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Clinical implications of novel diagnostic and surgical methods in the intraocular surgery of pediatric and adult patients

(Klinische Implikationen neuartiger diagnostischer und chirurgischer Methoden in der intraokularen Chirurgie von pädiatrischen und erwachsenen Patienten)

Habilitation thesis
to obtain the venia legendi in Ophthalmology
at the Faculty of Medicine of the Justus Liebig University Giessen

presented by
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Giessen 2021

to my parents, Marta and Mychailo

CONTENT:

ABBREVIATIONS:

ACCC	Anterior continuous curvilinear capsulorhexis
AI	Artificial intelligence
AIIRP	Argus II Retinal Prosthesis System
AL	Axial length
BIL	Bag-in-the-lens
BSS	Balanced salt solution
ERM	Epiretinal membrane
HCMD	Hydraulic centripetal macular displacement technique
ILM	Internal limiting membrane
IILMFT	Inverted internal limiting membrane flap technique
iOCT	Intraoperative optical coherence tomography
IOL	Intraocular lens
IOP	Intraocular pressure
iSD-OCT	Intraoperative spectral domain optical coherence tomography
IVI	Intravitreal injection
LIB	Lens-in-the-bag
MH	Macular hole
OCT	Optical coherence tomography
PC	Posterior capsule
PCCC	Posterior continuous curvilinear capsulorhexis
PCO	Posterior capsule opacification
PPV	Pars plana vitrectomy
RD	Retinal detachment
ROP	Retinopathy of prematurity
SB	Scleral buckling
TMH	Traumatic macular hole
UKGM	University Hospital Giessen and Marburg GmbH
VAR	Visual axis reopacification
WAVS	Wide-angle non-contact viewing systems

1. Introduction

Understanding of implication of novel diagnostic and surgical techniques in the intraocular surgery in patients of different age groups and its importance requires an overview into the major anatomic features of the eye and available surgical approaches. The following section is dedicated to the anatomy of the eye with regard to the surgical techniques, development of intraocular surgery and surgical techniques on anterior and posterior eye segment.

1.1. Applied anatomy for intraocular surgery

Ophthalmic microsurgery is indispensably linked to the surgical anatomy and ophthalmic pathology of the eye (Naumann et al.1997, Remington 2005). Without a deep understanding of the different specific features of the surgery in general, any surgical intervention can end with adverse consequences for the patient (Daley et al. 1997, Dimick et al. 2010).

The main goals of an eye surgeon are to recognize the failure of the diseased eye with its particular pathophysiologic features and to restore the anatomy and function of the eye segments, or to bring them to the best possible condition. Accurate preoperative identification of the disease with knowledge about its natural course allows for choosing an adequate and optimal surgical solution.

In this chapter, the anatomy of the eye will be discussed in order to provide a basis to better understand the presented studies of the cumulative habilitation thesis. A separate attention will be payed to the anatomy of the lens, vitreous body and central retinal area, the macula.

Anatomy of the eye

The eye consists of three concentrically located layers of tissue complexes that enclose the transparent and clear optic media (Figure 1) (Forrester et al. 2002). The most external layer comprises the corneo-scleral envelope, which contains a completely transparent cornea and a white and solid sclera with an approximate square ratio of 1/6 to 5/6, respectively (Adenis and Morax 1998). The middle layer, which is called uvea, includes the choroid, ciliary body and the iris. All these structures are highly vascularized and accomplish a nutrition function for the surrounding tissue. In addition, the iris forms the pupil, through which the light reaches the posterior part of the eye. The third and most internal layer of the eye consist of a photosensitive structure - the retina, which facilitates initial perception, processing and transfer of visual information through photoreceptors and downstream connected neurons. The central area of the retina, the macula, containing the fovea, is responsible for visual fixation and accomplishes the function of central vision (Garner and Klintworth 1994).

An important aspect for any surgeon is the division of the eye into two segments: anterior and posterior segment (Figure 1, dashed line). Anterior segment begins at the anterior surface of the cornea and encloses all intraocular structures up till the posterior surface of the lens. Posterior segment of the eye includes all structures behind the lens, including vitreous body, retina and optic nerve head (Hart 1992, Warwick 1976).

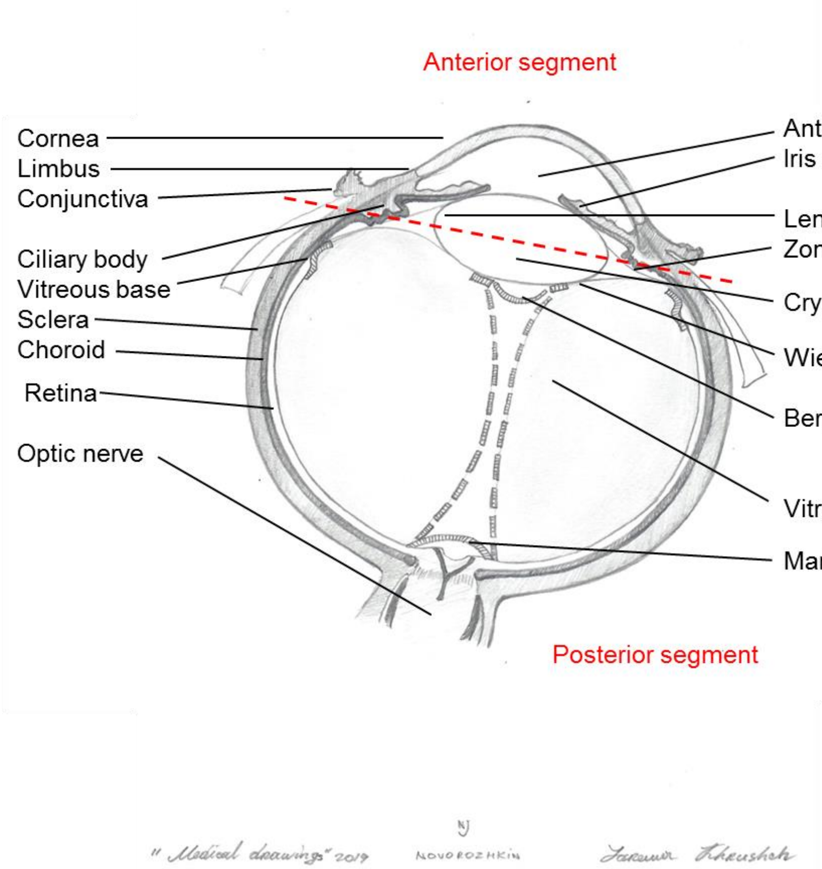

Figure 1. Schematic drawing of the human eye. *The red dashed line divides the eye into anterior and posterior segment (explanation in text) (Created by J. Khrushch).*

Anterior segment of the eye

The limbus delineates the junction between the cornea and sclera, and serves as a very important orientation landmark at the ocular surface (Figure 1) (Hart 1992). Almost all distance measurements in the posterior eye segment surgery or extraocular eye muscle surgery are being performed from the limbus (Van Buskirk 1989).

The optic system of the eye, namely its dioptric apparatus, consists of the tear film, cornea, anterior aqueous humor, lens and vitreous body. Among these structures the cornea and the crystalline lens are frequent targets for surgical manipulation (Hogan and Alvarado 1971). In anterior segment surgery, the cornea is perforated at the periphery and this wound serves as the entrance for intraocular instruments to reach intraocular structures.

The crystalline lens is the most significant refractive element of the optic system (Von Helmholtz 1962, Patterson and Delamere 1992, Bassnett et al. 2011), and surgical interventions at the crystalline lens belong to the most frequently performed surgeries in ophthalmology (Hogan and Alvarado 1971). Most often, different forms of lens opacification, called cataract, are the treatment targets. For this reason, understanding the lens anatomy in different age periods is crucial for every eye surgeon dealing with cataract patients.

The lens derives from the surface ectoderm with the optic vesicle, and plays an important role in regulatory processes during the prenatal and early postnatal development of the anterior eye segment (Kuszak and Brown 1994). Hence, the lens appeared to be very sensitive to the different kinds of embryonic developmental abnormalities, which can result in lens opacification (Kuwabara 1975). Development of the lens is determined by a complex regulation of the transcriptional network within the lens epithelial cells (Clark 1994, Lovicu and McAvoy 2005). Consequently, dysregulation of gene expression profile during the development process is a typical pathogenetic feature in hereditary congenital cataract (Shiels and Hejtmancik 2013, Cvekl et al. 2004). However, genetic factors are not the only causes of cataract, and further etiologic factors will be discussed in a subsequent chapter. During its normal growth, the lens loses its blood supply and innervation, and aqueous humor and vitreous body become responsible for lens nutrition and metabolism.

Lens anatomy and physiology facilitate its main functions: to maintain its own clarity, to refract the light beams and to provide the accommodation (Benedek 1983). Crystalline lens consists of the capsule, which envelopes lens epithelial cells, the cortex and the nucleus (Figure 2).

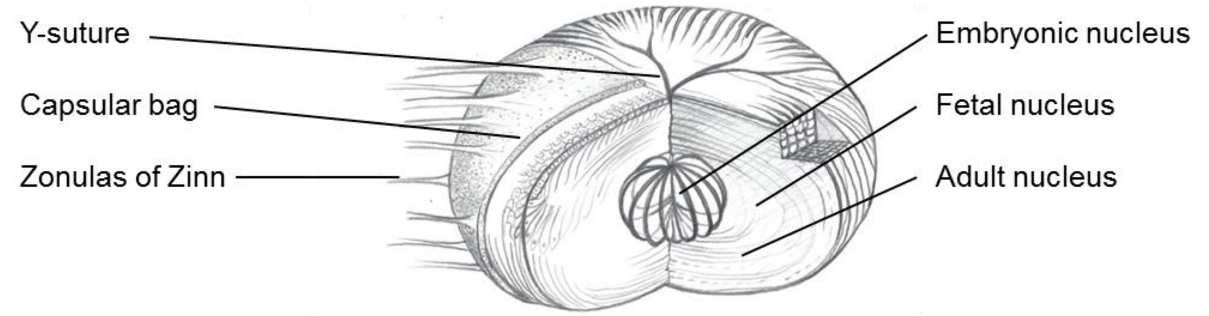

Figure 2. Structure of the lens. *Y-suture that is formed by lens fibers is situated at the anterior and posterior poles of the lens. The lens includes the following layers from the core to the surface: embryonic nucleus, fetal nucleus, adult nucleus, cortex and lens capsule (Created by J. Khrushch).*

The nucleus in adults consists of the three parts: embryonic, fetal and adult nucleus (Assia and Apple 1992 a, b) (Figure 2, 3). The lens is positioned at its place by thin but strong fibers - zonulas of Zinn, which are inserted into the anterior, equatorial and posterior part of the lens capsule and are attached to the pars plicata of the ciliary body (Assia et al. 1991) (Figure 2).

The zonular fibers belong to the suspension apparatus of the lens and have a diameter of 5-30 µm. Lens epithelial cells possess high mitotic activity and integrate into the lens fibers during their migration towards the periphery. Continuous crowding of the lens fibers and displacement of the older fibers to the center of the lens induce formation of the dense but still transparent embryonic, fetal and adult nucleus (Augusteyn 2007). The lens capsule is formed by biologic elements, which are secreted by lens epithelial cells, and serves as a basal membrane for the lens epithelium. It is composed mostly of collagen type IV (Berman 1994) and appears to be elastic, transparent and homogenous. In adults, the thickness of the capsule is 17-23 µm in the periphery and 4 - 5 µm in its central part. In contrast, in children, the lens capsule is much thinner and less elastic and contains the embryonic and fetal nucleus, but not the adult one.

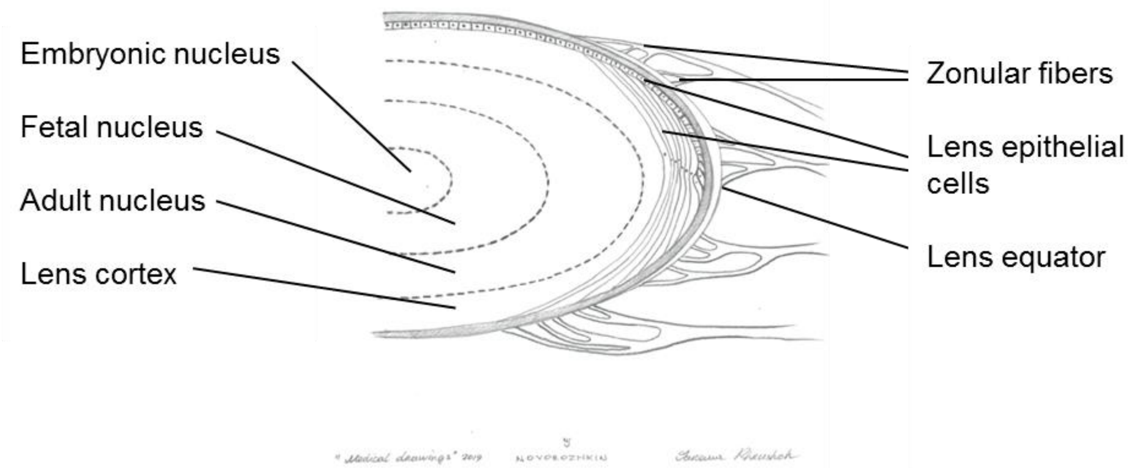

Figure 3. Schematic illustration of the adult lens. *Depicted are the nuclear zones, cortical zones and zonular fiber attachment relatively to the lens capsule (Created by J. Khrushch).*

Posterior segment of the eye

The vitreous body is the optic medium located behind the lens. It slightly refracts the light, similarly to water, and does not possess accommodative properties (Hart 1992, Sebag 2014) (Figure 1). However, almost every surgery on the posterior eye segment is associated with removal of the vitreous body in order to release vitreoretinal traction and to facilitate the access to the retina. The vitreous body fills out almost 2/3 of the volume of the eyeball. It is formed by the transparent gel of hyaluronic acid, which contains up to 98% of water, and is penetrated by fine embryonic fibrils of collagen. The strongest vitreoretinal attachments exist in the area of the vitreous base (periphery of the retina and ciliary body), at the optic disc and in macular area (Figure 1). Wieger's ligament demarcates a concentric attachment of the anterior vitreous to the posterior lens capsule, and forms a retrolental Berger's space that in healthy conditions is free from vitreous adhesion (Figure 1). Similarly, at the posterior pole, a Martegiani's ring delineates the attachment of the vitreous to the optic nerve head. The vitreous body undergoes aging with loss of its structure and can be naturally detached from the retina with the risk of retinal tear formation.

An outgrowth of the brain, the optic cup, creates the scaffold for the development of the retina (Warwick 1976). The outer wall of the optic cup differentiates into the retinal pigment epithelial (RPE) layer, while the inner wall becomes the neural part of the retina. The latter contains light-sensitive photoreceptors (rods and cones) and the second (bipolar cells, horizontal cells, amarcrine cells) and third (ganglion cells) neurons of the visual pathway (Hart 1992). The separate origin of retina and RPE explains why retinal detachment usually develops with the splitting between RPE and photoreceptors of the retina. The extension of the retina is limited by the ora serata anteriorly (junction with pars plana of the ciliary body) and the optic nerve head posteriorly (Schachat 2018). The total surface square of the retina in adults is approximately 266 mm^2 (in healthy emmetropic eye), with maximal thickness of 560 µm near the optic nerve head and 100 µm in the periphery. The macula with its central area, fovea centralis, is responsible for high visual acuity and color vision (Figure 4).

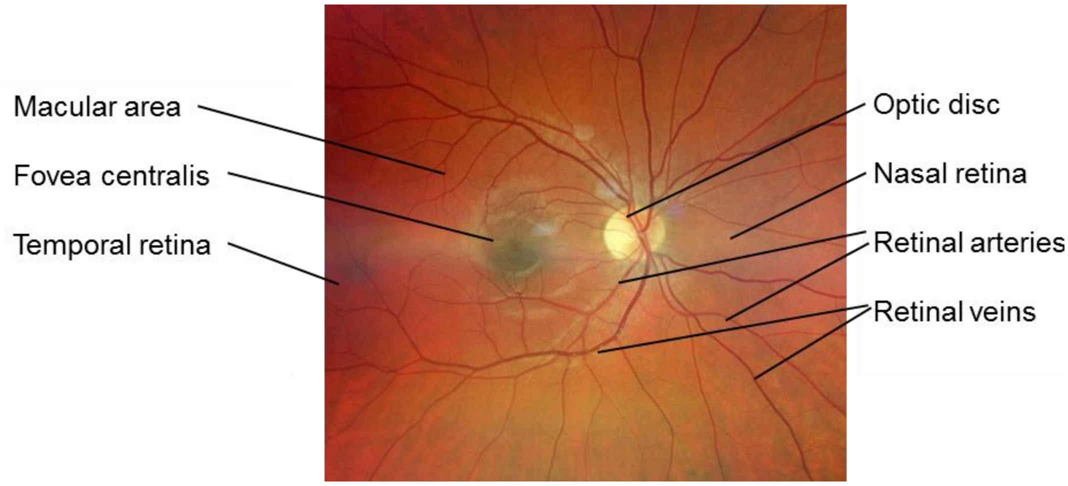

Figure 4. Fundus photography of the human retina in adult eye (right eye). *Different anatomic structures can be identified. Among them the optic disc, where the axons of ganglion cells leave the retina, the macula area, which is slightly pigmented, and the fovea centralis, the spot where humans possess highest visual acuity and color vision. (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

The retina consists of 10 layers (Figure 5), which can be identified on histologic slides. A huge increase in the knowledge about the in vivo morphology of the retina was observed when a new technology revolutionized ophthalmology about 15 years ago: optical coherence tomography (OCT) (Huang et al. 1991, Fercher et al. 2003). This imaging technique, comparable to an ultrasound B mode, but created by light, allows to view and assess the morphology of the retina in vivo with high spatial resolution (3-4 µm). For example, it allows to describe the foveal depression at the center of the fovea, where the inner retinal layers have moved to the side, thus allowing the light to reach the photoreceptor outer segments directly (Figure 5, 6 A) (Yaqoob at al. 2005).

Similarly, the use of the OCT allows assessing the morphology of the optic cup, which is an important diagnostic parameter in a variety of different ocular diseases (Figure 6 B). The underlying choroid facilitates the nutrition of the outer retinal layers, while the retinal vessels deliver the nutrition to the inner retina (Yaqoob at al. 2005, Fujimoto et al. 2000).

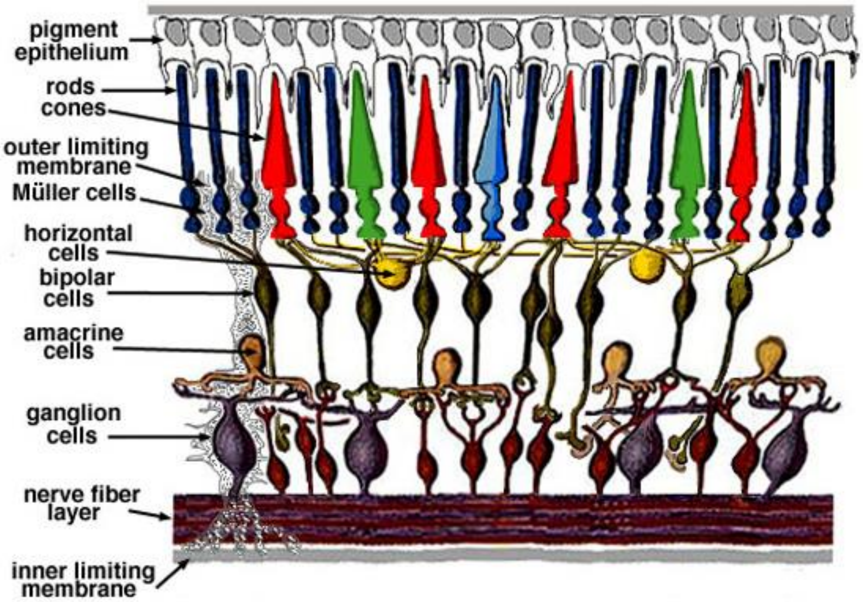

Figure 5. Simple diagram of the organization of the retina (webvision.edu, open access).

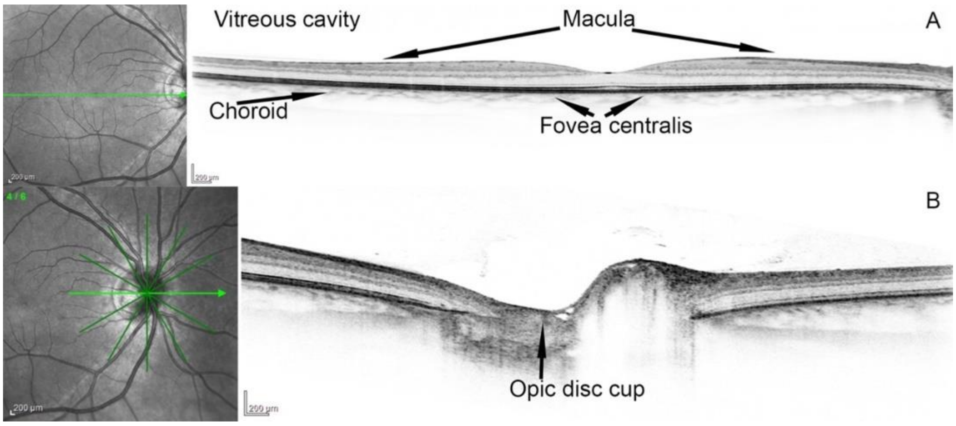

Figure 6. Spectral domain optical coherence tomography of the macula (A) and optic nerve (B) in the healthy eye (right eye). *The foveal depression can be seen in (A), where the inner part of the retina moves to the side, thus allowing direct exposure of the photoreceptors to the light. (SPECTRALIS OCT, Heidelberg Engineering, Heidelberg, Germany) (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

1.2. Surgical approaches for intraocular surgery

1.2.1. Development of intraocular surgery

Intraocular surgery has developed into the microsurgery field after the introduction of the operating microscopes, which enabled the performance of very precise microsurgical maneuvers within the limited surgical field (Machemer and Parel 1978). The microscopic approach with magnification up till 40 folds facilitates more precise control during surgical manipulations and clear identification of the pathologic areas that are adjacent to healthy tissues (Figure 7).

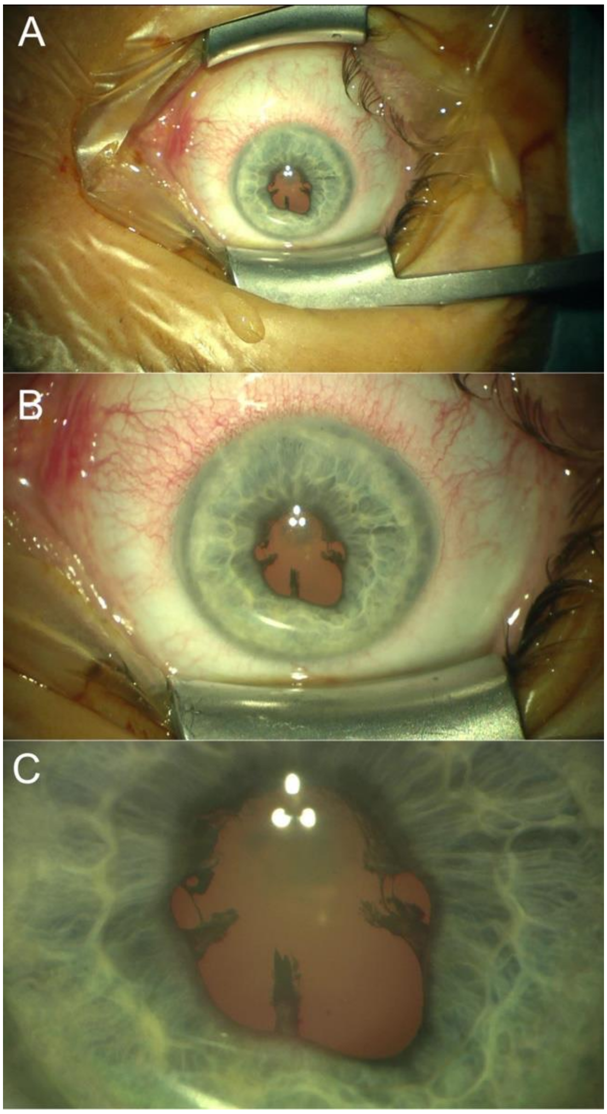

Figure 7. Imaging of an eye with posterior synechia and complicated cataract recorded with minimal (A), moderate (B) and highest (C) magnification (microscope OPMI LUMERA 700, Zeiss Meditech, Oberkochen, Germany). *Motorized zoom system with zoom ratio 1:6 and magnification factor 0.4x-2.4x allows for detailed imaging of the finest intraocular tissues of anterior eye segment (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

In this section the development of most important surgical innovations will be discussed with regard to cataract and vitreoretinal surgery. The most revolutionary innovations in anterior and posterior eye segment surgery are presented in Table 1 and Table 2, respectively.

Table 1. Development of the surgery of anterior eye segment.

Name of the author	**Year and type of innovation**
von Graefe, Germany	1856 - Iridectomy for angle closure glaucoma
Critchett, UK	1858 – Principle of filtrating surgery for glaucoma treatment
Ridley, UK	1949 – First implantation of a lens implant made of polymethylmethacrylate (PMMA) after extracapsular cataract extraction
Harms, Germany	1955 – Introduction of operating microscope and microinstruments for eye surgery
Kelman, USA	1965 – Ultrasound phacoemulsification for cataract extraction
Fankhauser, Switzerland **Aron-Rosa, France**	1975 - First YAG-laser iridotomy and capsulotomy
Balazs, USA	1979 - Introduction of viscoelastic materials to stabilize anterior chamber
Buratto, Italy	1990's - Minimally invasive cataract surgery
Ahmed, USA	2000's - Minimally invasive glaucoma surgery

New technologies and operating systems

Over the last three decades, technological developments in anterior and posterior eye segment surgery facilitated safe and highly controlled performance of the standard surgical procedures, such as cataract, glaucoma and retina surgeries. Through the use of modern operating cataract and vitrectomy machines during anterior and posterior segment surgery, the intrasurgical fluctuations of the intraocular pressure, which increase the risks of complications, are not relevant anymore (Alio et al. 2004, Alio et al. 2006). Modern surgical instruments and systems secure the tightness of the surgical entrances and wounds, maintaining intraocular pressure in its physiologic range. Consequently, in cataract surgery, the risk of intraocular hypotension and anterior chamber instability was considerably reduced (Kelman 1967, Kelman 1974). Furthermore, the use of modern viscoelastic liquid materials with different cohesive properties allows for protecting the corneal endothelial cells and supporting of anterior chamber stability during all steps of the cataract surgery.

Table 2. Development of the surgery of vitreoretinal disorders.

Name of the author	Year and type of innovation
Gonin, Switzerland	1920's – Reattachment of the retina through the perforation of the eyeball with Paquelin's thermocautery on the area of retinal hole with incarceration of its edges by withdrawal of the needle
Custodis, Germany	1930's - Scleral buckling procedure
Meyer-Schwickerath, Germany	1949 –„Light surgery" for retinal detachment
Schepens, USA Fison, UK	1950's - Binocular indirect ophthalmoscope for visualization of the retina
Lincoff, USA Bietti, Italy	1970's - Cryoretinopexy
Cibis, USA	1970 – Silicon oil endotamponade
Machemer and Parel, USA	1970's – 20-gauge pars plana vitrectomy
Spitznas, Germany	1987 - Wide field non-contact visualization systems
Chang, USA	1990's – Introduction of perfluorocarbon heavy liquids to stabilize the retina during the surgery
Adamis, USA	1996 – First report about anti-VEGF therapy for ischemia associated eye diseases
Fujii, Japan	2001 - Small-gauge minimally invasive vitreoretinal surgery
Abulo and Charles, UK	2009 - Valved trocars to eliminate the sudden intraoperative ocular hypotony
Binder, Austria	2009 – Microscope integrated intraoperative OCT system
Chaves de Oliveira, Canada	2010's - High speed vitrectors for vitreous removal
Rodrigues, Brazil	2010's – „Chromovitrectomy"
Sakaguchi and Oshima, Japan	2012 - Chandelier assisted vitrectomy with bimanual technique
Eckardt, Germany	2014 – Heads-up 3D ocular surgery

Due to modern innovations, a standard cataract surgery has been transformed into the ambulatory type of surgery with very low risk of complications (Alio 2006, Kahraman et al. 2007, Soscia et al. 2002). Introduction of the acrylic foldable intraocular lenses (IOL), which can be implanted through a small incision (1.8-2.8 mm), decreased the need of suturing the incisions, as the wounds are created in self-sealing manner.

Similarly, pars plana vitrectomy (PPV), which was introduced in the early 1970s, became a much safer procedure (Machemer et al. 1971, Machemer et al. 1972). This was possible due to improvements of the three-port vitrectomy with automated control of fluidic circulation, vitrector/cutter performance, and better delivery of the illumination and laser energy. The use of the state of the art highly purified vitreous substitutes enabled the surgery of complicated cases with better postoperative visual and anatomical outcomes. In modern vitrectomy systems, the vitrector probes, which possess a double function of cutting and aspiration, can perform removal of the vitreous body with the speed of up two 7.500-16.000 cuts per minute (cpm) (initial cutting speed was 200 cpm) (Mitsui et al. 2016). The improved duty-cycle, the proportion of a single cutting cycle during which the vitrectomy port is opened, together with high cutting speed facilitates an optimal, exceptionally controlled and fast removal of the vitreous body, thus reducing the time of the surgery by 35%-50% (de Oliveira et al. 2016, Pavlidis 2016, Mariotti et al. 2016). The development of vitreoretinal surgery enabled the treatment of the complex vitreoretinal diseases in children. However, in case of pediatric vitreoretinal surgery, application of the most recent technological achievements necessitates a thorough preoperative planning, examination and cooperation with anesthesiology team.

Minimally invasive surgery

Introduction of the minimally invasive cataract surgery was facilitated by the use of small size knifes to construct tunnel shaped incisions with the size of 1.8-2.8 mm. In adult patients, the hydration of the small incisions with balanced salt solution (BSS) at the end of the surgery allows for self-sealing of the incisions with almost no risk for wound reopening. In contrast, suturing of the wounds during cataract surgery is mandatory in children.

After a long history of using 20-gauge (outer diameter 0.9 mm) systems for pars plana vitrectomy, the instrumentation was miniaturized to the size of 23, 25 and 27 gauge (outer diameter 0.64, 0.5, 0.4 mm) (Figure 8). The use of small gauge vitreoretinal surgery converted it to a sutureless surgical approach by performing transconjunctival sclerotomies (Chang 2008). The insufficient stiffness of the first small gauge surgical instruments was significantly improved during the last decade, giving rise to a less traumatic 27-gauge surgery of various retinal diseases (de Juan and Hickingbotham 1990, Fujii et al. 2002, Sborgia et al. 2019). Introduction of the valved cannulas to the modern trocar systems enabled to work with the closed eye system by limiting and controlling the exit and entrance of the fluids inside the eye (Figure 9, A). It also reduced intraocular turbulence and vitreous incarceration, which is responsible for the formation of iatrogenic peripheral retinal holes (Abulon and Charles 2014, Oellers et al. 2015).

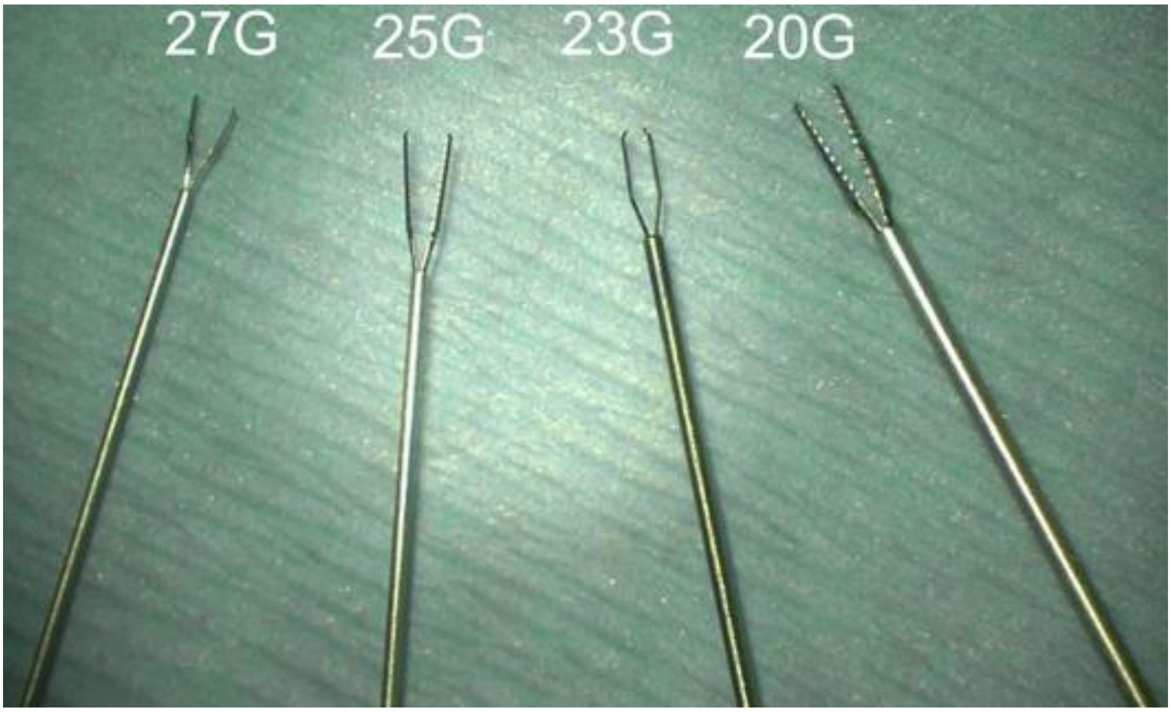

***Figure 8. Comparison of the size of 20, 23, 25, and 27-gauge forceps for vitreoretinal surgery** (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

In order to enable a sufficient illumination of small gauge light probes, the new vitrectomy systems utilize either xenon or light-emitting diode (LED) light sources (Chow 2014) with incorporated short-wavelength filters in order to reduce the possible phototoxicity on the retina. With the use of additional illumination, the performance of bimanual surgery became possible.

Intraoperative imaging

Intraoperative imaging during anterior eye segment surgery is mainly facilitated by the magnified view of the microscope (Figure 7). For conventional corneal, cataract and glaucoma surgery, this view enables a sufficient differentiation of the intraocular structures with satisfactory depth of focus. For glaucoma surgery with manipulations on an anterior chamber angle additional goniolenses are required.

