranstaltet. Alle Beiträge sind in englischer Sprache verfasst.

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Subretinal Implants: *In Vitro* and *In Vivo* Investigations on Blind P23H Rats

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With 3 Figures

Abstract

To contribute to the development of retinal prosthesis, we examined the activity of retinal ganglion cells in P23H rats, an animal model of retinitis pigmentosa, and their responses to electrical stimulations. We developed a surgical procedure to insert implant prototypes into the subretinal space of P23H rats for *in vivo* testing the material biocompatibility and the stimulation effectiveness.

Zusammenfassung

Als Beitrag zur Entwicklung der Retina-Prothesen untersuchten wir die Aktivität von retinalen Ganglienzellen in P23H-Ratten, einem Tiermodell für Retinitis pigmentosa, und deren Antwort auf elektrische Stimulation. Wir entwickelten ein Operationsverfahren, um Implantprototypen in den Subretinalraum der P23H-Ratten einzusetzen und so *in vivo* die Materialverträglichkeit und die Effektivität der Stimulation zu testen.

1. Introduction

Photoreceptor degeneration causes blindness in both hereditary diseases such as retinitis pigmentosa and non-hereditary retinal diseases such as age macular degeneration (AMD). In these diseases, the photoreceptor loss is followed by a substantial secondary degeneration of other retinal neurones (Humayun et al. 1999). In very advanced states of the disease, this degenerative process can induce a profound reduction of up to 70–80 % of retinal ganglion cells (RGCs) (Humayun et al. 1999) which integrate and transmit visual information to the brain through the optic nerve. Another consequence of the photoreceptor loss is the major reorganization of the retinal network (Milam et al. 1998). Retinal prostheses propose to restore vision by targeted electrical stimulation of these remaining retinal cells. The concept has been validated in several clinical trials showing that patients were able to follow moving light targets and identify known contrasted objects (Humayun et al. 2003). However, the current resolution of individual electrodes preclude the production of arrays

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containing 600 densely packed independent electrodes that are required for complex tasks such as text reading or visually guided locomotion (Cha et al. 1992, Sommerhalder et al. 2004).

In dystrophic animal models, the retinal tissue is also undergoing a massive reorganization (Marc et al. 2003), as previously described in clinical studies. At the cellular level, retinal neurones postsynaptic to photoreceptors, such as bipolar cells and horizontal cells, were also shown to undergo major morphological changes (Strettoi and Pignatelli 2000, Strettoi et al. 2002). In ON bipolar cells, for instance, their synaptic glutamate receptor, mGluR6, was even found to delocalize from the dendritic tips to their axons (Strettoi and Pignatelli 2000). Surprisingly, some authors have recently reported that RGCs maintain their normal morphology (Margolis et al. 2008, Mazzoni et al. 2008) whereas previous studies had concluded at RGC degeneration (Villegas-Perez et al. 1998, Wang et al. 2000). Similarly, some recent studies have shown abnormal RGC spontaneous and light-induced activity in the rd mouse retina during photoreceptor degeneration with a potential increase in background discharge rates (Stasheff 2008) or occasional rhythmic spiking activity (Margolis et al. 2008).

To assess the efficacy of electrical stimulations, RGC responses were recorded *in vitro* on embryonic chicken retinas (Stett et al. 2000) or rabbit retinas (Jensen and Rizzo 2006) when using subretinal electrodes. Similar experiments were also performed using epiretinal electrodes (Fried et al. 2006, Jensen et al. 2005a, b, Jensen et al. 2003), that triggered one spike with a short latency and additional delayed spikes. The use of synaptic blockers indicated that the delayed spikes were related to the electrical activation of RGC presynaptic neurones (Fried et al. 2006). Surprisingly, very few studies have measured individual RGC responses to electrical stimulations on an *in vitro* retina of an animal model of retinitis pigmentosa (Ye and Goo, 2007, Zrenner et al. 1999), although their retina is undergoing the same degenerative process as those of patients. Similarly, very few studies were performed *in vivo* on the retina of dystrophic animals. The RCS rat model was for instance used to demonstrate that the surgical introduction of a subretinal implant can generate a neuroprotective effect at distance from the implant (Pardue et al. 2005). It was also used to demonstrate the functionality of wireless subretinal implants (DeMarco et al. 2007). Blind dogs were well tolerated to an epiretinal implant that generates cortical responses to the electrical stimulation of the retina (Guven et al. 2005).

To contribute to the development of retinal prosthesis, we examined the activity of RGC in P23H rats, an animal model of retinitis pigmentosa, and their responses to electrical stimulations. Furthermore, we developed a novel surgical approach to insert implant prototypes into the subretinal space of P23H rats for *in vivo* testing the material biocompatibility and the stimulation effectiveness (Salzmann et al. 2006).

2. Results

2.1 In Vitro Recording

Blindness in P23H rats older than one year was attested *in vivo* by the lack of behavioral responses to visual stimuli and by the absence of a recordable electroretinogram (Yang et al. 2009). Specific immunolabeling of retinal ganglion cells with the Brn3a antibody indicated a loss of retinal ganglion cells at this age. To determine if the remaining RGCs were still

generating action potentials, they were recorded with the multielectrode array (MEA) technique as previously reported (KOLOMIETS et al. 2006). In all P23H rats (n = 10), recordings showed spikes with a clear signal to noise ratio (Fig. 1*B*) and with classic action potential features (Fig. 1*A*). Figure 1*C* illustrates that RGC activity could be monitored simultaneously at different electrodes. When individual recordings were examined in more detail, they clearly showed spikes of different amplitudes. Individual spikes did not show

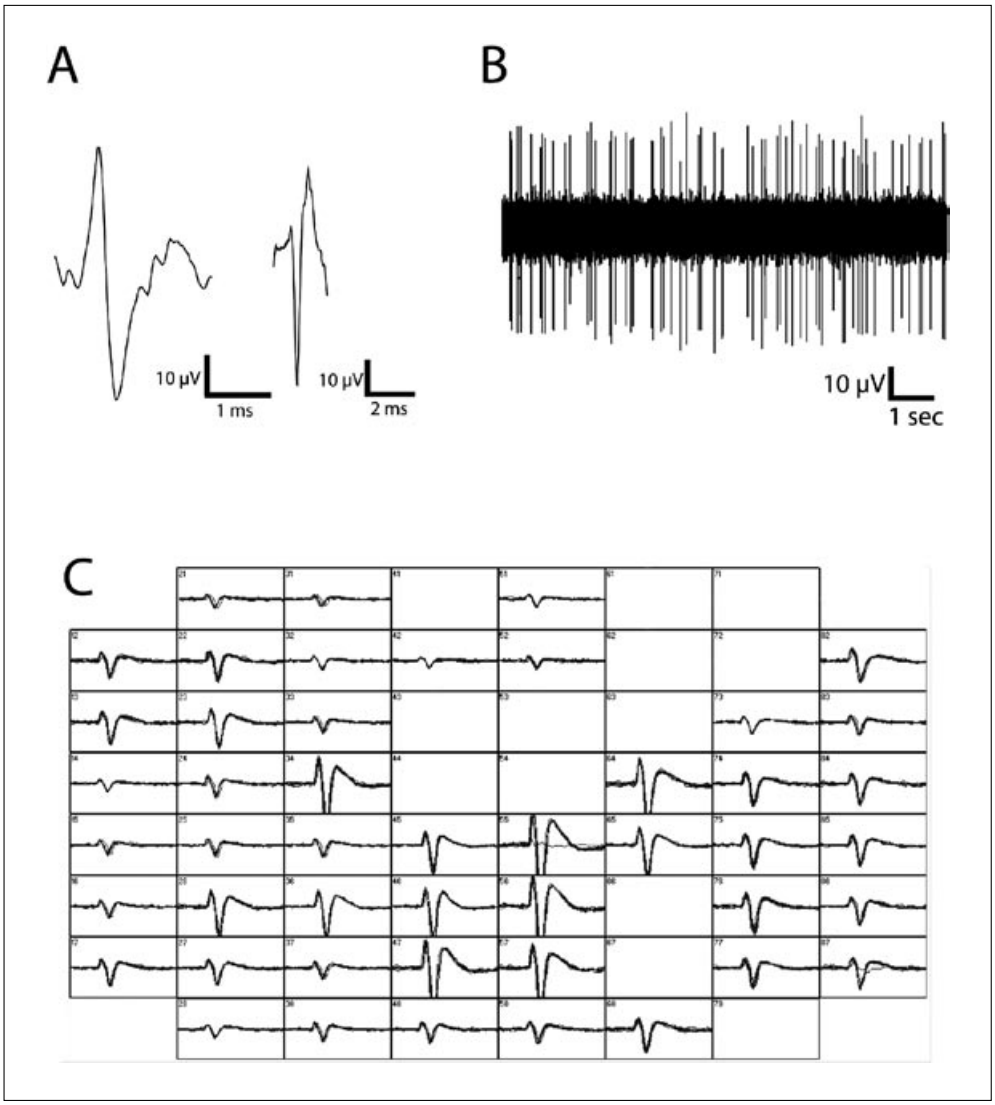

Fig. 1 Spontaneous activity in retinal ganglion cells of P23H rat retina recorded with the multielectrode array technique. (*A*) Somatic and axonal action potentials recorded in ganglion cells of P23H blind retina. (*B*) Sustained activity recorded at a single MEA channel. (*C*) Overlay plot of spike cutouts recorded in P23H rat retina at multiple MEA channels (200 µm spacing between channels). Empty plots represent no or multiunit activity. Channels numbers indicated in the top left corner of each plot.

any abnormal shape, duration, amplitude, or temporal pattern (Fig. 1*A*). On the basis of their waveform, the origin of action potentials could be attributed either to ganglion cells or their axons, as described previously in classical pioneer retinal studies (KUFFLER 1953). There was no difference between retinal spike shapes in sighted control and blind P23H rats. In contrast to control rats (KOLOMIETS et al. 2006), the spontaneous activity was not modulated by light stimulation. A complex analysis of the RGC firing rates indicated some functional changes.

When the retinal tissue was electrically stimulated with electrodes of the multielectrode array, local excitatory responses were measured on RGCs recorded on nearby electrodes at latencies comparable to those seen in control animals. Figure 2 illustrates the raster plot and the post-stimulus histogram following electrical stimulation. Responses show an early spike at a very short latency and more delayed spikes. As previously reported in normal animals (FRIED et al. 2006), the short latent spike may result from direct stimulation of the recorded RGC whereas delayed spikes may rely on the activation of presynaptic neurons. These results indicated that RGCs from the degenerated retina can also be very efficiently stimulated with an epi-retinal electrode. Ongoing experiments are now evaluating the efficacy of subretinal electrical stimulations because the remaining retinal tissue may feed the appropriate information into the different visual information processing channels to the brain (ROSKA and WERBLIN 2001).

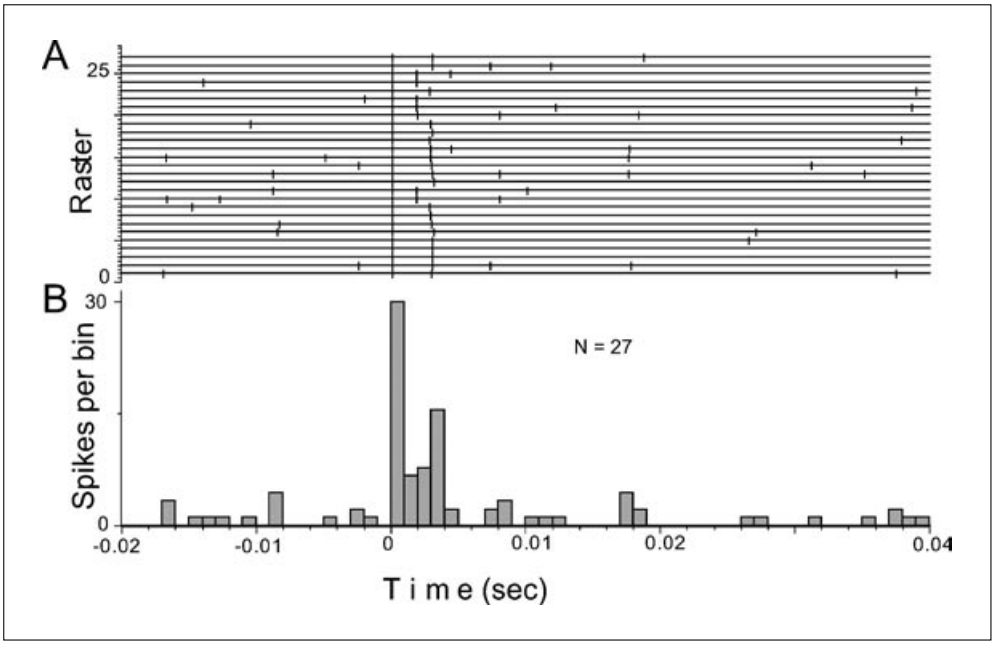

Fig. 2 Raster plot (*A*) and PSTH histogram (*B*) of responses to electrical stimulations in one retinal ganglion cell from a blind P23H rat. Responses contains both an early spike presumably antidromic (due to direct soma stimulation with regular (27/27) spike occurrence and latency fluctuation < 0.5 ms) and late orthodromic spikes (synaptic, with fluctuating [2–4 ms] latency on raster histogram) components. Responses were generated by bipolar activation via pair of nearby (200 µm spacing) MEA electrodes (53 [ground] and 54 [+I]) using square pulses (5 µA, 200 µs, 0.5 Hz, Number of stimuli 27, bin width 1 ms).

2.2 In Vivo Experimentation

A surgical procedure was designed to introduce retinal implants in the subretinal space of P23H rats. As previously described (SALZMANN et al. 2006), these implants were first examined with the scanning laser ophthalmoscope at the eye fundus. Figure 3 illustrates the examination of a subretinal implants after one and a half months of implantation under fluorescein angiography. Blood vessels are observed to run over the retinal implants confirming the subretinal implantation. No major tissue reaction can be detected at this level *in vivo*. Because the scanning laser ophthalmoscope was limiting the daily observation of animal implanted eyes, we developed a new technique allowing the examination of the all eye compartments. This technique relies on an endoscope and enables the investigator to obtain images from the anterior and posterior chambers at the same time by simply changing the orientation of the probe. After having developed this technique to examine retinal implants, we have demonstrated its potential use not only for rat eyes but also for mouse eyes (PAQUES et al. 2007) and even eyes of larger animals such as cats, dogs, and monkeys (GUYOMARD et al. 2008). This imaging technique was used to discriminate animals with hemorrhage or major fibrous reactions following a subretinal implantation. The morphological state of the tissue was correlated to *in vivo* measures of electrode impedances. In experiments with a good morphological aspect, these measures showed an increase in electrode impedance that stabilized within a month after implantation surgery. This impedance increase was attributed to the change in tissue/implant interface state over time. Indeed, the implant is introduced in a sub-retinal space created by a retinal detachment. The measure suggests that a month is required for the retina to reattach and to adhere to the implant. In parallel, we are investigating the potential increase in retinal gliosis at the implant/tissue interface. These *in vivo* studies could therefore be very interesting for investigating the biocompatibility of new materials and the *in vivo* efficacy of new electrode geometry.