Intraoperative imaging during posterior segment surgery is more challenging, because a microscope necessitates additional optic elements, such as contact lenses, or viewing systems that are usually attached to the microscope (Figure 9, 10). Today, the wide-angle non-contact viewing systems (WAVS) are used as a standard for vitreoretinal surgery during the learning curve and in every day practice (De Oliveira et al. 2016) (Figure 9 B). Modern WAVS include an integrated microscope inverter, which inverts a double reversed image to the standard view. A wide-angle view is especially important for managing of complicated cases of retinal detachment with proliferative vitreoretinopathy, and during vitrectomy in children. Due to these developments, vitreoretinal surgery with WAVS enabled the surgery even in cases with narrow pupil. Application of WAVS in combination with the bimanual technique, additional illumination systems, and scleral indentation, allows for manipulating on the far periphery of the retina and on the ciliary body.

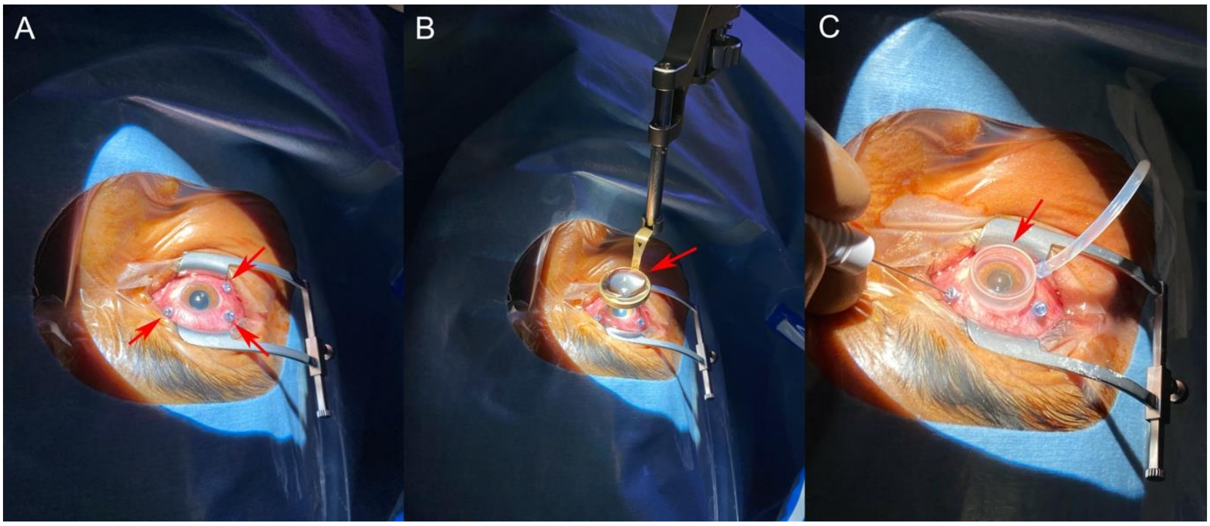

Figure 9. Depiction of operating field without (A) and with additional optic elements (B, C). *A - view of the three port PPV approach with the use of valved cannulas (red arrows); B – distal lens of wide-angle non-contact viewing systems (red arrow) for vitreoretinal surgery; C – contact lens for surgery on the macula (red arrow) (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

In the past 10 years, a new concept of endoscopic vitrectomy was introduced into intraocular surgery for cases with opaque optic media (Marra et al. 2013). Endoscopic probes enable direct visualization of the intraocular structures, which is transmitted onto the screen as a 2-dimentional (2D) image. Currently, there is only one operating system available on the market (Endo Optiks®, Waltham, MA, USA). Endoscopic probes, which accommodate triple function of camera, light probe and endolaser probe, are available in 20 gauge and 23 gauge and allow for approaching any area of the retina, ciliary body and all the structures of the anterior chamber (Lee et al. 2016). Endoscopic vitrectomy belongs to the first heads-up approaches used in the treatment of eye disorders.

Starting from 2014, a completely novel approach of intraoperative visualization was developed and introduced by Eckardt (Eckardt and Paulo 2016). Anterior and posterior segment surgery became virtually assisted through the use of a 3-dimentional (3D) camera to the optic axis of the microscope. The 3D signal is transmitted via the computer in real time to the large 3D screen with high resolution. The surgeon wears 3D glasses and operates looking straight forward onto the screen. The 3D heads-up surgery enables a much larger magnification. The dynamic range of the camera leads to decreased light levels, thus decreasing the risk of retinal phototoxicity. Moreover, the implemented intraoperative imaging can be projected onto the screen and can overlay the real-time image of the surgical field in large magnification. Not least, the use of the 3D heads-up surgery improves the teaching process through the enhanced observation possibilities. The learning curve with the new system was reported to be very short, lasting few surgeries. In addition, performance of the surgeries with heads-up 3D systems improves the ergonomics of the surgeon during difficult and long surgeries.

Intraoperative optical coherence tomography (iOCT) imaging is a supplementary intraoperative viewing method which allows for real-time scanning of the living eye tissues with an immediate observation of the surgical procedure and tissue behavior without interruption of the surgical flow (Binder et al. 2010) (Figure 10 B). One of the following chapters (Chapter 3.1.) is dedicated to this technology and will describe this topic more detailed.

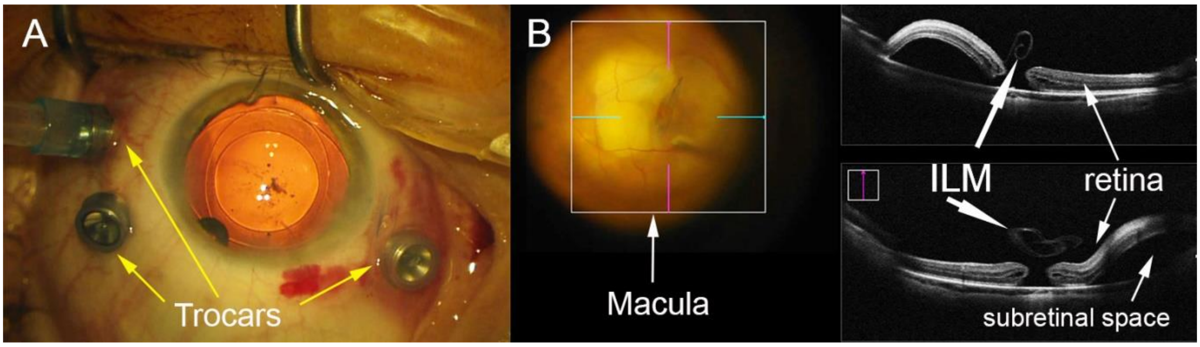

Figure 10. iOCT assisted standard three-port pars plana vitrectomy in a patient with macular hole. *A – three trocars are inserted through the pars plana part of ciliary body (yellow arrows). B – intraoperative OCT imaging shows manipulation on the macula with removal of the internal limiting membrane (white arrows) (microscope OPMI LUMERA 700 Rescan®, Zeiss Meditech, Oberkochen, Germany) (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

Modern approaches of intraoperative imaging in ophthalmic microsurgery are being developed together with the progress in technologic and computing systems. Introduction of eye tracking systems into the viewing microscopes enabled precise marking of the tissues during complex surgical steps (Figure 11). Additionally, integration of artificial intelligence (AI) into the ophthalmic diagnostics has become a standard for software-based screening of some retinal diseases (Schmidt-Erfurth et al. 2018).

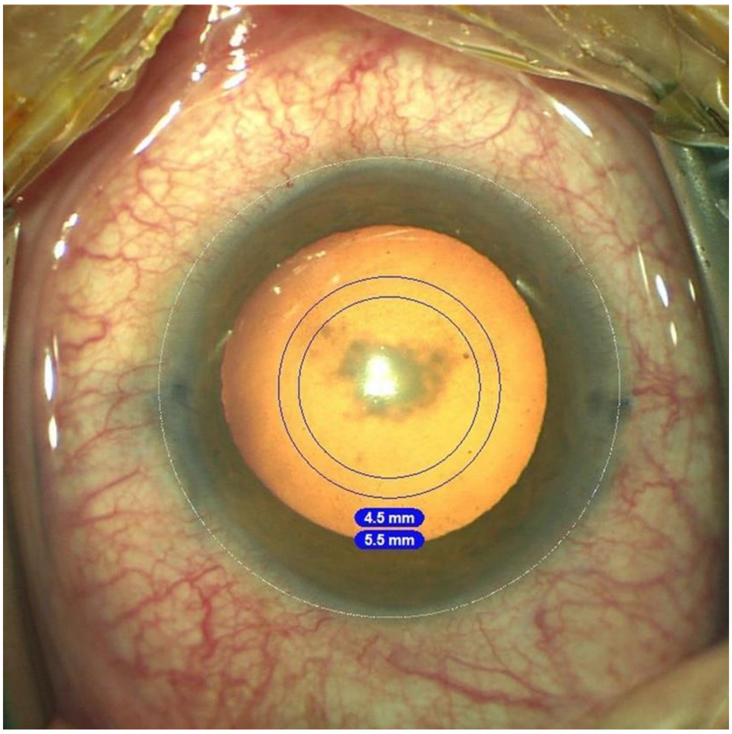

Figure 11. View of the virtually superimposed marking of the limbus (outer ring) and preset size of anterior curvilinear continuous capsulorhexis (4.5mm-5.5mm). *The surgeon can see the marking through one of the oculars of the microscope with heads-up function (microscope OPMI LUMERA 700 Rescan™, Carl Zeiss Meditech, Oberkochen, Germany) (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

1.2.2. Surgical intervention on anterior and posterior eye segment

Intraocular tissues are among the most delicate structures of our body and therefore most vulnerable. Any intraocular surgery is associated with the risk of tissue damage that can lead to irreversible consequences.

There are three main perforation routs that are necessary to perform during intraocular intervention: clear corneal, limbal or limbo-corneal, and sclero-corneal approach (Boote 2019) (Figure 12/1 A, B). In opposite, non-mechanical surgical approaches, such as intraocular laser photocoagulation, cryocoagulation, and photo-dynamic therapy are performed without the creation of iatrogenic perforating wounds (Leysen et al. 2000). While choosing the wound location, the surgeon needs to consider all advantages and disadvantages of every wound type in relation to the pathologic condition. The main rule of invasive surgery remains as follows: every created wound shall be closed at the end of the surgery in order to minimize the risk for infection and ocular hypotony. Every opening of the eyeball, either in the anterior or posterior eye segment, is associated with a sudden drop of intraocular pressure (Wang et al. 2019). This leads to the inner blood-retinal or/and blood-aqueous barrier breakdown (Naumann 2003, Blankenship 1982). The choice of the wound location also determines its healing mechanism, such as avascular, in the case of corneal wound, or vascular, in the case of limbal or sclero-corneal wounds (Chen and Tseng 1991). Among three major types of approaches for intraocular surgery, including wide-open sky, minimally invasive, and non-invasive, particularly the minimally invasive approach is considered to be the most effective with relatively low rates of intra- and postoperative risks for complications. Planning of surgeries on only one remaining eye requires separate attention, as the undesired complication can result in dramatic outcome for the patient (Henke et al. 1988).

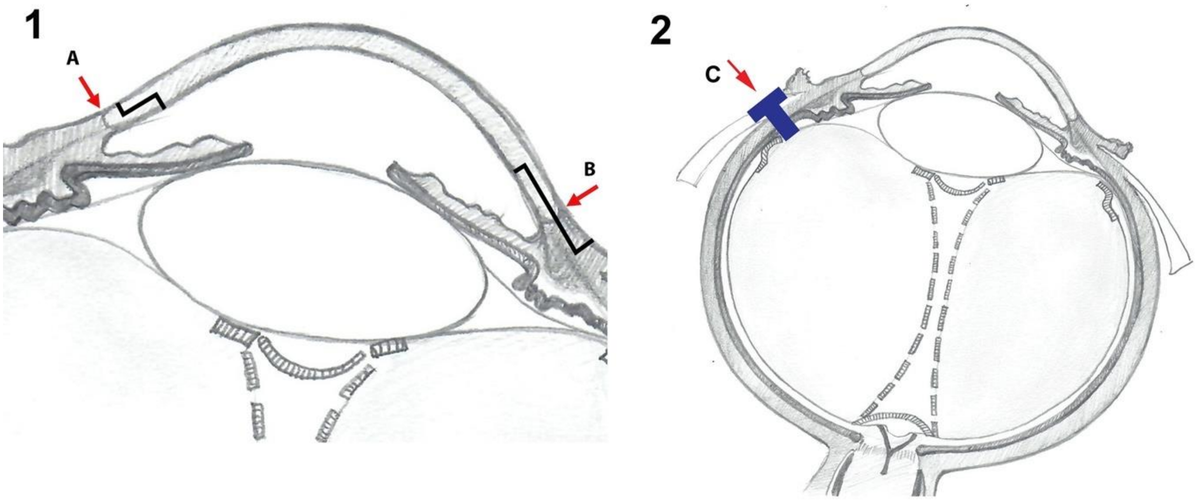

Figure 12. Schematic illustration of main perforation routs during the surgery on anterior (1) and posterior (2) eye segment (red arrows). *A – three-step clear corneal incision; B - three-step sclero-corneal incision; C – standard transscleral placement of valved trocars through pars plana of ciliary body during three-port PPV (Created by J. Khrushch).*

Intraocular surgery on the anterior segment

This kind of surgery is performed within the limited space of the anterior and posterior chamber of the eye. The inner structures, such as pupil or trabecular meshwork, shall be well-preserved. All surgical wounds shall be precisely created and remain adapted during the surgery in order to maintain the circulation of the intraocular fluid and balance of the intraocular pressure. Among the most vulnerable structures of the anterior eye segment are: endothelial cell layer located on the inner surface of the cornea, anterior chamber angle, iris and anterior lens capsule (Chang and Campbell 2005).

Anatomically and physiologically underdeveloped structures and functions of the anterior chamber of the newborn child, which are responsible for the equilibrium of the intraocular pressure, react usually more aggressive to the surgical intervention compared to those in adults (Alvarado et al. 1981, Auffarth et al. 2000). With growth of the patient, the condition of the intraocular tissues undergoes age-associated changes. For example, the anterior chamber depth plays an important role, as it can change depending on the age and entity of the eye disorder ranging from 0 mm to 3-5 mm. Corneal endothelial cells are most exposed to the surgical intervention in children as well. Limited capability of endothelial cells for proliferation and regeneration in the case of surgical trauma can lead to immediate loss of corneal clarity and endothelial decompensation. Surgery related trauma of the iris results in postoperative inflammation and iris atrophy with ischemic changes and loss of function (Hinzpeter et al. 1974). Regarding the lens surgery, a more anterior insertion of the zonular fibers into the anterior capsule in children should be considered while performing anterior capsulorhexis (opening of the anterior capsule) during cataract surgery (Figure 3) (Naumann 1987). Manipulations with the fine instruments in cataract surgery undergo in the close proximity to the corneal endothelium and iris (Figure 13).

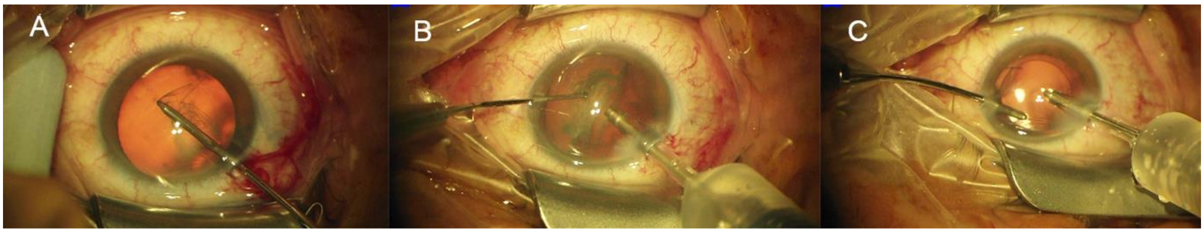

Figure 13. Major steps of conventional lens-in-the-bag cataract surgery: *A – anterior capsulorhexis (opening of the anterior capsule), B – phacoemulsification (removal of the crystalline lens with ultrasound device), C – implanted artificial intraocular lens in the capsular bag. Intraocular instruments are hold in close proximity to corneal endothelium (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

Intraocular surgery on the posterior segment

During surgery on the posterior eye segment, the surgeon approaches a much larger space of vitreous cavity compared to the anterior chamber. However, the view of this space can be limited by the size of the pupil and clarity of the optic media. The periphery of the vitreous cavity, including peripheral retina and ciliary body, is obscured by the iris. For this reason, intraoperative scleral indentation is an essential technique, which allows for exposing of the peripheral structures into the operating field of view. The most important areas of natural vitreous attachment together with posterior zonula insertion and posterior lens surface shall be treated and operated with maximum attention. Intraocular hypotony can lead to intra- or postoperative complications, such as postoperative uveitis, choroidal effusion, or even expulsive hemorrhage. The use of irrigation solutions for intraocular surgery with temperatures higher than room temperature can create an additional risk for tissue damage (Rinkoff et al. 1986; Zilis et al. 1990).

Surgical manipulations onto the retina surface shall be performed with high level of attention, as the neurosensory retina in physiologic conditions appears to be transparent and hardly visible. The use of proper lenses and adequate magnification is required in order to distinguish between the pathologic and normal layers within the retina (Figure 9, B, C). Intraoperative optical coherence tomography (iOCT) can assist to recognize the retinal surface pathology in challenging cases. The innermost layer of the retina – the internal limiting membrane (ILM) – undergoes pathologic changes with anterior-posterior and/or tangential constriction in certain retinal diseases. That is why it shall be removed with the aim to release the traction (Figure 10, B). The removal of the ILM affects the Müller cells, which play an important role in structural and metabolic homeostasis of the retinal layer (Franze et al. 2007, Reichenbach et al. 2007). For this reason, the removal of the ILM has to be carefully considered in each case, as the iatrogenic impact can prevail over the therapeutic intentions.

Exudation, caused by disruption of inner and outer blood-retinal barriers, can lead to epi-, intra- and/or subretinal accumulation of fibroblast-like cells with active proliferation. Gradual growth of the proliferative membranes with the traction and risk for retinal re-detachment is a hallmark of proliferative retinopathy (PVR) with different severity grade and hence, with different visual and anatomical prognosis (Cardillo et al. 1997).

An intravitreal approach or extraocular surgery of retinal disorders requires manipulations close to RPE, Bruch's membrane and choroid. The removal of strongly adherent subretinal membranes or transscleral evacuation of subretinal fluid is always associated with the risk of choroidal hemorrhage, which remains among the most severe complications due poor visual outcomes.

Additionally, an intravitreal approach requires sclerotomies that are placed transscleral in the projection of the pars plana of the ciliary body (Figure 12/2, C) (Boote 2019). Surgical instruments inserted through the sclerotomies pass close to the posterior lens capsule, posterior zonula and ciliary body. Preoperative assessment of the size of the eye globe requires exceptional concern. The surgery on the small or large eyes necessitates special attention in regard to the different dimensions and transformed interrelations between ocular structures (Wang et al. 2011).

2. Aims of the studies

The growth of knowledge about etiology, pathophysiology and the natural course of eye disorders requires modern surgical treatment methods with the use of minimally invasive surgical procedures, where the targeted tissue is addressed during the surgical intervention and nearby laying structures remain untouched. The latest developments of surgical approaches in ocular surgery demonstrated their favorable impact on the postoperative outcome and assistance during the treatment of complex cases in general (McClintock and Rezaei 2015, Thomas and Kuriakose 2000).

In this thesis the following innovations in ophthalmic surgery investigated and developed by the author are presented and discussed with regard to their importance to the field:

1. **New diagnostic techniques.** This chapter will describe the novel intraoperative imaging method – intraoperative optical coherence tomography, and how it can improve performance of standard cataract surgery and novel techniques of complex vitreoretinal procedures.
2. **New surgical techniques.** To this topic belong the description of the development, improvement and clinical application of a new technique for surgery of an anterior and posterior segment in adults and children.
3. **New surgical instruments.** This chapter will describe the development and clinical implication of new instrumentation for vitreoretinal surgery, which were developed by the author of this thesis during recent years.

The central focus of this work is to show the implementation of the innovative techniques into the real-life intraocular surgery, and to discuss their influence on the intraoperative flow and postoperative outcomes.

3. Results

3.1. New diagnostic techniques

3.1.1. Intraoperative optical coherence tomography (iOCT)

Optical coherent tomography (OCT), since it was first introduced in ophthalmology almost three decades ago, has radically revolutionized the field and brought the understanding of the ocular pathology to the qualitatively higher level (Huang et al. 1991, Fercher et al. 2003, Yaqoob et al. 2005). OCT is a non-invasive diagnostic method that often is compared to *in vivo* non-contact biopsy, as the detailed data, which are obtained within iOCT, resemble histological samples of the tissue (Fercher et al. 2003, Fujimoto et al. 2000). Further development of this technology brought an OCT diagnostic imaging technique into the operating room, allowing for simultaneous imaging of the extra- and intraocular tissues without interruption of the surgery flow. It became possible after the full integration of an OCT system into operating microscope with emerging of a new field in ophthalmic imaging – intraoperative optical coherence tomography (iOCT). The majority of current iOCT systems use a spectral domain intraoperative OCT source (iSD-OCT), which delivers very fine resolution of image (3-5 μm in tissue).

The iSD-OCT imaging belongs to one of image-guided intervention methods (Cleary and Peters 2010). Using OCT principle, microscopic view and software, the iSD-OCT systems facilitate in real-time an imaging of the ocular tissues that overlays the microscopic imaging (Feldchtein et al. 1998, Zivelonghi et al. 2014, Hanna et al. 2005, Ehlers et al. 2014). It allows the surgeon to observe a completely different view of the surgical field. A high resolution of 3-5 μm enables visualization of almost all layers of the cornea and retina – the two most applicable tissues that have been operated with the use of iSD-OCT.

iSD-OCT systems. The field of iOCT is considered to be a relatively new branch of intraoperative eye diagnostics. The number of commercially available iOCT systems is limited and the progress in development of this new approach is related to additional costs. Currently, there are three commercially available iOCT systems, which obtain very similar technical parameters, but differ with its software and hardware (Table 3). In 2014 the company Carl Zeiss Meditech (Oberkochen, Germany) presented the first iOCT system Rescan™700, which was fully integrated into the operating microscope OPMI Lumera 700 and accomplished with the software CALLISTO eye® (Rescan™ 700, Carl Zeiss Meditech https://www.zeiss.com/meditec/int/product-portfolio/surgical-microscopes/ophthalmic-microscopes/opmi-lumera-700.html Accessed 09 July 2015) (Figure 14, A). The image of the dynamic iOCT scanning is injected into the one of the oculars of the microscope and simultaneously is projected onto the screen of CALLISTO eye® system (Figure 14, B).

Additionally, the surgeon, an assistant and operating nursing staff can follow the flow of the imaging on the external screen. The control of the imaging can be performed by the surgeon itself using a foot control pedal.

Table 3. Technical characteristics of the fully microscope integrated iOCT systems that are available on the market.

Characteristics	**Rescan™700 (Zeiss, Oberkochen, Germany)**	**Bioptigen SDOIS (Bioptigen, Morrisville, NC, USA)**	**iOCT® (Optomedical Technologies GmbH, Lübeck, Germany)**
OCT source	spectral domain	spectral domain	spectral domain
OCT Image	27.000 A-scans/ second	32,000 A-scans/sec	10,000 A-scans/second
Depth Resolution	5.5 µm in tissue	3.3/2.4 µm in air/tissue	10 µm in air
Scan Range Depth	2.0-5.0 mm	3.4 mm (2.5 mm in tissue)	4.2 mm
Scan Beam Wavelength	840 nm	830±30 nm	800 nm
Lateral scan width	3-16 mm (scan rotation 360°)	16 mm	5-30 mm dependent on microscope zoom
Recording options	videos, snapshots	videos, snapshots	videos, snapshots, 3D-images

The second microscope integrated system was assembled using already existing hand-held OCT system Bioptigen Spectral Domain Ophthalmic Imaging System (SDOIS) (Bioptigen, Morrisville, NC, USA) and Proveo 8 microscope (Leica Microsystems, Wetzlar, Germany) (Bioptigen Envisu https://www.leica-microsystems.com/company/news/news-details/article/leica-microsystems-to-acquire-oct-company-bioptigen/ Accessed 09 July 2015). This system necessitates additional personnel in order to operate with the iOCT imaging. The third iOCT system was developed by the company OptoMedical Technologies GmbH (Lübeck, Germany), and was integrated with the operating microscope HS Hi-R NEO 900A NIR (Haag-Streit GmbH, Wedel, Germany) (iOCT® Haag-Streit https://www.haag-streit.com/de/haag-streit-deutschland/produkte/mikrochirurgie/ophthalmologie/ioct/. Accessed 09 July 2015). In this system the iOCT camera is integrated into the microscope and uses the same microscope optic pathway. This system is less used during the studies.

The most important issues, which are studied with iOCT imaging, are the intraoperative tissue behavior, iatrogenic influence of surgical maneuvers on the living tissues, and the new data about tissue-tissue and/or tissue-implants interaction in cases of severe and rare diseases. Moreover, the use of iOCT systems allows for instant decision making during the surgery and for creating the possibility to accomplish necessary surgical steps regarding the newly detected conditions. Additionally, one of the main advantages of the new iOCT assisted surgery remains the possibility to decrease the range of intraoperative iatrogenic trauma.

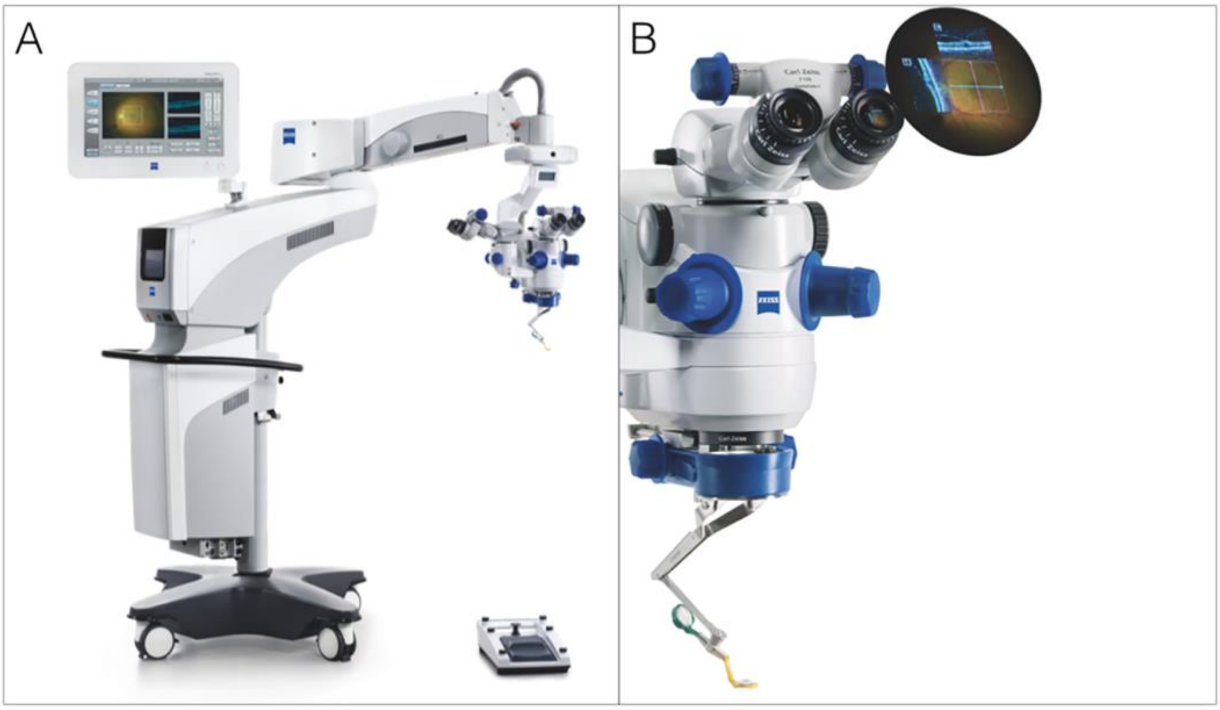

Figure 14. Microscope integrated iSD-OCT system Rescan™700 (Carl Zeiss Meditech, Oberkochen, Germany). *General view of the system (A). iOCT image is injected in the right ocular of the microscope and is overlaid onto the microscopic view of the operating field (B) (Lytvynchuk L, Glittenberg C, Binder S (2017) Intraoperative Spectral Domain Optical Coherence Tomography: Technology, Applications, and Future Perspectives. In: Meyer CH, Saxena S, Sadda SR (eds.) Spectral Domain Optical Coherence Tomography in Macular Diseases. Springer, New Dehli, India, pp 423-443. Permission granted).*

The indications for iOCT assisted ocular surgery include surgeries of the anterior and posterior eye segment. Development and improvement of modern keratoplastic surgeries was evolved by the implication of iOCT (Juthani et al. 2014, De Benito-Llopis et al. 2014, Miyakoshi et al. 2014, Xu et al. 2014, Steven et al. 2013, 2014). In terms of cataract surgery, the use of iOCT assists during the learning curve and guides the surgeon of complicated cases. In glaucoma surgery, the iOCT use is limited. However, the future of the iOCT use for glaucoma surgery *ab interno* is studied further (Heindl et al. 2014). Vitreoretinal disorders belong to one of the most widely considered indications for the iOCT assisted surgery. It is crucial to maintain optimal clarity of the optic media of the anterior chamber, in order to perform efficient iOCT assisted surgery on the posterior eye segment. Numerous studies have revealed new information about the pathophysiology of certain vitreoretinal disorders and iatrogenic influence on the living tissues.

A book chapter, which is attached as Appendix 1 of this habilitation thesis, is dedicated to this topic.

Appendix 1

Intraoperative Spectral Domain Optical Coherence Tomography: Technology, Applications, and Future Perspectives.
Lytvynchuk L, Glittenberg C, Binder S (2017) In: Meyer CH, Saxena S, Sadda SR (eds.) Spectral Domain Optical Coherence Tomography in Macular Diseases. Springer, New Dehli, India, 423-443.

3.1.2. Clinical applications of the iOCT

Appendix 2

Evaluation of intraocular lens position during phacoemulsification using intraoperative spectral-domain optical coherence tomography.
Lytvynchuk L, Glittenberg C, Falkner-Radler C, Neumaier-Ammerer B, Smretschnig E, Hagen S, Ansari-Shahrezaei S, Binder S. J Catarct Refract Surg. 2016;42(5):694-702.

iSD-OCT for cataract surgery

Introduction. One of the first iOCT imaging of conventional cataract surgery documented the flow of the standard lens-in-the-bag (LIB) implantation technique and revealed the dynamic of the different steps of lens extraction and implantation of artificial intraocular lens (IOL) into the capsular bag (Figure 15) (Lytvynchuk et. al 2017). It showed that iOCT imaging can facilitate the control during creation of self-sealed incisions, hydrodissection of the lens from its capsule, removal of the lens and correct flow of IOL implantation. Such a control is most important during the learning of the cataract technique by young surgeons and fellows. It was also reported, that the measurements of the anterior chamber depths performed with iOCT can serve as an additional intraoperative calculation parameter, which improves the prediction error of preoperative IOL power calculation (Hirnschall et al. 2013, 2015).

The standard LIB technique is pretty straight forward and delivers a relatively favorable postoperative result, but the risk of postoperative complications, which influence visual function, still exists (Figure 13, 18). The most common complication after LIB cataract surgery remains a posterior capsule opacification (PCO) (Pandey et al. 2004, Sinha et al. 2013). The reason for this is a slow-going proliferation of the remaining lens epithelial cells onto the inner surface of the posterior capsule (PC). A number of factors can exacerbate

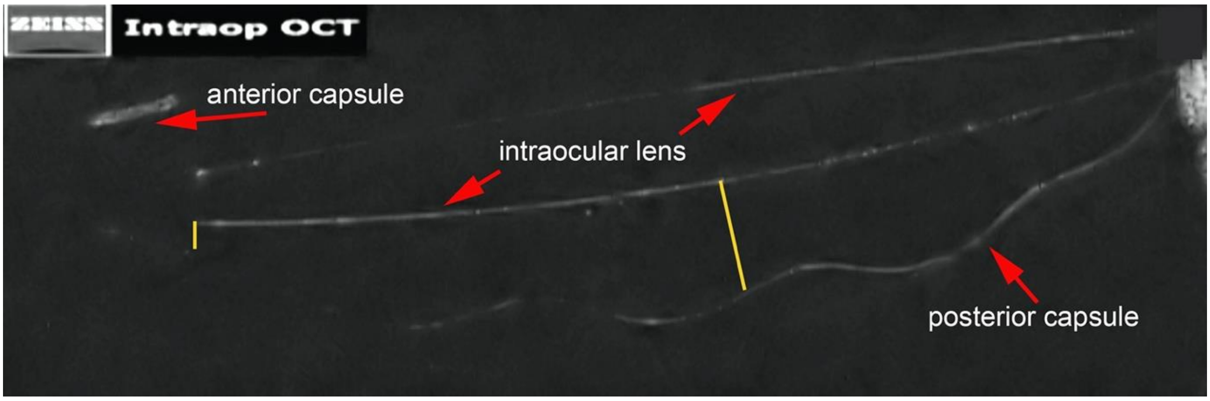

Figure 15. iOCT imaging of the implanted IOL into the capsular bag at the end of the surgery. *Yellow lines indicate the distances between posterior IOL surface and posterior capsule. Red arrows indicate anterior capsule, intraocular lens and posterior capsule (L. Lytvynchuk et al. Evaluation of intraocular lens position during phacoemulsification using intraoperative spectral-domain optical coherence tomography. J Cataract Refract Surg. 2016; May; 42(5):694-702. Permission granted).*

and speed up the development of PCO (postoperative inflammation, IOL material, implantation technique, concomitant ophthalmic conditions) (Lombardo et al. 2009, Ram et al. 2001). The studies reported that implantation of the IOL with squared edge being in contact with posterior capsule can prevent the development of the PCO (Kohnen et a. 2008, Peng et al. 2000). The reason for this is the contact between the squared IOL edge and posterior capsule, which mechanically slows the proliferation and migration of lens epithelial cells from the periphery toward the IOL optic center. Nevertheless, the risk of PCO after standard cataract surgery remains significant. The relationship of the contact between the IOL posterior surface and posterior capsule at the end of the surgery was not studied. Analysis of the IOL position during and at the end of the surgery with iOCT imaging could answer this question and guide future studies that are focused on the prevention of the most often vision threatening complication after conventional cataract surgery.

Aim of the study. The study was aimed to evaluate the position of standard intraocular lenses (IOL) with improved squared edge design using intraoperative spectral-domain optical coherence tomography (iOCT) at the end of phacoemulsification performed with LIB implantation technique.

Methods. This prospective single-center study included 101 cases (74 patients) with diagnosis senile cataract. As exclusion criteria served the presence of concomitant eye diseases or previous eye surgery. All patients underwent an eye surgery (phacoemulsification technique) with implantation of IOL and assistance of iOCT imaging. A standard phacoemulsification technique with implantation of foldable IOL with squared optic edge was applied by five experienced surgeons. The surgery consisted of limbo-corneal main incision, one paracentesis, anterior curvilinear continuous capsulorhexis (4.5-5 mm in diameter), hydrodissection, phacoemulsification of the lens, aspiration of cortical material, implantation of the IOL with push-back maneuver, and removal of ophthalmic viscoelastic device at the end of the surgery (Figure 16).