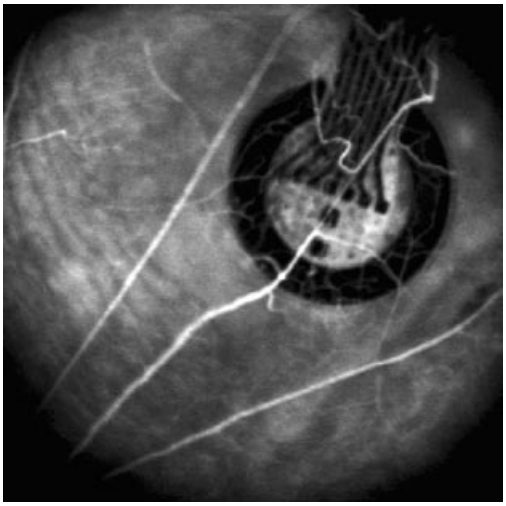

Fig. 3 Retinal implant viewed at the eye fundus of a P23H *in vivo* rat with a scanning laser ophthalmoscope under fluorescein angiography. Blood vessels are seen to pass above the implant head containing the electrodes (diameter of 1 mm) attesting of its subretinal position (SALZMANN et al. 2006).

3. Conclusions, Perspectives

The concept of retinal prostheses has been validated in different clinical trials. However, their resolution has not yet reached a level sufficient for text reading and independent locomotion. Different approaches including 3D electrode designs (Palanker et al. 2004) have been proposed to increase the resolution of individual electrodes. The development of new biocompatible materials is also an important matter for the implant longevity. We are currently testing the biocompatibility of diamond materials on different retinal cell cultures prior to *in vivo* testing (European project: DREAMS). We hope that this work on P23H rats will contribute significantly to the development of retinal prostheses.

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Wüsten –
natürlicher und kultureller Wandel in Raum und Zeit

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Wüsten üben eine eigenwillige Faszination aus: Sie sind heute einerseits attraktive, mystifizierte, abenteuerträchtige Reiseziele, andererseits aber noch immer extrem lebensfeindliche Naturräume. Die aktuelle Diskussion um den globalen Klimawandel und seine möglichen Folgen wirft ein Schlaglicht auf die lebensarmen Wüsten der Erde. Im vorliegenden Band werden vielfältige Aspekte des Lebens- und Wirtschaftsraumes „Wüste“ anhand von Beispielen aus der Sahara und der Namib-Wüste in Afrika, der Atacama in Südamerika und den Wüstengebieten Zentralasiens thematisiert, z. B. die Rekonstruktion der klimatischen und landschaftlichen Geschichte, die kulturelle und kulturgeschichtliche Bedeutung, der aktuelle Wandel und die zukünftige Entwicklung dieser Regionen. In diesen Kontext ordnen sich auch archäologische Forschungsbefunde ein und liefern erstaunliche Erkenntnisse über frühere Kulturmilieus. Aber auch Fragen des Wüstentourismus in der Gegenwart werden kritisch beleuchtet. Die Beiträge zum sozialen, wirtschaftlichen und politischen Wandel in wüstenartigen Gebieten zeigen, welche – teils unerwartete – Rolle solchen Grenzräumen der Ökumene zukommt. Es wird deutlich, wie verletzlich diese Naturräume sind, welche – teils verderbliche – Rolle der Mensch in vielen dieser Ökosysteme spielt und welches gesellschaftlich-politische Konfliktpotenzial sich darin verbirgt. Klimatologische Modellierungsansätze werfen einen Blick in die mögliche zukünftige Entwicklung der Wüsten vor dem Hintergrund des aktuellen Klimawandels in einer stark anthropogen beanspruchten und veränderten Welt.

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Considerations in Designing Optimal Stimulation Electrodes for Retinal Prostheses

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With 3 Figures

Abstract

To move beyond retinal prostheses that provide rudimentary visual capacity to blind patients to ones that provide vision close to that which one might call normal will require the use of arrays of small-tipped electrodes positioned close to the neurons they seek to stimulate. Here we describe technology which makes possible the fabrication of both monopolar and bipolar small-tipped electrodes and some modelling and experimental work aimed at determining safe limits for electrical stimulation. A major finding is that generating pulse shapes which minimize high frequency components should be considered in the design process since such pulses can – in all likelihood – provide effective and safe stimulation of neurons at greater separation than the conventional rectangular pulse shape.

Zusammenfassung

Um von Retina-Prothesen, die rudimentäres Sehvermögen für blinde Patienten erlauben, zu solchen zu gelangen, die eine fast normale Sehfähigkeit gestatten, bedarf es der Verwendung einer Reihe von leicht geneigten Elektroden, die in der Nähe der Neuronen, die sie stimulieren sollen, eingebracht werden müssen. Hier beschreiben wir Verfahren, die die Herstellung von solchen monopolaren und bipolaren Elektroden ermöglichen sowie die Modellierung und experimentelle Testung der Sicherheitsgrenzen für die elektrische Stimulierung. Ein wesentliches Resultat der Untersuchung ist es, die Erzeugung solcher Pulsformen, die hochfrequente Komponenten minimieren, bei der Gestaltung des Prozesses besonders zu beachten, da solche Pulse – aller Wahrscheinlichkeit nach – eine effektive und sichere Stimulierung der Neurone mit größerer Trennschärfe als die herkömmlichen rechteckigen Pulse liefern.

1. Introduction

Perhaps the two primary considerations when designing stimulation electrodes for retinal, or indeed for other neural prostheses, are the biological substrate that one seeks to stimulate and the behavioral outcome desired from that stimulation. For the case of retinal prostheses, the two major neural targets for stimulation are the retinal cone bipolar cells (subretinal prosthesis) and the retinal ganglion cells (epiretinal prosthesis). The desired behavioral outcome is obviously restoration of as close to normal visual performance as attainable. Standard measures of visual performance generally include visual acuity, the extent of the visual field and contrast sensitivity. Visual field extent is dependent on the size of the electrode array. Visual acuity depends on the spacing of electrodes in the array and

the spread of the electrical fields their stimulation produces in the plane of the target neurons. Contrast sensitivity will be limited by how many distinct levels of neural response can be achieved when stimulus amplitude is varied.

While these three constitute the standard metrics of visual performance, it is recognized widely that normal vision is a richer experience than can be captured simply by these measures alone. Color vision and the perception of movement are visual capacities that are not probed with standard tests of the visual field, acuity, or contrast sensitivity. Because of the parallel organization of the visual system, which is seen as early as the level of cone bipolar cells (Boycott and Wässle 1991) and extends through the higher areas of visual cortex (Ungerleider and Pasternak 2004), we can suppose that vision approaching that of a normal person is possible only when the parallel components of the visual pathway are activated appropriately. This need is perhaps no more manifest then when considering the differential electrical stimulation of OFF- and ON-center retinal ganglion cells or of OFF (hyperpolarizing to light) and ON (depolarizing to light) cone bipolar cells. The division of the retinal output into OFF and ON parts indicates a differential system of neural signaling and, if these two components are not stimulated differentially, the resultant signal transmitted to the brain will likely be self-canceling. Overlaid on this OFF and ON subdivision is a more complex coding scheme involving more than 10 types of cone bipolar cell and even more varieties of retinal ganglion cell – a coding scheme that remains incompletely characterized and thus incompletely understood (Boycott and Wässle 1991, Troy and Shou 2002).

For patients who would be considered candidates for retinal prostheses, those with photoreceptor degenerative diseases, it is believed that the inner retinal structure remains largely intact, although it is also well accepted that significant cell loss will have occurred among these inner retinal neurons. Hence, the main challenge we face in designing an optimal retinal prosthesis is to couple its stimulating electrodes to a patient's remaining retinal infrastructure in such a way that retinal neurons can be driven as close to their natural functioning state as possible. Given the generally close packing of the target cone bipolar or retinal ganglion cells, this need would seem to imply that close proximity between the neurons and the stimulating electrodes is required. To accomplish this task, one necessarily requires stimulating electrodes with tip dimensions that are smaller in size and spacing than the neurons that one seeks to stimulate, meaning tips no larger than a few micrometers in size. In the body of this report we describe progress we have made through experimental and modeling work towards the goal of making electrodes of this size and stimulation strategies that encourage safe electrical stimulation of individual neurons. This work constitutes an important step along the path to developing high resolution retinal prostheses, which can potentially restore a high level of visual capacity to patients with diseases of photoreceptor degeneration.

2. Results

2.1 Monopolar and Bipolar Stimulating Electrodes

A number of methods exist to fabricate monopolar stimulating electrodes with tips from as small as 100 nm up to a few micrometers (e. g., Levick 1972, Qiao et al. 2005). Bipolar stimulating electrodes in either side-by-side or in coaxial configurations with very small

tips can also be made, and have the advantage of producing electric fields that are more localized than those resulting from monopolar electrodes. One can fabricate glass-insulated platinum bipolar electrodes in the side-by-side configuration by threading platinum wire into theta quartz glass and pulling the composite with a laser glass puller like the P-2000 of Sutter Instruments (Novato, CA, USA). The disadvantage of this fabrication approach is that one has limited control over the separation of the bipolar electrode tips. The separation is fixed by the geometry of the theta glass. However, very small coaxial bipolar electrodes can be made using templating techniques developed for nanofabrication (Masuda and Fukuda 1995, Shelimov and Moskovits 2000). This approach permits far greater control over electrode design. Hence, the technology exists today to make very small stimulating monopolar or bipolar electrodes of many designs. What remains unresolved, however, is what should be the tip size, material composition, and configuration of such electrodes for producing optimal electrical stimulation with retinal prostheses. The key determining factor for tip size is how much charge one must deliver to stimulate a target neuron and whether or not this charge can be delivered in a manner that results in little or no tissue damage or erosion of the electrode tip. The remainder of this report focuses on work we have undertaken to investigate strategies to minimize tissue or electrode damage with small sized stimulating electrodes.

2.2 Modeling the Electrode-Electrolyte Interface

Because current is carried by electrons in metal and by ions in electrolyte there is a barrier to charge transfer at the interface between a metal electrode and biological tissue. Depending on the operating parameters, the impedance of this barrier can be very significant, constituting by far the biggest component of impedance for electrical stimulation. Surprisingly, until recently, the impact of this important interface on neural stimulation has been poorly characterized. Some recent modeling work of ours (Cantrell et al. 2008) has gone some way to addressing this vital gap in our understanding of electrical stimulation of neural tissue. Relying on the empirical descriptions provide by Richardot and MacAdams (2002) for the interface between platinum and saline and by Bousse and Bergvold (1983) for the interface between silicon dioxide and saline, we constructed a finite element model of current flow from glass-insulated platinum electrodes into physiological saline. The model was set up and run in the COMSOL (Burlington, MA, USA) multiphysics modeling environment. We examined the behavior of current flow as functions of both stimulus amplitude and stimulus frequency. The range of amplitudes investigated was 10–500 mV, which corresponds to the range of empirical results collected by Richardot and MacAdams (2002), and the range of frequencies was 100 Hz to 100 kHz. Among the major findings of this modeling work was the observation that the electrode-electrolyte impedance, in addition to restricting current flow from the electrode into tissue, serves, under specific circumstances, to ensure that the current density distribution over the electrode's active (metal) surface is comparatively uniform. Uniformity of current density is likely to have benefit both in reducing electrode tip erosion and tissue damage. Unfortunately, these beneficial effects are lost when high stimulus voltages or high frequencies of stimulation are applied, since the current density distribution over the electrode surface then becomes much less uniform with high current density focused at points of high curvature (Fig. 1).

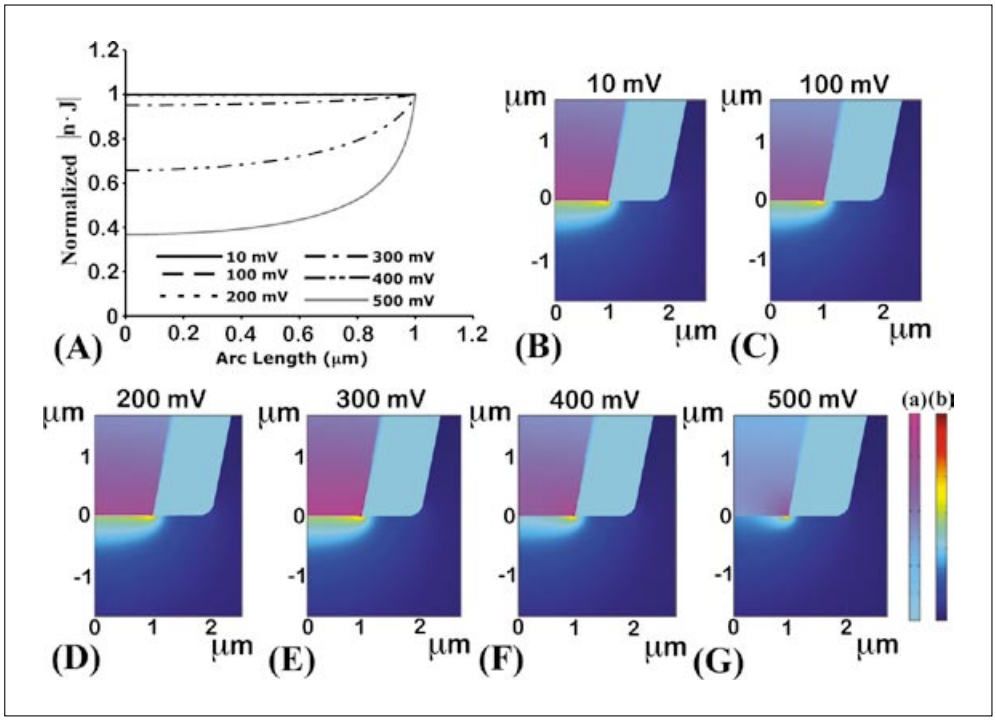

Fig. 1 Current density profiles (*A*) and the surface plots of the norm of the current density (*B*–*G*) generated for a disk electrode including the effects of the electrode-electrolyte interface. The solutions presented in this figure were obtained at 10 KHz while varying driving potential amplitudes. Panels (B)–(G) show current density distributions of cross-sections through half of a 2 μm diameter platinum (mauve) in glass (light blue) electrode immersed in physiological saline (deep blue). Panel (A) shows the norm of current density across the platinum surface where 0 μm is the midpoint of the platinum and 1 μm is its outer edge. Note how the current density distribution remains approximately uniform over the electrode surface for an amplitude of 300 mV or less. The linear color scales apply to panels (*B*)–(*G*). The minimum of both scales is 0 A m^{-2} for all panels. The maxima in units A m^{-2} differ however by panel: panel *B*, (a) 300, (b) 180; panel *C*, (a) 1,500, (b) 1,000; panel *D*, (a) 3,800, (b) 2,400; panel *E*, (a) 22×10^3, (b) 13×10^3; panel *F*, (a) 170×10^3, (b) 100×10^3; panel G, (a) 580×10^3, (b) 380×10^3. Figure reproduced from Cantrell et al. (2008) with permission from IOP Publishing Ltd., Bristol, U. K.

Following from the results of McCreery et al. (1990) and Shannon (1992), it may be concluded that optimal electrical stimulation of neurons – where optimal means minimal tissue damage or electrode erosion – requires a uniform current density distribution over the electrode surface. Hence, our modeling results imply two important implications for the design of safe retinal prostheses. The first is that one would wish to constrain stimulus amplitude to a range that permits a uniform current density distribution over the electrode surface. From a design perspective, this translates into setting a limit on how far a stimulating electrode can be from its target, since lower voltage amplitudes applied to an electrode will be needed to evoke threshold voltages at a neuron when the electrode is closer to that neuron. The second implication is that there should be a pulse shape – one that reduces high frequency components in its waveform – that preserves uniformity of

current density over the electrode surface for the maximum range of stimulus amplitudes. This means that by optimizing pulse waveform one can achieve safe neural stimulation without moving the electrode as close to its target as would be needed with a sub-optimal waveform. In many cases, this could avoid some significant design challenges faced when the distance needed for safe stimulation between an electrode and its target neuron is very small. We therefore investigated both theoretically (modeling) and experimentally whether modifying the shape of stimulus pulses could produce more uniform (less damaging) current density distributions over an electrode's surface without compromising stimulation effectiveness.

2.3 Choosing an Optimal Stimulus Waveform

2.3.1 Modelling Results

Pulses of rectangular time-course are mostly used for electrical stimulation, commonly in a biphasic form with the aim that chemical reactions driven by the anodic or cathodic phases are reversed during their respective counterphases. We investigated three stimulus waveforms. One is the standard rectangular pulse, which we called a squarewave pulse. A second was a pulse shaped as a truncated Gaussian function, which we refer to as a Gaussian pulse. The third was a pulse shaped like half the cycle of a sine function, here called a sinusoid pulse. Since the frequency spectrum of the square pulse contains more high frequency components than either the sinusoid or the Gaussian pulse, our expectation was that the latter two pulses would create, when matched to the square pulse in terms of effectiveness in stimulating neurons, more uniform current density distributions over the electrode surface than the square pulse. To test this we created a finite-element model in the COMSOL multiphysics environment that included an electrode, its interface to physiological saline and a model retinal ganglion cell. The ganglion cell model was morphologically simple (it was a sphere) but its membrane properties were realistic incorporating Hodgkin-Huxley dynamics of the membrane's voltage-sensitive sodium and potassium channels as well as the involvement of calcium ions in neural excitability as modeled previously by FOHLMEISTER et al. (1990).

With the model we were able to increase stimulus pulse duration for all three waveforms until action potentials were evoked from the model retinal ganglion cell. We could then use the threshold for activating a single action potential as a way to normalize effectiveness for the different wave shapes in driving ganglion cell discharge. When compared in this way, we found that essentially the same total charge must be injected to fire an action potential irrespective of the stimulus waveform. But, comparing the current density distributions over the electrode surface for the three waveforms, as expected, we found that the distribution was considerably less uniform for the square pulse than for either of the sinusoid or Gaussian shaped pulses. This difference could be quantified easily by tracking either the surface variance of current density or the peak current density as a function of time. Both measures showed that the distribution of current density over the rectangular pulse was substantially less uniform (Fig. 2).

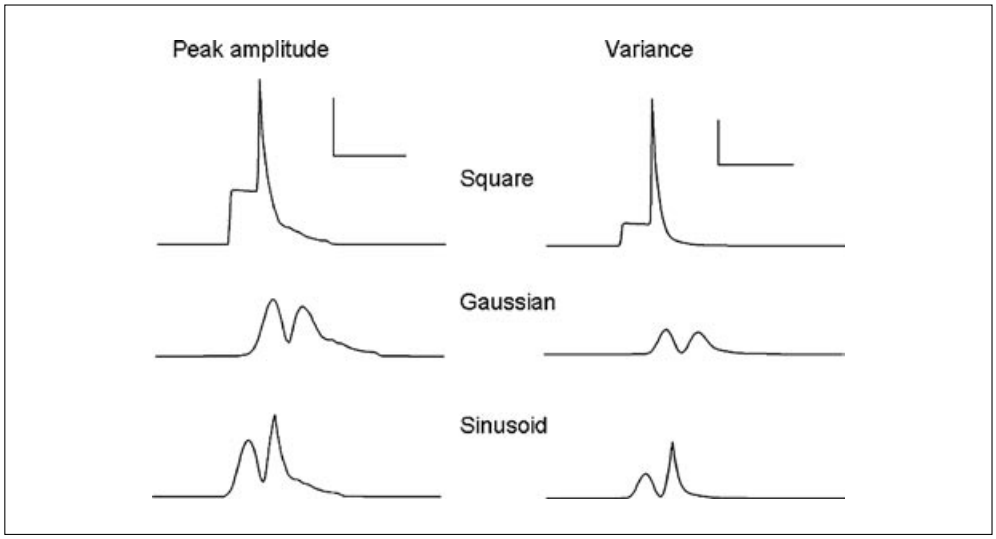

Fig. 2 Properties of the current density distribution on the electrode surface at the threshold required to activate a retinal ganglion cell for stimuli of different waveforms. The left-hand traces show the peak current density and the right-hand traces the variance of current density as a function of time. Note that the peak and variance of current density for the square-wave stimulus show significantly greater excursions in amplitude than is the case with either the Gaussian or sinusoidal waveforms. Scalebars: Time in both cases is 0.5 ms; Amplitude for the left-hand traces is 0.1 $mA m^{-2}$ and for the right-hand traces is 0.05 $mA^2 m^{-4}$.

2.3.2 Experimental Results

Using an *in vitro* preparation of mouse retina we investigated the relative effectiveness of the square, sinusoid, and Gaussian waveforms in driving retinal ganglion cell discharges experimentally. Applying the same approach to normalize responses for stimulus effectiveness experimentally that we did in the modeling exercise – matching stimulus strength to evoke equal amplitude discharge rates – we found that the sinusoid and Gaussian stimuli were somewhat more effective than the rectangular stimulus (Fig. 3). They require slightly less charge transfer to evoke equal responses from ganglion cells to the rectangular stimuli. Furthermore, the average charge density of these stimuli shows less variation as a function of time than does that of the rectangular stimulus. It remains to be determined experimentally whether the sinusoid and Gaussian stimulus waveforms produce less tissue damage for equivalent stimulus strengths than the square pulse but this seems likely and is under investigation. We are also attempting to determine the stimulus wave shape which will create the least tissue and electrode damage and fulfill some other requirements of optimality. For example, pulse widths must be constrained by the requirements of repetitive stimulation and the generation of some pulse shapes might be costly from the perspective of energy consumption. It seems probable that there are wave shapes other than the sinusoid or Gaussian forms that meet the requirement of a more uniform current density distribution and some of these may carry additional advantages. In summary, it seems clear that using stimulus pulses with waveforms that minimize high frequency components in retinal prostheses is likely to have some advantage.

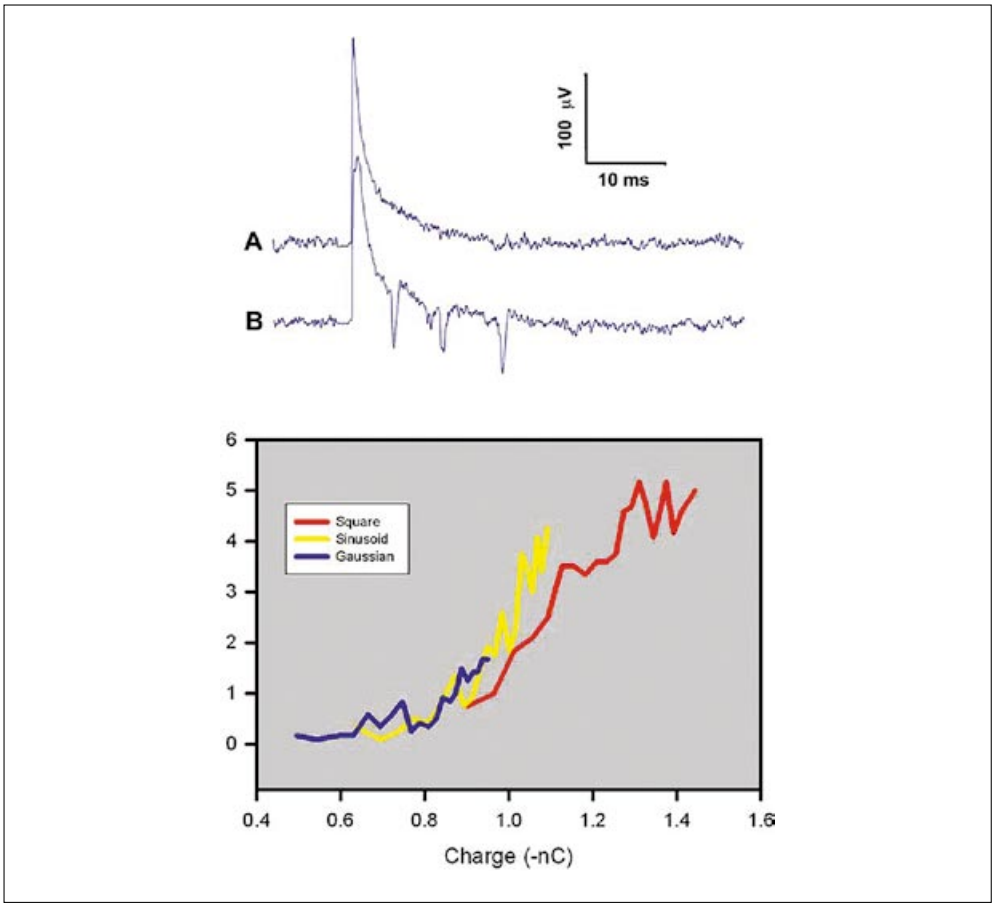

Fig. 3 Upper traces are raw voltage recordings from a 60 µm TiN electrode of mouse retinal ganglion cell spikes following electrical stimulation (the residue of the stimulus artifact is evident at the start of the response). Trace *A* demonstrates the absence of spikes to this stimulus intensity. Trace *B* shows the evoked discharge of three spikes following a stronger stimulus pulse. Such measurements were made for a range of stimulus strengths and for each of the square, Gaussian and sinusoidal pulse waveforms. The lower panel shows the number of spikes evoked (ordinate) by stimuli of different net charge injection for each of the three pulse types. The sinusoidal and Gaussian pulses would appear to be more effective stimuli than the square-wave pulse.

3. Conclusions

There are three main conclusions to the work reported here. Firstly, stimulating electrodes with tips no larger than a few micrometers and placed comparatively close to their stimulation targets are needed to generate high quality visual images in patients with diseases of photoreceptor degeneration. Secondly, such electrodes with current technology can be fabricated in either monopolar or bipolar configurations. Thirdly, if the electrodes can be positioned sufficiently close to their targets and the stimulation pulse is appropriately optimized, tissue damage and erosion of the electrode tip can be minimized.

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Implantation and Explantation of Active Subretinal Visual Prostheses Using a Combined Transcutaneous and Transchoroidal Approach

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With 5 Figures

Abstract

We are reporting on the surgical technique for implantation and explantation of subretinal visual implants with extra-ocular and extra-corporeal parts. We have thus far implanted 11 patients successfully. Visual percepts ranged from recognition of simple geometric forms up to letter recognition which technically was corresponded to a visual acuity of more than 0.02. Surgery was performed in all cases without complications. Histology showed that the implant is tolerated well. Future implants will have a prolonged implantation period and be wirelessly controlled.

Zusammenfassung

Wir berichten über die chirurgische Technik zur Implantation und Explantation von subretinalen Sehimplantaten mit extra-okularen und extra-korporalen Anteilen. Es wurden bisher 11 Patienten erfolgreich operiert. Die Seheindrücke schwankten zwischen der Wahrnehmung von einfachen geometrischen Formen bis hin zur Erkennung von Buchstaben, was rechnerisch einer Sehschärfe von über 0.02 entsprach. Die Chirurgie konnte in allen Fällen komplikationsfrei durchgeführt werden. Histologische Ergebnisse zeigen, dass das Implantat sehr gut toleriert wird. Künftige Implantate werden eine deutlich verlängerte Tragedauer haben und drahtlos gesteuert sein.

1. Introduction

Active subretinal implants receive energy from external sources to elicit visual perceptions by electrical stimulation of retinal cells (Rizzo et al. 2001, Zrenner 2002a). Since electrical energy from solely microphotodiode based is not sufficient (Stett et al. 1998, 1999, 2000), external energy is mandatory and has been supplied by a cable connection in our group recently (Besch et al. 2008, Gekeler et al. 2008, Zrenner et al. 2009). Retinal implants are primarily designed for patients suffering from degenerative retinal disease such as retinitis pigmentosa (RP) where outer retinal cells deteriorate while inner retinal cells stay intact a longer time (Santos et al. 1997, Stone et al. 1992) and can be used to transmit electronically generated signals to the brain.

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Implantation surgery has been described before for extra-ocular/orbital surgery (Besch et al. 2008, Gekeler et al. 2008) and vitreal surgery (Sachs et al. 2000, 2008, 2009). Here we are reporting on our experience in implantation surgery in 11 consecutive patients suffering from RP (Zrenner et al. 2009). Special attention is paid to the explantation procedure which was usually performed several months later as required by our local approval institutions. In light of recently reported adverse events where rapid explantation is required as well as in light of patients' requests for newer generation implants, in our opinion explantation has thus far been undervalued. This prompted us to investigate the explantation procedures in our patients who were implanted with an active subretinal prosthesis with a permanent extra-corporeal connection.

2. Material and Methods

2.1 Patients

We included 11 patients with end stage RP (10 males, 1 female). Remaining vision was required to be 'of no use in daily life'. In all subjects electrical excitability was ensured by prior trans-corneal electrical stimulation with DTL-electrodes (Gekeler et al. 2006c). All experiments were undertaken with the understanding and written consent of each subject respecting the Code of Ethics of the World Medical Association (Declaration of Helsinki) and in accordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC). The study was approved by the local university's ethics committee which granted permission for a study period of 4 weeks in the first 8 patients and 4 months in the last 3 patients.

2.2 The Subretinal Prosthesis

The prosthesis consisted of four parts (Fig. 1).

- The subretinal part (*i*). – with (*a*) the MPDA with 1,550 photodiodes and titanium-nitride electrodes driven by light falling onto it through the optics of the eye and powered by external energy transferred via gold connection lanes on the polyimide foil strip, and (*b*) 16 titanium-nitride electrodes in a 4 × 4 array for direct, light independent, electrical stimulation; each electrode is connected to an outside stimulus generator via connection lanes on the trans-sclerally, trans-choroidally implanted foil strip.
- The extra-ocular part (*ii*). – After choroidal and scleral penetration the foil strip is flipped to lay episclerally. It then leads under the lid to the lateral orbital rim. For fixation, a patch of polytetrafluoroethylene glued to the foil is sutured onto the sclera. At the end of the foil strip a silicone patch is fixed by sutures in two holes through the lateral orbital rim.
- The subdermal part (*iii*). – The foil strip connects in the temporal fossa to a silicone cable with spirally twisted, isolated wires, which lead subperiostally beneath the temporal muscle to the retro-auricular space where it surfaces into a plug. There the device is fixed to the bone by a stainless steel clamp.
- An extra-corporeal part (*iv*). – The play connects to a stimulus generator.

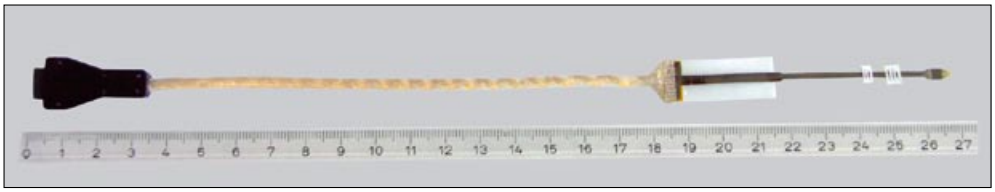

Fig. 1 Photograph of the active subretinal implant. It consists of four parts: (*i*) The subretinal part (polyimide foil strip, 20 µm thick, 3.2 mm wide, approximately 22 mm long) with: a 4 × 4 array of titanium-nitride electrodes (diameter 50 µm, spacing 280 µm) and a microphotodiode array with 1,550 photodiodes and electrodes (electrode diameter 70 µm, spacing 70 µm, thickness 70 µm) which lies para-foveally. (*ii*) The extra-ocular part (polyimide foil) carrying 22 golden connection lanes to the external connection and the reference electrode. At length 12 and 26 mm from the tip two polytetrafluoroethylene pads are mounted for fixation on the sclera. At approximately 55 mm from the tip a silicone pad is glued to the polyimide foil for suture fixation to the lateral orbital rim. (*iii*) The subdermal part (silicone cable, diameter 3 mm) leads the connections on the polyimide foil to the external part by 22 spiraled gold flexes. The silicone cable perforates the retro-auricular skin. (*iv*) The external part consists of the silicone cable which connects via a plug to an external generator for control signals, energy, and stimuli.