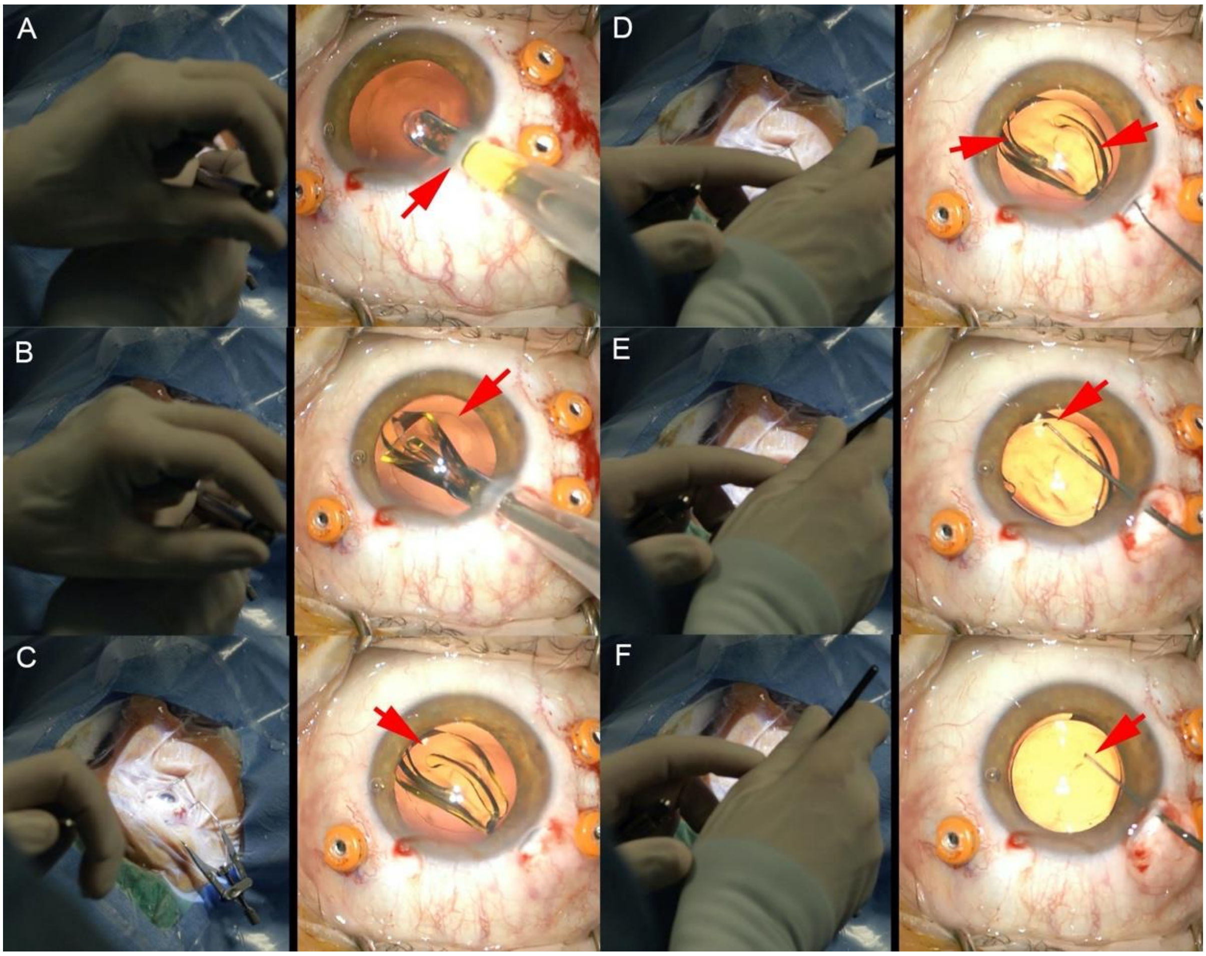

Figure 16. Implantation of foldable IOL during conventional lens-in-the-bag cataract surgery. *Red arrows indicate position of the IOL during different steps of implantation: A, B – insertion of the tip of injector into the main limbo-corneal incision and implantation of the IOL into capsular bag; C, D, E – unfold of the previously folded IOL inside capsular bag; F – centration of the IOL inside the capsular bag with push-back maneuver (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

In order to study the possible influence of the IOL design on postoperative IOL position, two type of foldable IOLs were used: Acrysof IQ SN60WF IOL (Alcon Laboratories, Inc.) in Group 1, and Tecnis IOL (Abbott Medical Optics, Inc.) with improved posterior surface design in Group 2. Intraoperative imaging of the IOL position was performed by every surgeon at the very end of the surgical procedure with the use of iOCT system Rescan™ 700 (Carl Zeiss Meditec AG, Oberkochen, Germany), which is fully integrated in the surgical microscope foot stand (Opmi Lumera 700). iOCT scanning was performed using video and image modes with the focus on the center of IOL optic, IOL edges, and posterior capsule (Figure 15). After iOCT data were exported they were post-processed using graphic software ImageJ (version 1.48v). In all cases the distance between posterior IOL surface and PC in different areas was measured twice on iOCT images. The areas of measurement included the IOL optic center, IOL squared edge and IOL haptic element. The distance values were measured in pixels as the distances in iOCT scans due to technical limitations are not calibrated. The following relation between IOL and capsular bag were evaluated: contact between the IOL haptic and the posterior capsule, wrinkling of the posterior capsule, contact between the anterior capsule and IOL, and the presence of anterior vitreous hyperreflectivity. The results were statistically analyzed with p-value less than 0.05 as statistically significant.

Results. Within 74 patients (101 eyes) there were 39 men (38.61%) and 62 women (61.39%) with mean age 71.43 years (range 49 to 91 years). In 59 eyes (58.6%) the Acrysof IQ SN60WF IOL was implanted (Group 1) and in 42 eyes (41.6%) the Tecnis IOL in (Group 2).

The analysis of Intraocular Lens Central Optic to Posterior Capsule Distance (Central Distance) showed, that in 99 eyes (98%), a space between the IOL central optic and the posterior capsule was present with the mean central distance was 0.72 pixel (range 0.06 to 1.38 pixels. In 88 eyes (87.13%) there were no contact observed at all between the IOL central optic and the posterior capsule (Figure 17 A, 22 B). In 11 eyes (10.89%) a partial contact between the IOL central optic was detected and only in 2 eyes (1.98%) a full contact was observed. It was detected a significant correlation between the central distance and the axial length. Hence, an increase in the AL resulted in an increase in the central distance (with p-value 0.213).

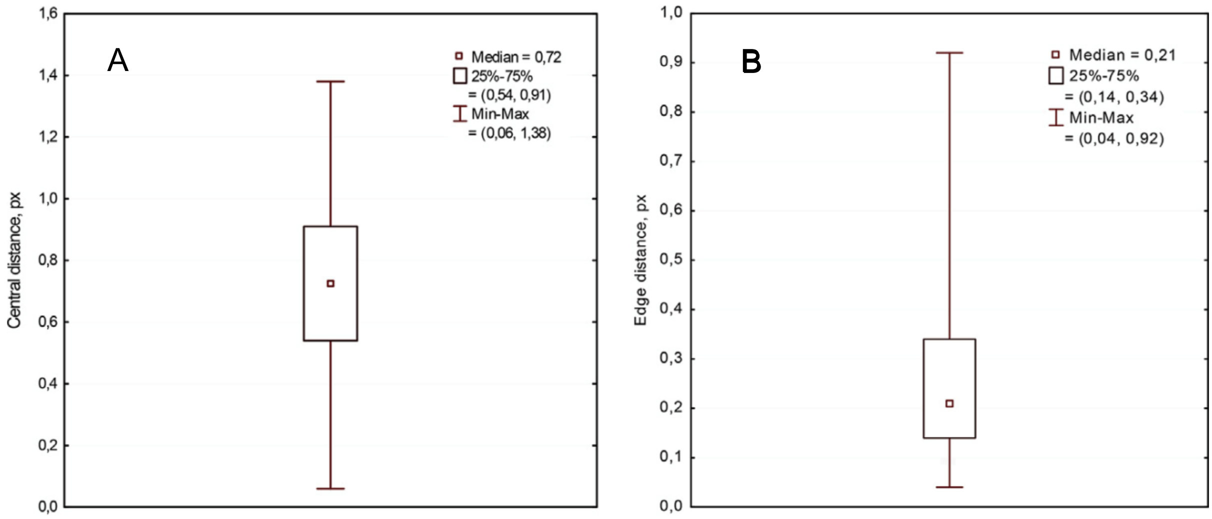

Figure 17. Results of the mean central distance between the IOL and the posterior capsule (A), and the mean edge distance between the IOL and the posterior capsule (B) in pixels. *Box-and-whisker plots (L. Lytvynchuk et al. Evaluation of intraocular lens position during phacoemulsification using intraoperative spectral-domain optical coherence tomography. J Cataract Refract Surg. 2016; May; 42(5):694-702. Permission granted).*

The analysis of Intraocular Lens Edge to Posterior Capsule Distance (Edge Distance) showed that in 73 eyes (72.3%) 360 degrees of the IOL edge were detectable with iSD-OCT at the very end of the surgical intervention (Figure 15, 18 B, C). The mean parameters of the edge distance were 0.21 pixel (range 0.04 to 0.92 pixel) (Figure 17 B, 18 B, C). A complete absence of contact between the IOL edges and the posterior capsule was detected in 31 eyes (42.47%). A partial contact between the IOL edges and the posterior capsule was observed only in few cases and was considered as insignificant.

Among the additional findings there were following changes of intraocular tissue position. Posterior capsule wrinkling which was observed in 63 eyes (62.38%) could arise as the result of reduced capsular bag volume after phacoemulsification (Figure 15). Anterior vitreous hyperreflectivity was detected in 20 cases (19.8%) mostly in patients with mean age of 69.8 years (range 53 to 81 years). The contact between IOL and anterior capsule was identified in 7 (9.6%) of 73 eyes with sufficient intraoperative mydriasis. However, the clinical significance of these finding shall be studied further.

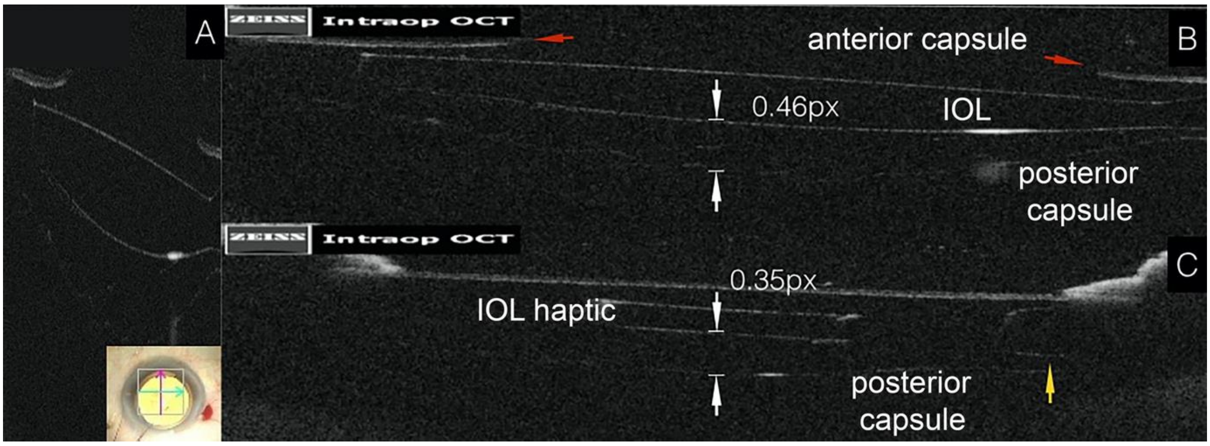

Figure 18. iSD-OCT imaging of the IOL inside the capsular bag at the end of the cataract surgery (A). *Post-processed images of the same eye (B, C). White arrows indicate the absence of the contact between the central optic area and posterior capsule (B) and the squared edge and posterior capsule (C). The absence of the contact between IOL haptic and posterior capsule are is indicated with yellow arrow (C). Slightly elevated anterior capsule edges IOL are marked with red arrows (B) (L. Lytvynchuk et al. Evaluation of intraocular lens position during phacoemulsification using intraoperative spectral-domain optical coherence tomography. J Cataract Refract Surg. 2016; May; 42(5):694-702. Permission granted).*

Discussion. Among a variety of postoperative complications after standard cataract surgery, PCO is considered to be the most common, which can be detected to a certain extent almost in every case with lens-in-the-bag IOL implantation. The area of PCO development correlates with surgical technique, IOL design and postoperative inflammatory reaction. To the best of our knowledge, our study was the first of its kind to investigate the role of IOL position in regard to PCO development in real-life surgery. One of the study arms was to compare lens-capsule interaction in cases with two different IOL designs: Tecnis®

IOL and AcrySof® IQ. The first type possesses improved 3-point fixation design to increase the adhesion between IOL and posterior capsule. The results showed that in cases of Tecnis® IOL the distance between central IOL optic area and posterior capsule was slightly shorter, but the difference was not statistically significant. Axial length appeared to be the single parameter that significantly correlated with the distance between IOL and PC. The condition of the vitreous body that can be hydrated during the surgery can also influence the forward movement of the posterior capsule toward IOL (Oh et al. 2014). However, this question is not studied enough. Another concern that arises from the study result is that the absence of IOL-capsule contact can cause IOL instability and lead to its dislocation with decreased visual outcome.

Summary. The application of iSD-OCT system for the first-time allowed imaging of the precise anatomical position of IOL in the capsular bag at the end of standard cataract surgery. Study results demonstrated that contact between the IOL central optic and central posterior capsule appeared to be uncommon. The reason for this might be the bigger size of the capsular bag or posterior capsule in comparison to the size of the IOL. The contact between the square edge of IOL and the posterior capsule, which purposes to reduce rate of posterior capsular opacification, was only partial and was detected in 57.53% of eyes.

In the vast majority of cataract surgery cases the surgeons implant the IOLs with the same dimensions into the capsular bags with different sizes. The results of this study could hypothesize that implantation of IOLs with bigger optic diameter could improve the contact between the IOL edge and the posterior lens capsule. The new findings allow for better understanding of the failures of the standard cataract surgery, suggesting that new designs of IOLs could be personalized and adapted to the size of the capsular bag of every patient. Hence, it could decrease the rate of posterior capsular opacification and eliminate the necessity for additional intervention with optimization of postoperative results and reduced costs for cataract surgery.

iSD-OCT for retinal surgery

Appendix 3

Dynamic intraoperative coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery.

Lytvynchuk L, Falkner-Radler C, Krepler K, Glittenberg C, Ahmed D, Petrovski G, Lorenz B, Ansari-Shahrezaei S, Binder S. Graefes Arch Clin Exp Ophthalmol. 2019;257(8):1649-1659.

Introduction. The most common indication for the use of iOCT during retinal surgery remain macular diseases, including epiretinal membranes (ERM), macular holes (MH), subretinal hemorrhages, vitreomacular traction syndrome (VMTS) and macular edema (Ehlers et al. 2013, 2014, Lee and Srivastava 2011, Binder et al. 2010, 2011). In order to remove ERM, the use of intraocular dyes is recommended. However, the retinal toxicity of the intraocular dyes is frequently studied and discussed (Ehlers et al. 2010, Matz et al. 2012). The internal limiting membrane (ILM) can be pathologically changed and shall be removed during the same surgery. Unfortunately, ILM remains invisible for iOCT. Only after initiation of the ILM flap, the iOCT scanning is able to detect the ILM (Figure 10 B). The reason for this is the thickness of ILM, which is only 0.5 to 1.4 µm, and is strongly adherent to the retinal nerve fiber layer. In contrast the resolution of iOCT systems is between 3.5 and 5 µm in tissue.

Full thickness macular holes require special attention (Hayashi et al. 2011, Ehlers et el. 2014, Wykoff et al. 2010). This macular disorder can cause a sudden loss of central vision and lead to irreversible changes of the foveal area (Figure 19 A). Chronic and long-standing macular holes are characterized by hypertrophy and proliferation of the retinal pigment epithelium cells on the retinal surface (Figure 19 A yellow arrows). The use of conventional PPV and ILM peeling for large macular holes (diameter ≥400 µm) is considered to be less effective, and prognosis is usually poor in approximately 50% of cases. During the last decade, a number of novel techniques emerged aiming to treat and close large and chronic macular holes. One of the new methods proposes to use the parts of peeled but still attached ILM in order to cover the orifice of the MH (Michalewska et al. 2009, 2015) (Figure 19 B, C). There are a lot of difficulties that can complicate the surgery and lead to its failure, including the loss of the ILM flap or displacement of the inverted ILM flap at the end of the surgery, i.e. iatrogenic intraoperative trauma. The learning curve of this technique remains still challenging.

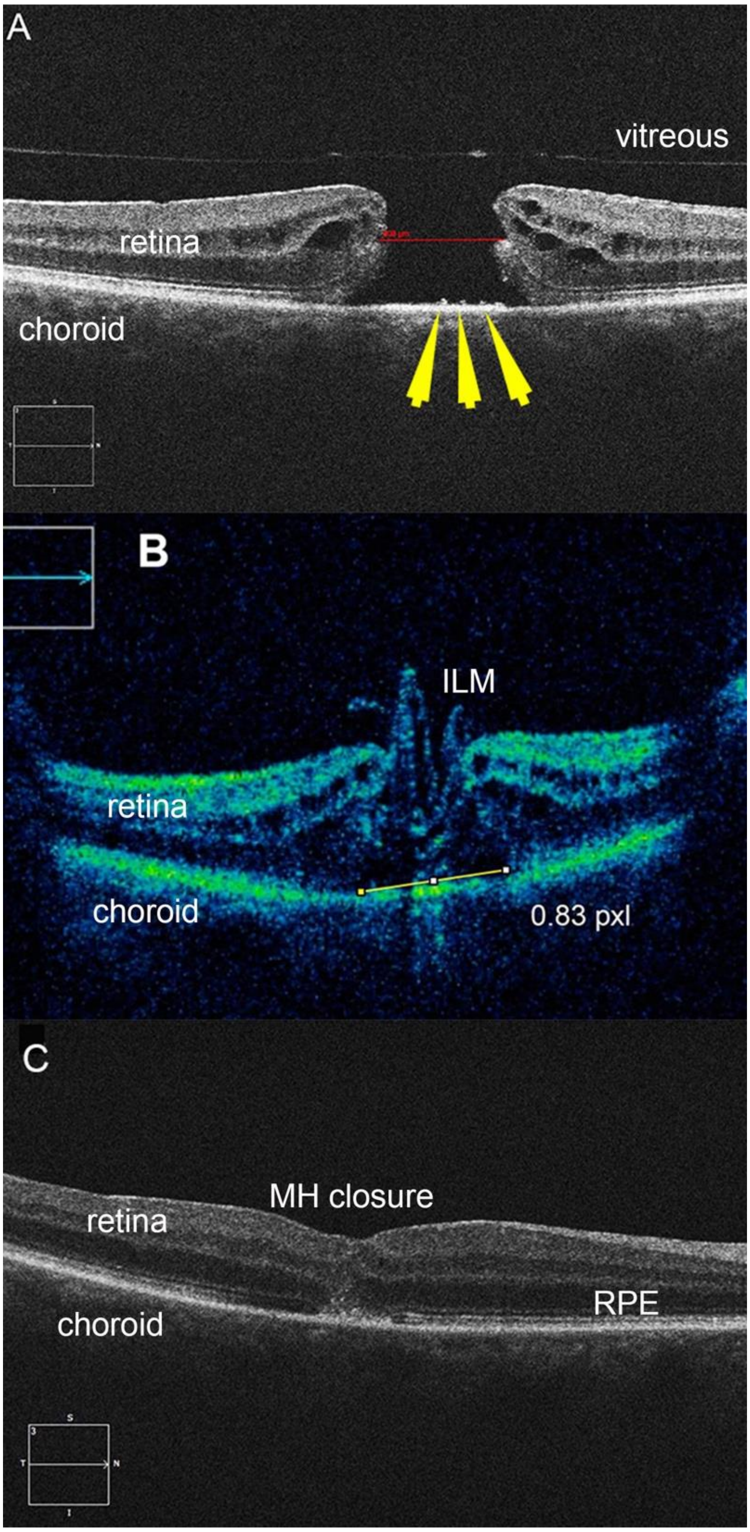

Figure 19. OCT and iOCT imaging of macular hole. *A - Preoperative OCT of the full-thickness MH. The red line indicates the size of the MH (806 µm) with visual acuity of 0.05 decimal. The yellow arrows indicate the hypertrophy of RPE layer of the retina, which is the hallmark of the chronic and longstanding MH. B – intraoperative OCT image of the MH covered with the ILM. The yellow line shows the size of the MH base. C – postoperative OCT in 2 weeks after the surgery demonstrates complete closure of the MH with improved visual acuity from 0.05 to 0.16 decimal (L. Lytvynchuk et al. Dynamic intraoperative optical coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery. Graefes Arch Clin Exp Ophthalmol. 2019; Aug; 257(8):1649-1659. Permission granted).*

Aim of the study. This study aimed to assess the value of dynamic intraoperative spectral-domain optical coherence tomography imaging for a novel technique - inverted internal limiting membrane flap technique (IILMFT), in large and chronic macular hole surgery. An additional purpose was to reveal new information about the surgery-induced influence of the vitreoretinal intervention, manipulations on the retina and new pathophysiologic features of the MH dynamic during the surgery.

Methods. To this prospective non-randomized observational study were enrolled 7 patients (8 eyes) with large and chronic MH with mean age 63.29 years (range 32-75 years). As inclusion criteria was the maximal diameter of large MH > 700 µm. The maximal diameter (size) of MH was defined as longest distance between external limiting membrane (ELM) on horizontal OCT images. All patients underwent a standard ophthalmologic examination pre- and postoperatively including spectral domain OCT imaging. The surgical procedure included 23-, 25-, or 27-gauge pars plana vitrectomy. In order to stain the ILM, a Membrane Blue Dual ® (D.O.R.C. International, Zuidland, The Netherlands) was used. In seven eyes a classical IIMLFT was performed, and in one eye - a free ILM flap technique was applied. Both MH closure techniques followed by parafoveal retina massage aiming to re-appose the edges of MH closer. At the end of the surgery, an incomplete fluid-air exchange (80–90% of air) with infused air pressure of 25 mmHg was facilitated. After the surgery, all patients were positioned face down over one night. Intraoperative imaging was facilitated during every surgery using microscope integrated iOCT system Rescan™ 700 (Zeiss, Oberkochen, Germany) and EnFocus™ UltraHD (Leica Mikrosysteme Vertrieb GmbH, Wetzlar, Germany) (Table 3). Heads-up display of the iOCT system, which is injected into the ocular of the microscope allowed for visual controlling of the surgery without interruption of the surgical flow. During the postoperative analysis of the efficacy of dynamic iOCT imaging for large MH surgery the following steps of the surgery were overviewed: scanning of the MH during PPV, scanning of the ILM, imaging of the vitreoretinal instruments, imaging of the relations between instruments and the retina, imaging of apposition of MH edges, dynamics of the MH base during ILM peeling, and scanning of the MH with inverted ILM flap after fluid-air exchange (Figure 20 a, b, c, Figure 21 a, b, Video 1 – Supplemental material 1 on USB-Stick).

iOCT data were recorded as snapshots and videos. All data was post-processed using graphic software ImageJ 1.48v (Wayne Rasband, NIH, USA). Enhancement of the clarity of the subtle structures of MH and ILM inside the iOCT data was facilitated with 3D visualization and a voxel-based system. During post-processing the raw iOCT data sets were exported from the iOCT system, Z-aligned with following noise reduction. The outcoming data was imported into graphic software Cinema 4D™ (Maxon Computer GmbH, Friedrichsdorf, Germany) and rendered using a custom-made plugin.

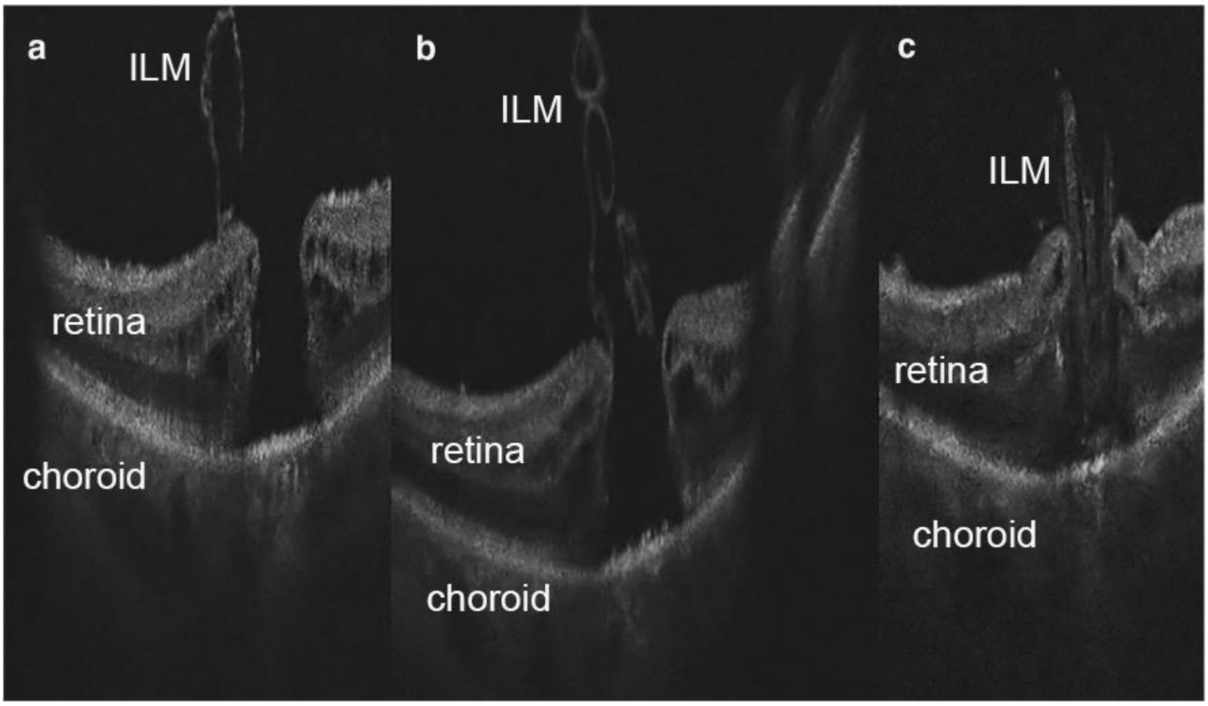

Figure 20. iOCT imaging of stages of inverted ILM flap technique. *a - Initiation of the ILM flap. b - Shortening of the ILM remnants attached to the MH edge. c - Inversion of the ILM flap into the MH. (L. Lytvynchuk et al. Dynamic intraoperative optical coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery. Graefes Arch Clin Exp Ophthalmol. 2019; Aug; 257(8): 1649-1659. Permission granted).*

Results. The study group included seven cases (6 patients) with large chronic full thickness MH and 1 case with recurrent full thickness MH. The mean size of MHs in this case series was 730.9 μm (range 439–1149 μm). The mean preoperative best corrected visual acuity was 0.19 (ranged 0.02 to 0.5 Snellen). The mean postoperative best corrected visual acuity was 0.28 (ranged 0.06 to 0.6 Snellen). Postoperative examination with hard definition OCT confirmed the closure of the MH in seven cases (cases 1–6, 8). Only in case 7 (recurrent MH) the size of the MH became smaller. All surgeries went without local or systemic complications in relation to the novel inverted or free ILM flap technique.

Dynamic iOCT imaging facilitated visualization of the retinal structures and microsurgical instruments during the whole surgery with IILMFT. In cases 1–6, and 8 iOCT system was able to visualize the ILM flap and cover the MH orifice with inverted ILM flap (Figure 19 B, Figure 20 c). In case 7 (recurrent MH) the free ILM flap was also visualized on the MH bottom. Intraoperatively the ILM flap that covered large MH after partial fluid-air exchange was visualized in all cases.

Analysis of iOCT imaging during pars plana vitrectomy with ILMFT demonstrated the decent quality of the data, which made it possible to reveal clinically significant findings.

During initial stage of the surgery, the use of iOCT allowed for imaging of the hypertrophic RPE at the bottom of the MH. As it was stated earlier, iOCT was not able to detect ILM, which became visible immediately after initiation of the ILM flap. It was possible to document all steps of inverted ILM flap technique: ILM flap formation, shortening, and inversion of the ILM flap attached to the 360° of hole edge (Figure 20). During imaging of the vitreoretinal instruments (end-gripping forceps, silicon tipped aspiration cannula) iOCT data revealed that steel tubing of the forceps and cannula caused a complete iOCT signal shadowing, which obscured the visualization of the area of interest. However, the jaws of the ILM-forceps caused very small and insignificant shadowing of the signal. The very tip of silicon tipped cannula demonstrated semitransparency in relation to the iOCT signal with a very small shadowing.

Analysis of iOCT data of response of the retinal tissue during IILMFT revealed the following entities: depression of retinal tissue during ILM flap initiation and peeling, appearance of hyporeflective zones in subretinal space caused by ILM, distance between the tips of the jaws of the ILM forceps and retinal pigment epithelium (RPE). Slight massaging of the retina during mechanical apposition of MH edges necessitated application of the pressure onto the retinal surface and resulted with indentation of the retinal layers. Nevertheless, the apposition of the MH edges allowed for decreasing of the size of the MH base (Figure 21). Hence, the mean preoperative MH base size before the massaging was 1.1 px (range 1.23–0.97 px), and after - 0.89 px (range 1.05–0.79 px). Dynamic iOCT imaging demonstrated that centripetal direction of the ILM peeling during IILMFT didn't induced the enlargement of the MH in opposite to conventional circular direction of the ILM peeling, as the tractional forces were heading the center of the macular hole, but not the side. iOCT imaging allowed for confirming the correct position of the ILM flap at the very end of the surgery with partial fluid-air exchange (vitreous cavity was filled up to 80–90% with sterile air). The results of post-processing of the iOCT data with 3D visualization showed a detailed depiction of the MH before and after ILM inversion (Figure 22). After analysis of 3D images, an appearance of superficial focal irregularities onto the retinal surface and splitting of the retinal layers after ILM peeling were revealed (Figure 22 D).

Discussion. The results showed, that the use of real-time iOCT imaging enabled visualization of almost all steps of the surgery with inverted ILM flap technique. The iOCT assisted surgical approach enabled to reassure the correct position of the inverted ILM flap onto the retinal surface after incomplete fluid-air exchange at the very end of the surgery (Figure 19 B, 20 c, 21). iOCT imaging revealed an important information about massaging of the retina, showing that this surgical maneuver causes the depression of the foveal area and can be potentially harmful if performed without iOCT control. It was detected that anterior-posterior direction of the peeling forces leads to the appearance of hyporeflective zones under the retina, that resemble to local damage of photosensory retina (Figure 22, D). At the same time, a tangential direction of the peeling forces could prevent potentially damaging consequences of the ILM removal. The distance between the retinal layers and surgical instruments was controlled with iOCT, as well.

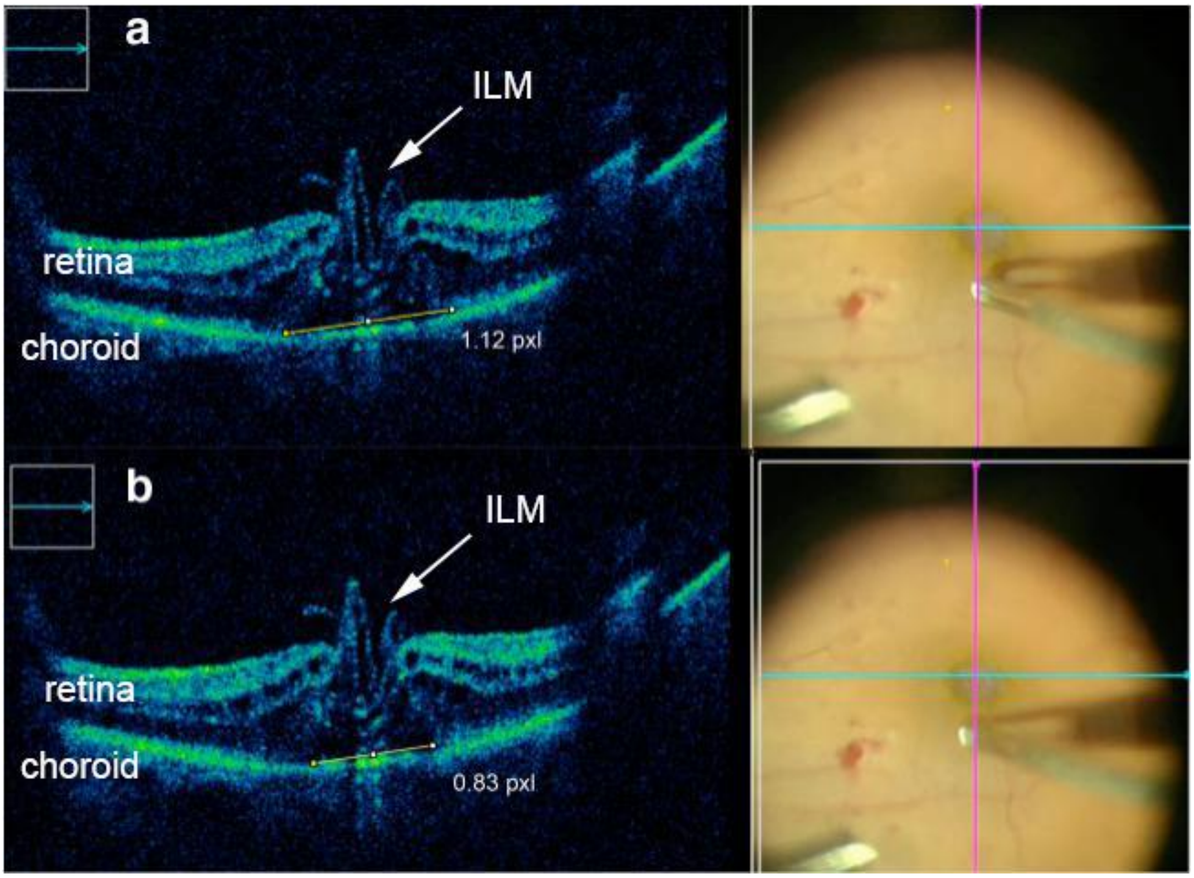

Figure 21. Decrease of bottom size of MH after mechanical apposition of the MH edges. *a - Before the apposition. b - After the apposition. The distance expressed in pixels (L. Lytvynchuk et al. Dynamic intraoperative optical coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery. Graefes Arch Clin Exp Ophthalmol. 2019; Aug; 257(8):1649-1659. Permission granted).*

The use of iOCT for inverted ILM flap technique was reported to be efficient but also to have some limitations (Borrelli et al. 2018, Maier et al. 2018). The authors reported that that the use of iOCT enabled to control the correct position of the ILM flap after complete fluid-air exchange. However, the data presented in their publications does not show the air meniscus in front of the retina. In our study we performed an incomplete air-fluid exchange at the end of the surgery, as complete filling of the eye with air was reported to be a risk for optic nerve dehydration with postoperative visual field loss (Hirata et al. 2000, Kokame 2000, 2001). Our study results demonstrated that slight massaging of the retina during the surgery decreases the size of the MH base which predisposes the healing of the full-thickness defect. Due to resolution limitation (3.5-5 μm in tissue) the iOCT imaging is unable to detect the ILM, which firmly adheres to the retinal nerve fibers layer. The 3D reconstruction of the iOCT data enabled to detect hyporeflective zones and epiretinal tufts, which clinical significance shall be investigated in the future (Figure 22 D).