2.3 Histology

Tissue samples surrounding the extra-corporeal implant were taken during explantation at various sites. Tissue was embedded in paraffin in the usual manner. 4–5 µm thick sections were stained with hematoxylin-eosin (H&E), Periodic acid Schiff (PAS), and Masson's trichrome. Moreover, various immunohistochemical stains like CD4, CD8, CD68, sm-actin, and KI67 and were performed.

3. Results

3.1 Implantation Surgery

The implantation procedure was carried out sequentially in the following steps as has been previously described in more detail (Fig. 2) (Besch et al. 2008, Gekeler et al. 2008). In short, the skin was incised in the retro-auricular space. Approximately 2 cm by 2 cm of bone were exposed and two holes drilled to fix a metal clamp fixed with osteosynthesis screws. Then a prolonged brow incision was performed to expose the lateral orbital rim. Two holes were drilled 2 mm superior and inferior to the *sutura zygomatico-frontalis* and threads were inserted. Preparation proceeded laterally into the *fossa temporalis* elevating the temporalis muscle and the periosteum. From the subconjunctival space in the upper temporal quadrant a tunnel was bluntly prepared through the septum to the brow incision and was kept patent by a small silicone tube. A specially made trocar was advanced from the periorbital region subperiosteally until it reached the retroauricular area. The implant could then be advanced inside in anterior direction and the trocar removed leaving the implant in place. The intra-ocular surgery comprised a pars-plana-vitrectomy, creation of a subretinal bubble and trans-choroidal penetration in the upper lateral quadrant of the eye. Then, the fixation pad was sutured onto the sclera and the retina re-attached by perfluorocarbon liquids and filled with silicone oil for endotamponade.

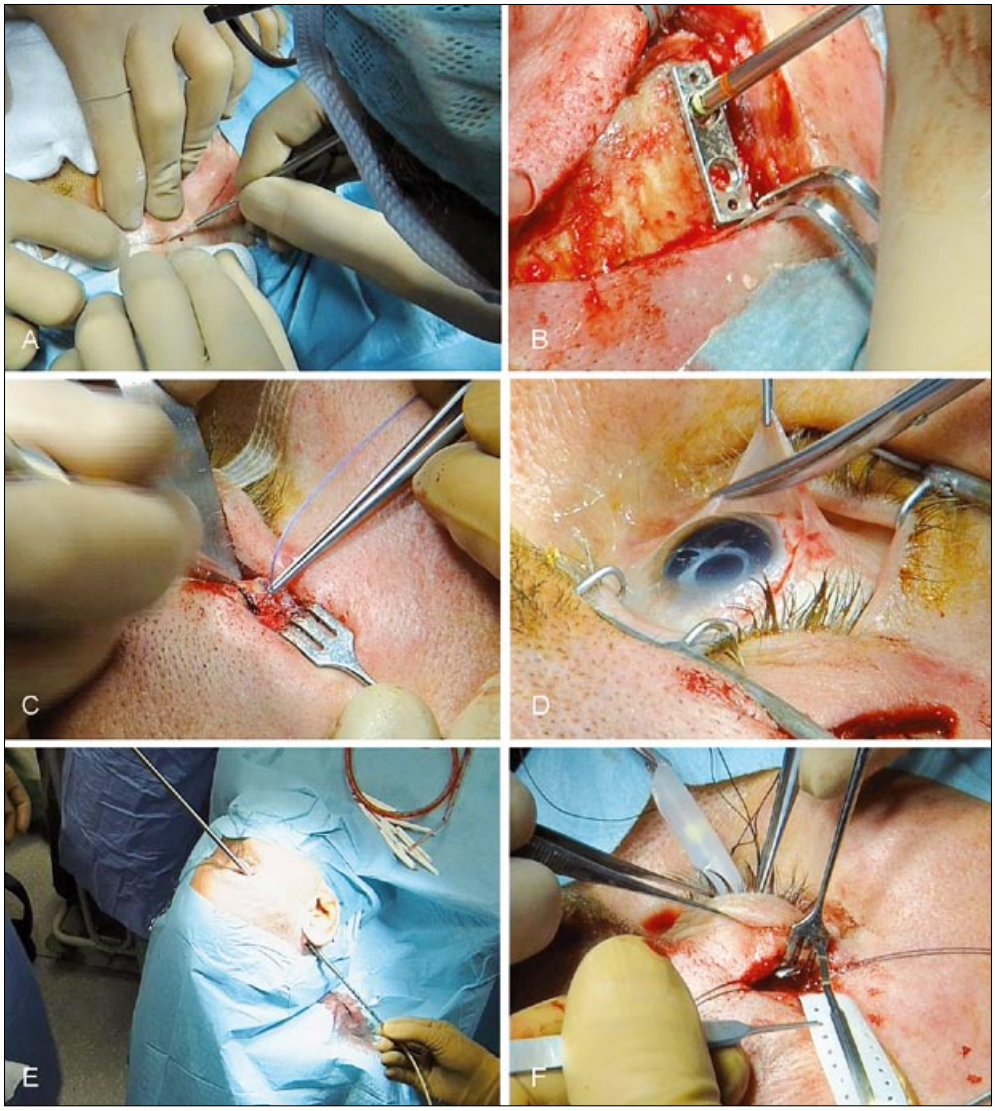

Fig. 2 Photographs of the decisive surgical steps for implantation. (*A*) Performing the retro-auricular cut. (*B*) Fixation of the base of the fixation clamp with two osteosynthesis screws. (*C*) Pulling threads through the two holes through the lateral orbital rim (2 mm above and below the *sutura zygomatico-frontalis*) for fixation of the implant. (*D*) Lifting the conjunctiva before the 360° incision. (*E*) Using the trocar in anterior-posterior direction in which the implant is inserted in opposite direction. (*F*) Insertion of the implant to the subconjunctival space.

The surgical procedure provided no major difficulties. The procedure of subperiostal implantation from the retro-auricular space to the orbital rim using the trocar proved to be well controllable in all cases. In general, the most challenging part was the protection of the implant during all steps of the surgery; touching the MPDA or the electrodes was not possible with any instrument and even fine threads could easily tear the polyimide foil and

lead to disruption of the gold wires (besides constituting a predetermined breaking point). Of this, an especially delicate part turned out to be pulling the polyimide foil with the subretinal parts through the opening from the lateral orbital rim under the lateral lid to the subconjunctival space. First, because the fairly large protecting silicone tube exerted considerable pressure onto the globe leading to a marked increase in intraocular pressure requiring fast maneuvers. Second, because the delicate subretinal parts had to be protected against mechanical injury by placement inside of the silicone tube while pulling the tube through the iatrogenic access. To facilitate this and provide better protection for the globe and the implant, a metal cartridge has been used in the last three patients. The cartridge was smaller in diameter, and a thread could be attached to pull it through the iatrogenic access (Fig. 1*F*); it considerably reduced pressure increases on the globe and helped to protect the implant's tip. Coagulation by monopolar or bipolar diathermia was to be avoided in the proximity of the implant because high-frequency electrical fields could damage the MPDA which acted as an antenna. To protect the implant a large spatula (touching the sclera to conduct any currents) was placed between it and the coagulating tip. During the following intra-ocular surgery the implants tip was kept away inside of the silicone/metal tube taped to the surgical drape.

In all 11 patients the implantation surgery, extra- as well as intra-ocular, could be performed as planned. No intra-operative complications were encountered. Surgery was performed in all cases without damaging the prosthesis. Figure 2 shows selected surgical steps in one patient. Time for extra-ocular surgery was 1.5 to 2.5 h; the whole surgery lasted 6 to 7 h.

3.2 Surgical Outcome

During the first postoperative days moderate edema and hematoma in the periorbital region were noticeable. The subdermal passage to the retro-auricular space proved to be unproblematic in all cases, leading to only minimal swelling and almost no pain. Two patients complained about a mild jaw closure blockade noticed during chewing which had disappeared one week postoperatively. A possible cause is an irritation of the temporal muscle or some fibers of the facial nerve in this region of the cable passage. Conjunctival chemosis and injection were observed in all patients comparable to other intraocular procedures such as pars-plana-vitrectomy. After approximately 5 days conjunctival chemosis, edema and hematomas had almost completely resolved and patients were discharged.

All wounds healed properly and no signs of infections or wound dehiscence were noticed. The skin penetration of the silicone cable proved to be well tolerable and unproblematic over the whole examination period.

Computed tomography scans of one patient and 3-dimensional reconstructions are shown in Figure 3.

The retina was attached immediately post-operatively until explantation in all cases. In the early postoperative days some retinal edema over the MPDA was present in optical coherence tomography. The amount of edema decreased during the first post-operative week. Fluorescein angiography could show capillaries in fine detail over the MPDA because the opaque MPDA totally blocked background fluorescence from the choroid. In the periphery (upper temporal part) of the MPDA capillary rarefication was noticeable, which could either be due to mechanical obstruction from the thickness of the soldering points of the MPDA in this region or due to pre-existent changes in RP retinas (Gekeler et al. 2007).

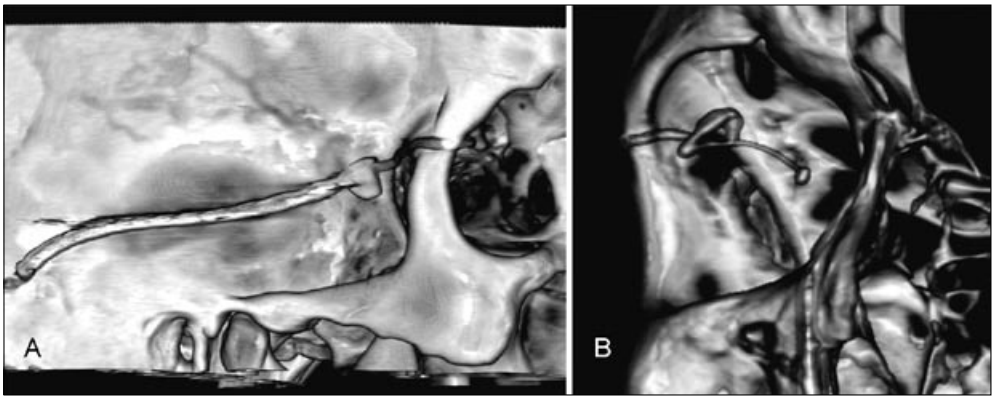

Fig. 3 3D reconstruction of computed tomography scans of one patient approximately 2 years after implantation. (*A*) Side view of the reconstruction which shows the path of the silicone cable from the retro-auricular region through the temporal fossa around the lateral orbital rim. The ticker part in the temporal fossa is the transition from the silicone cable to the polyimide foil. (*B*) Frontal view showing the polyimide foil within in the orbit, the episcleral part and the subretinal part where the thicker ending of the implant constitutes the microphotodiode array and the direct stimulation electrodes.

3.3 Explantation Surgery

First, the skin was re-opened in the retro-auricular space and in the brow region posteriorly to the temporal fossa. The implant was then carefully exposed by blunt preparation. Especially under the conjunctiva there was considerable scar tissue which had formed around the implant. This tissue, however, was not adherent to the implant's structures, but rather formed a capsule in which the implant could slide. Then the silicone cable was dissected at the junction with the polyimide foil in the temporal fossa. The screws of the clamp in the retro-auricular space were removed and the silicone cable pulled posteriorly which posed almost no measurable resistance due to the capsule also found in this region. The basal plate of the clamp and the bone screws were removed and the skin closed again. Following that intra-ocular parts of the implant were removed by loosening the scleral fixation pad and the scleral access was re-opened to pull out the intra-ocular parts. No intra-ocular procedure was required. All wounds were finally closed in layers. Silicone oil was removed approximately 3 months later, depending on the individual situation. Several steps of explantation surgery are shown in Figure 4.

Prostheses were explanted after 4 weeks in patients 2, 3, and 4; and after 5 weeks in patients 5, 6, and 7. The elongation of the study period was permitted by the local ethics committee. Patient 1 refused to have the device explanted.

At explantation the implant was surrounded by scar tissue, which was – due to the inert nature of the polyimide, silicone, and expanded polytetrafluoroethylene materials – not connected to any of the implant's parts. Therefore, after careful dissection of this tissue using microscissors and removal of episcleral and bone sutures the device could simply be pulled out as described above. Explantation was uneventful in all 6 cases and patients could be discharged on the following day.

3.4 Functional Results

Eight patients reported topical correct visual percepts by the direct stimulation array and 6 patients also by light stimulation through the MPDA (Zrenner et al. 2006, 2009). Details will be published in upcoming publications.

3.5 Histology

Histology showed the formation of scar tissue (condensed connective tissue) along the extra-corporeal implant as a morphological correlate of the described capsule. Fibroblasts invaded the polytetrafluoroethylene pad covering the polyimide foil. There was a moderate inflammatory reaction consisting of CD4, CD8, and especially CD68 positive cells along the extra-bulbar implant. Foreign body giant cells were primarily seen in the vicinity of the polytetrafluoroethylene pad (Fig. 5).

4. Discussion

We have developed a surgical procedure that allows safe implantation and explantation of active visual prostheses with extra-corporeal parts. The study in 11 patients has proven that the surgical access is feasible for a period of at least four weeks. Surgery was successful in all cases and lead to stable placement of the prosthesis. No postoperative complications were encountered, such as infections or displacement of implants. Patients altogether felt astonishingly little irritation from the surgical procedure and the presence of the device. The trans-cutaneous connection proved to be uncomplicated and usable for repeated connection and disconnection of the stimulator.

Since in previous animal experiments small dislocations of the implant's subretinal parts have lead to retinal tears and retinal detachments (Gekeler et al. 2006b), multiple tension relief points were introduced along the course of the implant: flexible pads for fixation on the sclera, two sutures through holes in the bone of the lateral orbital rim, and by a metal clamp on the scull bone in the retro-auricular space for the silicone cable. Consequently, no retinal detachments or dislocations were noticed.

Explantation was required in our case by local ethics committee after 4 weeks in the first 8 patients and after 4 months in the three last patients. However, there are several more situations when explantation is required, such as major complications (e. g. endophthalmitis has been reported by other groups; Humayun 2009) or when patients request more up-to-date implants. Therefore, the finding that explantation of devices with extra-ocular parts (which most groups now favor) is feasible is of great value. Explantation surgery required extra attention due the scar tissue found especially in the subconjunctival space, but was successful in all cases and implants were available for further technical examination. The implant itself was not connected to any tissue due to the inert materials used (polyimide, titanium, silicone).

Histology showed the usual condensation of connective tissue at the host tissue-implant interface. Inflammation was generally moderate but recognizable with a foreign body reaction (giant cells) especially in the vicinity of the polytetrafluoroethylene pad and polyimide foil.