The use of standard vitreoretinal instruments during macular surgery produced the shadowing of the area of interest on the retina, as the steel made tubing parts of the instruments block the penetrance of the iOCT signal. This limitation has not been resolved up till now and necessitates additional studies with development of the new instrumentation.

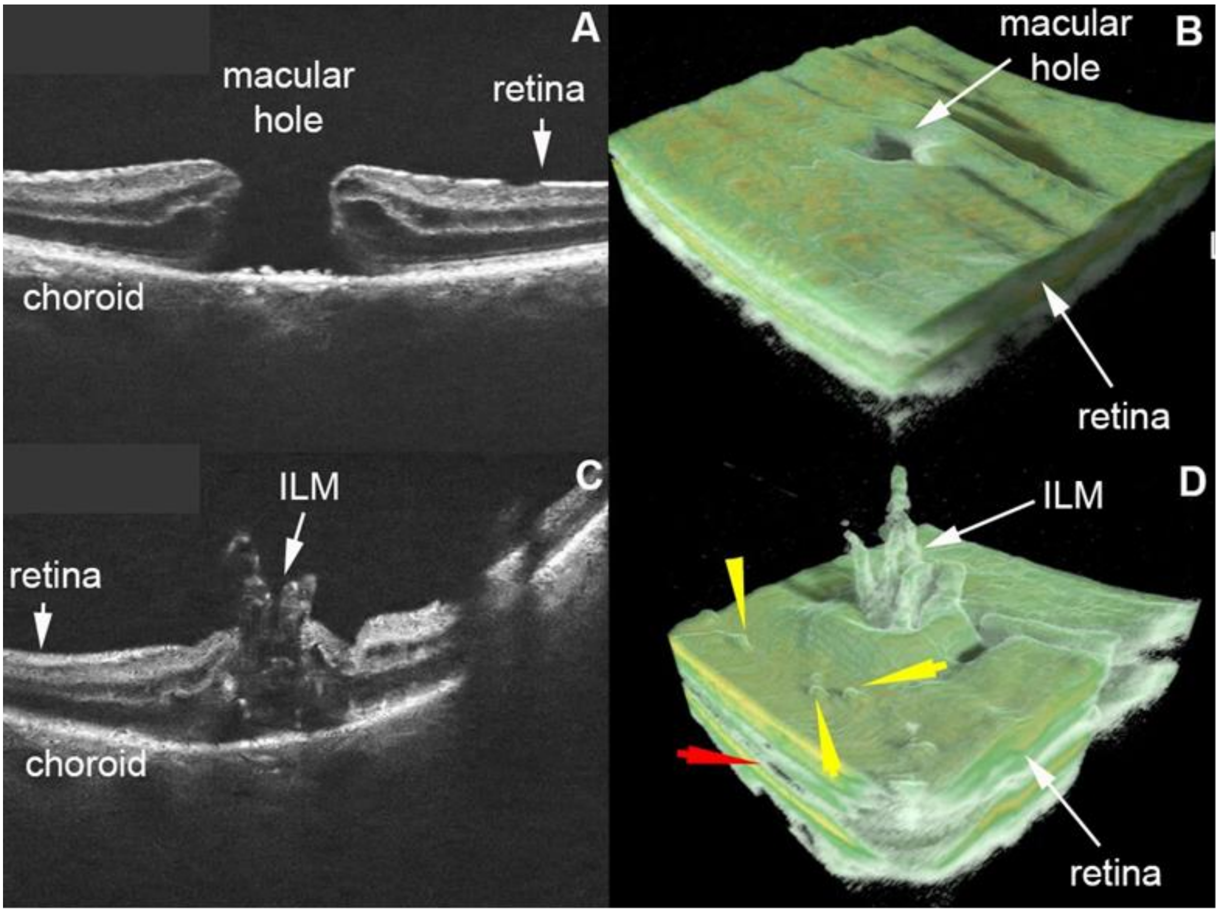

Figure 22. Intraoperative OCT imaging of the MH: *before (A, B) and after (C, D) the surgery with inverted ILM flap technique. D - Post-processing of iOCT images with 3D reconstruction enabled to detect hyporeflective zone (red arrow) and epiretinal tufts (yellow arrow) (L. Lytvynchuk et al. Dynamic intraoperative optical coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery. Graefes Arch Clin Exp Ophthalmol. 2019; Aug; 257(8):1649-1659. Permission granted).*

Summary. To conclude, the use of iOCT imaging appears to be an effective approach for learning curve and performing of a controlled and secure inverted ILM flap technique in patients with chronic and large MH. The real-time iOCT visualization has been shown not to be time consuming, and its value and clinical significance shall be investigated in future studies. Nevertheless, the clinical significance of the novel iOCT findings shall be further studied and interpreted in order to deepen our knowledge regarding the tissue response and healing mechanisms of the large MH.

3.1.3. Novel indications for iOCT imaging

Appendix 4

Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography.
Lytvynchuk L, Falkner-Radler C, Grzybowski A, Glittenberg C, Shams-Mafi F, Ansari-Shahrezaei S, Binder B. Spektrum für Augenheilkunde 2020(1);1-9.

Introduction. The complex and multifunctional structure of the retina makes it vulnerable for development of genetically determined disorders, which can affect only one or more retinal layers (Stieger and Lorenz 2010). Retinitis pigmentosa (RP) is one of these disorders, characterized by gradual loss of RPE and photoreceptor cells, while other layers remain functionally active (ganglion, bipolar, amacrine, horizontal, retinal nerve fiber cells). Among the new therapeutic methods of the genetically determined retinal diseases the most promising appear to be subretinal cell therapy, subretinal gene therapy and implantation of intraocular prosthesis (Lorenz et al. 2010). The main idea of these new therapeutic strategies is either to renew or to substitute the missing function of certain cellular complexes. Cell based therapies currently are being studied in several human clinical trials (Kundu et al. 2014, Schwartz et al. 2015, StemCells Inc. Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Age-Related Macular Degeneration), including subretinal implantation of stem cells that are meant to differentiate into the RPE cells, or differentiated RPE (Falkner-Radler et al. 2011, Binder et al. 2007, Xian et al. 2015). Subretinal injection of the cell suspension, subretinal implantation of the cell-supporting cell sheets and cell monolayer supported by the membranous scaffold belong to the main cell delivery techniques (Yaji et al. 2009, Hynes and Lavik, 2010, Sheridan et al. 2009). Gene based therapy also requires an injection of the gene modified therapeutic substance into the subretinal space, creating the conditions for expression of the transgenes within the retinal layers. Cell based therapy and gene therapy would be impossible without the development and improvement of the subretinal delivery techniques and instruments. Cellular suspension or genes containing substance are usually injected through a thin cannula (41-gauge). The success of the cell based or gene-based therapy is strongly dependent and correlates with the realization of surgical maneuvers, as the complications can even worsen the preexisting anatomical and functional condition of the retina.

Introduction into the clinic of principle of the bionic medicine became an alternative approach to treat certain degenerative retinal disorders, such as RP and age-related macular degeneration (AMD). Several intraocular prostheses were developed, tested and clinically applied during the last three decades. The studies showed favorable results in the matter of substitution of the photoreceptors' function. The main goal of the bionic eye treatment approach is to implant an intraocular prosthesis onto or under the central retina, which will take over the conversion of the light energy into the electrical impulse. To the most frequently implanted and studied intraocular prosthesis belong the Argus II Retinal Prosthesis System (AIIRP; Second Sight Medical Products, Inc., Sylmar, CA, USA), which was tested in patients with end stage RP and the atrophic form of AMD (Figure 23). The use of AIIRP aims to deliver electrical stimuli to the retina using epiretinal array of the prosthesis (Figure 23, C – intraocular part). It consists from the following parts: 1 - camera that is integrated into the glasses, 2 – videoprocessor, which transforms color signal to black and white signal, 3 – antenna, which transfers the signal to the extraocular part of the AIIRP (Figure 23 B).

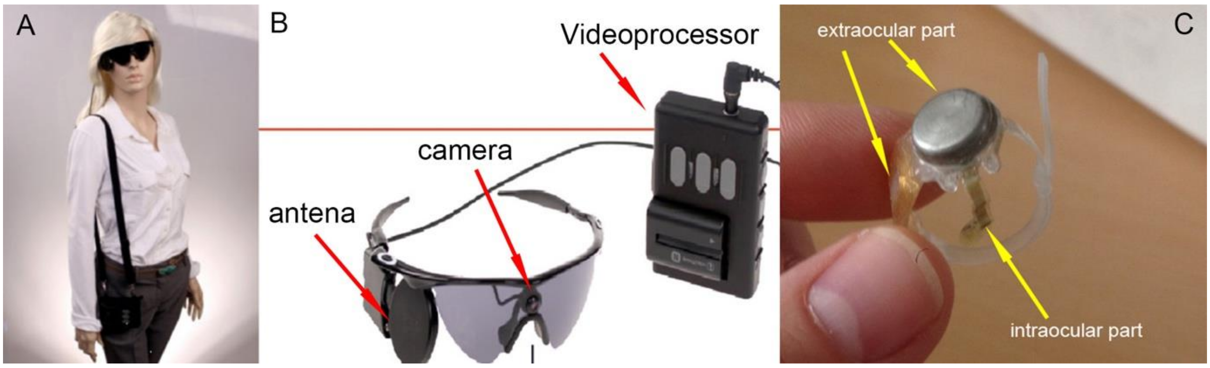

Figure 23. Argus II Retinal Prosthesis System. *A – general view of the patient using Argus II Retinal Prosthesis System. B – External parts of the system including camera, antenna and videoprocessor. C - Argus II Retinal Prosthesis with depiction of its extraocular and intraocular (array) parts (Binder S, Lytvynchuk L. Argus II Retina Implantat bei an Retinopathia pigmentosa erblindeter Patientin: Ein Fallbericht. Spektrum der Augenheilkunde 2016; 30:100-5. Permission granted).*

In patients with RP the inner retinal layers remain to be functionally active. That is why, delivered stimuli can be transmitted further to the optic nerve and optic pathways, creating a kind of visual perception of flashes. These shall be later interpreted by the patient.

A standard pars plana vitrectomy with epiretinal membrane removal remains a basic approach, which facilitates safe and efficient implantation of intraocular part of the prosthesis (Binder and Lytvynchuk 2016, Luo and da Cruz 2016, Rizzo et al. 2014).

The use of iOCT during cell based, gene therapy or implantation of intraocular prosthesis was recently reported and its feasibility was confirmed in a number of studies (Xue et al. 2017, Ehlers 2016, Kashani 2019, Lervin et at. 2004). With the assistance of iOCT imaging the surgeon can control the performance of the surgery and detect and treat complications, such as retinal hole or epiretinal membrane. After all manipulations are done, it is very useful to observe and document the condition of the operated retinal area at the very end of the surgery.

There are limited data about the use of iOCT imaging during implantation of epiretinal prosthesis (Rachitskaya et al. 2016, Binder and Lytvynchuk 2016). It was reported that iOCT imagining assisted to place correctly and fix an array on the macular area in relation to the foveal and optic nerve.

The residual distance between the retina and the posterior surface of the array determines the strength of the signal, which can be adjusted after the surgery in order to create effective stimuli. This distance can be measured with iOCT and the adjustment of the signal can be planned in ahead. Nevertheless, there are certain limitations of the application of iOCT during implantation of intraocular prosthesis. It was reported that surgery can last from 2 to 8 hours (Rachitskaya et al. 2016). The extended duration of the complex surgery can lead to the decompensation of the corneal epithelium with consequent corneal edema and opacification. This condition can influence the flow of the surgery and decrease the quality of iOCT signal. Even slight corneal opacification, which appears to be insignificant for the surgeon, can impact the quality of the iOCT signal and hereby reduce iOCT control of the procedure.

Aim of the study. The main aim of this study was to assess the impact of human eye optic media on intraoperative spectral-domain optical coherence tomography (iOCT) imaging of Argus® II retinal prosthesis (AIIRP) and retina surface during the surgery. As the iOCT assisted control of AIIRP imaging is becoming a gold standard during the surgery with bionic eye, this issue of iOCT image quality and resolution remains of a great interest.

Methods. In this comparative observational study we analyzed, compared and summarized the difference between AIIRP and retina iOCT-assisted imaging in a test eye without optic media and in a human eye with optic media in real-time conditions. It was reported that the mean duration of the surgery in patients was 3.5 hours (Rachitskaya et al. 2016).

The aim of Argus® II retinal prosthesis implantation, as a part of the Argus® II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA, USA) is to create the visual perception and improve quality of life of patients with RP, which developed to its end stage. The Argus® II retinal prosthesis (a sterile medical device) consists of the following elements: the implant coil, the electrode array, the electronic case, and a scleral band. During the surgery its extraocular part is placed and fixed onto the sclera and its intraocular part is placed and fixed with standard retinal tack onto the retinal surface (Figure 23 C). Intraocular part (electrode array) consists of 60 electrodes (6x10) and wire conductors, which are hermetically covered with silicon. Electrodes are connected with the electronic case placed onto the sclera.

Implantation of the AIIRP, exactly of its intraocular part, was the main object of the study, in which two AIIRPs were used: 1 - a sterile AIIRP used during implantation in patient with RP; 2 - a non-sterile AIIRP used during implantation in the test artificial eye. In both cases (in the human and test eye) a standard implantation technique of the electrode array was applied. However, a test polymer eye model was without all optic media: cornea, lens, and vitreous body. This created the conditions to compare the iOCT imaging of the array during its implantation in the eye with and without optic media in order to reveal their role for imaging quality.

iOCT imaging of the electronic array of the AIIRP was performed with iOCT system Rescan™ 700 (Zeiss, Oberkochen, Germany) (Table 3). The surgeon performed the visual control of iOCT imaging through the heads-up display. Fully integrated iOCT system facilitated the imaging of the implantation process without interruption of the surgical intervention.

For analysis of iOCT scans a graphic software ImageJ 1.48v (Wayne Rasband, NIH, USA) was used. The iOCT data were exported and post-processed. For image quality analysis an option “Histogram” of ImageJ 1.48v was applied. This option calculates the distribution of gray values in the selected image. The certain parts of the AIIRP array as well as retinal layers near and underlying the array were selected and analysed. The average histogram data were extracted and compared for imaging of the AIIRP in human and test eye. The results were statistically analyzed using Student’s t-test and the Mann–Whitney U test for continuous parameters as well as fort two independent Samples using software SigmaPlot Version 14.0 (Systat Software Inc., Chicago, IL, USA).

Results. Application of iOCT system allowed for a good visualization and imaging of the AIIRP array during and after its implantation in human and in test eye (Figure 24). In both cases the use of microscope-integrated iOCT imaging facilitated satisfactory quality of videos and snapshot. In the human eye the semitransparent AIIRP array enabled the imaging of the space and the retina under the posterior surface of the array.

The duration of the surgery in the human eye was 3 hours and 25 minutes. iOCT scanning of the array was performed before and after its fixation to the retina with the retinal tack (approximately 40 min before the end of surgery). The clarity of the first optic media – cornea, was maintained by covering the cornea with ophthalmic viscoelastic device. Intraocular lens and vitreous cavity remained clear during the whole surgery as well. The absence of the optic media opacifications enabled the imaging of all parts of the array. A slight hyperreflectivity was produced by the anterior and posterior surface of the array. However, the semitransparency of the polymer cover allowed for visualization of the underlying retina. The steel electrodes themselves blocked iOCT signal causing the shadowing onto the retina. The surgeon was able to bring into the focus any part of the array using foot control in order to prove the correct position of the entire array surface onto the retina.

iOCT imaging of AIIRP array in the test eye demonstrated satisfactory quality as well. Similar to the human eye it was possible to visualize the retinal surface of the test eye underneath the array in spite its slight hyperreflectivity.

Analysis of the quality of iOCT images and videos showed that the mean gray values of the histogram of the anterior and posterior surface of the AIIRP array in the human and the test eye were not statistically significant: p= 0.985 for anterior surface; p= 0.063 for posterior surface (Table 4).

Table 4. The mean gray values of the histograms of different areas of the AIIRP depicted in pixels in a human and a test eye *(Lytvynchuk, L.M., Falkner-Radler, C.I., Grzybowski, A. et al. Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography. Spektrum Augenheilkd. 34, 1–9 (2020). Permission granted).*

Imaging of ARIIRP	Eye	Mean	Min	Max	SD
Anterior surface of ARIIRP	Human eye	39.2	13	101	20.9
	Test eye	40.4	13	115	21.5
Posterior surface of ARIIRP	Human eye	39.6	15	103	19.1
	Test eye	39.2	13	134	20.8
Anterior-posterior surface of ARIIRP	Human eye	28.0	8	140	9.7
	Test eye	26.0	8	94	7.2

Analysis of iOCT imaging data of the retina under the AIIRP array and nearby demonstrated satisfactory quality. The difference of gray value of the histograms between underlying and lying near AIIRP array retina appeared to be statistically insignificant with p-value 0.566 (Table 5, Figure 25).

Table 5. The mean gray values of histograms of human retinal areas underlying and lying near the AIIRP array depicted in pixels *(Lytvynchuk, L.M., Falkner-Radler, C.I., Grzybowski, A. et al. Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography. Spektrum Augenheilkd. 34, 1–9 (2020). Permission granted).*

Imaging of the retina	Mean	Min	Max	SD
Retina under the ARIIRP	38.4	11	94	15.2
Retina near the ARIIRP	37.1	13	90	13.7

Discussion. During AIIRP implantation surgery, iOCT assisted surgical approach enable delivery of the real-time information about epiretinal adhesion of the vitreous body, epiretinal membrane, location of the AIIRP and condition of the underlying retina (Binder and Lytvynchuk 2016). Throughout iOCT imaging there was no interruption of the surgical flow and significant time consumption. Correct position of the AIIRP relatively to the optic disc and retinal surface appeared to be very important for delivery and intensity of stimuli (Seider and Hahn 2015, Rachitskaya et al. 2016). As the intraocular part of AIIRP consists of wires and electrodes that are coated with soft polymer, it limits its elasticity. Only in rare cases an AIIRP can be placed directly onto the retina. The intensity of the stimuli correlates with the distance between AIIRP and retina and can be adjusted postoperatively. iOCT approach allows for measuring the distance between AIIRP and retina, enabling calculation and prediction of the intensity of the stimuli in postoperative period (Seider and Hahn 2015).

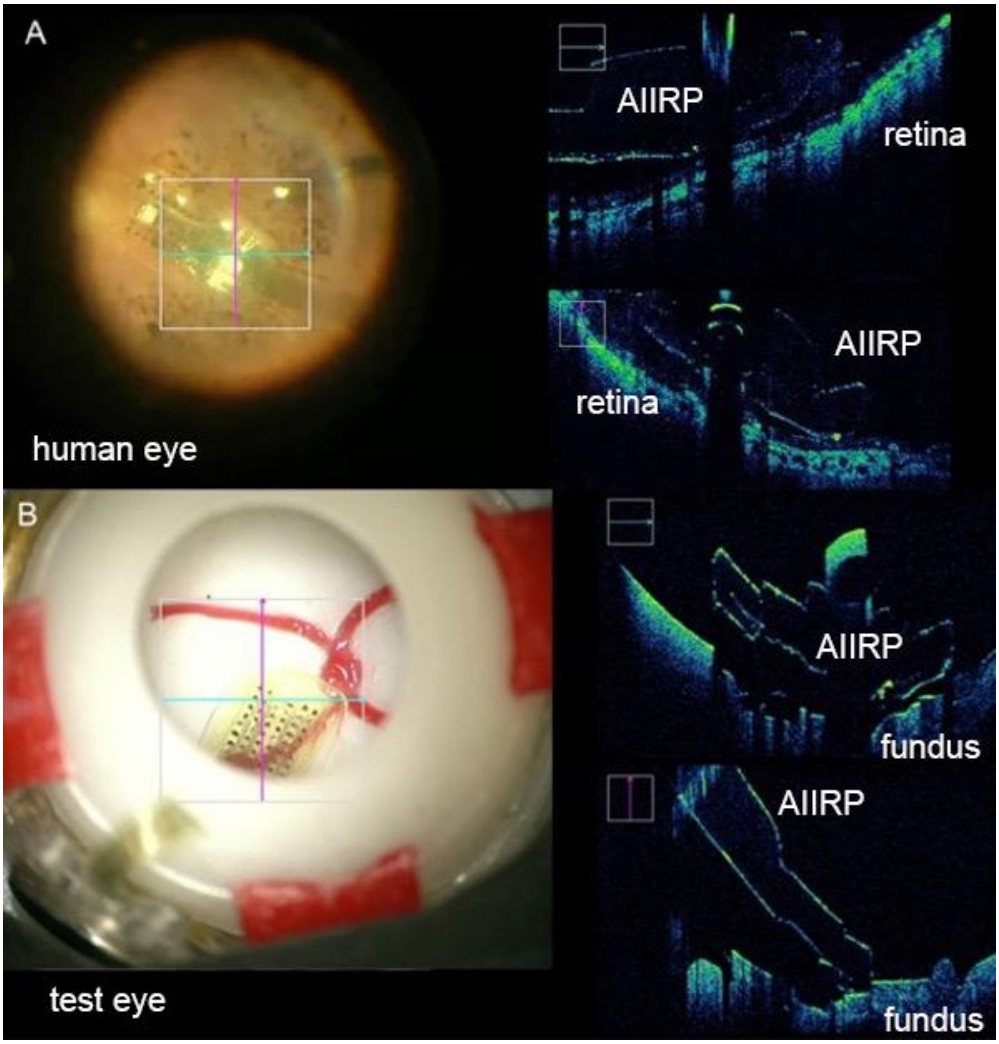

Figure 24. Microscopic view and iOCT imaging of intraocular part of AIIRP: *in human (A) with and in test eye (B) without optic media (L. Lytvnchuk et al. Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography. Spektrum für Augenheilkunde 2020(1): 1-9. Permission granted).*

The study results revealed the usefulness of the iOCT application for surgery with Argus II retinal prosthesis implantation. During iOCT assisted pars plana vitrectomy it was possible to reassure the complete removal of the vitreous body and ERM from the retinal surface in the area of the following AIIRP implantation and fixation (Video 2 – Supplemental material 2 on USB-Stick). This step considered to be crucial due to possible complications, such as ERM progression and retinal detachment. The quality of images of AIIRP appeared to be satisfactory and delivered useful information about prosthesis position and condition of the retina (Figure 24). The semitransparency of the intraocular part of the AIIRP to iOCT scanning beam allowed for controlling the condition of the underlying retina with comparable image quality of the near-lying retina (Figure 25).

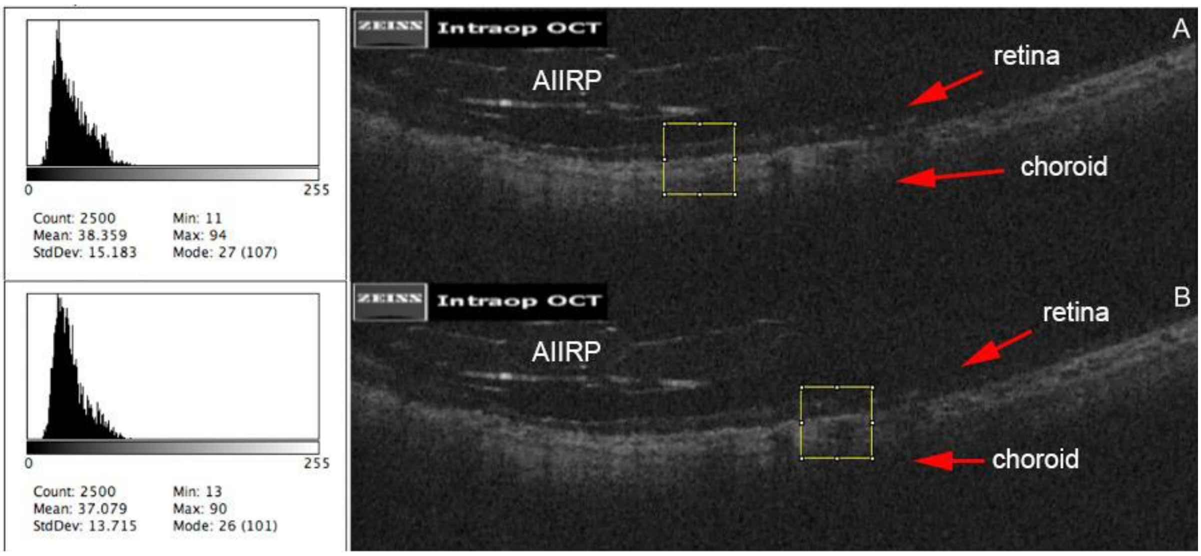

Figure 25. Analysis of histogram and iOCT signal quality of human retina: *retina underlying the AIIRP (A) and near laying (B) to AIIRP (yellow square). Red arrows indicate choroid and atrophic retina (L. Lytvnchuk et al. Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography. Spektrum für Augenheilkunde 2020(1): 1-9. Permission granted).*

Summary. The iOCT-assisted implantation of AIIRP allowed for imaging of the AIIRP array during its implantation. The quality of AIIRP array iOCT imaging was not impacted by uncompromised human optic media and the iOCT signal was not reduced significantly during all steps of the average lasting surgery (Figure 24). The influence of the opaque cornea in long lasting surgeries on the iOCT scan quality during AIIRP implantation shall be investigated further.

Future studies will explore the use of iOCT in new kind of the surgical approaches, which remain to be the most challenging part of the cell-based, gene therapy and bionic eye implantation.

3.2. New surgical techniques

3.2.1. Challenges and innovations in the treatment of pediatric cataract

Pediatric cataract is the most common disease of the lens in children (Solebo et al. 2017, Lambert and Drack 1996, Foster & Gilbert C 1992, Haargaard 2015, Chan et al. 2012, Gilbert at al. 1999, Zetterstrom et al. 2005). Congenital amblyopia or blindness initiate the entire row of life difficulties for a child and his or her family including developmental, socioeconomic, integration into the society (Lenhart et al. 2014, World Health Organization. Global initiative for the elimination of avoidable blindness. WHO 1997).

Epidemiology of pediatric cataract including its prevalence and incidence is dependent on the evaluation methods, reliabilities of the studies, different methods for data collection and difficulties by evaluating the visual functions in children (Trivedi and Wilson 2014, Liu 2017, Lambert and Lyons 2017, Zetterström et al. 2005). The incidence of pediatric cataract varies from 1 to 15 cases per 10,000 of children population (Foster et al. 1997). The prevalence of cataract-associated blindness in industrialized countries is around 0.1 to 0.4 per 10,000, when in developing countries the prevalence is significantly higher with the rate of 1 to 7 cases per 10,000 (Trivedi and Wilson 2014). It was estimated that over 200,000 pediatric patients remain blind on both eyes. The number of bilateral cataract cases in developing countries was reported to be around 10 children per 1,000,000 per 1 year (Trivedi and Wilson 2014).

Etiology of pediatric cataract is not always clear (Chan 2011, Merin 1991). The diagnosis necessitates the multimodal examination not only of the affected child but also the parents and sometimes relatives. Determination of the origin of pediatric cataract is crucial, as it can influence treatment indications and visual prognosis (Chan et al. 2012). Regarding to the age of appearance, pediatric cataract can be differentiated into congenital (present at birth), infantile (developing during the first two years of life) and juvenile (developing within first 10 years of life). In relation to the etiological factor pediatric cataracts are divided into hereditary, non-hereditary and idiopathic forms. It was reported that the incidence of idiopathic cataract can be up to 2/3 of all cataract cases (Haargaard et al. 2004). The presence of systemic and ocular infection plays an important role in development of pediatric cataract (Lorenz et al. 2002).

Morphology. It is important to know and understand the specifics of anatomical development of crystalline lens of the healthy lens including its physiology and functional performance (Brown 1977) (Figure 2, 3). Similarly to the majority of elements of visual system, the crystalline lens continues to develop and grow in non-linear fashion after the birth. During the first years of life the developmental changes undergo in all lens structures, including, capsular bag, lens epithelial cells, zonular fibers. Additionally, the lens increases in dimensions, in weight and volume. The elasticity of the capsular bag is changing, as well as lens position related to the iris, vitreous body and retina (Chen et al. 2017, Krag S et al. 1997). The standard classification of the pediatric cataract based on its morphology divides the cataract onto the following morphologic types, which could be a relative or absolute indication for surgical intervention: 1. Diffuse/total; 2. Anterior polar; 3. Cortical lamellar; 4. Fetal nuclear; 5. Posterior polar; 6. Posterior lentiglobus; 7. Posterior (and anterior) subcapsular; 8. Persistent fetal vasculature; 9. Traumatic (Parks 1982, Parks 1993). Differentiation of morphologic subtypes of pediatric cataract can serve often as prediction parameter for intra- and postoperative complication, as well as postoperative visual improvement. According to the Infant Aphakia Treatment Study (IATS), over 50% of congenital cases present with fetal nuclear opacities (Wilson et al. 2011). This type of cataract can be associated with persistent fetal vasculature and can necessitate an extensive surgical intervention.

Genetics of pediatric cataract. Modern knowledge in the field of genetic studies revealed a great number of etiologic factors, which can explain the cause of hereditary cataract in children (Lorenz 2007, Shiels A, Hejtmancik 2013). Approximately in 70% of hereditary cataract cases the isolated lens opacifications are present, and the rest 30% of case can be associated either with concomitant ocular abnormalities, or with systemic genetic disorders (Hejtmancik 2008, Graw et al. 2006). These cataract cases mainly are inherited via autosomal dominant transmission. However, autosomal recessive or X-linked transmission is possible as well. Disease causing mutations are associated with following genes: crystalline genes, regulatory genes of transcription factors, cytoskeletal protein genes, membrane protein associated genes, GCNT2 gene, growth factor genes, ferritin light-chain gene, chromatin-modifying protein genes. For example, mutation in genes that encode crystallines is responsible for more than 50% of hereditary pediatric cataract. Mutations in membrane protein genes, which are related to cataract formation, can be detected in gap junction protein (GJP), a major intrinsic protein of lens fibers, and lens intrinsic membrane protein-2 (LIM-2) (Wu et al. 2017). A typical Y-shaped structural cataract develops as a result of mutation in cytoskeletal protein genes (Beaded-Filament Structural Protein) (Liu 2017).

Hereditary cataracts linked to systemic abnormalities may be associated with a mutation of the paired-like homebox-containing gene 6 (PAX6), ferritin L-related gene, and chromosome linked genes (Lorenz 2007, Fold and Weingiest 1990, Cotlier and Rice 1971, Tripathi et al. 1986, Liu 2017, Pearce 1972, Falls et al. 1960). To chromosomal diseases that are associated with hereditary cataract belong trisomy 21, trisomy 13, Turner syndrome and Klinefelter syndrome (Liu 2017). Genetic diagnosis of hereditary cataract is becoming possible due to developments in the fields of molecular biology, mapping of the genes related to hereditary cataract and screening of the mechanisms of mutation (Lorenz 2019). Application of highly specific genetic diagnostic methods, such as, linkage analysis, direct sequencing of candidate genes, whole-exome and whole-genome sequencing allow establishing a clear clinical diagnosis.

3.2.2. Surgical treatment of pediatric cataract

The main purpose of cataract treatment in children is to restore the clarity of the visual axis and visual function as much as possible in order to facilitate the optimal visual rehabilitation and avoid amblyopia (Wilson et al. 2003, Obstbaum 1994, Zetterström & Kugelberg 2007, Nihalani & VanderVeen 2010, Wilson & Trivedi 2009). One of the main issues of pediatric cataract surgery remains the timing of the surgical intervention (Birch et al. 2009, Eriksen 2006, Bradford et al. 1994). The surgery of the pediatric cataract as well as adult cataract underwent a number of evolutionally developmental changes. Currently used surgical approaches could be divided into two main groups: with implantation of the IOL and without. Among the modern approaches there are lensectomy and anterior vitrectomy, lens-in-the-bag implantation technique and implantation of the IOL with optic capture technique (Gupta et al. 2014, Kim et al. 2012, Haargaard et al. 2009, Zetterstrom et al. 2007, Kuhli-Hattenbach et al. 2016, Wilson 2004, Vasavada and Vasavada 2017, Gimbel 1996). One of the most common complications of cataract surgery with IOL implantation in children is secondary visual axis opacification. Regarding to the fact that posterior capsule of the lens is removed during the majority of the conventional surgical approaches with IOL implantation, the rate of posterior capsule opacification (PCO) and visual axis reopacifications (VAR) still remains significant (Trivedi et al. 2004, Planger et al. 2014, Hosal & Biglan 2002, Trivedi et al. 2011, Plager et al. 2002). Other complications related to the current surgical approaches are anterior capsule rupture, posterior synechia, intraocular hypertension and uveitis (Gradin & Mundia 2011, Kirwan et al. 2010, Knight-Nanan et al. 1996, Plager et al. 2014, Zetterberg et al. 2015, Tassignon et al. 1996, Kirwan and O'Keefe 2006).

The achievement of the optimal postoperative anatomical and visual outcomes is strongly dependent on the choice of surgical technique, as every cataract surgery can be associated with postoperative complications including posterior capsular opacification, glaucoma, endophthalmitis, retinal detachment, choroidal detachment, etc. (Freedman et al. 2015, Vasavada et al. 2011, Agarkar et al. 2017, Gradin & Mundia 2011).

In the 90’s a Belgian ophthalmologist developed a novel and very promising surgical technique for pediatric cataract treatment – bag-in-the-lens (BIL) (Tassignon et al. 2002, Tassignon et al. 2007, Tassignon 2014) (Figure 26 B). It showed already superior results compared to the conventional approaches. Because the BIL IOL technique is considered to

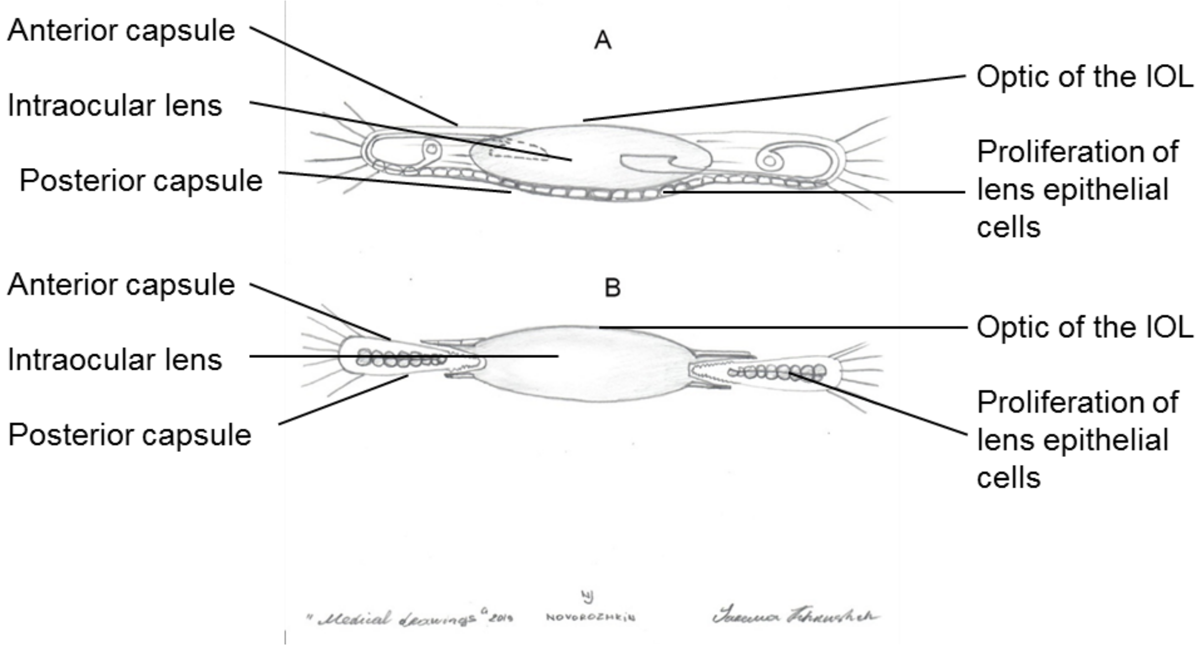

Figure 26. Schematic illustration of conventional lens-in-the-bag (A) and bag-in-the-lens (B) IOL implantation technique (Created by J. Khrushch).

be more challenging it is not yet widely accepted. However, the use of iOCT imaging during BIL IOL implantation enables to control the correct insertion and position of the new lens and can serve as a very efficient controlling tool during the learning curve (Figure 27).

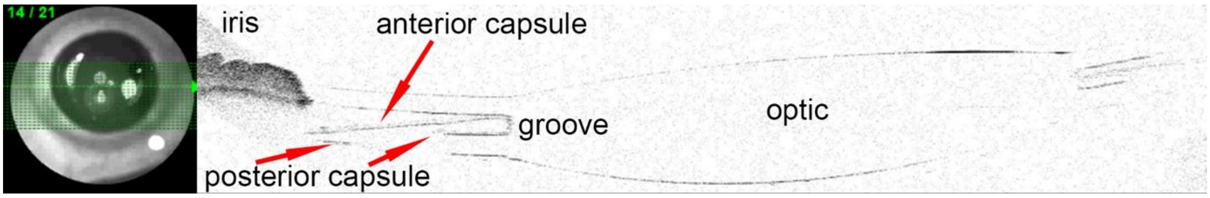

***Figure 27. Intraoperative OCT imaging of the correctly implanted BIL IOL.** Both anterior and posterior capsules (red arrows) inserted into the IOL groove (imaging with SPECTRALIS Flex Modul, Heidelberg Engineering, Heidelberg, Germany). Intraocular acrylic IOLs possess a low reflectivity (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

Modern surgical techniques, which are applied for treatment of pediatric cataract, allowed for making the surgery minimally invasive and relatively safe and short (Nischal 2016, Vasavada & Vasavada 2017, Dahan and Salmenson 1990). In spite increased knowledge about the pediatric eye, cataract pathophysiology, causes of intra- and postoperative complication, and progress of surgical systems, instrumentation and foldable IOLs, the role of major postoperative complications remains significant during the postoperative period in children (Harsum et al. 2010).

Two book chapters are dedicated to this particular topic:

Appendix 5

Preparing Pediatric Cataract Patients for BIL Cataract Surgery
Lytvynchuk L, Kuhn D, Sander M, Lorenz B. In: Tassignon M-J, Dhubhghaill S, van Os L (ed.). Innovative Implantation Technique: Bag-in-the-Lens Cataract Surgery. Springer Nature. Switzerland AG 2019: 197-206.

Appendix 6

Visual Outcomes and Complications After BIL in the Peadiatric Population
Lytvynchuk L, Lorenz B. In: Tassignon M-J, Dhubhghaill S, van Os L (ed.). Innovative Implantation Technique: Bag-in-the-Lens Cataract Surgery. Springer Nature. Switzerland AG 2019: 206-225.

In these book chapters, the information about conventional and novel approaches regarding preparation and treatment of pediatric cataract patients is summarized.

3.2.3. Calculation of the intraocular lens power in children

Appendix 7

Precision of bag-in-the-lens intraocular lens power calculation in different age groups of pediatric cataract patients: report of the Giessen Pediatric Cataract Study Group.
Lytvynchuk L, Thiele L, Schmidt W, Lorenz B. Journal of Cataract & Refractive Surgery. 2019; 45:1372–1379.

Introduction. Calculation and selection of intraocular lens power in children differs from those in adults (Dahan & Salmenson 1990, Wilson et al. 2001, Wilson & Trivedi 2007, Eibschitz-Tsimhoni 2007). Almost always the main aim of the IOL power calculation in adults is postoperative emmetropia. In contrast, in children the main purpose during IOL power selection is to target emmetropia in adulthood, as the eye grows from infancy to adulthood resulting in a significant decrease in the refractive power (Lorenz et al. 1993). As there may be significant deviations from the physiological decrease in power in real life, target refraction is still a matter of debate. Moreover, during IOL power calculation the surgeon and the whole team shall keep in mind that the cataract surgery is only the beginning of the entire treatment process, including the long period of follow-ups, aggressive amblyopia treatment and visual and social rehabilitation. The choice of IOL is strictly dependent on the preoperative target refraction and postoperative plan of the surgeon regarding amblyopia treatment (Lambert et al. 1999, Bowman et al. 2007).

Calculation of the IOL power necessitates a thorough ocular examination with measurements of preoperative refraction (if possible), axial length, corneal radii, anterior chamber depth, and lens thickness of both eyes. All formulas for IOL power calculation were designed for adult eyes, as they are based on the numerous calculation protocols of the adult patients. Some formulas were modified for so called *short eyes* with axial length <21 mm (Hoffer & Savini 2017, Hoffer 1993). Even though, these formulas did not bring the desired precision during IOL calculation in children (Long et al. 2012, Plager et al. 2002).

There are two types of formulas for IOL power calculation: theoretical and regressive (Mezer et al. 2004). To the most frequently used formulas for IOL power calculation belongs Hoffer Q, Haigis, Holladay, SRK/II, SRK-T (Hoffer 1993, Retzlaff et al. 1990, Thanapaisal et al. 2015). According to the reports, the mean calculated absolute prediction error for these formulas in adult cataract surgery is <0.6 D (diopters) (Mezer et al. 2004). Numerous studies have demonstrated that the prediction error in children is higher compared to adults (Mezer et al. 2004, Andreo et al. 1997, Moore et al. 2009, Enyedi et al. 1998, Andreo et al. 1997). A number of factors can influence the increase of prediction error in children (Eibschitz-Tsimhoni et al. 2007, Vasavada et al. 2016, Tromans et al. 2001, Vanderveen et al. 2013). Precise examination of pediatric cataract patients requiring surgery during the first 3 years of life is usually possible only in general anesthesia with the use of hand-held instrumentations. This can cause the larger error and influence precision of the measurements. It was shown that the use of SRK/T formula leads to the least prediction error in pediatric patients with axial length <20 mm (Vasavada at al., 2016, Kekunnaya et al. 2012, Lee et al. 2018). In the last decade there were proposed the 4th generation formulas, such as, Barrett Universal II formula, Hill-RBF formula, and Olsen formula (Roberts et al. 2018, David et al. 2016). With these formulae surgeons can calculate and predict the postoperative refraction more precisely. The reason for that is that these formulas use additional parameters of the eye, which are measured with the optical devices that use a diode-light beam (https://rbfcalculator.com/online/). In order to perform such measurements, the patient needs to be compliant. This is not possible in children. The limitation of the commonly used formulas can be explained also, as the improvement of each formula usually is based on the huge volume of the previously operated eyes, and these eyes are adult eyes. Moreover, conventional formulas are developed to calculate the IOL power when it is implanted in the lens bag. It makes the use of these formulas limited in the cases of alternative or newly developed IOL implantation techniques in children.

Selection of the correct IOL power in children remains challenging as well (Trivedi & Wilson 2011, Kumar & Lambert 2016). The dimensions of the eye change together with the optic system. This results in a decrease in refraction, the so-called myopic shift, and makes it difficult to predict the final refraction of the operated eye in adolescent age. It was reported that an average myopic shift can vary from 5.5 D to 6.2 D during first 12 to 22 months after the surgery (Lambert et al.1999, Hoevenaars et al. 2011). In previous practice the surgeons used to implant in children IOLs with a power that was usually implanted in adults (Hiles 1984, Burke et al. 1989). The vast majority of pediatric cataract surgeons choose to target hyperopia of different grade as an ideal refraction. One of the first reports dedicated to the target refraction in children describes the recommendation for implantation and suggest choosing +5.0 D as initial target refraction in cases with congenital cataract with slow decrease of the diopters to 0 at age of 13 years (Plager et al. 2002). Since then a number of recommendation tables were proposed by different authors, which are mainly oriented on postoperative hyperopia after the surgery in first months with reduction to emmetropia at the age between 7 and 14 years (Enyedi et al. 1998, Plager et al. 2002, Trivedi and Wilson 2017). The target refraction shall be carefully considered in each single case as there are many other additional factors that can influence the selection of the target refraction, including possibility to regularly follow-up the patient, social family situation, alternative surgical approaches (Bradford et al. 1994). For BIL IOL power calculation in children the SRK/T formula was used (Tassignon et al. 2007; Van Looveren et al. 2015; Nyström et al. 2018, Gobin et al. 2011). One of the most important issues during the preparation to the BIL IOL implantation surgery remains the congruence between target refraction of the chosen IOL power and postoperative achieved refraction in pediatric cataract patients. This concern is also challenging for conventional techniques. For this reason, the study of precision of BIL IOL power calculation is very important, in order to demonstrate similarity of the novel technique and to promote it in regard of its positive clinical results, that have been already reported.

Aim of the study. In this article we present one of the study arms of the Giessen Pediatric Cataract Study - the study of precision of the BIL IOL power calculation in pediatric cataract patients in different age groups. An absolute prediction error (PE) – the difference between target refraction and achieved refraction – was in the main focus of this study, as it is very important to be able to predict postoperative refraction in children in accordance to the planning of postoperative amblyopia treatment and in accordance to the expected decrease in refraction over time, the so-called myopic shift. Additionally, we analyzed correlation between an absolute prediction error and axial length, corneal radii and postoperative astigmatism.

Methods. To this retrospective non-randomized single-center study were enrolled 56 consecutive pediatric patients (85 eyes) with diagnosis of cataract (Table 6). All patients in this cohort underwent cataract surgery with bag-in-the-lens IOL implantation. Study period was from January 2008 till May 2018. The presence of pediatric cataract and use of hydrophilic acrilic IOL Morcher Type 89A (79 eyes)/Type 89A Toric (2 eyes)/Type 89F (4 eyes) (Morcher GmbH, Stuttgart, Germany) were the basic inclusion criteria. All patients underwent specific ophthalmologic examination before and after the surgery. For better data analysis all patients were divided into four age groups: 1st group - 0-younger than 3 months, 2nd group - 3 months but younger than 12 months, 3rd group - 12-36 months, 4th group - older than 36 months up to 17 years of age.

One of the most challenging examinations for this study were autokeratorefractometry and biometry. In uncooperative patients examinations were performed with a hand-held device Retinomax (Righton, Selangor, Malaysia) and with ultrasound contact method using Alcon Ocuscan RxP (Alcon Lab., Fort Worth, TX, USA) in general anesthesia. Older and cooperative patients were examined preopreratively with non-contact autokeratometry and non-contact biometry using an Auto Refractometer AR-610 (Nidek Co., Ltd., Aichi, Japan) and with IOLMaster 500 (Carl Zeiss Meditech, Oberkochen, Germany), respectively.

Calculation of BIL IOL power. In this study the calculation of BIL IOL power was performed using the SRK/T formula in all age groups. The IOL power was calculated with the IOLMaster Software Version 7.7.4.0326 (Carl Zeiss Meditech, Oberkochen, Germany) using the A constant (118.2) of BIL IOL from the manufacture company (Morcher GmbH, Stuttgart, Germany). The highest BIL IOL power used in our operating facility was 36.5 D. All refraction readings were obtained after instillation of a combination of tropicamide 1.0%, and atropine 0.5% eye drops (0.1% atropine eye drops in infants <3 months of age).

Surgical technique. All patients underwent surgical treatment in general anesthesia. In all cases a standard technique for BIL IOL implantation which was described by Tassignon at al. was applied. After mydriasis was reached, a temporal approach and additional 1 or 2 paracentesis were performed. Anterior continuous curvilinear capsulorhexis (ACCC) (opening of the anterior lens capsule) was performed using caliper ring Type 4L with diameter 4.3 mm (Morcher GmbH, Stuttgart, Germany), which was positioned on the surface of the anterior capsule and then removed. The lens was aspirated in all cases without use of ultrasound. After that an anterior and posterior capsule were brought together with sodium hyaluronate 1.2% and through the perforation of the posterior capsule (PC) the anterior vitreous was separated from the posterior capsule with injection of sodium hyaluronate

1.2%. Then a posterior continuous curvilinear capsulorhexis (PCCC) was performed. The BIL IOL was implanted through a 2.2 mm cartridge (Medicel AG, Thal, Switzerland) and edges of both capsulorhexises were inserted into the groove of the BIL IOL using gentle right-to-left movement. Finally, the pupil was constricted with injection of Myochol 2-5 mg. The corneal wounds were closed with Vicryl 10.0. At the end a 0.05 ml of cefuroxime was injected in anterior chamber for prophylaxis of infection.

Analysis of BIL IOL power calculation. To analyze the precision of BIL IOL power calculation the following parameters were analyzed in regard to each age group: target refraction, early postoperative refraction, prediction error, and change in corneal astigmatism. The desired target refraction (DTR) was determined as follows: 1st group (0-3 months) + 10.0 diopters (D), 2nd group (>3<12 months) - +8.0 D, 3rd group (12-36 months) - +6.0 D - +3.0 D, and 4th group (>36 months - 17 years) - +2.0 D - 0.0 D. The selected target refraction (STR) of the IOL was chosen based on available IOL power. In unilateral cases the DTR and STR were chosen depending on the refraction of the contralateral eye. All IOL (power in diopters) were calculated using SRK/T formula. Postoperative achieved refraction (AR) was defined as postoperative spherical equivalent. The precision of IOL calculation - the prediction error (PE) – was described as absolute difference between STR and postoperative achieved refraction (AR) (absolute value in diopters). Additionally, the influence of axial length, corneal radii, age and time of the surgery on the precision of the calculation of IOL power was analyzed in all age groups. Postoperative astigmatism relatively to the main incision was in 10 eyes (8 patients).

Statistical methods. The results were analyzed using Student's t-test and Mann-Whitney U-test for continuous parameters and fort two independent samples, respectively. The PE was analyzed using the t-test, with $p < 0.05$ considered as significant (SigmaPlot Version 14 (Systat Software Inc., Chicago, IL, USA)).

Results. Eighty-five eyes of 56 patients were included to the study with 22 females (39.3%) and 34 males (60.7%). The distribution of the age and characteristics of axial length and corneal radii are presented in Table 6**.** Unilateral cataract was present in 27 patients (48.2%), and bilateral cataract - in 29 patients (51.8%). The mean follow-up period was 1.93 month (range 0.03-10.82 months) with the following distribution in age groups: 1st group - 1.56 months (range 0.16-4.44 months), 2nd group - 2.52 months (range 0.03-10.09 months), 3rd group - 3.18 months (range 0.03-10.82 months), 4th group - 1.21 month (range 0.03-4.14).

Analysis of BIL IOL power calculation. The mean power of BIL IOL that was implanted in the entire group was 24.78 D (range 8-36.5 D). The mean postoperative achieved refraction (AR) for the whole group was 2.95 D (range 3.75-13.25 D). Drop of AR toward 0.00 diopters was noticed in each age group. Additionally, a myopisation of refraction in age groups 3 and 4 was present. The mean PE was highest in the 1st age group with a mean value of 3.43 D. It decreased gradually to 1.33 D in the 4th age group (inverse correlation with age) with statistically significant difference of PE between the 1st and the 4th age group (p=0.020). The difference of PE in patients younger and older than 36 months was statistically significant (p=0.039). The mean PE was higher in eyes with AL < 20mm with 2.67 D than in eyes with AL ≥ 20mm with 1.44 D, and the difference was statistically significant (p < 0.001). The correlation of PE with corneal radii did not show a statistically significant difference (p=0.110) (Table 6).

Table 6. Analysis of prediction error (PE): *The red figures are showing the mean PE related to the age, AL and corneal radii (L. Lytvynchuk et al. Precision of bag-in-the-lens intraocular lens power calculation in different age groups of pediatric cataract patients: report of the Giessen Pediatric Cataract Study Group. Journal of Cataract & Refractive Surgery. 2019; 45:1372–1379. Permission granted).*

				Prediction error, D				
Groups		**Patients**	**Eyes**	**mean**	**median**	**min**	**max**	**SD**
Entire group		56	85	1.79	1.23	0.01	7.02	1.63
Age at surgery	**1st age group**	5	9	3.43*	3.33	0.21	7.02	2.45
	2nd age group	13	19	2.14	2.17	0.01	4.41	1.54
	3rd age group	13	18	1.60	1.12	0.07	6.93	1.59
	4th age group	25	39	1.33*	0.91	0.02	5.82	1.16
Axial length	**<20 mm**	16	24	2.67●	2.34	0.21	6.12	1.65
	≥20 mm	40	61	1.44●	0.89	0.01	7.02	1.50
Corneal radii	**<7,3 mm**	8	15	2.45	1.64	0.27	6.12	1.96
	≥7,3 mm	45	66	1.66	1.12	0.01	7.02	1.57

*, ● – statistically significant difference.

The mean preoperative astigmatism of 10 eyes (8 patients) was -2.35 D (range -0.37 D - -8.00 D), with mean axis of 36.5°(range 166°- 2°). The mean postoperative astigmatism was -1.55 D (range -0.5 D - -5.75 D) with mean axis 64.5°(range 180°- 4°). A temporal corneal tunnel was performed in 9 eyes and a superior tunnel on 1 eye. For right eyes: the mean preoperative astigmatism was -2.7 D (range -0.86 D - -8.0) with axis 62°(166°-6°), and the mean postoperative astigmatism was -1.45 D (range -0.75 D - -2.5 D) with axis

22.6°(67°- 5°). For left eyes: the mean preoperative astigmatism was -1.998 D (-0.37 D - -3.75 D) with axis 11°(16°-2°), and the mean postoperative astigmatism was -2.15 D (-0.5 D - -5.75 D) with axis 106.4°(180° - 4°).

Discussion. Primary implantation of IOL during uncomplicated pediatric cataract surgery becomes the standard protocol in many eye centers worldwide. Selection of the target refraction as well as IOL power remains challenging. Postoperative refraction is dependent on the planned postoperative amblyopia treatment. Introduction of the novel surgical method with bag-in-the-lens implantation technique, which significantly reduced the rate of PCO and VAR, faced with the similar issues regarding IOL power calculation and selection. Moreover, there is no consensus which calculation formula shall be used.

Among the most precise formulas that showed better preoperative prediction of postoperative refraction in children are SRK/T, SRKII and Holladay 1 (Vanderveen et al. 2013, Kekunnaya et al. 2012). The developer of the BIL IOL technique reported the use of SRK/T formula for children.

To the factors that can influence the postoperative refraction during calculation of BIL IOL power belong: choice of formula for IOL calculation, measurement of postoperative refraction, age at the time of surgery, and changes of axial length during the growth of the eye.

In our study we report the results of analysis of postoperative refraction after BIL IOL implantation in children of different age groups with regard to axial length, corneal radii and postoperative astigmatism. The study was focused on the evaluation of postoperative refraction in pediatric patients after BIL IOL implantation that was calculated with SRK/T formula. The results of our study demonstrated that the prediction error with BIL IOL technique appeared to be comparable to that in reports, which studied lens-in-the-bag implantation technique. Postoperative prediction error (PE) showed a strong inverse dependence with age at surgery: PE was highest in children in the youngest age group (mean PE 3.43 D), and lowest in 4th age group (mean 1.33 D). The PE appeared to be higher in eyes with AL <20 mm (mean PE 2.67 D), compared to eyes with AL≥20 mm (mean PE 1.44 D) with statistically significant difference (p=0.001). However, there was no significant impact of different corneal radii on PE (p=0.110).

The predictability of formulae for IOL calculation in infantile eyes with unilateral congenital cataract in the Infant Aphakia Treatment Study Group was reported by Vanderveen et al. The authors showed that SRK/T and Holladay 1 formulas presented better results of IOL calculation compared to other formulas. Kekunnaya et al. also analyzed the predictability of SRK II, SRK/T, Holladay I, and Hoffer Q formulas for cataract surgery in children. The study results demonstrated superiority of SRK II for pediatric eyes. The highest PE was revealed in children younger than 2 years of age. Tassignon at al. and Van

Looveren et al. first reported the results of BIL IOL implantation in a pediatric population. For BIL IOL calculation they used SRK/T formula. Additionally, Nystrom at al (2018) reported the results of BIL IOL implantation in children but without indication of formula for IOL power calculation. In our study we used SRK/T formula for all cases as it was first used by developer of BIL IOL and first published for this technique, accordingly.

The correlation of the PE with the age of the patient for non-BIL IOL implantation technique was reported by Tromans et al. They showed that PE was significantly higher in eyes of children younger than 36 months (mean PE 2.56 D) in comparison to in eyes of children older than 36 months (mean PE 1.06 D). The analysis of PE in patients younger and older than 36 months was also performed in our study with implantation of BIL IOL. The results were comparable to the data for mentioned above study with mean PE of 2.19 D in children aged <36 months, and mean PE of 1.33 D in children aged ≥36 months (p-value 0.039).

To the limitations of this study belong first of all an unequal number of patients in each age group. As pediatric cataract is one of the rare diseases, it is difficult to plan the study with equal number of patients of different age. The measurement of the postoperative refraction is also an issue in children in early postoperative period and is not always possible direct after the surgery, especially in young children. The general anesthesia as an alternative support for such autokeratometry was not considered, as it has possible systemic reaction. The use of a single of SRK/T formula for BIL IOL calculation could be another limitation. The 4th generation formulas reported to be more accurately. However, the implication of these formulas for children is limited, as these formulas necessitate optically measured biometric data, which is not possible to obtain in vast majority of pediatric patients. The Haigis formula could be an alternative formula. It requires an additional value - anterior chamber depth. This value is, however, not absolute, as it changes constantly with the growth of the eye.

The modification of the formulas for bag-in-the-lens IOL implantation technique probably shall be considered.

Summary. The prediction error (PE) of IOL power calculation in pediatric cataract cases is larger than that in adults. Moreover, it was already reported for LIB technique, that PE is larger in pediatric eyes younger than 36 months and in eyes with axial length smaller than 20 mm. However, all these data is only relevant to lens-in-the-bag implantation technique with or without posterior capsulorhexis and with or without optic capture technique. In contrary, the position of the BIL IOL after its implantation seems to be more stable. This can influence the precision of the BIL IOL. The results of our study for the first time showed the values of the PE in relation to the different age groups, axial length, corneal radii and postoperative astigmatism especially for BIL IOL implantation technique.

Comparison of the similar studies of lens-in-the-bag technique with our data for BIL IOL technique demonstrated that there was no superiority of the LIB IOL implantation technique. BIL IOL technique in the matter of prediction of IOL power appeared to be safe, well tolerated and repeatable. The outcomes of our study support the efficacy of the novel surgical technique with implantation of BIL IOL in children and shall serve as a promoting argument for its wide use among the surgeons worldwide dealing with pediatric cataract.

3.2.4. Complications after pediatric cataract surgery and its management

Appendix 8

Analysis and management of intraoperative and early postoperative complications of bag-in-the-lens intraocular lens implantation in different age groups of paediatric cataract patients: report of the Giessen Paediatric Cataract Study Group.
Lytvynchuk L, Thiele M, Lorenz B. Acta Ophthalmol. 2020;98(2):e144-e154.

Introduction. Posterior capsular opacification (PCO) or/and visual axis reopacification (VAR) are among the most common postoperative complications after pediatric cataract surgery. During conventional lens-in-the-bag technique the posterior capsule remains intact and serves as a scaffold for postoperative proliferation of the lens epithelial cells obscuring the visual axis. Despite the fact primary posterior continuous curvilinear capsulorhexis (opening of the posterior lens capsule during the primary surgery) was introduced in children, the rate of VAR was reported to be from 8% to 80% of cases (Trivedi et al. 2004, Plager et al. 2002). The development of VAR usually is seen in the early postoperative period (within first 6 months). This complication necessitates additional surgical intervention due to secondary visual deprivation, which is certainly associated with new challenges, difficulties and risks. In order to solve this problem a new concept of IOL and implantation technique was introduced and applied in clinical practice in the early 2000s by Professor Marie-José Tassignon from Antwerp, Belgium (Tassignon et al. 2005, De Groot et al. 2005, Tassignon 2014). Initially, a newly developed bag-in-the-lens (BIL) IOL implantation technique was applied routinely during cataract surgery in adults (De Groot et al. 2006, Verbruggen et al. 2007, Tassignon et al. 2011). The first clinical results were reported and showed the considerably decreased rate of PCO with almost no use of neodymium:YAG laser after the surgery for posterior laser capsulotomy (Tassignon et al. 2002, Tassignon et al. 2006, 2011, 2006, Leysen et al. 2006). After 4-year experience on adults the BIL technique was introduced to pediatric cataract surgery with the advantageous results regarding to the reduction of PCO and VAR (Tassignon et al. 2007, Tassignon et al. 2009, Van Looveren et al. 2015, Nyström et al. 2018). In opposite to LIB, BIL IOL implantation technique is more complex and necessitates extra skills, especially during performance of capsulorhexes. However, the complexity is not comparable to the favorable postoperative results.

The BIL IOL implantation technique includes the performance of anterior continuous curvilinear capsulorhexis of a well-defined diameter (4.3 mm to 5.0 mm) and removal of the lens in a standard manner. However, instead of filling of the capsular bag with ophthalmic viscoelastic device and implanting IOL into the capsular bag, additional manipulations are required. The anterior chamber only shall be filled with ophthalmic viscoelastic device, bringing the remnants of the anterior capsule and posterior capsule together. Then, through the small punctured opening in the posterior capsule, with the help of injected ophthalmic viscoelastic device the anterior vitreous shall be separated from the posterior capsule. Anterior vitreous surface shall be left intact. After creation of space behind the posterior capsule, primary posterior continuous curvilinear capsulorhexis is performed. Consequently, the implantation of the BIL IOL into anterior chamber is completed. The next step is the implantation of both circular edges of ACCC and PCCC into the 360 degrees groove of the bag-in-the-lens IOL (Figure 26, 27).

One of the most important features of this technique is the closure of residual capsular bag space. In these conditions the proliferation of lens epithelial cell is limited and can undergo only on the periphery leaving optical part of the BIL IOL clear (Tassignon et al. 2002) (Figure 26, 31).

The BIL IOL is produced by German company Morcher GmbH and is made of acrylic hydrophilic material (Coacryl) which contains 28% of water (http://www.morcher.com/nc/en/products/foldable-iols.html Assessed on 28.06.2019). There are three types of BIL IOL: 89A (a standard), 89D (designed for small eyes) and 89F (modified for adult eyes). All these types are foldable IOLs, which enables the implantation through 2.2-2.5 mm main incision using an injector system. The overall length of the standard Type 89A IOL is 7.5 mm with the optic 5.0 mm. In Type 89F IOL the optic has 5 mm but the overall length is 8.5 m with anterior haptic element longer compared to posterior. After the surgery there is a risk of capture of the iris into the BIL IOL groove (Figure 28). The larger haptic of BIL IOL (Type 89F) and application of intracameral myotics are recommended to reduce this risk.

The first publication about the use of the BIL IOL implantation technique in children showed the significant reduction of visual axis reopacification compared to the conventional IOL implantation techniques (Tassignon et al. 2007). Later in 2015 there was report from the same group about long-term follow-up in children after BIL IOL implantation. Recently another group of authors presented a study, which analyzed the results after BIL IOL implantation in children (Nyström et al. 2018). The authors of both publications reported the postoperative visual and anatomical outcomes after BIL IOL implantation and concluded that BIL IOL technique appeared to be effective, well tolerated and easy to teach surgical method for the treatment of pediatric cataract. Moreover, the BIL IOL can be also exchanged in order to update the diopter (Dhubhghaill et al. 2015). Hence, the number of reports about the use of BIL IOL technique in children is limited, further studies of this perspective surgical method remain to be in focus of the current thesis.

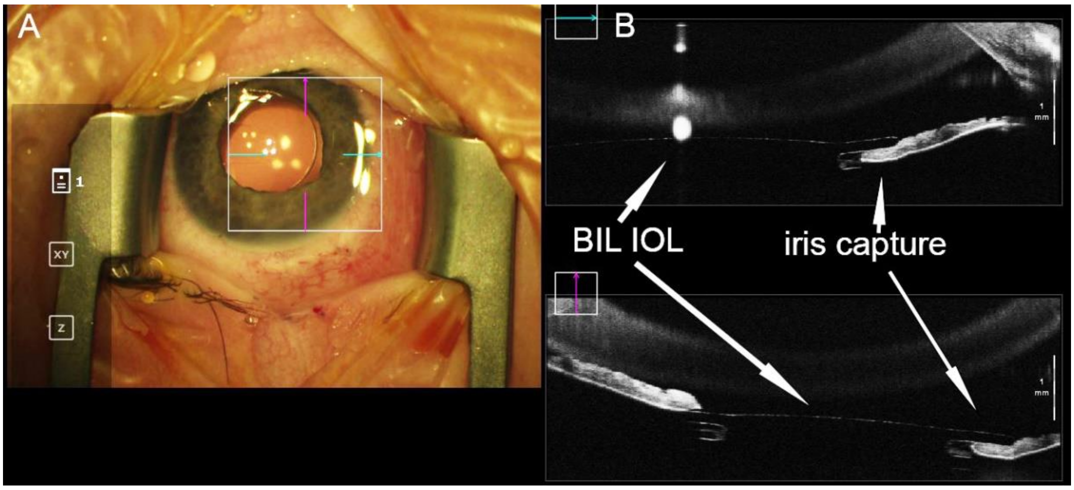

Figure 28. The appearance of iris capture on the next day after the surgery with implantation of BIL IOL Type 89A IOL (female, age at the surgery 4 months). *A – microscopic view of the iris capture. B – intraoperative OCT imaging (horizontal and vertical scan) of the iris capture (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

Implementation of the BIL IOL technique into surgical treatment of pediatric cataract was initiated and introduced in the Eye Clinic of the University Hospital Giessen and Marburg GmbH (Campus Giessen), in 2008 by Prof. B. Lorenz. Recently, the department has been also linked to the European Union initiative network of health care – European Research Network - Eye (ERN-EYE), which makes it a center for rare pediatric eye disorders, including cataract, with a significant number of referred patients. Since 2008 the department became one of the first eye care centers in Germany, where pediatric patients could benefit from this novel surgical technique. Even though, this technique for the past 10 years became only slightly more admired by pediatric cataract surgeons all over the world. Clinical experience of our site resulted in several and ongoing studies of the BIL IOL such as refractive, visual and anatomical results, of a relatively large cohort of pediatric cataract cases – the Giessen Pediatric Cataract Study Group.

The implementation of BIL IOL technique into clinical practice necessitates a learning process, which can be associated with intra- and postoperative complication. According to

Tassignon, the duration of the learning curve is between 30 and 60 cases. The risk of certain complications can be different for different age groups of pediatric patients.

Aim of the study. This study was focused on intraoperative and early postoperative complications after BIL IOL implantation and their management in pediatric patients in Giessen Pediatric Cataract Study Group. The main aim of this study was to analyze the rate of complications specifically related to BIL IOL technique and the optimal ways of its management.

Methods. This retrospective non-randomized single-center study (Giessen Paediatric Cataract Study Group) analyzed intra- and postoperative complications of paediatric cataract cases operated with bag-in-the-lens IOL implantation at the Department of Ophthalmology, Justus Liebig University, University Hospital Giessen and Marburg GmbH (Campus Giessen) from January 2008 to December 2018. The study group (60 patients, 90 eyes) included the following age sub-groups: 1st - 0-<3 months, 2nd – 3-<12 months, 3rd– 12-<36 months, 4th–>36 months-17 years of age. To main inclusion criteria belonged: paediatric cataract treated with implication of bag-in-the-lens IOL implantation technique. The following three types of BIL IOL were implanted in pediatric patients: Type 89A, Type 89A Toric and Type 89F (Morcher GmbH, Stuttgart, Germany). The standard pre- and postoperative examination was performed in all patients.

Surgery. In all cases the surgery was performed in general anesthesia with implication of standard bag-in-the-lens IOL implantation technique as proposed by Tassignon et al. (Video 3 – Supplemental material 3 on USB-Stick). Through the main 2.4 mm incision (sclerocorneal or limbocornea) the ring caliper Type 4L with outer diameter 4.3 mm (Morcher GmbH, Stuttgart, Germany) was introduced into the anterior chamber in order to perform an anterior continuous curvilinear capsulorhexis with diameter ≈4.3-5.0 mm. The soft crystallin lens was aspirated. Then after the injection of sodium hyaluronate 1.2% the anterior and posterior capsule were approached to each other. The posterior capsule was punctured and anterior vitreous surface was separated from the posterior capsule by injection of sodium hyaluronate through the puncture. After that a posterior continuous curvilinear capsulorhexis with similar diameter to ACCC was performed. The bag-in-the-lens IOL was injected into anterior chamber and both capsulorhexes were inserted into the 360° groove of the bag-in-the-lens IOL. In certain cases, which are, associated with vitreous prolapse an anterior vitrectomy was performed. The corneal wounds were closed with Vicryl 10.0 and 0.025 mg of cefuroxime was injected in anterior chamber.