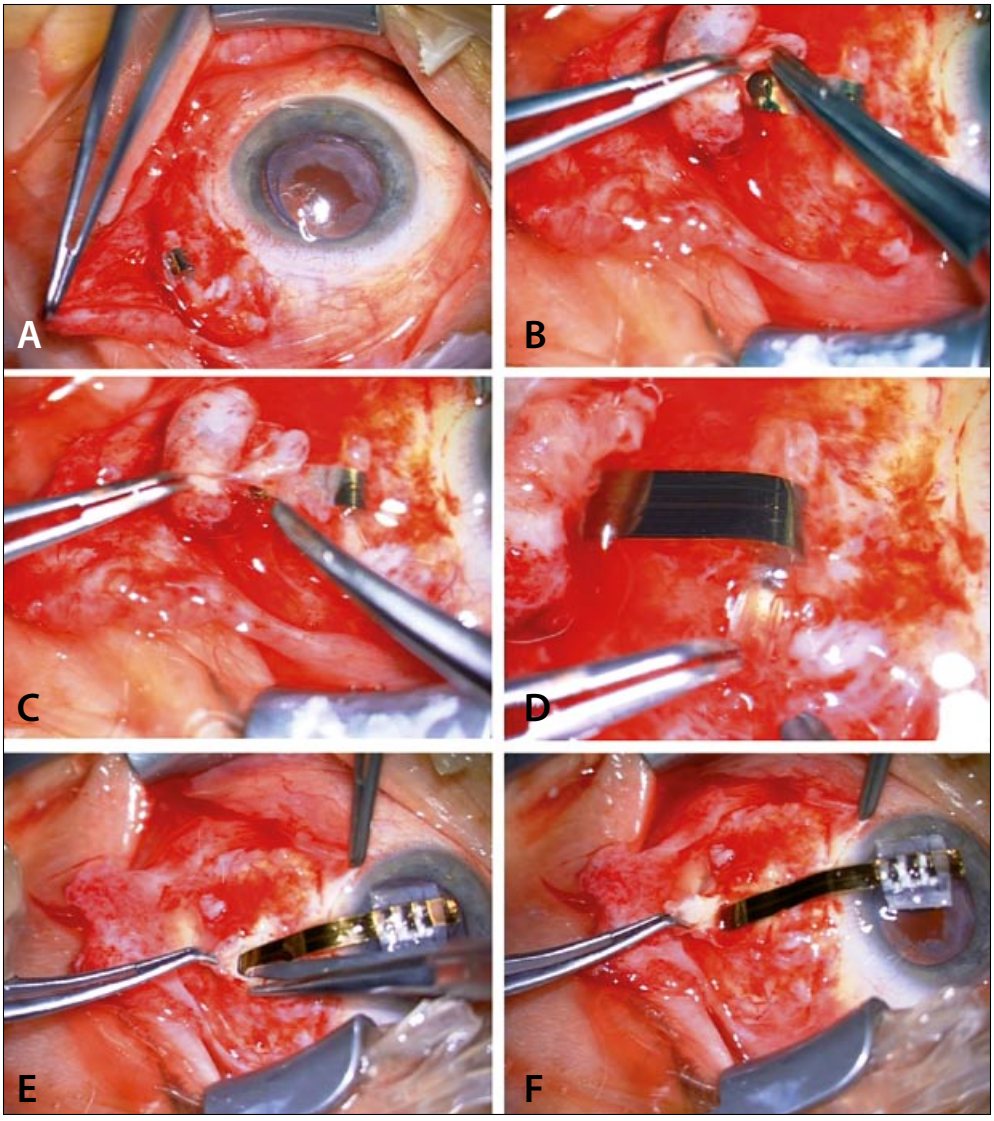

Fig. 4 Photographs of the decisive steps for explantation. (*A*) The polyimide foil can be seen after lifting the conjunctiva in the upper temporal quadrant of the left eye of this patient after 3 months. (*B*) and (*C*) The foil is surrounded, but not adherent to scar tissue which produces a kind of capsule that is incised carefully. (*D*) Removal of the artificial hypomochlion made from silastic tubing that was placed to protect the foil from potential damage of sharp bends. (*E*) The scar tissue is opened more posteriorly. (*F*) The original scleral flap is prepared (lifted up here by the forceps).

As a first step in this study, an extra-corporeal connector was used through a trans-cutaneous cable in order to be able to directly measure charge transfer and impedance of individual electrodes. Using a direct connection we were also able to optimize the control settings for the MPDA, which will be used for the next implantations with a wirelessly controlled implant. An extra-corporeal connection does certainly not qualify for permanent and rou-

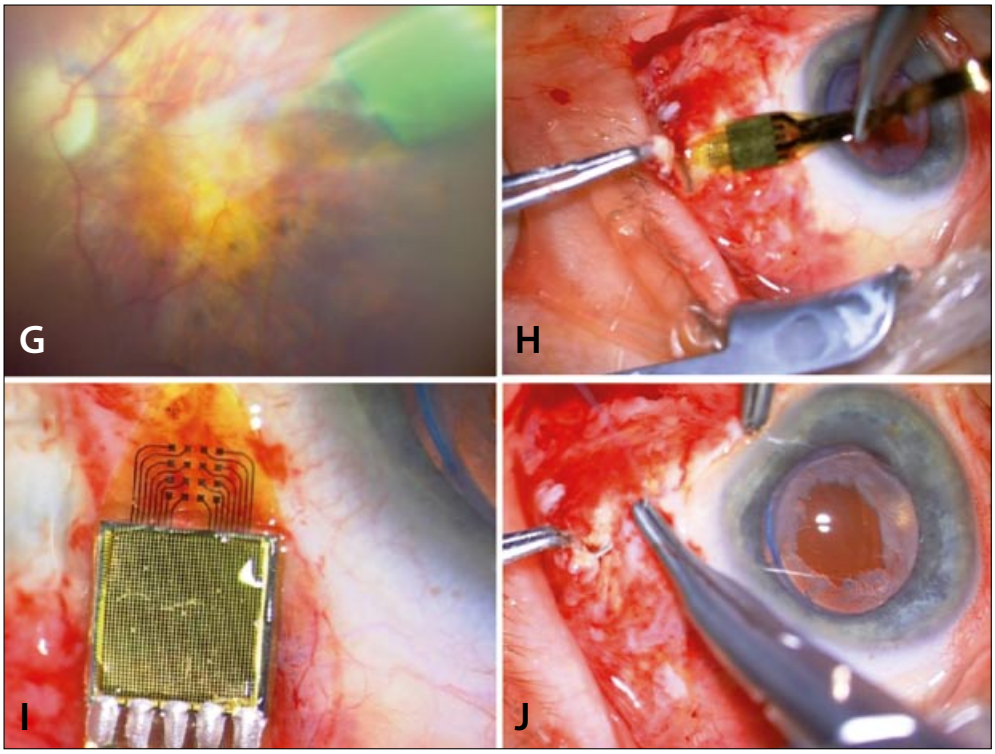

Fig. 4 (*G*) Fundus view (taken through the operating microscope) showing the implant already partially removed, which leaves a depigmented area in the original place. (*H*) The implant can simply be retracted with silicone oil in place. (*I*) A first glimpse at the implant after explantation under the microscope reveals completely intact structures: 16 direct stimulation electrodes at the top and the microphotodiode array with approximately 1,600 diodes on the bottom. (*J*) Suturing of the scleral flap for globe closure.

tine use. We feel, however, that this step was justified in regard of the very positive results of the study and the low complication rate.

Other groups have already placed wireless systems either in the retro-auricular space (Humayun et al. 2003), episclerally (Rizzo et al. 2008), or even intra-ocularly as a modified intra-ocular lens in the capsular bag (Alteheld et al. 2007). A totally intra-ocularly implantable device is still, even when using up-to-date technology, large in size and the trauma inferred for implantation is considerable since it requires a large limbal opening and combined anterior and posterior segment surgery with a wired connection e. g. from the capsular bag to the episcleral surface (Alteheld et al. 2007), or possibly even to the subretinal space. The easier surgical access and the additional room in the extra-ocular space give more freedom in the choice of the receiver coils and control circuitry. In our opinion therefore, a system where the receiver and control units of a wireless system are placed extra-ocularly bears significant advantages. In particular, in regard of the unproblematic trans-choroidal, trans-scleral penetration with a wired connection in our cases and in the literature (Besch et al. 2008, Gekeler et al. 2006a, 2007, Sachs et al. 2005, Humayun et al. 2003) a completely intra-ocularly implantable system does not seem essential. Several steps of the extra-ocular surgery presented in our study can contribute to implan-

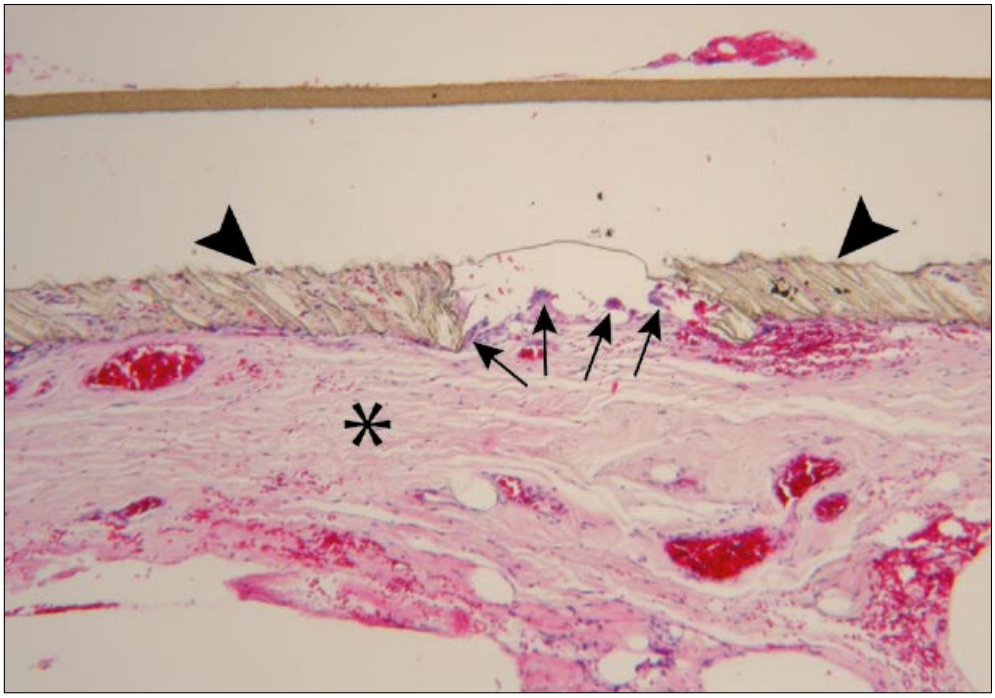

Fig. 5 Histological section of tissue surrounding the implant (polytetrafluoroethylene pad polyimide foil) taken at the time of explantation after approximately 2 months. Fibroblasts have invaded the porous polytetrafluoroethylene pad patch (arrow heads) which is lined by foreign body giant cells (arrows). Connective tissue seems condensed besides the implant (asterisk) with mainly longitudinal orientation of the collagen fibers (H&E).

tation of such a prosthesis and also under other circumstances in ophthalmic research, e. g. when intra-ocular technical devices have to receive or transmit signals, such as intra-ocular pressure (e. g. Walter et al. 2000) or temperature sensors (e. g. Sailer et al. 2007), epi- or sub-retinal prostheses, and also optic nerve head prosthesis (in Rizzo et al. 2001, Zrenner 2002 b).

In conclusion, our study in eleven patients has proven the feasibility of a trans-cutaneous, trans-choroidal cable connection to the subretinal space using the described surgical procedure. Implantation and explantation were highly successful and led to stable placement in all cases. Functional results are extremely promising (Zrenner et al. 2009).

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Subretinal Implant: The Intraocular Implantation Technique

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With 1 Figure

Abstract

Purpose: The size of subretinal active film bound visual prostheses and their necessary connection to extraocular structures for energy supply requires a transchoroidal surgical implantation procedure. A safe surgical transchoroidal subretinal access is mandatory for successful chronic implantation in humans.

Method: Eleven legally blind, volunteer patients were implanted with a transdermal cable bound device. A transchoroidal subretinal implantation of the stimulation device (active implant) was carried out. The implant consisted of a stimulation chip on a polyimide film and additional stimulation electrode array with 16 TiN electrodes. The energy which was required for the stimulation was delivered via a retroauricular plug transdermal by a cable and transchoroidal by a polyimide film with supply lines. Thus, subretinal stimulation experiments could be carried out successfully in chronic subretinal implanted patients for the first time. According to the schedule the implants had to be removed after 30 days and after 3 months for the last 3 patients. Careful radiodiathermy with precise adjusted parameters allowed to penetrate the choroid without bleeding. A specially designed guide film was used as an implantation instrument. Silicone oil served as a tamponade.

Results: Implantation was successfully performed in 11 patients. No surgically induced adverse events (choroidal bleeding, retinal detachment, inflammation, etc.) were observed during the surgical procedure or the follow up period lasting up to 3 years. The implants remained stable in all cases. All but one of the implants were explanted according to schedule approx. 30 days or 3 months after implantation. One patient refused the explantation and kept the implant. This patient was closely monitored for 3 years.

Conclusions: A newly developed transchoroidal implantation and explantation procedure was successfully established in humans. This procedure enables a safe chronic stable subretinal implantation and explantation of large scale electronic prostheses. With these results a possible exchange option of subretinal implants is given if necessary.

Zusammenfassung

Hintergrund: Geeignete operative Verfahren zur Implantation von Sehchips standen nicht zur Verfügung und mussten deshalb entwickelt werden. Besonders die Größe von aktiven subretinalen Implantaten (Retina-Implant) und die Notwendigkeit von außen Energie zuführen zu müssen erfordert einen transchoroidalen chirurgischen Zugangsweg zum Subretinalraum, der in dieser Form als nicht machbar galt. Ein sicherer operativer Zugang ist entscheidend für Erfolg oder Misserfolg einer prothetischen Versorgung.

Methode: Elf an degenerativer Netzhauterkrankung erblindete Patienten wurden im Rahmen der Studie mit einem Retina-Implant versorgt. Das Implantat bestand aus einem Chip auf einer Polymidfolie sowie zusätzli-

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chen 16 Stimulationselektroden. Die für die Stimulation benötigte Energie wurde über eine Kabelverbindung aus dem Subretinalraum heraus von außen zur Verfügung gestellt. Über diesen Zugang kann von außen eine Energiezufuhr erfolgen. So konnten subretinale Stimulationsexperimente sowohl mit dem Chip als auch mit Stimulationselektroden durchgeführt werden. Die Implantate mussten entsprechend dem Versuchsplan nach 30 Tagen oder nach 3 Monaten entfernt werden. Die Behandlung der Aderhaut mittels Radiodiathermie mit entsprechend angepassten Parametern, erlaubte es, die Chorioidea ohne jede Blutung zu penetrieren. Für die Implantation des Chips wurde eine speziell angefertigte Führungsfolie entwickelt.

Ergebnisse: Die Implantation konnte bei allen 11 Patienten erfolgreich durchgeführt werden. Es gab keine chirurgischen Komplikationen, wie choroidale Blutungen oder Netzhautablösungen. Auch während der Nachsorge zeigten sich keine Komplikationen. Alle Implantate (mit einer Ausnahme) wurden entsprechend dem Protokoll nach 1 oder 3 Monaten entfernt, was jeweils auch komplikationslos verlief. Ein Patient verweigerte die Explantation und trägt dieses komplikationslos seit 3 Jahren.

Schlussfolgerungen: Der für dieses Verfahren neu entwickelte transchoroidale Zugang ermöglicht eine komplikationslose Implantation und Explantation des Retina-Implants. Die vorher durchgeführten Versuchsreihen an Hausschweinen ermöglichten die Entwicklung einer komplexen Operationsmethode, die komplikationslos auf den Menschen übertragen werden konnte. Diese Operationsprozedur ermöglicht die Implantation von größeren subretinalen Implantaten und die Energieversorgung von außen. Darüber hinaus ergeben sich für diesen Zugang optimale Explantationsmöglichkeiten, wie auch die Möglichkeit, derartige Implantate zu wechseln.

1. Introduction

Various groups worldwide are developing visual prosthetic devices to restore vision for blind or visually handicapped patients who are blind due to photo receptor degeneration (Zrenner 2002, Schanze 2005). All the retinal based implants in current use try to activate remaining retinal neuronal cells by electric stimulation (Rizzo and Wyatt 1997). One main issue is the resulting visual field which is determined by the size of the implant and has an impact on the surgery. Another decisive factor is the energy supply for the stimulation process. Technical problems concerning biocompatibility, biostability, or the implantation procedure itself have to be solved. According to the various approaches, different surgical techniques have been developed to guarantee a safe implantation of the device. Subretinal implantation was first carried out with micro photo diode arrays (MPDA's) (Chow and Chow 1997) which were placed completely into the subretinal space. The energy supply for the MPDA's, which were supposed to stimulate the degenerated retina, was the available light falling into the eye.

Animal experiments by our group made clear that the stimulation process requires an additional energy supply to stimulate the retina under ambient light levels. Therefore the concept of an active subretinal implant was developed which feeds the necessary energy for the stimulation process from external electronic parts into the subretinal space. A permanent (cable) connection into the subretinal space is mandatory in this concept. A suitable surgical procedure for this concept had to be developed. In this concept a transchoroidal placement of the implant (combined *ab externo* and *ab interno* procedure) seems to be the method of choice. Such, the retina is protected to provide optimal conditions for the stimulation process. Hence, this is a new and complex surgical maneuver, and attention has to be focused on the crucial sequences. They have been studied in detail in animal experiments. Especially the bloodless penetration of the choroid has to be guaranteed to reach an optimal surgical result. The extraocular and extra orbital surgical procedure which describes the path of the subdermal cable is described in detail elsewhere (see Gekeler 2010, in this volume).

2. Material and Methods

Twelve legally blind male RP patients were recruited for the study. The residual vision was determined to be of no use in their daily life to fulfill the requirements of the local ethics committee. The patient with the best residual vision had light perception without any light localization. All these patients with end stage RP had extensive diagnostic work-up including family history for pattern inheritance, electric retinography, FA, OCT, SL examination and funduscopy. To ease the complex implantation process, cataract surgery with the implantation of a posterior chamber IOL was carried out weeks prior to subretinal implantation surgery. Written consent of each subject respecting the Code of Ethics of the World Medical Association (Declaration of Helsinki) was present.

3. The Implant

The complete implant is composed of different elements which fulfill the needs of the respective anatomical structure. The requirements of the subretinal space, the extraocular path and the subdermal path had to be fulfilled. In principle the implant consists of a polyimide foil strip with direct stimulating electrodes on the tip of the foil strip followed of the chip for subretinal stimulation. Both these elements cover the implanted tip of the foil. The tail of the foil contains the conductive wiring which is connected to a subdermal silicone cable containing gold wiring. The distal cable ends in a micro plug which can be connected to the stimulation unit during the trials. The silicone cable leaves the skin in the retroauricular region. The micro plug is extra corporal (see Gekeler 2010, in this volume).

4. The Ocular and Subretinal Part

The shape of the foil was designed and empirically tested in animal models (Sachs et al. 2004). The size of the chip determined the maximum width of the implant. A successful penetration of the choroid is eased by the design and shape of the foil. This design especially the form of the tip is helpful for the subretinal advancement and left room for the additional direct stimulating (DS) electrodes. These electrodes are important for parameter determination and basic electrophysiological experiments. The 16 DS electrodes are situated on the tip of the foil followed by the stimulation chip with 1,550 photodiodes. The chip, which is square shaped, has the photodiodes with the equal number of TiN electrodes arranged in a rectangular manner. The chip is powered by external energy which is delivered via the supply lines on the polyimide foil. Light falling onto the chip (MPDA) drives the device. The 16 DS electrodes can be directly connected to an external stimulator and are used for light independent stimulation trials. The width of the foil tail is determined by the wiring and the need for stability during the process of subretinal foil advancement and proper placement. The foil leaves the eye in the (pre-) equatorial region through the choroid and is covered for approximately 5 mm by a scleral flap. The extraocular foil has small polytetraflourethilene-like patches glued onto it to ease episcleral fixation. This fixation is intended to neutralize the tensile stress. The foil reaches the fornix where it is rather loose to guarantee the mobility of the eye.

The path of the subdermal cable starts at the orbital rim and ends at the retro auricular region. The cable has to be fixed to the bone with the help of screws to avoid tensile stress which could affect the more vulnerable PI-foil.

5. The Transition from MPDA to Active Subretinal Implants

Surgery was developed using different animal models. Pigs were primarily used to develop or improve the critical surgical steps. For the required electrophysiological experiments cats were of great value (Schanze et al. 2002). The experience of this model gave rise to the decision to develop an active implant. Information on retinal stimulation gathered from cat brains revealed that the MPDA-concept without additional energy supply was not successful. The decision to build a cable bound implant was the result of acute (intraoperative) stimulation film experiments in cats and pigs which were transformed step by step to a chronic experiment.

The surgical knowledge which was necessary to plan a transchoroidal procedure in humans was achieved by a series of implantations of cable bound stimulation film devices in domestic pigs. Engaging this animal model, the parameters for a bloodless penetration of the choroid were determined.

6. The Transchoroidal Subretinal Implantation in Humans in Detail

The surgical team responsible for the extraocular surgery (the path of the cable – see Gekeler 2010, in this volume) starts the surgery and hands over to the intraocular surgical team after finishing their part and opening the conjunctiva. The stimulation foil enters the orbit beneath the upper temporal quadrant of the eye lid. A standard 3-port vitrectomy is carried out and vitreous is removed as far as possible. A critical step is the search for a suitable (choroidal) penetration site which should allow the creation of a visible subretinal fluid bleb in the equatorial region. This bleb, which is created by injection of BSS through a 41G Teflon canula (DORC, Netherlands, Dual bore BSS injection needle, 41G tip), is stabilized with viscoelastic solution (Healon, 10 mg/ml AMO, Uppsala, Sweden) injected with a subretinal injection needle (Subretinal injector, curved, Glaser, 32G tip). The size of the bleb is kept small, just big enough to meet the demands of retinal protection in the corresponding area which was determined in advance on the sclera as the suitable implantation site. A trapezoid scleral flap with its base corresponding to the subretinal bleb is created. The width at the base is 4 mm (the implant size is 3.5 mm), and the length of the flap is 5 mm. The flap is prepared full thickness in the equatorial region to expose the choroid. No supra choroidal tissue should be left. This maneuver is carried out in hypotony (the intermediate used scleral plugs are removed) to prevent the choroid from prolapsing. Care is taken to avoid any choroidal bleeding. The choroid is completely exposed in an area of 2×4 mm and radiodiathermy is applied in this region. The best and most constant results have been achieved with an Ellmann Surgitron Radiofreuency device in the Fulguation mode 4 mHz (Ellmann, NY, USA). In this mode with a spark gap waveform maximum penetration and hemostasis is achieved. A ball electrode (2 mm) is used and discrete whitening of the choroid in the treated area is achieved. Thus the choroid can be punctured with a sur-

gical knife without any bleeding. The subretinal space is entered by gaining access to the viscoelastic bleb from outside of the globe. This tiny choroidal opening is widened by a specially designed lancet shaped guiding foil.

Its rigidity and shape allows a safe subretinal advancement of this device into the desired subretinal posterior target area. A smooth mechanical separation of the retina is achieved and the vulnerable electronic device can be advanced behind this shield into the desired macular region. After placement of the stimulation chip the shield can be withdrawn easily. The scleral flap is immediately closed by one situation suture (Vicryl 7.0) the moment the guide film is removed. Gentle pressure onto the sclera next to the cut edge removes the viscoelastic from the subretinal space. The infusion is turned on and inspection of the intraocular situation can be carried out. If the desired position is not yet reached, a repositioning by gently pulling back the implant and again advancing it is possible. With the implant in its destination the scleral flap is sutured several times with Vicryl 7.0. The implant leaving the scleral flap is turned over and fixed with patches onto the sclera. The extraocular region of the flap and the visible foil are covered by a Gore Tex patch which was cut to the desired size. This patch is also fixed to the sclera. Its purpose is to minimize scaring and therefore to ease a removal of the implant after the implantation period. The loose part of the foil is buried in the fornix region without suturing it. Silicone oil is used as a tamponade medium.

7. Results

The feasibility of a transchoroidal implantation of retina implants was proven. All eleven transchoroidal subretinal implantations were carried out successfully. No adverse event occurred. All surgical maneuvers were in accordance with the originally planned procedure. The transfer of the critical sequences of the surgical steps from the situation in laboratory animals to humans turned out well. The parameters determined in animal models were extremely helpful in the human surgical situation. Unforeseen problems did not occur. The vulnerable electronic components were left undamaged during the surgery. This was repeatedly monitored in post explantation function tests. A step by step approach of the transchoroidal procedure is given in Figures 1*A* and 1*B*.

There are remarkable differences in the tissue of the RP patient which influence the surgery. It is merely possible to punch the retina with a 41G Teflon canula due to a increased rubber like resistance of the tissue. When injecting the subretinal fluid through this canula the bleb appears in a different, flatter, way than in a normal retina. The mechanical separation of the RP retina from the underlying pigment epithelium seems to be harder to achieve. A slightly increased resistance exists when advancing the guide foil. Incomplete penetration of the choroid with the implant results in a ping pong effect when advancing the foil. To avoid this, the presence of a clear sign of a complete penetration is mandatory. A clear sign of penetration into the subretinal space is when viscoelastic solution is emerging after puncture of the choroid. Due to the fact that visual control of the foil advancement in the penetration site is not possible, these indirect signs seem to be important. Retracting the scleral flap and carrying out the maneuver under visual control leads to unintended loss of viscoelastic solution and hinders pressurizing the eye again. The implantation process is rather dynamic and best carried out beginning in hypotony (infusion closed, scleral

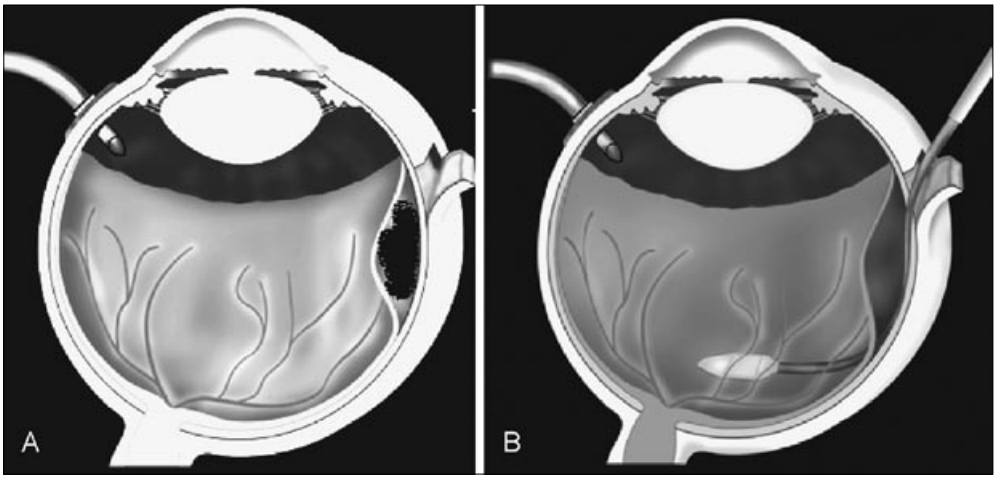

Fig.1 (*A*) Subretinal bleb containing viscoelastic solution and scleral flap before choroidal penetration. (*B*) Position of the implant after choroidal penetration and subretinal advancement (guide foil removed)

plugs removed) for the choroidal puncture and after slightly injecting the guide foil turning over the scleral flap temporally suturing it so that the advancing forces are tangential. After temporally suturing the flap, the eye can gently be repressurized. This seems to prevent the guide foil from running via falsa and rolling up in the originally created subretinal viscoelastic bleb.

8. Discussion

The transchoroidal access to the subretinal space in combination with a pars plana vitrectomy is a newly developed surgical procedure. Due to severe theoretic possible complications a lot of critical views were mentioned during the development period especially in the phase of the animal experiments. The chance of choroidal bleeding was discussed extensively. In this phase the complex implantation procedure was divided into single steps which have been optimized. The development of the bloodless choroidal puncture was well taken care of and radiodiathermy enabled optimal results. The optimized steps were combined again and adapted to each other. Thus a procedure resulted which could be transferred from the animal models to the human situation without adverse events. The feared disastrous choroidal bleeding did not appear in any of the 11 cases. To avoid uneventful penetration of the retina during the implantation process a guiding tool was developed. This tiny instrument protects the retina during the implantation of the chip and is of enormous importance for a successful implantation. The ideal performance of the material, the rigidity and the flexibility were determined empirically. The choice of adequate animal models to acquire this information was decisive to reach this goal. Minipigs turned out to be a proper model to develop this procedure.

With 11 surgically successful implantations out of 11 human implantations a manageable procedure is now available to implant electronic components of relevant size into the

subretinal space. The persistent connection of the subretinal space to the extraocular environment has been shown to be manageable via this foil implantation procedure. The stability and safety of this situation in the postoperative period has been proven and therefore an important step for a long lasting implantation has been made by developing this new surgical access to the eye. Other applications for this procedure seem possible but have not been examined so far.

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Elements – Continents

Approaches to Determinants of Environmental History and their Reifications

Leopoldina-Workshop
Deutsche Akademie der Naturforscher Leopoldina in Zusammenarbeit mit dem DFG-Graduiertenkolleg Interdisziplinäre Umweltgeschichte

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Zu den Gebieten, die zurzeit verstärktes Interesse finden, gehört die Umweltgeschichte. Der Band konzentriert sich auf Grundfragen des umwelthistorischen Diskurses durch Rückbesinnung auf elementare Mensch-Umwelt-Beziehungen durch zwei Annäherungen: „Elemente“ und „Kontinente“. Mit Hilfe dieses kleinen wie großen Maßstabes wurde der Bedeutung am Konkreten und im historischen Aufriss nachgegangen. Unter der Überschrift „Elemente“ werden Feuer, Wasser, Luft und Erde als unmittelbare, für das Leben determinierende Qualitäten, die sich im ökologischen Prozessgeschehen abbilden, analysiert. So wird etwa die Rolle der Feuerökologie am Beispiel mitteleuropäischer und nordamerikanischer Wälder behandelt oder dem Element Wasser und seinen Aggregatzuständen in der Bedeutung für die Geschichte der Niederlande nachgegangen. Hinzu kommt als weitere Dimension die Biosphäre. Die „Kontinente“ Afrika, Amerika, Asien, Australien und Europa bilden das thematische Äquivalent. Insbesondere werden hier die Auswirkungen der naturräumlichen Grundausstattung auf die wirtschaftliche und kulturelle Entwicklung thematisiert. Die Palette der Themen reicht dabei vom „europäischen Sonderweg“ bis zur chinesischen Umweltgeschichte. Darüber hinaus liefern Beiträge von Nachwuchswissenschaftlern einen Einblick in die Bandbreite laufender umwelthistorischer Projekte.