Analysis of intra- and early postoperative complications was performed in entire cohort in order to reveal typical surgical complication related solely to BIL IOL implantation technique.

Analysis of management of intra- *and postoperative complications* was based on 39 video-documented consecutive cases with follow-up up to 12 months for early postoperative complications. To the most clinically significant complications belonged: iris capture (partial and total), visual axis reopacification, secondary postoperative ocular hypertension or glaucoma, BIL IOL dislocation.

For statistical analysis a Fisher's exact test was used to examine the associations between two kinds of classifications. The p-value of $p < 0.05$ was considered as statistically significant, for data analysis and presentation, we used R i386 3.3.2, R Core Team (2014) (R Foundation for Statistical Computing, Vienna, Austria).

Results. Within the study group there were 24 females (40%) and 36 males (60%). The mean age at the time of surgery was 45.25 months (range 1.05-200.28). Unilateral cataract was present in 27 patients (45%), and bilateral cataract – in 33 patients (55%). The mean follow-up for 56 patients (93.3%) was more than 12 months. The mean power of implanted BIL IOL in entire group was 24.78 D (range 8-36.5 D).

Table 7. Intraoperative complications during BIL IOL implantation technique in pediatric patients of different age groups *(Lytvynchuk L, Thiele M, Lorenz B. Analysis and management of intraoperative and early postoperative complications of bag-in-the-lens intraocular lens implantation in different age groups of paediatric cataract patients: report of the Giessen Paediatric Cataract Study Group. Acta Ophthalmol 2020;98(2):e144-e154. Permission granted).*

Intraoperative complications	Entire group	0-<3 months	3-<12 months	12-<36 months	36 months-17 years
Number of eyes	90	10	21	19	40
Vitreous prolapse	26 (28.9%)*	2 (20%)	6 (28.6%)	9 (47.4%)	9 (22.5%)
Iris hemorrhage	2 (2.2%)	0 (0%)	1 (4.8%)	0 (0%)	1 (2.5%)
Iris prolapse	2 (2.2%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Iris capture	1 (1.1%)	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)
Anterior capsule rupture	12 (13.3%)	0 (0%)	6 (28.6%)	3 (15.8%)	3 (7.5%)
Posterior capsule rupture	2 (2.2%)	0 (0%)	0 (0%)	2 (10.5%)	0 (0%)
BIL IOL dislocation after implantation	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)

*- Among 26 vitrectomy cases 23 were operated between 01/2008 and 12/2015, and 3 - between 01/2016 and 12/2018.

Analysis of intraoperative complications. Vitreous prolapse into anterior chamber was noted in 26 cases (28.9%) which required a transcorneal vitrectomy (Table 7). Among minor intraoperative complications there were 2 cases (2.2%) of iris hemorrhage, 2 cases (2.2%)

of iris prolapse, 1 case (1.1%) of iris capture, 12 cases (13.3%) of rupture of the anterior capsule, 2 cases (2.2%), 7 cases (7.8%) of persisting mydriasis at the end of the surgery. There was no significant difference with Fischer's Test comparing different age groups.

Table 8. Early postoperative complications after BIL IOL implantation technique in pediatric patients of different age groups *(Lytvynchuk L, Thiele M, Lorenz B. Analysis and management of intraoperative and early postoperative complications of bag-in-the-lens intraocular lens implantation in different age groups of paediatric cataract patients: report of the Giessen Paediatric Cataract Study Group. Acta Ophthalmol 2020;98(2):e144-e154. Permission granted).*

Early postoperative complications ≤ 12 months	**Entire group**	**Age at the time of the surgery**			
		0-<3 months	**3-<12 months**	**12-<36 months**	**36 months-17 years**
	n=90	**n=10**	**n=21**	**n=19**	**n=40**
Visual axis reopacification (VAR)	5 (5.6%)	2 (20%)	1 (4.8%)	1 (5.3%)	1 (2.5%)
Intraocular hypertension*	7 (7.8%)	2 (20%)	1 (4.8%)	2 (10.5%)	2 (5%)
Secondary glaucoma	2 (2.2%)	1 (10%)	1 (4.8%)	0 (0%)	0 (0%)
Intrapupillary membrane	1 (1.1%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
Anterior peripheral synechia	2 (2.2%)	1 (10%)	1 (4.8%)	0 (0%)	0 (0%)
Iris capture	2 (2.2%)	0 (0%)	1 (4.7%)	1 (5.3%)	0 (0%)
Hyphema	2 (2.2%)	0 (0%)	0 (0%)	2 (10.5%)	0 (0%)
Uveitis	6 (6.7%)	0 (0%)	3 (14.3%)	2 (10.5%)	1 (2.5%)
BIL IOL glistening	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)
BIL IOL luxation	3 (3.3%)	1 (10%)	2 (9.5%)☼	0 (0%)	0 (0%)
Peripheral corneal opacification	2 (2.2%)	2 (20%) #	0 (0%)	0 (0%)	0 (0%) #

*- postoperative intraocular hypertension was defined as IOP ≥ 12 mmHg measured with applanation tonometry Perkins Tonometer Mk2 (Haag-Streit, Essex, UK) in general anesthesia or as IOP ≥ 20 mmHg with iCare® PRO (Model: TA03, Icare Finland Oy, Vantaa, Finland) in awake state.
#- statistical analysis showed a significant difference with p=0.037.
☼- in one of two cases in this age group the BIL IOL was dislocated in vitreous cavity.

Analysis of early postoperative complications (≤ 12months after the surgery). Visual axis reopacification was noticed in 5 cases (5.6%) (Figure 29 A, Table 8). Removal of the visual axis reopacification and reinsertion of the posterior capsule into the BIL IOL groove is shown on figure 29. Intraocular hypertension was documented in 7 cases (7.8%) and could be treated with topical medications. Majorly an intraocular hypertension developed in the youngest age group of the patients (20% of cases). Secondary glaucoma was diagnosed in 2 cases (2.2%) and required secondary surgical intervention. Iris capture was noticed in 2 cases (2.2%) and only in 1 case it necessitated a surgical intervention, as the application of the mydriatics didn't help. Postoperative uveitis was diagnosed in 6 cases (6.7%).

Analysis of management of complications related specifically to the learning curve of the BIL technique was based on video documentation of 39 consecutive cases and was divided into two sections: 1. Management of intraoperative complications; 2. Management of early postoperative complications (Table 9).

Management of intraoperative complications. To incision related problems belonged the issues of the main corneal or corneoscleral incision size which was of 2.2 mm. However, it was insufficient for BIL IOL implantation. It was solved through an enlargement of the main incision to 2.4 mm. This allowed for uncomplicated implantation of a foldable Type 89A or 89F IOL a with optic size 5.0 mm and diopter's range from 8 D to 36.5 D (Lytvynchuk et al. 2019).

To caliper ring related problems belonged a slight displacement of the caliper ring during performance of ACCC and damage of caliper ring in 6/39 cases (15.4%) during its removal. Centration of caliper ring was performed based on the first and third Purkinje reflexes. Removal of the caliper ring was then improved and performed by gripping of the ring with gentle pressure from the jaws of the forceps. In 12/39 cases (30.8%) where ACCC or PCCC were smaller than the caliper ring (<4.3 mm) an enlargement of the capsulorhexis using anterior chamber scissors and capsular forceps was performed. Vitreous viscodissection problems or insufficient viscodissection of the vitreous from the posterior capsule was noted in 4/39 cases (10.3%). In these cases, a limited anterior vitrectomy behind posterior capsule was performed and BIL was successfully implanted. Mydriasis related problems associated with insufficient mydriasis were observed in 5/39 cases (12.8%). It was solved through the separation of posterior synechia or by employing of flexible iris retractors (Alcon Grieshaber, Schaffhausen, Switzerland). Intraoperative bag-in-the-lens IOL dislocation was documented in 5/39 cases (12.8%) and was only partial. It was managed through re-implantation of the capsulorhexis edges into the BIL IOL groove. Damage of the BIL IOL was noticed in 1/39 cases (2.6%) as a crack of the IOL optic during its re-implantation. It followed by the removal of the damaged IOL and implantation of the new BIL IOL (Type 89A).

Management of early postoperative complications. One of the most typical but not dangerous postoperative complication after BIL IOL implantation remains capture of the iris associated with posterior synechia (in 2/39 cases (5.1%))(Figure 28). In one case (partial iris capture) it was treated conservatively with instillation of mydriacyl 1% and then pilocarpin 1% aiming to dilated the pupil and release the capture, and then to constrict the pupil. One case of circular complete iris capture required surgically intervention. Visual axis re-opacification (VAR) was documented in 2/39 cases (5.1%). VAR were caused by improper implantation of BIL IOL and postoperative dislocation of the posterior capsulorhexis (Figure 29 A). As the consequence the capsular epithelial cells continued to proliferate on the anterior surface of the vitreous body behind the lens optic, which led to VAR. These cases were treated surgically with vitrectomy and re-implantation of the capsular edges into the IOL groove (Figure 29 B, C). Dislocation of BIL IOL in the vitreous body was diagnosed in 1/39 cases (2.6%) and was caused apparently by inappropriate (too large) capsulorhexis. The lens was removed and a 3-piece IOL was implanted in the sulcus. Pigment precipitates on the BIL IOL optic occurred in 2/39 cases (5.1%). However, these findings appeared to be insignificant and didn't necessitate any treatment.

Table 9. Inra- and postoperative complications related solely to BIL IOL implantation technique *(Lytvynchuk L, Thiele M, Lorenz B. Analysis and management of intraoperative and early postoperative complications of bag-in-the-lens intraocular lens implantation in different age groups of paediatric cataract patients: report of the Giessen Paediatric Cataract Study Group. Acta Ophthalmol 2020;98(2):e144-e154. Permission granted).*

	Intraoperative complications related to BIL								**Postoperative complications related to BIL**			
Number of cases with video documentation	Incision related problems	Caliper ring related problems	ACCC oversized	ACCC or PCCC too small	Vitreous viscodissection problems	BIL IOL implantation related problems	BIL IOL dislocation	BIL IOL damage	Iris capture with posterior synechia	Visual axis reopacification	BIL IOL dislocation	BIL IOL precipitates
39 eyes 100%	5 12.8%	6 15.4%	5 12.8%	12 30.8%	4 10.3%	5 12.8%	5 12.8%	1 2.6%	2 5.1%	2 5.1%	1 2.6%	2 5.1%

Discussion. BIL IOL implantation technique (first described by M-J. Tassignon) appeared to be an alternative surgical method for pediatric cataract treatment.

The use of this novel surgical method allows for reduction of the most threatening complication after cataract surgery in children – visual axis reopacification. Our study results support the efficacy of BIL IOL technique reported previously (Tassignon et al. 2007, Van Looveren et al. 2015, Nyström et al. 2018). However, to the best of our knowledge, this is the first study, that analyses the rate of the most common complications of BIL technique in pediatric patients of different age groups. Furthermore, the management of the common undesired events linked to bag-in-the-lens IOL implantation was described as well.

First description of the use of bag-in-the-lens technique in children referred to publication from 2002 by Tassignon at al. (Tassignon et al. 2002). In 22 months of follow up in one case with bilateral cataract in a 4-year-old girl there were no complications, BIL IOL was centered with visual acuity of 0.6 (decimal) on both eyes. In 2007 the same group of Tassignon at al published the first case series of BIL technique in 22 children (34 eyes, age range: 2 months – 14 years) (Tassignon et al. 2008). The authors have described the following intraoperative complications: incorrect implantation of BIL IOL and vitreous prolapse, which necessitated vitrectomy. In one case one week after the surgery a luxation of the BIL IOL into the vitreous cavity was documented. It was treated with vitrectomy and reimplantation of the IOL into the sulcus. Also, the authors described one case of iris capture and two glaucoma cases postoperatively. In our cohort we did not implant BIL IOL into the sulcus. In one case within the cohort a dislocation of BIL IOL was documented. It was treated with vitrectomy, removal of the BIL IOL and implantation of the posterior chamber IOL into the sulcus. Iris capture was noticed in two cases (2.2%) and postoperative intraocular hypertension - in 7 cases (7.8%). Two cases (2.2%) of secondary postoperative glaucoma were treated surgically.

In regard to secondary intraocular hypertension it remains difficult to acquire an accurate measurement data of intraocular pressure in children of younger age-groups. There are two main reasons for that. First, young children are uncooperative and it is impossible to measure IOP with the applanation tonometry methods (the most accurate methods) without anesthesia. Second, the use of general anesthetics impacts IOP usually making it lower and the data are inaccurate again. Up till now there is no unique approach to diagnose postoperative intraocular hypertension and secondary glaucoma in children after the cataract surgery. As the postoperative period brings different causes for intraocular hypertension in different age groups, it also remains difficult to differentiate postoperative intraocular hypertension and secondary glaucoma in early postoperative period. As example, Tassignon et al. considered IOP increase ≥20 mmHg to be a sign of secondary glaucoma (Tassignon et al. 2007). Nyström et al. diagnosed secondary glaucoma when IOP was ≥22 mmHg and following clinical feature were documented: buphthalmus, cornea enlargement, swelling of the corneal, glaucomatous changes of the optic disc, myopisation of the eye due to increase of axial length (Nyström et al. 2018, Zetterberg et al. 2015). In our study group we considered postoperative intraocular hypertension to be diagnosed when IOP was ≥ 12 mmHg measured with applanation tonometry Perkins Tonometer Mk2 (Haag-Streit, Essex, UK) in general anesthesia or when IOP was ≥ 20 mmHg with iCare® PRO (Model: TA03, iCare Finland Oy, Vantaa, Finland) in the awake state. Diagnosis of secondary glaucoma was applied according to the description of glaucomatous changes made by Nyström et al. (Nyström et al. 2018).

A rare complication such as damage of BIL IOL was noticed in our study cohort as well. Earlier Kahn and Dodick in 2012 reported about of IOL surface damage during implantation of high-powered hydrophilic acrylic IOLs which were implanted (injected) using a small cartridge injector system (Kahn & Dodick 2012). Optic surface damage was detected in 50% of cases. A different study showed that a manufacturer-supplied hexagonal nozzle injector induced scratches on the posterior surface of the hydrophilic acrylic IOL (Harsum et al. 2010). In our case series we noticed two cases of IOL damage (1 case - scratches, 1 case – BIL IOL break during reimplantation). In the case of scratches, the IOL was not exchanged as the damage was considered to be not clinically significant. In the case of IOL break we exchanged the BIO IOL. Additionally, Dhubhghaill et al. reported a case of BIL IOL opacification 11 years after the implantation (Dhubhghaill et al. 2015). After BIL IOL was exchanged and analyzed, it was discovered that granular opacification on the IOL consisted of calcium and phosphates. In our group we did not notice any BIL IOL changes. However, the mean postoperative follow-up period was still short. In some cases, we observed only tiny cellular precipitates (presumably they were pigmented cells) which were located on the IOL surface. The remaining postoperative complications happened sporadically and could be safely managed. Among the limitations of this study there were following: performance of the surgeries by two surgeons with slightly different implantation technique and individual learning curve, limited number of cases due to rare disease phenotype, video-documentation of only 39 cases.

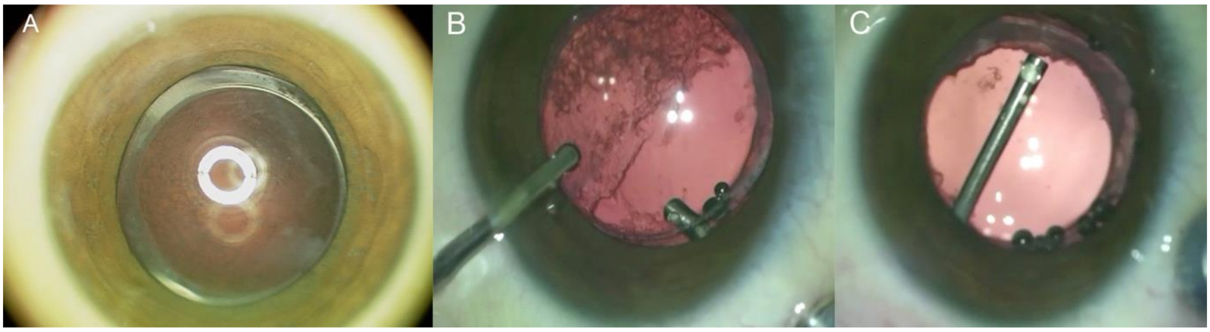

Figure 29. Rare case of visual axis reopacification that developed within 1 year after the surgery. *Opaque posterior surface of the IOL optic (A). Removal of VAR with pars plana vitrectomy and reposition of the BIL IOL during the second surgery (B, C) (Source: Department of Ophthalmology, Justus Liebig University, Giessen, Germany).*

Summary. The study results prove and support the efficacy of the BIL IOL implantation technique in children of different age groups with lens opacification. Regarding one of the most vision threatening complication – visual axis reopacification, postoperative observation demonstrated and supported superiority of the BIL IOL technique compared to the most used surgical techniques for treatment of pediatric cataract. Development of VAR was recorded in 5/90 cases (5.6%), with a success rate in 85/90 cases (94.4%). In spite the learning curve remains to be difficult, this surgical technique can be learned in adult cataract surgery, where the tools for management of complications are more advanced. The spreading and more frequent application of the BIL IOL implantation technique is believed to decrease significantly the rate of postoperative visual axis reopacification allowing for an adequate amblyopia treatment. The new implantation can decrease the frequency of postoperative complication and increase visual function in pediatric cataract patients of different age groups. Information about variety and management of intra- or postoperative complication specifically related to bag-in-the-lens IOL implantation technique and its learning curve shall improve the flow of the surgery and decrease the rate of undesired events.

3.2.5. New surgical treatment for traumatic macular holes

Appendix 9

Efficiency of the Hydraulic Centripetal Macular Displacement Technique in the Treatment of Traumatic Full-Thickness Macular Holes.

Ruban A*, Lytvynchuk L*, Zolnikova A, Richard G. Retina 2017;39 Suppl 1:S74-S83.

* - sharing first authors.

Introduction. Retinal disorders of the macular and especially of the foveal area cause immediate impact on the central vision of the patients with appearance of metamorphopsia and reduction of visual acuity. One of them is full-thickness macular hole (MH) with affection of layers at the fovea area (Gass 1987). The incidence of the MH is about 3.3 in 1,000 patients aged 55 and older (Casuso et al. 2001, Ezra 2001). Etiologically MH can be idiopathic, traumatic (TMH) and caused by the vitreo-foveal tractional syndrome. Approximately ½ of the MH belong to large MH with the diameter >400 μm.

Traumatic macular hole is associated with a complete different pathophysiologic mechanism, which is initiated by mechanical eye deformation, where the main cause is the anterior-posterior and/or tangential traction (Margheria and Schepens 1972, Johnson et al. 2001, Kuhn and Pieramici 2002, Miller et al. 2013). It was reported, that post-traumatic MH can have diameter from 200 to 500-700 μm and larger (Margheria and Schepens 1972). Spontaneous closure of the MH after the eye injury were reported as well (Kusaka et al. 1997, Yamashita et al. 2002, Yamada et al. 2002). But these cases are rather the exceptions.

Beside standard pars plana vitrectomy with ILM removal and gas endotamponade, a number of alternative surgical techniques were proposed to treat idiopathic large and traumatic MH. To the most studied surgical techniques belong arcuate retinotomy, perifoveal radial incisions, MH hydrodissection, the inverted ILM flap technique, the autologous lens capsular flap, and the autologous neurosensory retinal flap (Singh et al. 2019). These approaches can be differentiated into two main groups: techniques, which aim to cover the

MH and techniques, which aim is to re-appose MH edges in order to restore the initial anatomy of the fovea. The latter can be achieved using MH hydrodissection technique (Felfeli and Mandelcorn 2019). During this technique, after ILM peeling a small amount of balanced salt solution (BSS) is injected with the use of 41-gauge cannula into the subretinal space in order to initiate iatrogenic macular detachment. This allows for mobilization of the MH edges. After fluid-air exchange is performed, the MH edges are re-apposed with each other concentrically and the eye is filled with gas. The number of studies demonstrated favorable anatomical and visual outcomes (Oliver and Wojcik, 2011, Szigiato et al. 2016, Meyer et al. 2017, Fotis et al. 2019, Frisina et al. 2019). The surgical treatment of THM remains challenging.

In most severe cases, traumatic MH is associated with subretinal or intraretinal hemorrhage, choroidal rupture and chorioretinal fibrosis. The growth of the subretinal and chorioretinal fibrotic tissue appears to be an additional factor that can influence postoperative anatomic and functional results (Kuhn and Pieramici 2002).

There is no consensus regarding the optimal surgical approach to treat THM, which course is sometimes unpredictable. One of the reasons is the presence of chorioretinal changes located in the foveal area. Subretinal hemorrhage or/and posttraumatic inflammatory reaction with exudation cause enforced adhesion between RPE and neurosensory retina. Chorioretinal fibrotic tissue can reach inner retinal layers preventing MH closure after the surgery.

Aim of the study. The main aim of this study was to propose the new technique - hydraulic centripetal macular displacement technique with fibrotic scar dissection - for treatment of traumatic macular hole.

Methods. To this retrospective consecutive case series study were enrolled 7 patients (7 eyes) with TMH. In all cases the development of TMH was caused by various eye injuries including: a gunshot wound (n = 2), a hit with tennis ball (n = 2), and a blow from a cork from sparkling wine (n = 3). To inclusion criteria belonged: presence of full-thickness TMH, and postoperative 12 months follow-up. All patients were examined before and in 1, 3, 6, 9 and 12 months after surgery using standard ophthalmological examination methods. The size of macular hole was measure according to a protocol described by the International Vitreomacular Traction Study (IVTS) Group. The level of retinal displacement after the surgery was evaluated by placing over of pre- and postoperative red-free digital retina photos.

In all cases a standard three-port sutureless 25-gauge pars plana vitrectomy was applied. The surgery included the following steps: posterior vitreous detachment, staining the internal limiting membrane and its peeling to 3–4 optic disc diameter in a circular manner, subretinal injections of balanced salt solution within the major retinal vascular arcades, dissection of retina-choroidal adhesion was done using vitreoretinal scissors and/or 25-gauge needle, perifoveal centripetal macular displacement of the detached retinal tissue through a gentle massage with a backflush cannula, complete air-fluid exchange and air-gas exchange (20% sulfur hexafluoride (SF_6) or 16% hexafluoroethane (C_2F_6) (Figure 30, Video 4 – Supplemental material 4 on USB-Stick). All patients were asked to keep a prone position for 5 days after the surgery. Collected data were analyzed statistically using descriptive statistics, frequency tables, correlation matrices and Student's *t*-test.

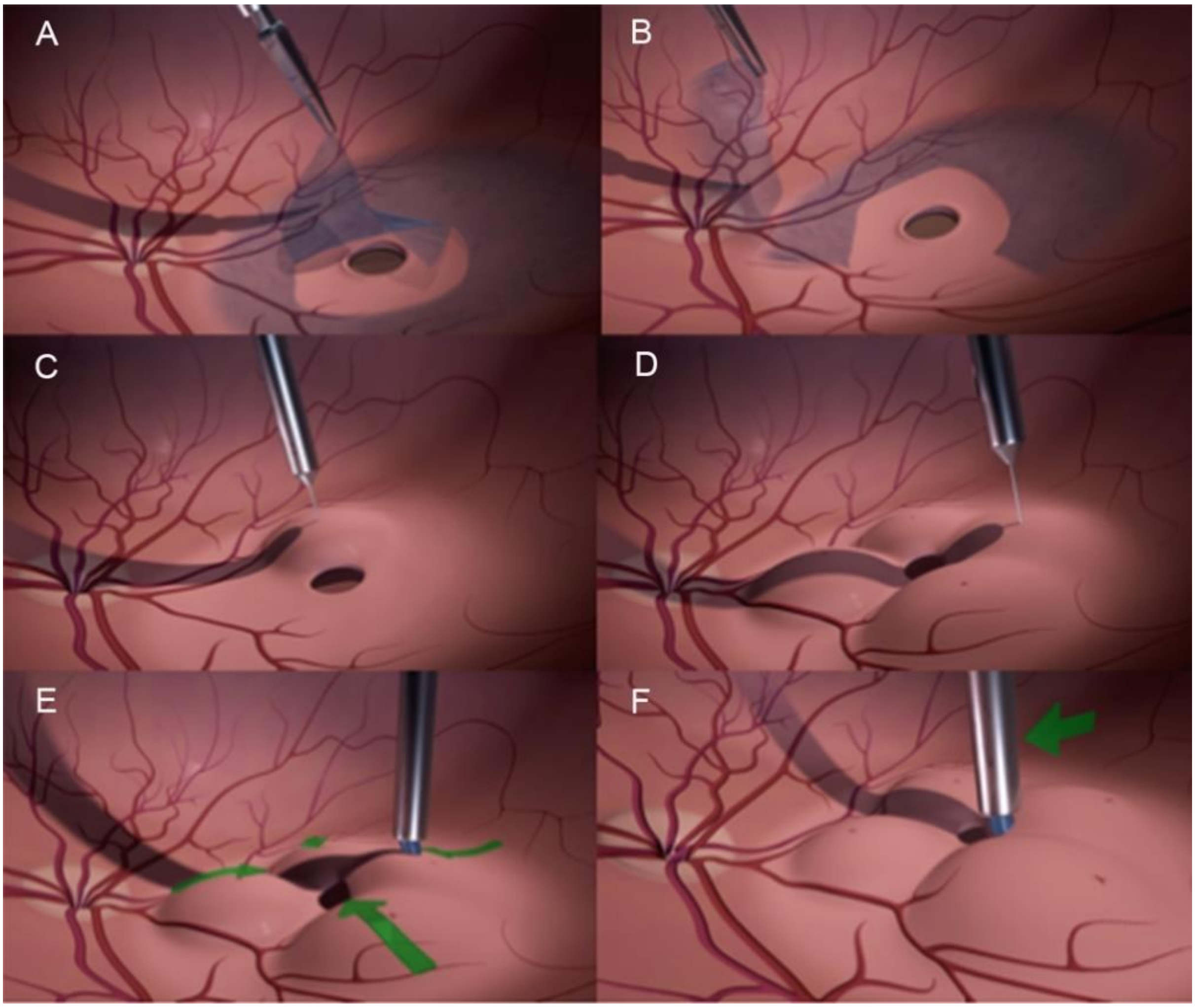

Figure 30. Schematic representation of the hydraulic centripetal macular displacement technique. *Standard peeling of the internal limiting membrane (ILM) around the traumatic macular hole (TMH) (A). Enlargement of initial area of ILM peeling to 3-4 optic disc diameters (DD) (B). Subretinal injections of balanced salt solution (BSS) using a subretinal cannula (C) in four quadrants (D). Centripetal displacement of macula (E, green arrows), followed by centripetal macular massage (F, green arrow) (Ruban A, Lytvynchuk L, Zolnikova A, Richard G. Efficiency of the Hydraulic Centripetal Macular Displacement Technique in the Treatment of Traumatic Full-Thickness Macular Holes. Retina 2017; 39 Suppl 1:S74:S83. Permission granted).*

Results. The study cohort included four males and three females (7 eyes) with mean age 38.1 ± 15.0 years (range 18–61 years). In four cases a combined surgery with phacoemulsification of the lens, IOL implantation and PPV was performed. In three cases –

only PPV was performed. Dissection of retina-choroidal scarring was applied in three cases. In two cases there was a postoperative intraocular hypertension, which was successfully treated with eye drops. Before the surgery the mean macular hole size was 825 ± 150 µm (range: 676–1130 µm). In 6 cases (85.7%) it was possible to achieve a complete closure of the TMH within the entire follow-up period, and in 1 case (14.3%) the size of TMH was significantly reduced. There were no complications that could be associated with puncture retinotomies. Displacement of the retinal tissue toward center of the macula could be confirmed in all cases (Figure 31).

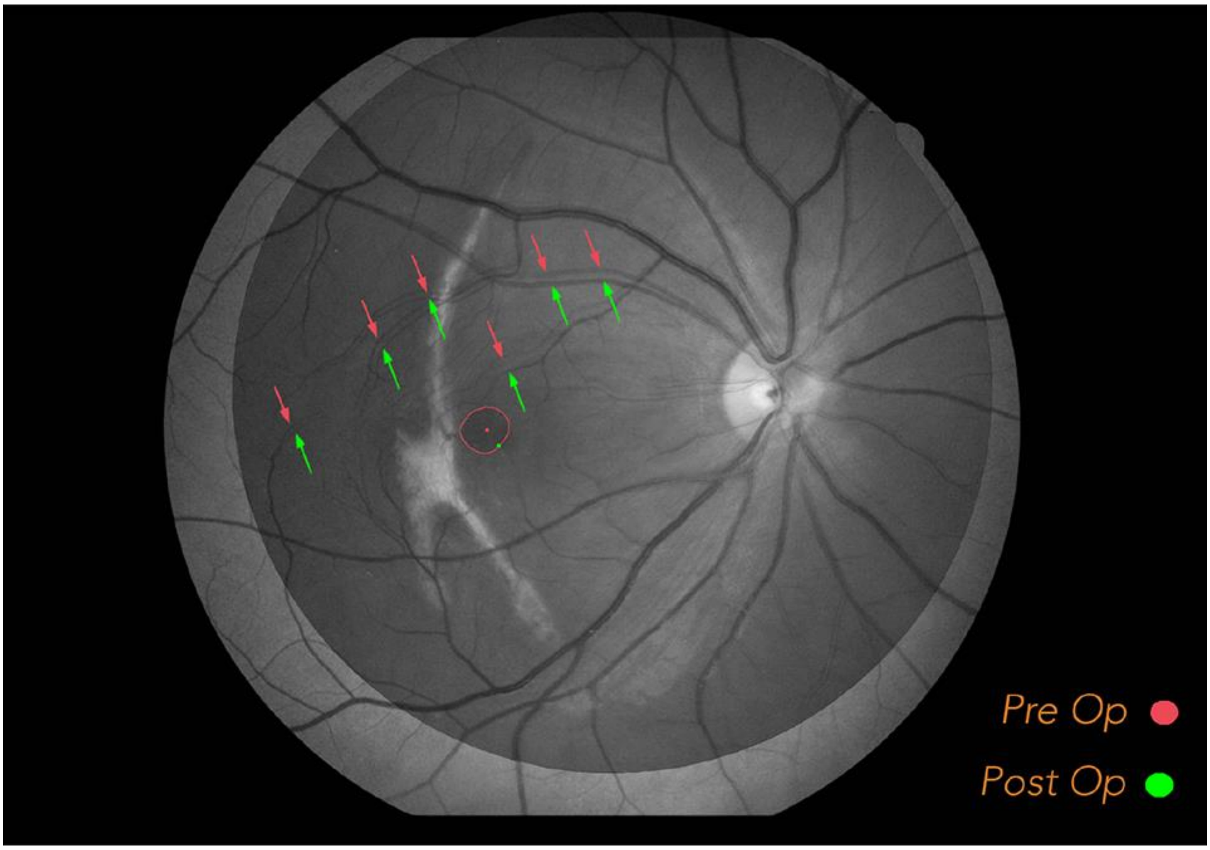

Figure 31. The degree of retinal displacement after superimposing of pre- and postoperative red-free digital fundus photos of the same eye (Case 3). *The position of the macular vessels and macular hole preoperatively and postoperatively is indicated with red and green color, respectively (Ruban A, Lytvynchuk L, Zolnikova A, Richard G. Efficiency of the Hydraulic Centripetal Macular Displacement Technique in the Treatment of Traumatic Full-Thickness Macular Holes. Retina 2017; 39 Suppl 1:S74:S83. Permission granted).*

Preoperative mean BCVA in the study group was 20/369 Snellen (1.16±0.26 logMAR, range 1.6-0.8). Postoperative mean BCVA increased to 20/166 Snellen (0.63 ± 0.33 logMAR, range 1.3-0.3), which was statistically significant ($t=8.8$; $p=0.001$). In one case of partial MH closure BCVA improved slightly (from 20/1000 to 20/400 Snellen, or from 1.6 to 1.3 in logMAR). Additionally, 6-month postoperative assessments of all patients revealed a negative correlation ($r = 0.76$; $p = 0.05$) between postoperative visual acuity and the time elapsed from the moment of the trauma, and a strong positive correlation ($r = 0.94$, $p = 0.002$) between the macular hole size and elapsed time from the injury.

Discussion. Traumatic macular hole remains one of the most serious and sight-threatening complication of a closed or opened globe injury. The pathogenesis of TMH is still unclear and its surgical treatment remains challenging. Posttraumatic complications, such as choroidal wound, retinal bleeding, and retinal detachment, usually affect anatomical and functional results after surgical treatment.

The first application of the novel techniques of macular detachment with subretinal BSS was reported in 2011 in one case of idiopathic MH (Oliver and Wojcik 2011). Since then there were a few publications describing macular displacement for large macular hole treatment (Szigato et al. 2016, Frisina et al. 2019). It was hypothesized that success rate could be improved through the reduction of retinal stiffness after subretinal BSS injection, which enables the apposition of the MH edges, and thus MH closure.

Since 2013 for the first time we started to use a similar technique independently under the name „hydraulic centripetal macular displacement technique" (HCMD) to treat traumatic MHs. The indications for this technique were large traumatic macular holes (600-800 μm and >800 μm in diameter) that were associated with chorioretinal fibrotic scaring. Besides standard displacement technique, our technique included additional steps, which in our opinion are very important for successful surgical outcome. These are: a massaging of the MH edges, centripetal retinal displacement with the use of atraumatic silicon tipped cannula, aspiration of subretinal fluid, and subretinal dissection of chorioretinal scaring through the macular hole orifice (Figure 32). The last step allows for increasing of retinal mobility and macular hole closure.

In our case series study, we report the use of an adjusted surgical technique (HCMD) that was applied in 7 patients (7 eyes) with TMH. In 3 cases an additional surgical separation of chorioretinal scarring was applied using either vitreoretinal scissors or 25-gauge needle. In 85.7% (6 cases) TMH was closed and in14.3% of cases (1 case) TMH became smaller with the size of the TMH significantly decreased.

Pars plana vitrectomy remains the standard surgical procedure for treatment of idiopathic macular holes with success rate over 90%. The technique, however, was many times modified and it is not clear which surgical approach is better in which case. Subretinal injection of BBS in treatment of idiopathic macular holes appeared to be efficient, especially in cases of persistent and recurrent MHs (Oliver and Wojcik, Szigato et al.). The hypothesis behind considered to be reduction of the tension and stiffness of the retina through subretinal BSS injection which allows for closing the MH edge due to its re-approximation.

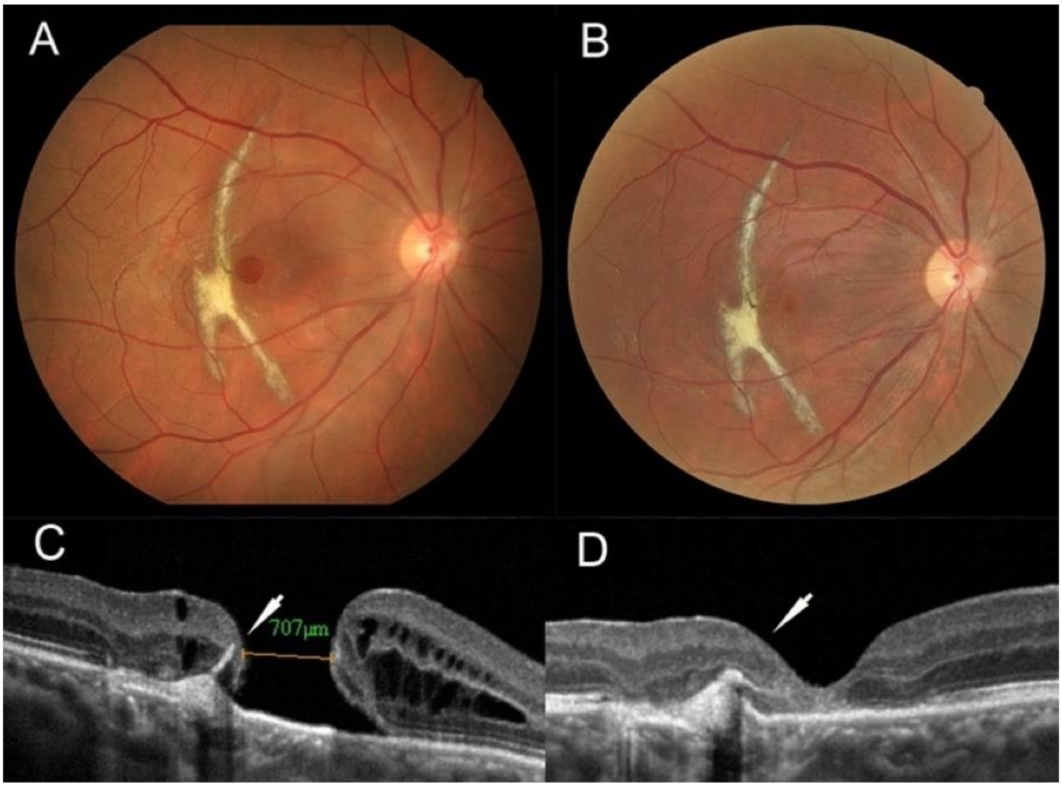

Figure 32. Traumatic macular hole of the right eye. *Preoperative (A) and postoperative fundus photo (B). Preoperative (C) and postoperative OCT image (D). White arrow shows the presence of retino-choroidal fibrotic adhesion preoperatively (C) and its absence postoperatively after it was dissected (D) (Ruban A, Lytvynchuk L, Zolnikova A, Richard G. Efficiency of the Hydraulic Centripetal Macular Displacement Technique in the Treatment of Traumatic Full-Thickness Macular Holes. Retina 2017; 39 Suppl 1:S74:S83. Permission granted).*

Our study included cases with large full-thickness TMH (>800 µm) and smaller TMH (600–800 µm) which were associated with chorioretinal scarring. The results support intrasurgical application of chorioretinal scarring, which enables the retina to be more mobile in the area of macular hole edges. Additionally, we realized that the larger the size of MH the larger the square of perifoveal retina that shall be displaced. However, the grade of macular tissue displacement was not the same in each direction. The major displacement of the retina was noticed the upper-temporal region (Figure 31).

Among the study limitations are: the type of the study (retrospective consecutive case series) and relatively short follow-up period. This could be explained with the low incidence of the TMH and difficulties by scheduling the long-term postoperative visits in patients traveling a long distance.

Summary. Pathogenetic mechanisms of traumatic macular holes are still not clear. Every available surgical approach could be used in order to reach macular hole closure and improvement of BCVA. The results of our study show that HCMD technique is an effective and safe method to treat TMH. Additional surgical steps, which are proposed by the authors, such as dissection of chorioretinal scarring, centripetal displacement of the retina and massaging of the MH edges, are considered to improve postoperative closure rate and postoperative visual function. Comparably to the results of alternative techniques for traumatic MH with success rate of closure in 83% with single-operation, our results showed a complete MH closure in 85.7% of cases (Rubin et al. 1995, Garcia-Arumi et al. 1997, Miller et al. 2013). However, we shall admit that the displacement of the retinal tissue was more prominent in upper-temporal quadrant (Figure 31).

Further studies with larger number of patients are required in order to understand the intraoperative and postoperative behavior of the retinal tissue in cases with TMH.

3.3. New surgical instruments

Development of instrumentation for treatment of vitreoretinal disorders arose simultaneously with the development of the vitreoretinal surgery itself. Initially proposed surgical technique to treat retinal detachment (RD) necessitated special instrumentation, which shall be adapted to the modern standards of minimally invasive surgery. An adequate design and feasibility of the instruments always played an important role in the surgery, as it can enable difficult tasks, shorten the duration of the surgery and influence postoperative results.

New instrument for scleral buckling surgery in retinal detachment

Appendix 10

New Scleral Depressor-Marker for Retinal Detachment Surgery.
Lytvynchuk L, Grzybowski A, Lorenz B, Ansari-Shahrezaei S, Binder S. Ophthalmology Retina 2019;3(1):73-76.

Introduction. Scleral buckling (SB) remains the gold standard procedure in young patients, in patients with localized small retinal breaks and in cases with retinal dialysis (Custodis 1956, Nam et al. 2013). The main goal of the scleral buckling procedure is to identify and localize retinal break or breaks with the use of binocular indirect ophthalmoscopy, then mark the location of the break on the sclera and suture the silicon-made buckle in this area, creating intraocular indentation.

Scleral indentation plays a crucial role during localization of the retinal breaks. During the surgery the extraocular muscles are fixed with the 4.0 suture, which allows manipulating with an eye and reaching most posterior areas of the back of the eye. Scleral indentation of 360° of the retinal periphery remains one of the most important steps of the surgery. It demands precise and thorough inspection of the retina. After the retinal break is detected and localized with scleral indentation, this area of indentation shall be immediately marked. Scleral buckle then will be fixed onto the sclera in the projection of the marking.

There are different instruments, which can be used for scleral indentation. The most important feature of these instruments is the presence of smooth and atraumatic tip that can slide on the scleral surface. The use of surgical forceps was described as well. However, the sharp edges of the forceps' tip can create the risk for scleral perforation. Marking of the localized area that correspond to retinal break is usually done after the indentation with the sterile marker pen of bipolar or monopolar diathermy. As alternative, a number of convention indenter-markers have been proposed and introduced by many surgeons (Ma et al. 2013, Chawla 1970, O'Connor 1971, Lincoff and Kreissig 1982, http://www.storzeye.com/products/7739/Other-Eye-Instruments/Schocket-Double-Ended-Scleral-Depressor/E5108.aspx). These instruments enable simultaneous indentation and marking due to slightly sharp edges of the tip which leave the grey short-lasting appearance on the sclera. Nevertheless, the indentation and marking procedure remains imperfect and requires training and experience.

The major disadvantage of the standard indenter-markers remains the long duration of the procedure and misinterpretation of primary indented area. Additionally, an eyeball shall be rotated forwards and backwards many times, switching between visual identification of indented area and explosion of the sclera many times in order to mark only desired area and to recheck the marking. Multiple rotations traumatize the extraocular muscles. With the use of conventional indenter-markers multiple marking can mislead the surgeon and result in improper buckle placement. The force that is being applied during indentation is also associated with pain, increase of intraocular pressure and risk for sclera damage (Trevino and Stewart 2015). These concerns inspired us to look for the solutions that could improve surgical performance of scleral indentation and marking, making it safer and more efficient.

Aim of the study. The main purpose of this study was to report the use of a new prototype of depressor-marker for scleral buckling (SB) procedure during retinal detachment treatment, which enables indentation and selected marking of the desired scleral area.

Methods. The study corresponded to the Declaration of Helsinki and was approved by local Independent Ethics Committee (Department of Ophthalmology, Rudolf Foundation Hospital, Vienna, Austria). The prototype was produced by company Vitreq (Vierpolders, The Netherlands, prototype № 17R006) and in cooperation with engineer V. Didenko (Kyiv, Ukraine). The new instrument was registered as an intellectual property (Justus Liebig University and TransMIT Geseltschaft für Technologietransfer GmbH, Giessen, Germany) under the title „Light-guided Scleral Depressor-Marker for Extrascleral Surgery by Lytvynchuk/Binder" in 2019. The construction of the new prototype comprised of two parts: a squeeze handle and a working part with two curved tubes (Figure 33 B, 34 A). There is a moving tip (1 mm diameter) with serrated surface hidden in the main tube (1.1 mm diameter). It shall be previously pre-stained with any surgical sterile dye or sin marker (Figure 33 A, 34 C). The second tube of the working part is aimed to integrate an instrument with chandelier fiber light in order to improve the precision of indentation making visible an indentation point.

The use of the prototype was evaluated in clinical conditions while performing a scleral buckling procedure in 11 eyes (11 patients). All patients have signed an informed consent. During the surgery after being pre-stained, the tip of the working part was placed onto the surface of the sclera and after the retinal hole was identified with binocular ophthalmoscopy and indentation, a distinct mark was placed onto the sclera by squeezing of the handle. Compatibility of the instrument with chandelier fiber light could aid during light-assisting sclera buckling surgery.

Results. In all patients, that were recruited to this study (11 eyes of 11 patients, age range 21-67 years) a diagnosed of primary rhegmatogenous retinal detachment was established. All cases could be managed with minimally invasive scleral buckling procedure. For visualization a binocular indirect ophthalmoscopy was used in five cases and a wide-angle non-contact viewing system assisted with endoillumination – in 6 cases. All surgeries were perform using only local anesthesia.

Indentation and marking were performed in every case without any local or systemic complications. It was very quick and required minimal indentation forces. A single staining of the tip allowed the surgeon to place multiple marks (up to 10) during a single indentation session without withdrawal of the instrument and re-staining. One of the primary results was the safety of the instrument, which was arranged by making the surface of the contacting tips blunt with smooth edges. It allowed for safe and atraumatic scleral indentation. The efficacy of the staining was improved by making the surface of the moving tip serrated. During the marking it was possible to put a tattoo-like scleral mark, which was resistant to BSS, wasn't wash out and remained visible during entire procedure. Separation of two functions (indentation and marking) allowed for performing of well controlled marking solely of desired scleral zone. The second thinner tube was used for fiber light assisted indentation and facilitated a transscleral illumination of the indented area showing on the retina the highest point of indentation.

The application of the new indenter-marker facilitates the indentation of the sclera with minimum of indentation forces (Video 5 – Supplemental material 5 on USB-Stick). It can decrease the risk for pain, rise of intraocular pressure and the risk of scleral perforation in cases with extremely thin sclera (high myopia, blue sclera, etc.). Light-assisted indentation can assist the surgeon by exposing of the highest indentation point. It can make the procedure more precise. Additionally, the light can illuminate retinal breaks from behind, making them more visible. There were no complications noted during 6-months follow-up period.

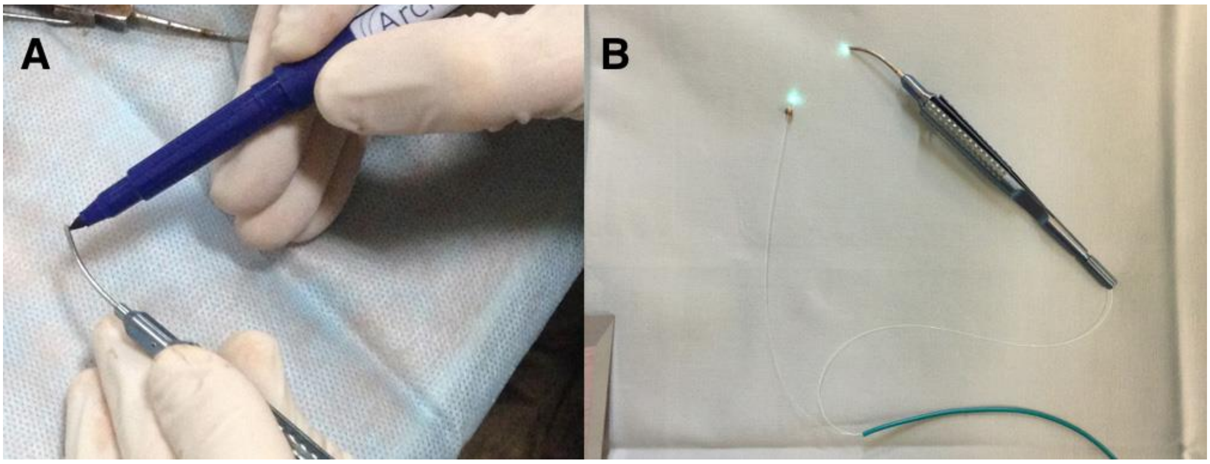

Figure 33. New indenter-marker. *Staining of the retracted tip of the new indenter-marker with conventional sterile surgical marker (A). Indenter marker is combiened with TwinLight Oshima chandelier for light-assisted scleral indentation (B) (L. Lytvynchuk et al. New Scleral Depressor-Marker for Retinal Detachment Surgery Ophthalmology Retina 2019; Jan; 3(1):73-76. Permission granted).*

Discussion. With development of pars plana vitrectomy the number of scleral buckling procedure decreases. However, this approach still remains a gold standard procedure to treat uncomplicated retinal detachment, especially in young patients. Standard scleral depression, which is performed during SB, induces an indentation of the inner eye wall. The indentation could be seen then well in vitreous cavity using binocular indirect ophthalmoscopy or wide-angle non-contact viewing system assisted with endoillumination. Scleral indentation remains a single effective and the only one manipulation that allows for identification of the retinal defects during SB surgery. Conventional scleral depressors or indenter-markers carry a risk of pain, IOP elevation and sclera damage. One of the most commonly used scleral depressor-markers is the O'Connor scleral depressor-marker or the Schocket double ended scleral depressor-marker (O'Connor 1971, http://www.storzeye.com/products/7739/Other-Eye-Instruments/Schocket-Double-Ended-Scleral-Depressor/E5108.aspx). The main disadvantage of conventional instruments is that the surgeon can depress and mark the sclera only simultaneously. It means that any indented area will be marked with a greyish short-lasting spot. This can mislead the surgeon during scleral placement and result in insufficient retinal defect closure and failure of the single surgery. Additional surgery for repositioning of the scleral buckle could be required.

The new concept of indenter-marker can convert a complex and important step of the scleral buckling procedure into easier and better controlled. Study results demonstrated that the use of new indenter-marker minimizes the need to rotate repeatedly the eye during indentation and marking, decreasing the trauma to eye muscles and decreasing the duration of this surgical step. Furthermore, the new indenter-marker can be applied during different ocular surgeries, which require indentation and/or marking of the sclera. To study limitations belongs the absence of commercially available instrument and additional cost of the surgery. However, the improved precision and safety of indentation and marking procedure can be an argument against the limitation related to additional surgery cost. In order to obtain more detailed information about efficacy of the new indenter-marker an additional prospective multicenter study would be required.

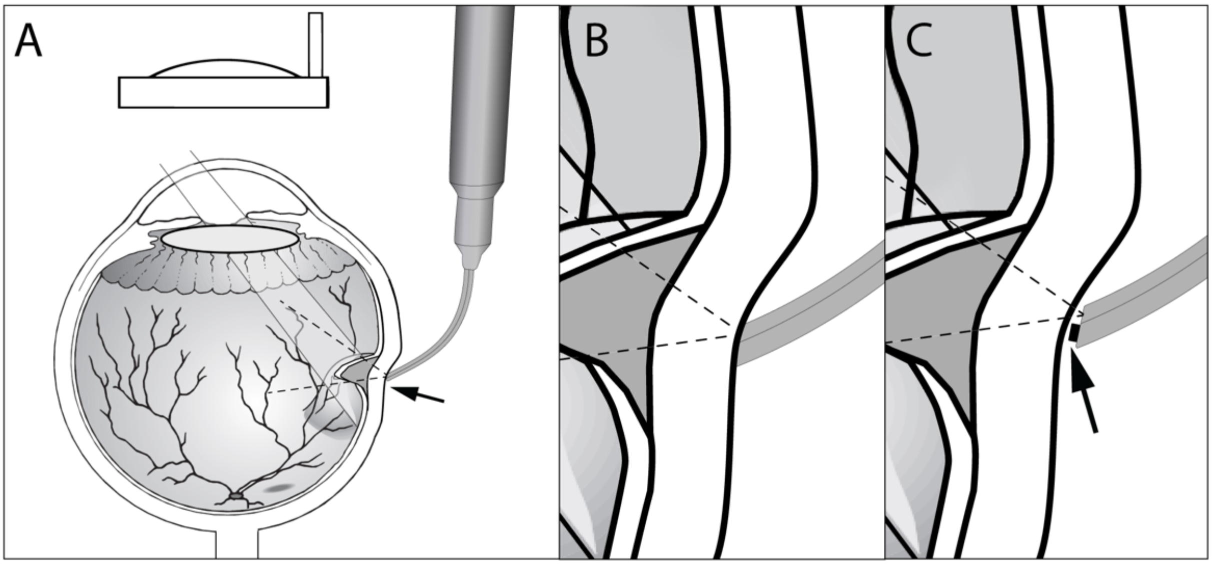

Figure 34. Schematic view of the light guided scleral depressor-marker during scleral buckling surgery. *General view (A). Close-up view of the tip of the instrument, depicting indentation (B) and marking (C) as separate steps of one procedure. Dashed lines illustrate the light from the integrated light source during light assisted scleral indentation (A, B, C) (L. Lytvynchuk et al. New Scleral Depressor-Marker for Retinal Detachment Surgery Ophthalmology Retina 2019; Jan; 3(1):73-76. Permission granted)****.***

Summary. Application of new instrument can improve scleral buckling procedure, making scleral indentation and marking as a separate independent step during the single session of the surgery. Therefore, an extent of repeated manipulations with the extraocular muscles and multiple rotation of the eye could be significantly reduced. Moreover, it can be used during any extraocular surgery, which requires marking of the sclera. The new instrument is available only as prototype and is not available on the market yet. This limitation could be solved in near future with the help of the marketing strategy.

Novel needle for Intravitreal injection of drugs

Appendix 11

Novel Needle for Intravitreal Drug Delivery: Comparative Study of Needle Tip Aspirates, Injection Stream and Penetration Forces.

Lytvynchuk LM, Petrovski G, Dam A, Hiemstra J, Wimmer T, Savytska I, Binder S, Stieger K. Clin Ophthalmol. 2021 Feb 19; 15:723-734.

Introduction. Pharmacologic therapy in the treatment of intraocular disorders, which are associated with increased concentration of proliferative factors, became the most important and significant tool for eye specialists. Vascular exudation, vascular and fibrovascular proliferation within the intraocular tissues, which are the main caracteristics of vasoproliferative intraocular disorders, can lead to the development of serious vison threatening complications, such as macular edema, sub- or intraretinal hemorrhage, choroidal and vitreous hemorrhage, etc. Vascular endothelial growth factor (VEGF) is one of the most targeted factors during antiproliferative pharmacologic therapy, which necessitates intravitreal injection (IVI) technique.

Intravitreal injection technique was introduced almost 100 years ago and currently is used for intraocular injection of gas, antibiotics and other drugs (Shikari and Samant 2016, Campbell et al. 2010). This kind of technique appeared to be very plausible and up till now remains a single delivery method for anti-VEGF therapy (Fagan et al. 2013, Lorenz et al. 2017). With the use of subcutaneous small-gauge needles ranging from 27 to 32 gauge the anti-VEGF drugs are injected into the vitreous cavity (Avery et al. 2014). Similarly to every surgical technique, the IVI is associated with the risks of complications and side effects (Van der Reis et al. 2011). One of the most vision-threatening complications is endophthalmitis - a severe inflammation of the intraocular tissues with the rate of 0.018% to 1.4% (Diago et al. 2009, Fintak et al. 2008, Klein et al. 2009, Sigford et al. 2015). It was reported that the use of standard hypodermic subcutaneous needles can play a role in development of this complication (Lytvynchuk et al. 2017). Every hypodermic needle that is used for IVI, has sharp inner and outer edges of the tip. It was shown that the inner edge of the tip cuts out the tissue column and the cut cellular material is injected into the vitreous cavity. Injected cellular content can contain intracellular infection and activate intravitreal immune response, which results in aseptic or septic intraocular inflammation (Lytvynchuk et al. 2017). There is no special needle on the market, which is designed especially for intravitreal drug delivery purposes. As possible solution a prototype of the new needle was developed and assessed in our study.

Aim of the study. This study was aimed to evaluate the features of a novel 30-gauge needle prototype, which was designed explicitly for IVI. During the study the new prototype was compared with the standard hypodermic 30-gauge needle. The following characteristics were evaluated: cellular content of the needle tip in experimental conditions, injection stream and penetration forces.

Methods. *New design of needle.* To visualize the concept of a new needle design, a schematic drawing was made with the depiction of its most important features (Figure 35, 36). Instead of front opening (Figure 35 A), the new needle has a side opening with the rounded smooth edges (Figure 35 B, C, Figure 36). In order to facilitate an accurate and desired dosage of the drugs, the dead space of the needle tip was filled out with the same steel material (Figure 36). In order to facilitate an adequate penetrance of the new needle, its tip was made similarly to the tip of standard hypodermic needle: beveled tip with an angle of 18˚ and total diameter of 30-gauge. The new designed 30-gauge (G) needle (NDN) was compared to a standard hypodermic 30 G needle that is regularly used for IVI (BD, Franklin Lakes, New Jersey, USA). Both needles had outer diameter of 0.31 mm, inner diameter of 0.16 mm, wall of 0.076 mm, bevel degree 12˚ (Abevel), and length of 13 mm (stainless steel). Intraoperative optical coherence tomography with Rescan™700 (Carl Zeiss Meditech, Oberkochen, Germany) was used to depict the difference between types of two needle tips. Schematic view of the needle tips was created with the use of graphic software CINEMA 4D (MAXON Computer GmbH, Friedrichsdorf, Germany) (Figure 37).

Intravitreal penetration and aspiration in rat eyes. An experimental part of the study was performed on 10 rat eyes (10 Wistar white outbred albino rats) in general anesthesia. The IVIs were performed on the right eye of the rat 1 mm posterior to the limbus with the 1.0 cc syringes, which were pre-loaded with 0.02cc of balanced salt solution and five novel needles and five standard needles. During the procedure instead of injection, an aspiration of 0.01 cc of vitreous was done.

Cytological analysis of needle tip aspirates. Cellular aspirates were withdrawn from the needles onto the glass slides. Fixation of cellular material was facilitated with 4% formalin and staining - with azure-2-eosin. The visual field of the slides was divided into 30 equal visual fields with size 160 μm^2 each. The number of every cell types was assessed in each visual field. For cytological analysis a light microscope HD Microscope Camera CC50HD (Leica Mikrosysteme Vertrieb GmbH, Wetzlar, Germany) with magnification of 100x and 400x was used. The damaged cells were characterized by the presence of granulated basophilic protein sediments.

Study of the injection stream. This part of the study was performed *in vitro* and in cadaver pig eyes, as well. For *in vitro* evaluation of injection stream from the new and standard needles, the syringes prefilled with trypan blue ophthalmic solution 0.06% Sida-Blue (IOL expert GmbH&Co.KG, Bamberg, Germany) were used. The injection strem was video documented under the microscope. Additionally, the injection stream was studied in cadaver pig eyes with two types of needles and syringes preloaded with Sida-Blue.The injection stream was video documented form the inside of the eyes with the help of E4 Ophthalmic Endoscopy System Endo Optiks® (BVI Medical, Waltham, MA, USA). The video data of two approaches were later prost-processed and analysed.

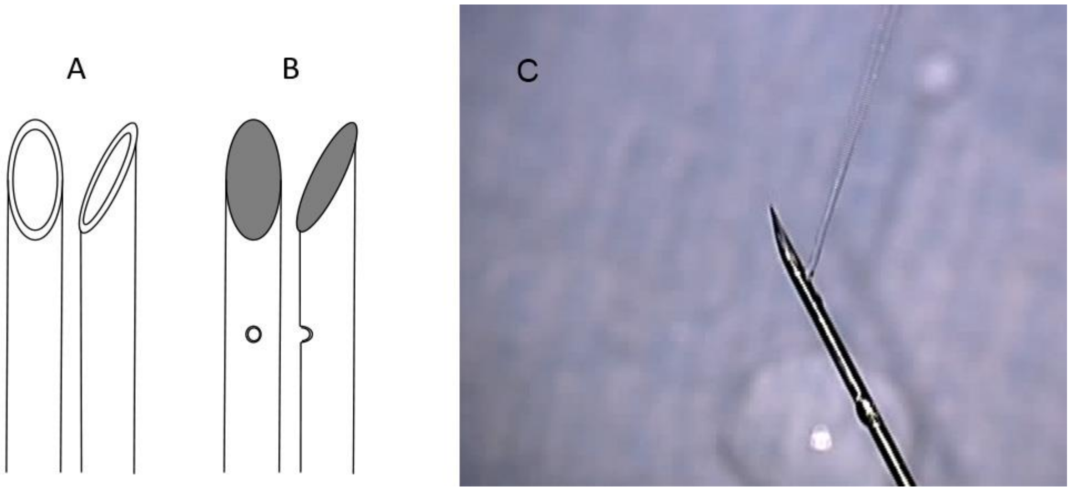

Figure 35. New needle for IVI. *Comparison of the standard hypodermic needle (A) and new needle (B, C). The front opening of the new needle is closed. The side opening is designed for drug delivery (C) (Created by L. Lytvynchuk).*

Penetration force. The penetration force of the two needles was measured in Newton (N) and tested with positioning of the needle tips perpendicularly at a distance of 1 mm to a 0.4 mm thick polyurethane Testing Foil Strips PU 04 (Melab, Leonberg, Germany), and applying a velocity of 100 mm/min (two tests).

All data of cytological study and penetration force study were statistically analysed.

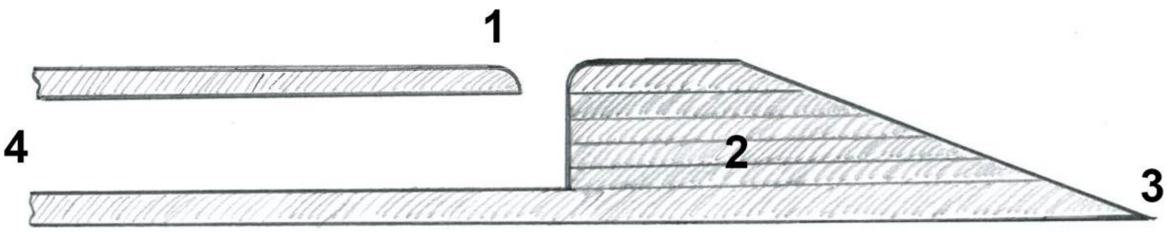

Figure 36. Schematic drawing of the new needle design for intravitreal injection. *1 – smooth edges of the side orifice of the needle tip. 2 – absence of the dead space. 3 – beveled tip. 4 – 30-gauge caliber of the new needle (Lytvynchuk LM, Petrovski G, Dam A, Hiemstra J, Wimmer T, Savytska I, Binder S, Stieger K. Novel Needle for Intravitreal Drug Delivery: Comparative Study of Needle Tip Aspirates, Injection Stream and Penetration Forces. Clin Ophthalmol. 2021 Feb 19; 15:723-734. Permission granted).*

Results. *New design of needle.* The main characteristics of the prototype of the needle for IVI appeared to be the absence of the anterior orifice with sharp outer and inner edges (Figure 37, E yellow arrow), and the presence of the side orifice (Figure 37, H yellow arrow), which facilitated injection of drugs (Figure 37, I yellow arrow). In opposite, the standard hypodermic needle has distinct sharp outer and inner edges (Figure 37, B yellow arrow). This facilitates the mechanical cut of the tissue and capturing the cellular material inside the neelde tip (Figure 37, C red arrow). Side port with smooth edges in new needle was designed to decrease the extent of potential tissue damage and cell capture during IVI (Figure 37, F red arrow). Closure of the front opening prevented from cutting of the ocular tissues' cells, which can stick inside the needle tip, and from injecting this cellular content into the vitreous cavity (Figure 36, 37, E yellow arrow). Therefore, the risk of the contamination of the vitreous body with active proteins, cellular content or infection agents could be reduced.

Needle tip aspirates. Cytological analysis of needle tip aspirates revealed the cellular content in each case of each needle type. However, the amount of different cell types including conjunctival, ciliary body epithelial cells was significantly less (about 50%) in aspirates taken from the new needle in comparison to the standard needle ($p<0.05$). The cellular damage marker (granulated basophilic proteins) was also higher in aspirates taken from standard needle tips: 885.3 μm^2 for NDN cases against 1442.75 μm^2 for SHN cases, and the difference was statistically significant ($p<0.05$).

Injection stream. Analysis of the injection stream *in vivo* and on cadaver pig eyes revealed the difference between the direction of blue dye distribution, showing the forward direction from the standard needle and an oblique direction (approximately 75º) from the new needle. In spite this difference, the oblique manner of injection stream of the new needle facilitated an adequate blue dye delivery into the vitreous cavity of cadaver pig eye.

Study of penetration force. The mean penetration force of the new needle was 39.8% higher (0.791 N) comparing to standard needle (0.566). Due to small number of samples the statistical analysis was not possible (Figure 38).

Discussion. The risk of vitreous contamination during standard IVI is associated with the intraocular immune response of different extent and could lead to vision threatening complications, such as acute endophthalmitis (Ven der Reis et al. 2011). The number of IVIs over the world constantly increases, making the number of affected eyes higher as well (Campbell et al. 2010). That is why an improvement of the standard intravitreal injection technique and development of the special needles aiming to reduce the risks of serious adverse events remains very important (Fintak et al. 2008, Klein et al. 2009, Sigford et al. 2015, Lytvynchuk et al. 2017, Lytvynchuk et al. 2019).

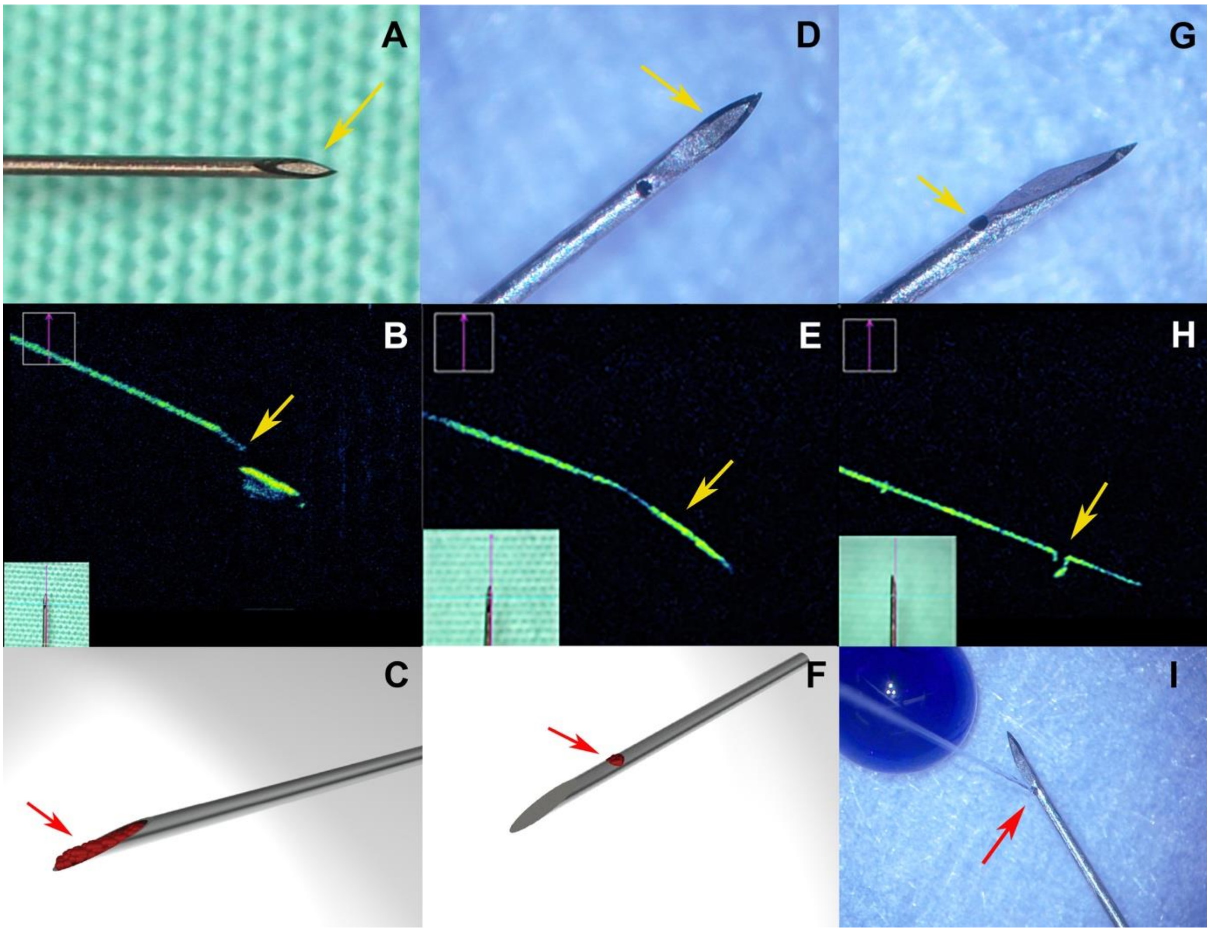

Figure 37. Enlarged view of needles used in experiments. *Enlarged view of the hypodermic 30G (A) and new designed needle 30G (D, G) needles. iOCT of the hypodermic 30G (B) needle and NDN 30G (E, H) needle. B - yellow arrow indicates the sharp inner edge of the tip of the hypodermic needles. E, H – yellow arrows indicate absence of tip orifice and side port, respectively. C, F - schematic view of the cellular content (red arrow) captured by hypodermic 30G and NDN 30G needles, respectively. I – the direction of the injection stream (yellow arrow) (Lytvynchuk LM, Petrovski G, Dam A, Hiemstra J, Wimmer T, Savytska I, Binder S, Stieger K. Novel Needle for Intravitreal Drug Delivery: Comparative Study of Needle Tip Aspirates, Injection Stream and Penetration Forces. Clin Ophthalmol. 2021 Feb 19; 15:723-734. Permission granted).*

After a biologically active or contaminated cellular content is unintentionally injected into the vitreous cavity, the risk for aseptic or septic reaction increases (Lytvynchuk et al. 2017). The vitreous body considered to be a natural cultivation medium. Its regulating factors can stimulate or inhibit proliferation of various cells (Forrester et al. 1986). In case of stimulation of proliferation, injected cellular material can become a scaffold for development of proliferative fibrotic membranes. Conventional technique of IVI and the needle's type and size considered to play an important role during process of contamination (Lytvynchuk et al. 2017).