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Artificial Sight: Perspectives with an Epiretinal Stimulator

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With 3 Figures

Abstract

The implantation of electronic retina stimulators appears to provide an opportunity future chance to restore vision at least partially in patients with retinal degeneration. Such concepts are not new but due to the general technical progress it has become more likely that a functioning implant will become a commercial reality. Visual prostheses are generally integrated in the visual system both subretinally and epiretinally implants, while others may also be connected directly to the optic nerve or the visual cortex. The epiretinal approach is the most promising at the moment, but the challenge of appropriate modulation of the image information is unsolved thus far. This will be necessary to provide an interpretable visual information to the brain. The present article discusses an epiretinal strategy.

Zusammenfassung

Die Implantation von elektronischen Retinastimulatoren bietet eine Möglichkeit, in Zukunft das Sehvermögen von Patienten mit Retinadegeneration wenigstens teilweise wieder herzustellen. Entsprechende Konzepte sind zwar nicht neu, aber dank des allgemeinen technischen Fortschritts ist es wahrscheinlicher geworden, dass ein funktionierendes Implantat verfügbar wird. Sehprothesen werden im Allgemeinen als subretinale oder epiretinale Implantate in das visuelle System integriert, während andere auch direkt mit dem Sehnerv oder dem visuellen Kortex verbunden werden können. Das epiretinale Verfahren ist zurzeit noch die vielversprechendste Herangehensweise, aber die Herausforderung einer angemessenen Modulation der Bildinformation ist bisher noch nicht bewältigt. Das aber wäre notwendig, um dem Gehirn eine interpretierbare visuelle Information weiterzuleiten. Der vorliegende Beitrag diskutiert eine epiretinale Vorgehensweise.

1. Background

Since ophthalmology is able to cure cataract and infectious diseases, degenerative retinal disorders became the most common cause for blindness particularly in the industrialized world. Among elderly persons the most important cause is age related macular degeneration (AMD). Nearly 30 % of all people over 70 years suffer from AMD (Knauer and Pfeiffer 2006). Among younger patients hereditary retinal degenerations play a leading role. Though these diseases are much rarer than AMD, it is obvious that a sufferer's quality of

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life and future prospects are strongly impaired. Even though our understanding of degenerative retinal disorders has improved through fundamental research, therapeutic options remain very limited. High expectations are attributed to neuroprotective therapies or stem cell based tissue replacement. In addition to these strategies in the 1990s a systematic development of electronic visual prostheses began. This became even more promising following the success of cochlear implants. The following article summarizes the development of electronic devices for artificial vision and outlines the challenges that are yet to be met for a clinical use of visual prostheses.

2. Methods of Integration into the Visual System

The visual system from the retina to the visual cortex is a complex interconnected system of four neurons with three of them located in the retina. It is a convergent system. That means one neuron of the visual cortex is not directly related to one photoreceptor. The convergency exists already in the retina, where multiple photoreceptors are combined to one receptive field. Starting at the ganglion cells the central visual system has a retinotope functional structure. In general, an implantation of a visual prosthesis might be possible at each part of the visual system, but anatomical and physiological circumstances of the desired implantation area as well as the pathophysiology of the disease have to be considered.

Most currently favored stimulation sites are located either epi- or subretinally, but there are also promising projects on a direct stimulation of the optic nerve by a cuff electrode or some attempts to stimulate the visual cortex directly. The authors' own work is focused on an epiretinal strategy, which is the subject of this article. It has to be emphasized that other approaches also show promising results. This has been reviewed in context with the authors' own project recently (Zeitz et al. 2009).

3. Epiretinal Implants

Humayun, Weiland et al. demonstrated that light perception might be achieved by stimulation of the inner retinal layers in blind patients with retinitis pigmentosa (Humayun et al. 1994). They reported on threshold levels from 160 to 3200 $\mu C/cm^2$ eliciting phosphenes (Humayun et al. 1996). This was done with platinum electrodes, but stimulation levels exceed the safe range. Therefore modifications became necessary (Shah et al. 2007). Today the same working group has performed implantations in several patients with retinitis pigmentosa and showed a successful assistance in accomplishing simple visual tasks (Yanai et al. 2007).

While subretinal stimulators replace the photoreceptors directly and use the optic apparatus of the eye to pick up the image information, epiretinal systems obtain their image from an external camera. The challenge, as well as the potential, of epiretinal stimulation, is the computerized reprocessing of the camera signal. The ganglion cell information does not correspond with the cortex in a bitmap-like manner. Furthermore, it is likely that not only the ganglion cells, but also deeper retinal layers, particularly bipolar cells, are stimulated by epiretinal electrodes. This could mean that the stimulation effect is in-

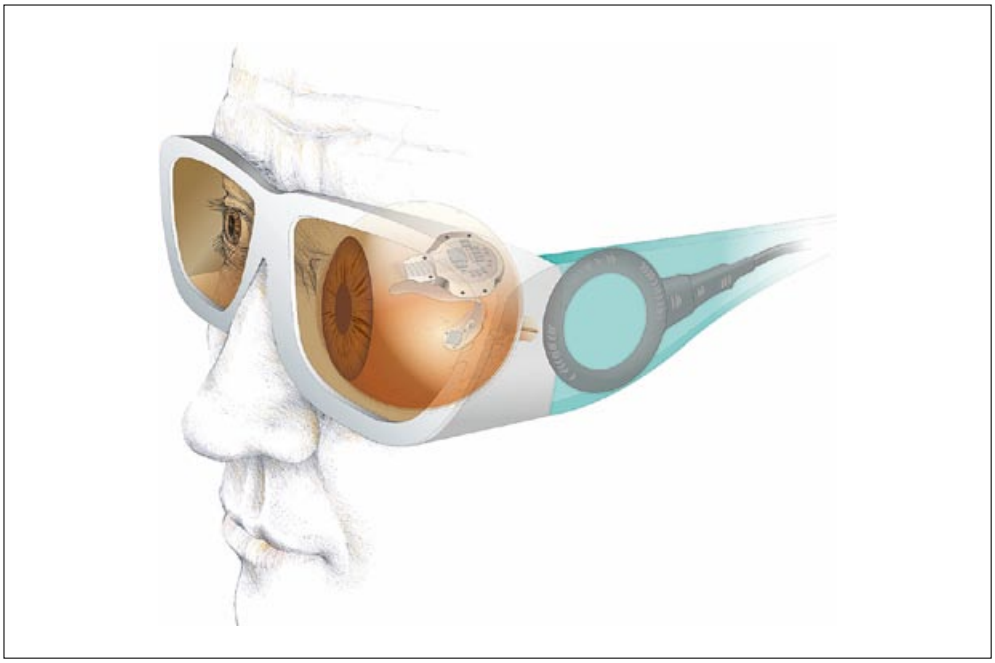

Fig. 1 The scheme illustrates the wireless energy supply of the implant by a specifically designed spectacle frame (© IMI Intelligent Medical Implants GmbH).

Fig. 2 The implant consists of an electrode array, which is connected to the control unit with a flexible foil conductor. The control unit is placed extraocularly sub-tenon (© IMI Intelligent Medical Implants GmbH).

dependent from a sub- or epiretinal stimulation localization. Recently, FRIED et al. (2008) showed a stimulation not only of ganglion cell somata, but also of distal ganglion cell axons by epiretinal electrodes.

ECKMILLER faced these problems of epiretinal stimulation with his concept of a learning Retina Implant (ECKMILLER 1997, ECKMILLER et al. 2005, ECKMILLER and BORBE 2008). A comparable system has been developed and improved by IMI Intelligent Medical Implants. Their device consists of an epiretinal stimulator that is attached to the retina with one retinal tack. A fully implantable processing unit is wirelessly addressed and inductively powered by a spectacle integrated camera and a HF-power transmitter. In addition to the completely intraorbital localization, the high electronic adaptability is a unique feature of this system. The pixel information of the captured image is not transmitted one-to-one to the electrode array, but individually processed by a so called "Ret-

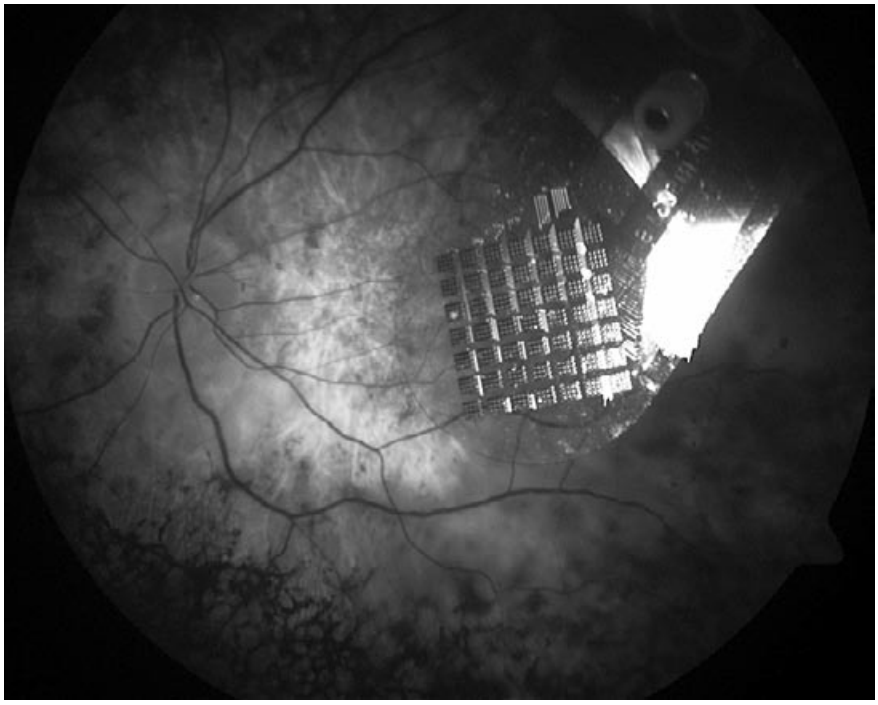

Fig. 3 The electrode array after implantation (© IMI Intelligent Medical Implants GmbH).

ina Encoder". The Retina Encoder can be individually adjusted to each patient. For example the stimulation parameters of a triangle are modified until the patient sees a triangle. This processing encoder bypasses the lack of knowledge of the exact connections in the retina underneath the electrodes. The parametrization of the Retina Encoder follows an iteration technique. According to recent studies less than 100 iterations are necessary for an individual adjustment. The electrodes of the IMI system are modified in a way that perceptions with threshold levels under 1 mC/cm^2 are already possible (Feucht et al. 2005). Clinical trials with the IMI device show no damage or alterations of the retina in OCT and FAG investigations over a long-term follow-up of up to 3 years after implantation in human retinitis pigmentosa patients (Keserü et al. 2008). Eliciting perceptions was also successful (Richard et al. 2008). Data transmission and power supply is completely wireless with the IMI system. Parts of the electronic are placed extraocularly under tenon's capsule and are connected with the electrode array via a transscleral tunnel (Keserü et al. 2008).

Prototypes of the device have been implanted in blind patients. In two patients the stimulation threshold and its course over time was studied extensively. The stimulation thresholds for the device were much lower than expected from previous studies and ranged on average below 30 nC. It was also shown that stimulation threshold is a dynamic measure in a certain range (Richard et al. 2009). The intelligent control of the device may compen-

sate for those fluctuations. Simultaneous stimulation of multiple electrodes revealed the ability of perception of simple geometric figures and a good ability for point-to-point discrimination.

4. Perspective

It is not proven, which approach to artificial vision is optimum. All different methods have advantages and disadvantages. The authors themselves are working on an epiretinal device with the advantage of standard vitreoretinal surgery techniques for the complex implantation procedure and relatively rare retinal and subretinal complications. Perhaps the functional integration of the visual prostheses in the neurophysiologic environment may be more important than the site of implantatio. More work is required before the final aim, i. e. to return reading capability to the patients, is met. In theory reading might be possible with an array of 60 electrodes (Sommerhalder et al. 2008). But this will only be possible, if the implant can produce a well interpretable signal for the brain. This will be the crucial point as microelectronic engineering and medical concepts are more advanced than neurobiologic research.

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Epiretinal Retinal Prosthesis

Peter WALTER (Aachen)

With 3 Figures

Abstract

It was demonstrated that electrical stimulation of the retina is a useful approach to specifically activate the visual cortex in animals. It was further shown that blind subjects suffering from retinitis pigmentosa (RP) had patterned light percepts when electrical current was applied to the retinal surface with microelectrode arrays placed on the retinal surface. Research groups and companies currently test implantable systems for electrical stimulation of the retina in blind patients suffering from RP in clinical trials. Preliminary results disclosed that the surgical procedures were well tolerated and that the patients had visual percepts possibly helping to improve the patient's mobility and performance under daily life conditions.

Zusammenfassung

Der Beitrag zeigt, dass die elektrische Stimulierung der Retina ein geeignetes Vorgehen ist, um den visuellen Kortex in Tieren anzuregen. Weiterhin konnte nachgewiesen werden, dass blinde Personen, die an Retinitis pigmentosa leiden, strukturierte Lichtwahrnehmungen hatten, wenn elektrischer Strom auf die Retinaoberfläche unter Verwendung von Mikroelektrodenspitzen, die in der Retinaoberfläche positioniert sind, appliziert wurde. Forschergruppen und Firmen erproben gegenwärtig in klinischen Versuchen Systeme für die elektrische Retinastimulierung an blinden Patienten, die an Retinitis pigmentosa erkrankt sind. Erste Ergebnisse zeigen, dass die Operationseingriffe gut vertragen wurden und die Probanden visuelle Wahrnehmungen hatten, die die Mobilität und Leistung des Patienten unter Alltagsbedingungen verbessern.

1. Introduction

Although significant progress has been made in the treatment of blindness-causing retinal diseases there are still conditions threatening patients with the loss of sight such as progressive photoreceptor dystrophies as in retinitis pigmentosa (RP).

In genetically homogenous diseases such as Lebers Congenital Amaurosis (LCA), which is associated with a RPE65 mutation, gene therapy is currently being investigated by several groups after it was shown that in a dog model of that disease a functional improvement was seen (ACLAND et al. 2001, BENNICELLI et al. 2008). However, retinal dystrophies are often genetically heterogenous and therefore the replacement of the gene may be difficult. In advanced cases of RP the vast majority of photoreceptors are lost and within the retina functional changes occur such as the migration of ganglion cells to more outer layers of the retina, the re-wiring of retinal neurons, the manifestation of axon and/or den-

drite conglomerates and new synapses. The retina in advanced cases of such dystrophies is not only a retina without photoreceptors. It is heavily reorganized and remodeled (Marc et al. 2003) bringing up considerable concerns regarding the effectiveness of gene therapy in end-stage RP. In the beginning of the 1990s several groups came up with ideas of bypassing the lost retinal functions by coupling technical implants to still functioning neurons of the visual system (Rizzo et al. 2001). These ideas were supported, and also motivated, by early results of functional electrostimulation of the visual cortex in blind subjects (Brindley 1970, Dobelle et al. 1974, Dobelle and Mladejovsky 1974). In general, it was discussed how implants should be designed for successful electrostimulation of the visual cortex, the optic nerve, or the retina.

2. The General Concept of an Epiretinal Retinal Prosthesis

The general concept of all retinal implants and more or less all visual prostheses is the idea that electrical stimulation will force retinal or other neurons in the visual system to change their membrane potential or to fire action potentials as if they have received input via the normal route. In retinal implants stimulating electrodes are implanted as close to the retina as possible either in an epiretinal approach onto the inner retinal surface where the electrodes are positioned close to ganglion cells or with a subretinal technique in the subretinal space where the electrodes are placed close to the postsynaptic cells of the outer retina. Usually biphasic pulses characterized by the duration of each phase, the amplitude, the duration of the inter-phase interval, and the repetition frequency are delivered at the electrodes. Thus each visual scene generates a data set of time and amplitude parameters for each pulse at each electrode – the spatiotemporal stimulation pattern. This data set together with the energy required for the implant has to be transferred to the implant.

Epiretinal Retinal Implants are complex systems usually consisting of an intraocular part carrying the stimulation electrodes and an extraocular part responsible for image acquisition, data processing and encoding, energy supply, and data transfer. The data transfer between the encoder unit and the stimulation array, as well as the energy supply of the intraocular part, can be managed either by cable connections or wirelessly. In the EPI-RET 3 system (Figs. 1, 2) both energy as well as data are transmitted via an inductive link without any cable connection from a transmitter unit mounted in front of the eye to the receiver part embedded into an artificial intraocular lens replacing the natural lens or a previously implanted artificial lens (Mokwa et al. 2008).

In the Intelligent Medical Implant (IMI) system the energy is provided by an inductive link between an antenna placed outside the eye and an episcleral receiver underneath the conjunctiva. A transscleral cable connection provides the energy from this external receiver to the intraocular part. The data stream is provided by an infrared optical link between an external IR-LED and an IR sensitive photodiode placed close to the stimulating epiretinal electrodes. The stimulation microchip is also placed in the episcleral part and consists mainly of a 232 channel stimulus ASIC with a size of 22 mm^2 (Ortmanns et al. 2007, Feucht et al. 2005).

In the Second Sight's ARGUS system energy and data are provided with cable connections from a receiver inserted underneath the skin in the earlobe area comparable to

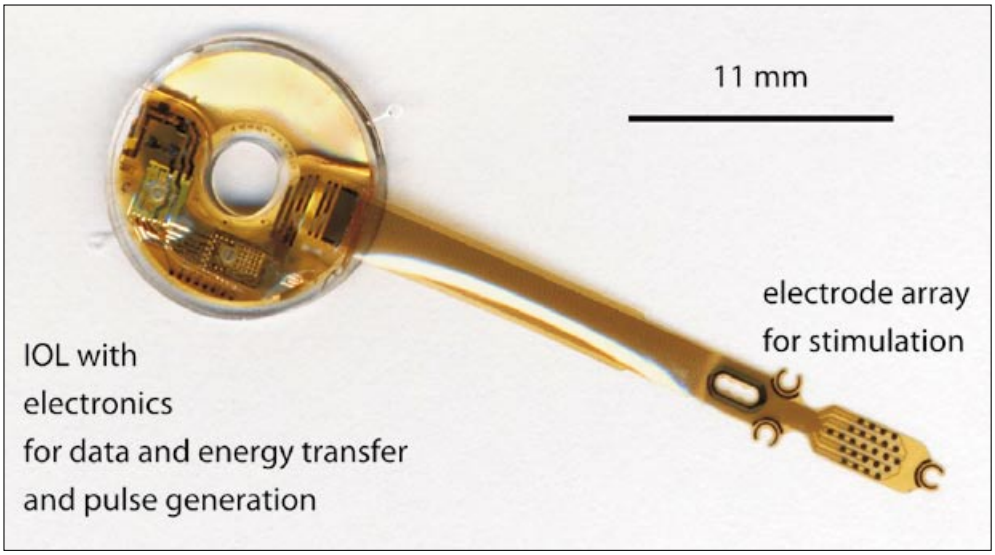

Fig. 1 Example of a complex epiretinal prosthesis (EPI-RET 3) with electronic circuits for data and energy transfer as well as for generating stimulation pulses for each electrode encapsulated in an artificial intraocular lens and the stimulator array with 25 electrodes.

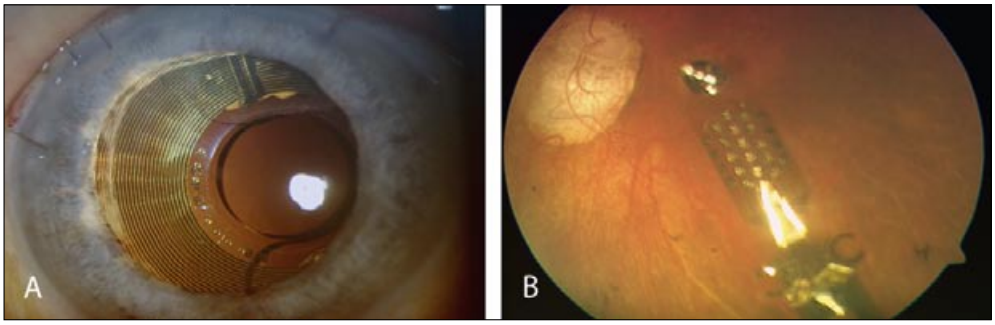

Fig. 2 (*A*): Anterior segment four weeks after implantation of the EPI-RET 3 system. (*B*): Fundus with the stimulator of the EPI-RET 3 system four weeks after implantation. No signs of adverse events.

cochlea implants. The data and energy transfer system is comparable to cochlea implant systems (Humayun et al. 2003). The IMI and the Second Sight systems are using transscleral cable connections similar to transscleral tubes used in glaucoma drainage devices.

3. Preclinical Studies

3.1 Material Toxicity

According to the prerequisites of regulatory authorities a number of preclinical tests have to be done before such implants are allowed to be implanted in human beings, either as investigational devices or as approved medical products. Any cytotoxicity of the implant has

to be excluded (Fig. 3). Therefore, L292 cells are usually incubated with the active implant and the viability of these cells is tested. It has to be excluded that the materials used in the implant such as polyimide or silicone, as well as the energy dissipated from the implant, is cytotoxic. One of the major issues concerning materials is the long-term hermetic seal of the electronics and their encapsulation in a biocompatible material. Usually Polydimethyl-siloxane is used, but additional insulation materials such as Parylene C may be helpful. Encapsulation can also help to facilitate the integration of the implant into the tissue. Several encapsulation measures and coatings have been tested, and it was demonstrated for subretinal devices that Parylene C and Iridium Oxide are well tolerated whereas Silicon Oxide induced the formation of a gliotic seal around the implant. It seemed that also the geometry of the device is an important factor for either integration or fibrotic encapsulation in the subretinal space (Butterwick et al. 2009). Energy dissipation was measured for cortical implants. It was described that under *in-vivo* conditions the tissue temperature will increase to 0.05 °C/mW when using the Utah multielectrode array (Kim et al. 2007). Temperature effects on the retina were studied by Piyathaisere and colleagues. They found no changes in the retina when the preretinal temperature was 2 degrees or the vitreous temperature was 5 degrees higher than normal. Therefore they suggested placing the electronics away from the retina (Piyathaisere et al. 2003).

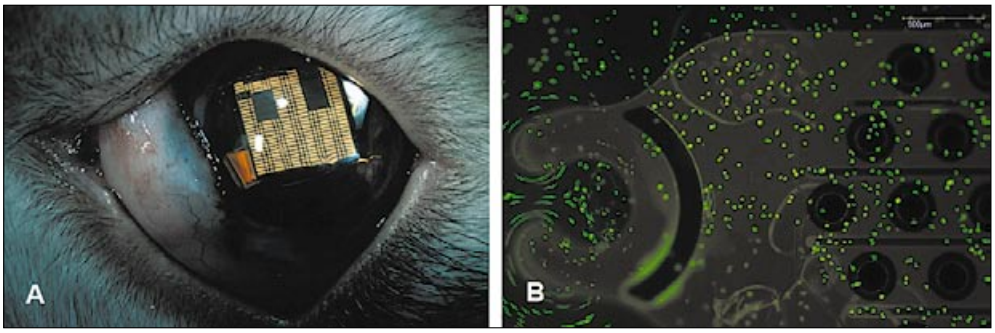

Fig. 3 (*A*) Preclinical studies to exclude material toxicity of epiretinal devices. Polydimethyl-Siloxane carrier with encapsulated silicone oxide microarrays implanted in the anterior chamber of a rabbit's eye six months after implantation with no signs of any adverse reaction. (*B*) Preclinical studies to exclude material toxicity of epiretinal devices. L929 cells grown on the surface of an epiretinal stimulator. Vital cells are stained green, dead cells are in red.

3.2 Development of Surgical Procedures

The key issue in the epiretinal approaches was the fixation of the electrode array onto the retinal surface. As a prerequisite to achieve a tight connection between the electrodes and the target neurons, the vitreous has to be removed completely. This can be achieved by a standard vitrectomy with detachment of the posterior vitreous cortex and removal of any epiretinal tissue and the inner limiting membrane. Researchers from the EPI-RET consortium and from Second Sight showed independently and simultaneously that the fixation of electrode arrays on the retinal surface is safe and stable when using retinal tacks (Majji et al. 1999, Walter et al. 1999). Tack fixation was tested in rabbits, dogs, pigs, and cats. Titanium tacks were used pressing the electrode array onto the retina. The implant has several holes for placing the tacks and the tack

itself is anchored in the sclera. Such a mechanical fixation, although very stable, may account for problems when removing the implant. Such tacks may also cause epiretinal gliosis. Therefore, researchers are looking for alternative techniques for the fixation of such implants, e. g. the use of glues or special coating such as pNiPAM (Tunc et al. 2007, 2008).

3.3 Functional Tests in Animal Experiments – Proof of Principle

All groups performed functional tests both *in vitro* with retinal explants, and in animals to demonstrate that electrical stimulation of the retina, or elsewhere in the visual pathway, can induce local activation within the visual cortex. To demonstrate cortical activity, EEP recordings were used in visual prosthesis research as a semiquantitative tool (Walter and Heimann 2000, Chowdhury et al. 2008, Siu and Morley 2008 a, b, Zhou et al. 2008, Tokuda et al. 2007, Shah et al. 2006, Fang et al. 2006, and Pardue et al. 2001). Much more detailed responses were obtained by recording field potentials from the visual cortex with penetrating microelectrodes or with surface multichannel electrode arrays. Eckhorn and his group showed that both – epiretinal or subretinal stimulation of the retina – may lead to percepts with a spatial resolution of 1° and to a temporal resolution of 25 frames per second. These tests were performed in healthy cats (Eckhorn et al. 2006, Chelvanayagam et al. 2008). With optical imaging metabolic changes can be detected in the primary visual cortex of the cat. With this technique it was shown that epiretinal stimulation activates a stimulus pattern in the visual cortex resembling the picture of ocular domain columns. The authors found that the activation of the visual cortex is strictly related to the retinal area of stimulation confirming that retinotopically correct activations were induced with this technique. The currents necessary to induce activation differ considerably from electrode to electrode. Factors for that variability may be the distance between each electrode and the retina, and/or the number, type, and density of ganglion cells around each individual electrode. However, in these healthy retinas under acute conditions stimulation was successful with stimulus currents of 4 μA inducing a field potential recorded from the optic tract comparable to the response obtained after visual stimulation with a bright light flash (Walter et al. 2005).

3.4 Acute Trials in Humans

Humayun and coworkers performed the first test in humans demonstrating that even in blind patients with a long history of retinal degeneration phosphenes can be elicited when the inner retinal surface is stimulated electrically. This finding could be confirmed by researchers from the IMI group and from the Nidek Group in Japan. It seemed that in patients with a very long history of blindness the stimulation efficacy is worse than in patients with a shorter period of blindness. Prognostic parameters to identify which patient is a good candidate for electrical stimulation have not been identified so far (Humayun et al. 1996, Hornig, et al. 2005, Fujikado et al. 2007).

3.5 Clinical Trials for Chronic Implantation of Epiretinal Implants

All three groups working on epiretinal implants started chronic clinical trials in which they implanted their prototype in blind patients suffering from RP. The Second Sight ARGUS trial was the first trial from which results were reported. They used a 16 electrode array

mounted on a 4 × 4 matrix. Perceptual thresholds were recorded by asking the patients about seeing light spots or anything with respect to stimulus currents. Typically the perceptual thresholds varied from electrode to electrode and from individual to individual. The main factor influencing stimulus threshold is the distance between the electrode and the retinal surface. A close contact between the electrode and the retina is the most important parameter to achieve a low threshold. Patients using the ARGUS system together with a camera interface in everyday conditions report some improvement in daily life performance (Yanai et al. 2007, de Balthasar et al. 2008, Caspi et al. 2009).

In the EPI-RET 3 trial stimulus thresholds given in charge density were on average 8.1 mC/cm^2. Patients reported the seeing of spots of lights, typically white or yellow in color, when single electrodes are activated. When lines of electrodes are activated they report lines or arcs. Discriminating two spots seemed to be more difficult than discriminating the orientation of lines (Roessler et al. 2009).

IMI has performed an initial clinical trial in three patients. It was reported that the implantation was safe and no side effects occurred. Stimulation data were given in terms of charge in one of the patients ranging from 8 to 36 nC (Keserue et al. 2009, Richard et al. 2009).

In all three epiretinal trials it was reported that the surgical procedure could be performed without major complications. Postoperatively, some inflammatory responses were observed which were successfully treated with steroids and antibiotics.

4. Perspective

The development of a visual prosthesis for the blind is a huge interdisciplinary effort. Compared to the mid-1990s when most of the projects were initiated and many retina experts doubted that such an approach could be successful, now the same experts conclude that the concept of retinal implants to restore sight in blind subjects is at least a possible option in the fight against blindness.

Currently, clinical trials are underway by three companies with epiretinal implants. It is not clear which company and which approach will have the best results. It is possible, and preliminary data points in that direction, that all companies will have more or less the same results because the major limiting factor is the retina itself with its significant remodeling processes associated with the chronic degeneration process.

Today it is not clear if retinal implants will be superior to molecular or genetic approaches. Maybe genetic or molecular approaches will be important in patients with a very short history of disease. And maybe the treatment should start in childhood or maybe even before birth, raising considerable ethical issues. It can be assumed that the indication for technical implants will be the advanced degeneration in which most of the photoreceptors are already gone. These cases will possibly not benefit from gene therapy.

Will retinal implants be superior to cortical implants which are also under development? This is not known. The advantage of cortical implants is that many more diseases may be treated by cortical stimulation, such as blindness from glaucoma. However, the spatial organization of the retina is very well known and therefore the stimulation paradigms can be more easily programmed. And will epiretinal implants be more successful than subretinal implants? This is also an open question. Both approaches have their pros

and cons. The next important steps in the development of epiretinal implants will be the development of large area microelectrode arrays to activate a larger area of the retina providing a large visual field, and to find new modalities in implant fixation such as coatings or cellular fixation. Innovative electrode materials will help to further reduce the energy necessary to activate cells in the retina. In a few years much more data will be collected and patients will already benefit from such early systems. Restoring light perception, hand movements, and localization of obstacles in one's surroundings will be achieved as a first step. Reading and face recognition will be the challenge for the next 10–15 years. But similar to the development of cochlea implants, retinal implants will have a place in the treatment options for RP or other outer retinal causes for blindness.

One can speculate that the pure technological devices in the future will be enhanced by cellular components such as cells producing neuroprotective or antiapoptotic signals. Such biohybrid implants combining pure electrical stimulation with features for biochemical interference with the degeneration process may be a goal for the next 20 years.

However, there will certainly be an ethical issue in retinal or cortical implants: Shall we accept that technical systems may have direct access to the central nervous system of humans? Isn't there a potential risk for the misuse of such systems to manipulate central nervous system functions by certain groups? It is necessary, and I would strongly recommend, that this discussion be started with patients, patient organizations, and specialists in the ethics of technology and medicine at a very early stage of development.

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350 Jahre Leopoldina – Anspruch und Wirklichkeit

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