The use of the new needle prototype presented in current study was already tested in experimental conditions (Lytvynchuk et al. 2019). The study demonstrated safety and efficacy during the IVIs in rat and in cadaver eye (Lytvynchuk et al. 2021). Statistically lower amount of different cell types in aspirates taken from the new needle tips could decrease the risk of postoperative immune reaction of different origin. The study of penetrating forces of a new needle showed no statistically significant difference compared to standard 30-gauge hypodermic needle (Lytvynchuk et al. 2021) and the injection stream of the new needle could provide a sufficient substance delivery into the vitreous cavity.

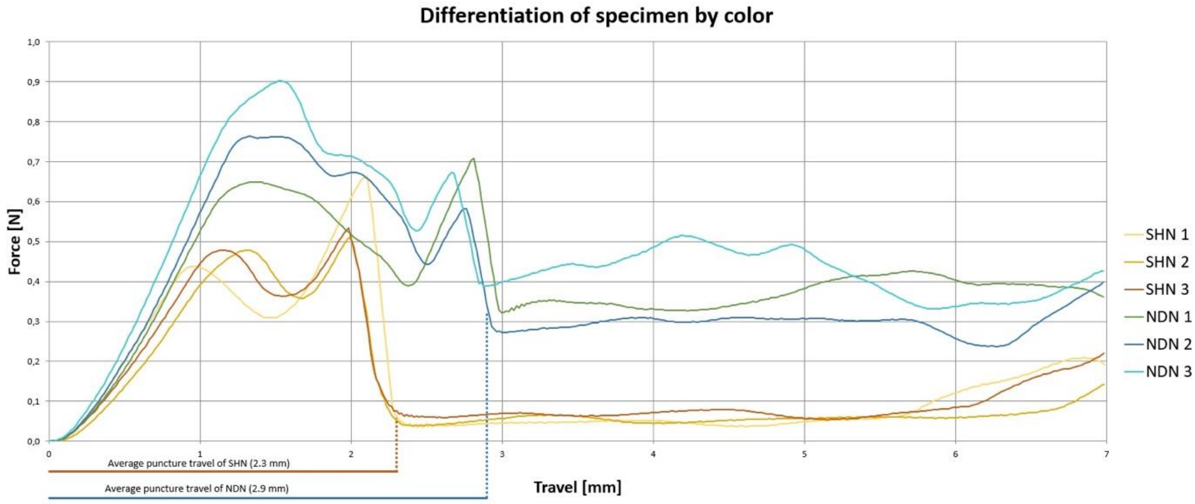

Figure 38. The penetration resistance of the standard hypodermic needle and new designed needle measured and plotted as a load-displacement diagram. Each needle was tested two times (red and black arrows). *The average maximal force for standard hypodermic needle was 0.791 N, and for new needle – 0.566 N (Lytvynchuk LM, Petrovski G, Dam A, Hiemstra J, Wimmer T, Savytska I, Binder S, Stieger K. Novel Needle for Intravitreal Drug Delivery: Comparative Study of Needle Tip Aspirates, Injection Stream and Penetration Forces. Clin Ophthalmol. 2021 Feb 19; <15:723-734. Permission granted).*

Summary. In spite the aseptic measurements during IVI are very strict in Europe and USA, the risks of vitreous contamination cannot be fully avoided. For this reason, the improvement of the IVI technique including perfection of the specially invented needles for IVI has to be considered, as the rate of inflammatory complications will rise due to increased amount of IVI worldwide.

In this study we proposed a new design of the needle for IVI, which aims to reduce ocular tissue damage and consequently capture of the cellular content inside the needle tip. It could play an important role to reduce the vitreous contamination. Penetrating force of the new needle appeared to be slightly higher compared to the standard hypodermic needle. The role of the cellular content injected into the vitreous has to be taken into consideration. Clinical significance of the new needle prototype shall be further investigated.

4. Discussion

4.1. New diagnostic techniques

The principal usage of iOCT in anterior segment surgery was established in earlier studies (Juthani et al. 2014, Heindl et al. 2014, Hirnschall et al. 2013, 2015). The iOCT assisted approach became an unreplaceable tool for different keratoplastik surgeries (De Benito-Llopis et al. 2014, Miyakoshi et al. 2014, Xu et al. 2014, Steven et al. 2013, 2014). However, only few reports are dedicated to the iOCT assisted cataract surgery. Hirnschall et al. focused their studies mainly on the prediction of the postoperative intraocular lens position and calculation of intraocular lens power on aphakic eyes during cataract surgery. One of their conclusions was that implantation of the capsular tension ring during lens-in-the-beg surgery allows for increasing of predictability of the postoperative IOL position, as well as postoperative refraction. Another conclusion was that iOCT assisted measurements of anterior chamber depth could serve as an addition to improve the accuracy of refractive outcome for lens power calculation.

One of the main vision-threatening complications after standard cataract surgery remains posterior capsular opacifications (Kohnen et al. 2008). It was previously reported that postoperative contact between intraocular lenses with squared edge and posterior capsule can reduce the risk of postoperative posterior PCO, and consequently the risk of reduction of visual acuity (Nishi et al. 1998, Peng et al. 2000, Kohnen et al. 2008). In spite of the existing concept "no space no cells" – a firm contact between posterior capsule and posterior IOL surface, which supports the primary use of the IOL with squared edge, a certain rate of PCO still exists. Our study was aimed to investigate the relationship between intraocular lens and anterior and posterior lens capsule. The main purpose was to investigate with iOCT the position of the IOL after standard lens-in-the-bag surgery with implantation of squared edge IOLs (Lytvynchuk et al. 2016). Our results demonstrated that after conventional lens-in-the-bag surgery in 87.13% of cases there was no full contact between posterior capsule and central portion of IOL, and the partial contact between squared IOL edge and posterior capsule was present only in 57.53% of cases. These findings could state that the reason for PCO remains the absence of desired postoperative contact between posterior capsule and square edge of the IOL. Consequently, a new IOL design should be considered and developed in order to increase the rate of posterior capsule adherence to the posterior IOL surface, which will prevent the development of PCO.

The feasibility of iOCT assisted surgical procedures for posterior and anterior segment surgery was reported by Binder et al. 2011. Among the most applicable surgical indications for iOCT remains the surgery of macular holes (Ehlers et al. 2014, Hattenbach et al. 2016). Development and clinical application of novel surgical techniques including inverted internal limiting membrane flap technique allowed to increase the rate of anatomical and functional success after macular hole closure up to over 95% (Michalewska et al. 2010, 2013, Rizzo et al. 2018). Modification of IILMFT, such as temporal inverted ILM flap technique could facilitate even less traumatic closure of the MH due to reduction of the square of ILM, which has been peeled (Michalewska et al. 2015). Elimination of the epiretinal tangential tractional forces and induction of gliosis onto the inner surface of inverted ILM flap belong to the main suggested mechanisms that facilitate closure of the MH after IILMFT (Michalewska et al. 2010, Andjelić et al. 2014). Nevertheless, the performance of this new technique and its learning curve remain challenging. Borrelli at al. in 2018 reveled that iOCT assisted IILMFT could be useful to detect the residual and subclinical epiretinal membranes, which could influence macular closure. Maier et al. in 2018 applied the iOCT approach for IILMFT and summarised that ILM peeling done in centripetal manner prevents the increase of the macular hole size and that iOCT allowed for visualizing the proper position of the ILM flap at the end of the surgery. In our study, we could widen the knowledge about application of iOCT during IILMFT. The improvement of ILM flap visualization with iOCT allowed us to use only incomplete short-lasting endotamponade with a sterile air (not with air-gas mixture) at the end of the surgery, which could decrease the risk of retinal and optic nerve dehydration due to residual meniscus of fluid (Lytvynchuk et al. 2019). In addition, we could document that the centripetal direction of the ILM peeling could not only avoid the enlargement of the macular hole size, but even reduce the bottom size of the macula hole. Moreover, the iOCT approach appeared to be very useful during the learning process of this new, complicated and challenging technique, documenting and demonstrating every step for the surgery. Step by step iOCT assisted learning of the IILMFT could avoid the risk of iatrogenic trauma of the foveal area and improve the macular hole closure rate.

With the current development in the fields of cell and gene therapy, and intraocular retinal prosthesis implantation to treat a variety of retinal dystrophies, the role of iOCT becomes more and more important (Luo and da Cruz 2016, Binder and Lytvynchuk 2016). Subretinal injection of cellular suspensions or subretinal implantation of cell carriers necessitates a perfect visual control. In the same way, a proper placement of epiretinal or subretinal intraocular prosthesis can be secured with an additional control, such as iOCT. Retinitis pigmetosa belongs to one of the first retinal dystrophies treated by the implantation of epiretinal prosthesis (Rizzo et al. 2014, Ghodasra et al. 2016).

In 2016, Binder and Lytvynchuk were first to report the use of the iOCT during implantation of Arguss II retinal prosthesis system to correct the visual perception in patients with retinitis pigmetosa. The authors also reported that the iOCT approach was useful during the detection of residual epiretinal membranes, which should be definitely removed before the placement of the Argus II prosthesis. Moreover, the iOCT was also used during the placement and fixation of the epiretinal prosthesis, in order to make these steps more precise and correct. Rachitskaya et al. reported the use of the iOCT approach in five cases of retinitis pigmetosa patients treated with implantation of Argus II epiretinal prosthesis. The authors described that the mean duration of the surgery was 3 hours 59 minutes, which led to corneal swelling with deterioration of intraoperative view and necessitated the corneal deepithelisation with the risk for postoperative corneal inflammation. Therefore, the condition of the optic media plays an important role during this type of surgery as it can impact the iOCT visualization as well.

In our study, we investigated the influence of the natural optic media of the human eye on the quality of iOCT imaging of an Argus II epiretinal prosthesis array and the retina in comparison to the quality of iOCT imaging in a training eye, which does not contain any optic media (Lytvynchuk et al. 2019). Our study results revealed that the use of the iOCT approach allowed for more controlled performance of the most important step of the surgery – the implantation of the intraocular part of the Argus II electrode array. The overall time of the surgery in our study in patient was 3 hours and 25 minutes. The findings showed that the quality of iOCT imaging through clear optical media of the human eye with uncompromised cornea does not differ significantly from the quality of images taken from the training eye. These results could only be applied to those cases, in which the duration of the surgery did not exceed more than three and a half hour and were not complicated by corneal edema. Moreover, we reported for the first time the impact of the semitransparent Argus II array on the underlying retina on iOCT imaging, which is crucial in order to examine the condition of the retinal layers in follow-up visits. The shell of the electrode array, made of silicon, does not produce a significant shadowing on the underlying retina. However, the areas, which are located directly under the metal electrodes of the Arguss II array, were exposed to shadowing. These areas, however, were relatively small. In addition, the residual distance between the array and the retina could serve during calculation of the signal intensity from the electrodes. In summary, the application of the iOCT approach for implantation of the epi- or subretinal prosthesis to treat retinal dystrophies has proven its important role to improve the precision of the surgical procedure and consequently to enhance the postoperative functional outcome.

4.2. New surgical techniques

Pediatric cataract surgery

Pediatric cataract belongs to the most common vision threatening eye disorders in children (Lambert and Drack 1996, Lorenz 2007, Solebo 2017). Based on the progress in surgical techniques and development of the new surgical strategies during the last two decades, cataract surgery in children has reached a new level of quality and safety (Wilson et al. 2009, Lin and Buckley 2010, Nischal 2016). Nevertheless, the high rate of the most common postoperative complication such as posterior capsule opacification or visual axis reopacification can lead to the failure of the primarily uncomplicated surgery (Zetterström and Kugelberg 2007, Medsinge and Nischal 2015). To reduce the incidence of PCO or VAR after the standard lens-in-the-bag implantation technique, two main approaches were proposed: posterior capsulorhexis with anterior vitrectomy and posterior capsular capture of the IOL optic (Gimbel 1996). In the 1990's Tassignon had developed and introduced a completely novel method of aphakia correction after cataract extraction – the bag-in-the-lens IOL implantation technique, which she first used in the cataract surgery in adults and then - in children (Tassignon et al. 2002, 2007). Since 2008, the BIL IOL implantation technique was introduced into the surgical treatment of cataract in children in Giessen. However, the complexity of the new cataract surgery technique in children required further studies.

Due to specific anatomical and developmental features of the growing and constantly changing eye in children, the calculation of the intraocular lens power and the prediction of postoperative refraction remained challenging (Vasavada and Vasavada 2017, Trivedi and Wilson 2017). Vanderveen et al. reported that particularly SRK/T and Holladay 1 formulas for IOL power calculation showed an improved predictability compared to other formulas in children (Vanderveen et al. 2013). Kekunnaya et al. reported the smallest prediction error of 1 diopter in children younger than 2 years with the use of SRK II formula (Kekunnaya et al. 2012). However, these studies described the experience with the lens-in-the-bag implantation or sulcus implantation of the IOL. During the first application of the new BIL IOL technique in children the SRK/T formula was used (Tassignon 2007).

In our study we aimed to analyse the accuracy and predictability of the SRK/T formula for BIL IOL implantation technique in different age groups of pediatric patients. The study results revealed that SRK/T formula appeared to be useful for BIL IOL power calculation. However, there are a number of factors that can influence the prediction error, or the difference between the target and achieved refraction. The most important factor is the age. The mean prediction error in children aged <36 months was 2.19 D, and in children aged ≥36 months it was 1.33 D. Another factor, which influences the refractive error is the axial length. In our study, the impact of corneal radius or preoperative astigmatism was not statistically significant. Overall, our study demonstrated for the first time that the refractive error for BIL IOL implantation technique was comparable and even lower to the prediction error for lens-in-the-bag IOL implantation technique regardless of the age of the patients. Furthermore, the rate of postoperative visual axis reopacification remains lower using the BIL IOL implantation technique. Our results suggest that calculation of BIL IOL power with SRK/T formula remains relatively accurate compared to conventional technique and that the use of this new surgical approach should be considered as a first-choice surgery in pediatric cataract.

In the second study related to this habilitation thesis we analysed the rate of intra- and postoperative complications of bag-in-the-lens IOL implantation technique in pediatric patients and the ways to manage them (Lytvynchuk et al. 2019). The main advantage of the BIL IOL implantation technique remains the significant reduction of the risk of postoperative capsular opacification (Tassignon et al. 2007, van Looveren et al. 2015, Nyström et al. 2018). It is facilitated through the performance of anterior and posterior capsulorhexes with similar size and further implantation of the remaining peripheral capsular edges into the groove of the newly designed BIL IOL (Tassignon et al. 2002). In this case scenario, the residual lens epithelial cells can proliferate and induce capsular opacification only within the closed space in the periphery of the capsular bag around the 5 mm optic of the IOL, which remains clear (Tassignon et al. 2002, 2007). Application of this new technique allowed for significant reduction of the rate of posterior capsular opacification after pediatric cataract surgery with improvement of success rate up to approximately 95% (Tassignon et. al. 2007, Van Looveren et al. 2015, Nyström et al. 2018). Among the most common complications other than PCO were intraoperative vitreous prolapse, postoperative intraocular hypertension, luxation of the IOL and BIL IOL opacification (Tassignon et. al. 2007, Van Looveren et al. 2015, Dhubhghaill et al. 2015, Nyström et al. 2018). As the data about the new BIL IOL technique remain limited, we studied those aspects further.

The result of our study demonstrated a success rate regarding development of PCO in 94.4% of cases, which correlated with other studies. Reopacification of the visual axis developed only in 5.6% of cases less than 12 months after the surgery and could be managed with a second intervention. Among the most common intraoperative complications in our study was a prolapse of the vitreous body into the anterior chamber, which necessitated vitrectomy in 28.9%. Most of these cases (69.2%) happened in children older than 12 months. Other intraoperative complications included iris hemorrhage, rupture of the anterior capsule, and persisting mydriasis. To the most common postoperative complications belonged visual axis reopacifications (5.6%), intraocular hypertension (7.8%), uveitis of different grade (6.7%), and luxation of the BIL IOL (3.3%).

For the first time on the large cohort of cases (90 cases) a detailed analysis of intraoperative and early postoperative complications of BIL IOL implantation technique for different age groups was performed. Moreover, we presented the challenges and complications of the BIL IOL implantation approach during its learning curve with description of the ways of its management. This study can serve as a guide during the training process for other surgeons, making them aware of possible risks and required additional surgical steps.

Macular hole surgery

Full-thickness macular holes belong to the group of retinal diseases that result in the sudden loss of central vision (Gass 1987). Surgical procedure appears to be the only approach to treat macular holes (Duker et al. 2013, Kelly and Wendel 1991). Postoperative outcomes usually depend on etiology of the MH, its duration and applied surgical technique (Kelly and Wendel 1991, Ullrich et al. 2002), with a success rate between 83% for traumatic macular hole and 98% for idiopathic macular hole cases (Chow et al. 1999, Miller et al. 2013, Rubin et al. 1995, Smiddy 2010, Reis et al. 2012). Cases with traumatic full thickness macular hole remain the most difficult for surgical treatment (Kuhn and Pieramici 2002, Johnson et al. 2001). The reasons include the unclear etiology, association with concomitant injury of other ocular tissue and high risk of postoperative complications (Miller et al. 2013, Garcia-Arumi et al. 1997).

Since the last decade, a number of new surgical approaches were proposed to treat idiopathic macular hole (Smiddy 2010, Reis et al. 2012), among them there was the macular detachment technique first described by Oliver and Wojcik (2011). After the internal limiting membrane is removed, a small amount of balanced salt solution is injected into the subretinal space in four quadrants forming four blebs. Following fluid-air/gas exchange, the patients should maintain a prone position after the surgery allowing superficial tension of the air/gas bubble to create a pressure on the central retina and to displace the retinal tissue toward the macula center supporting the closure of the hole. The authors reported macular closure rate of 90% (Oliver and Wojcik 2011). Centripetal displacement of retinal tissue was documented and reported by Yeun et al. in 2017 supporting the concept described by Oliver and Wojcik. Independently, in 2013 we started to use a similar technique to treat macular hole cases caused by ocular injury.

In our study, we aimed to apply this novel concept, which was implemented with few modifications, for the treatment of complicated traumatic full-thickness macular holes, calling this technique hydraulic centripetal macular displacement technique (Ruban et al. 2017). During our observational study, we investigated the anatomical and functional outcomes of pars plana vitrectomy, which was combined with HCMD technique. In addition to subretinal injection of balanced salt solution in every case, we performed a centripetal massage of the retina with silicon tipped cannula. Moreover, in cases with subretinal scarring and presence of chorioretinal fibrotic tissue, a dissection of the fibrotic scar with vitreoretinal scissors or the sharp tip of the hypodermic 27-gauge cannula was performed. The closure rate in our study was 85.7% compared to 83% with conventional surgery. To the best of our knowledge, this was the first study of application of this novel technique for MH caused by ocular injury. Nevertheless, the application of this technique should be studied further.

4.3. New surgical instruments

New scleral depressor-marker for retinal detachment surgery

Novel surgical instruments that quickly arise as a response to the more advanced requirements in ophthalmic surgery are of large interest and value (Charles 2004, Peyman et al. 2002). Retinal detachment belongs to the most often occurring emergency conditions in eye surgery. Scleral buckling with scleral indentation and identification of the retinal brakes still remains to be the first choice surgical approach in cases of uncomplicated rhegmatogenous retinal detachment (Custodis 1956). Combination of scleral buckling technique with endoillumination modernized the conventional approach (Nam et al. 2013). However, several issues related to surgical instrumentation remain unsolved (Trevino and Stewart 2015). Conventional scleral depressor-markers allow for simultaneous indentation and marking the sclera in areas of retinal brake in order to have an orientation for performing the cryoretinopexy and suturing scleral buckle (O'Connor 1971, Chawla 1970, Linkoff and Kreissig 1982). Nevertheless, the identification of this area remains challenging, as multiple indentations are required. Numerous marks performed during multiple indentations can confuse the surgeon and lead to failure of primary retinal detachment surgery.

Our invention of a new prototype of scleral depressor-marker was aimed to separate these two functions, indentation and marking, enabling the surgeon to perform the marking only of desired area (Lytvynchuk et al. 2019). The forceps-like type of the instrument’s handle during its squeezing facilitated an exposure of 0.5 mm of the internal pre-stained tip with serrated surface only when necessary, which could mark only the desired area of the sclera in a tattoo-like manner. In addition, we integrated into the new instrument an external light probe, which allowed for better visualisation of the highest indentation point during indirect ophthalmoscopy and consequently for more precise identification of the retinal breaks and marking. Overall, the use of the new instrument could decrease the indentation forces with less impact on pain and intraocular pressure rise, improve the indentation procedure staining of only desired areas of the sclera, decrease the number of scleral indentation and increase the precision of the marking with illumination assisted approach.

Surgical application of the new indenter-marker could be extended to the other fields of ocular surgery, such as treatment of intraocular tumors (radiotherapy or transscleral removal of the tumor).

Novel needle for intravitreal drug delivery

Intraocular injections into the vitreous body became one of the most often used routes of delivery of the drugs to treat a wide variety of ocular conditions, including vasculoproliferative and inflammatory diseases (Fagan and Al-Qureshi 2013, Campbell et al. 2010). Relative simplicity and low risks of the intravitreal injections of the drugs (IVI) made this procedure available in many in- and outpatient eye units (Campbell et al. 2010, Moisseiev and Loewenstein 2019). Variability of IVI techniques required the development of international guideline (Avery et al. 2014). Nevertheless, there is a risk of complications that could lead to severe visual loss (Van der Reis et al. 2011). The most serious adverse effects of the IVI technique include intraocular inflammation, varying form the local immune response with uveitis to postoperative endophthalmitis (Sigford et al. 2015, Jonas et al. 2007, Klein et al. 2009). There are several reports in the literature, which studied the possible causes of intraocular inflammation after IVI (Lytvynchuk et al. 2017, De Caro et al. 2008). De Caro et al. in 2008 demonstrated that contamination of the needle tip during IVI can happen even when topical antibiotic and povidone iodine were applied as prophylaxis of intraocular contamination. Nakashuizuka et al. in 2016 demonstrated in experimental conditions on enucleated porcine eyes that there is a risk of delivering of contamination directly inside the vitreous cavity during IVIs done with 27, 30 and 32-gauge needles.

The aim of our study was to evaluate the performance of a novel needle for IVI in vented by the author of this thesis, which is supposed to reduce cellular intake into the vitreous cavity. The new 30-gauge needle was compared to the standard hypodermic 30-gauge needle. Due to the specific design of the needle, cytological analysis of the needle tip aspirates revealed reduction of cellular material to almost 50% with subsequent reduction of the risk of vitreous contamination. Even though the penetration force of the new needle was higher due to the absence of industrial manufacturing of the new prototype, the study of the injection stream demonstrated satisfactory drug delivery properties. The impact of the new needle on inflammation frequency needs to be assessed as soon as the needle is approved for use in IVI. In addition, the possible clinical significance of the role of cellular material, which is injected during each IVI with the standard needle, needs to be analysed further.

5. Summary

Progress and improvement of the novel surgical approaches for intraocular surgery has advanced the field significantly. In this thesis, innovations are presented in the three area, which are of considerable importance to intraocular surgery: (1) new intraoperative diagnostics, (2) new surgical techniques, and (3) new surgical instruments.

1. *New diagnostic techniques*

Inventions of the intraoperative optical coherent tomography and its application into the clinical practice have modernized the field of the ocular surgery (Binder et al. 2011).

The first review of the commercially available iOCT systems and its feasibility for eye surgery was recently reported in a book chapter (Lytvynchuk et al. 2017). In this review the authors summarized the current information about technical characteristics of the iOCT systems, principles of intraoperative imaging, ways of data post-processing, as well as data regarding its application for anterior and posterior eye segments with presentation of clinical cases. It was demonstrated that the use of iOCT imaging enabled to investigate in real-time the pathophysiology of different eye disorders, revealing numerous intra-surgical findings, which have extended our understanding of the course of these diseases and the influence of the surgical procedure on the clinical outcomes.

In a second study, we applied the iOCT approach to investigate the real position of the intraocular lenses inside the capsular bag at the end of the standard lens-in-the-bag surgery (Lytvynchuk et al. 2016). This issue is significantly associated with the development of postoperative capsular opacification. For the first time, we were able to show that at the end of the surgery the contact between posterior lens capsule and IOL optic is a rare event (12.9%). This represents a new aspect to explain the residual rate of the PCO in spite of the use of square edge IOL with “no space – no cells” concept. These findings demonstrate that the absence of the contact between IOL and posterior capsule in the vast majority of cases results in postoperative proliferation and migration of the lens epithelial cells into the retrolental optical zone.

Within this thesis, the iOCT method was also applied during surgeries of the most sensitive area of the retina, the fovea centralis, with a particular emphasis on tissue reactions following surgical treatment of macular holes (Lytvynchuk et al. 2019). The inverted internal limiting membrane flap technique is a novel and very challenging approach to treat macular holes of different origin. In our study we applied iOCT during macular hole surgery with IILMFT to evaluate the possibilities and consequences of the new approach. The study results demonstrated the advantages of the new technique in comparison to convectional ILM peeling. We documented for the first time that IILMFT avoided the intraoperative iatrogenic enlargement of the macular hole size and even more, allowed to minimize the basal size of it. Additionally, the use of iOCT enabled to reassure the proper position of the inverted ILM flap at the very end of the surgery after air tamponade was done and visual control was impossible. Every step of the novel surgery could be visualized and was therefore well controlled, which improves the safety of such an approach.

Modern vitreoretinal surgeries for the treatment of degenerative retinal diseases might become an important field of application of iOCT. One of our studies was focused on the feasibility of iOCT imaging during Argus II retinal prosthesis implantation in patients with retinitis pigmentosa (Binder and Lytvynchuk 2016). The study results demonstrated that iOCT assisted surgery enabled the detection of residual epiretinal membranes in the macular area. These membranes need to be removed before Argus II implantation in order to decrease the risk of postoperative formation of a new gliosis. Evaluation of the influence of the human optic media on the iOCT imaging showed satisfactory results with almost no impact of the optic media on visibility of the implant and underlying retina. However, these results are valid only for cases with surgery duration shorter than 3.5 hours and with no corneal swelling. Focal shadowing from the array electrodes onto the retina surface was documented during the study as well, but appeared to be clinically insignificant, as the square of shadowing was minimal.

2. *New surgical techniques*

Pediatric cataract surgery is a complex and difficult. Frequently, the development of PCO or visual axis reopacification can lead to the failure of the surgery. Over 20 years ago, Dr. Tassignon in Belgium developed and introduced a completely novel method of aphakia correction after cataract extraction – the bag-in-the-lens (BIL) IOL implantation technique, which reduced significantly the rate of postoperative VAR (Tassignon et al. 2002). However, the performance of the BIL IOL implantation technique remains challenging and the reasons of the improved outcome after surgery remains debated (Tassignon et al. 2007).

In two book chapters, which are the part of this thesis, we summarized our experience of surgical care of pediatric cataract patients, including preparation of the patients, description of surgical complications and preliminary refractive and visual results (Lytvynchuk et al. 2019, Lytvynchuk and Lorenz 2019). Additionally, we performed two studies of use of BIL IOL implantation technique in different age groups of children with cataract. In the first report, we analyzed the postoperative refraction and prediction error in pediatric cataract patients at different age (Lytvynchuk at al. 2019). For the first time, our data demonstrated satisfactory and even slightly better precision of the BIL IOL power calculation in comparison to the data obtained in studies dedicated to conventional lens-in-the-bag or sulcus IOL implantation technique, supporting the efficacy of the new method.

The prediction error strongly inversely correlated with age and axial length of the pediatric eyes.

In the second study dedicated to BIL IOL technique, we analysed in a large cohort of patients at different age the rate of the most common intra- and early postoperative complications of the BIL IOL technique (Lytvynchuk et al. 2020). The study data demonstrated that the success rate with regard to VAR was 94.4%. There were no significant differences between the age groups concerning intra- or postoperative complications.

Another study, which is presented within this thesis, investigates the efficacy of a novel approach – hydraulic centripetal macular displacement – as first option treatment for traumatic macular holes (Ruban, Lytvynchuk et al. 2017). Our data showed that the macular hole closure rate in the group of patients with traumatic MH was 85.7%, which is slightly higher than previously reported. Postoperative TMH closure and improvement of the visual acuity was enabled by intraoperative centripetal displacement of the macula, removal of the chorioretinal scarring and gentle massaging of the macula in centripetal manner. Since the outcome of this new approach is very satisfactory, we suggested this novel technique to be an effective tool in the primary care for traumatic macular hole cases.

3. *New surgical instruments*

Rhegmatogenous retinal detachment remains one of the most frequent emergency situations, and the scleral buckling procedure is the first-choice surgical technique to treat uncomplicated RD. The most important step of this surgical technique is scleral indentation with marking of the retinal breaks onto the sclera. With our new prototype of new scleral depressor-marker we aimed to improve this step of the surgery, making it more precise with less risk for complications and shorter performance time (Lytvynchuk et al. 2019). We demonstrated its effectiveness in regard to separation of two major functions: scleral indentation and scleral marking, in contrast to conventional instrumentation. This could improve the accuracy of marking by placing the mark only onto the desired area. The combination of the light probe with the new instrument improves the precision of the scleral indentation indicating the highest indentation point with the light.

Modern development of pharmaceutical agents enables to treat a variety of retinal disorders by injecting them into the vitreous cavity. Intravitreal injection remains to be the most frequently used drug delivery method with relatively low rates of complications. However, since the number of IVIs constantly increases, the number of complications increases as well. Additionally, the reasons for the presence of epiretinal membranes after IVI, postoperative inflammation and retinal detachment remain elusive, making it difficult to further improve the method. The second invention presented here, a new needle for IVI, was aimed to decrease the trauma of the ocular tissues during the injection in order to decrease the risk of potentially injected cellular material, which can play a role in intraocular inflammation (Lytvynchuk et al. 2021). The new needle allowed to reduce the trauma of the ocular tissues and significantly decreased the capture of the cellular content inside the needle tip. Cytological analysis of aspirates taken from the new needle showed almost 50% less cellular content in comparison to a standard hypodermic needle. A custom-made needle prototype demonstrated a higher penetration forces, but the increased values were not statistically significant. Currently, new studies are underway to evaluate the new needle in preclinical and clinical settings.

The methods and techniques presented within this habilitation thesis have improved the surgical management of a number of ocular disorders. However, some of these new procedures have just entered clinical stage and remain to be further evaluated. It is therefore necessary and important to continue with the implementation of these techniques and to gather new data on safety and efficacy to ensure optimal outcome of the surgeries.

6. Zusammenfassung

Stetige Verbesserungen und Weiterentwicklungen von neuen chirurgischen Verfahren für die intraokulare Chirurgie haben dieses Feld der Augenheilkunde enorm vorangebracht. In dieser Habilitationsschrift werden Neuerungen auf drei Gebieten präsentiert, die für die intraokulare Chirurgie von großer Bedeutung sind: (1) neue intraoperative Diagnostik, (2) neue chirurgische Techniken, und (3) neue chirurgische Instrumente.

1. *Neue diagnostische Techniken*

Die Entwicklung der intraoperativen optischen Kohärenztomographie (iOCT) und die verschiedenen dadurch möglich gewordenen Anwendungsmöglichkeiten haben die okulare Chirurgie revolutioniert (Binder et al. 2011).

In einem Buchkapitel wurden die möglichen Anwendungen eines kommerziell erhältlichen iOCT Systems in der retinalen Chirurgie vorgestellt (Lytvynchuk et al. 2017). In dieser Übersichtsarbeit haben die Autoren die aktuellen Informationen über den technischen Stand der Methodik, die Prinzipien der intraoperativen Anwendung und Möglichkeiten der Nachverarbeitung gewonnener Daten beschrieben sowie die Vor- und Nachteile einer Anwendung im vorderen oder hinteren Augenabschnitt mit klinischen Fällen erläutert. Es konnte gezeigt werden, dass die Pathophysiologie von verschiedenen Netzhauterkrankungen in *real time* während der Operation untersucht werden kann, wobei verschiedene vorher unklare Befunde geklärt werden können. Dadurch können auch die Auswirkungen der chirurgischen Vorgänge auf den Krankheitsverlauf deutlich und besser dokumentiert und beurteilt werden.

In einer weiteren Arbeit zu diesem Thema wurde die iOCT Methodik zur Bestimmung der realen Position von Intraokularlinsen (IOL) innerhalb des Kapselsacks am Ende der standardisierten lens-in-the-bag Operation genutzt, da diese Fragestellung wichtig im Zusammenhang mit der Entwicklung von postoperativer Eintrübung der Kapsel (PCO) ist (Lytvynchuk et al. 2016). Zum ersten Mal konnte gezeigt werden, dass der Kontakt zwischen posteriorer Linsenkapsel und IOL ein seltenes Ereignis ist (12,9%). Diese Information kann die Rate an PCO erklären, obwohl *square edge* IOLs verwendet werden, die nach dem Konzept „*no space – no cells*“ funktionieren. Dadurch können bei einem Großteil der Fälle durch die Abwesenheit eines Kontaktes zwischen IOL und Kapselwand postoperative Proliferationen und Migration von Linsenepithelzellen in den retrolentalen Raum entstehen.

Im Rahmen der hier vorgestellten Arbeiten wurde die iOCT Technik auch angewendet, um Operationen im sensibelsten Teil des retinalen Gewebes, der Fovea centralis, durchzuführen. Hierbei wurde besonderes Augenmerk auf das Verhalten des

Gewebes in diesem Bereich auf chirurgische Manipulationen im Rahmen der Versorgung eines makulären Foramens gelegt. Die *inverted internal limiting membrane flap technique* (IILMFT) ist eine neue und besonders herausfordernde Methode zu dessen Behandlung. In der vorgelegten Studie wurde die iOCT Methode zur Evaluierung der IILMFT eingesetzt (Lytvynchuk et al. 2019). Mit Hilfe des neuen bildgebenden Verfahrens konnte gezeigt werden, dass die IILMFT Methode zur Vermeidung der iatrogen hervorgerufenen intraoperativen Vergrößerung des Foramens wichtig ist und sogar zu einer Verkleinerung des initial vorhandenen Foramens noch während der Operation führen kann. Durch iOCT konnte auch die korrekte Position des invertierten Flaps nach durchgeführter Luft-Tamponade und daraus resultierender nicht möglicher visueller Kontrolle trotzdem festgestellt werden. Die iOCT Methode ermöglicht in der Tat eine Kontrolle und Dokumentation jedes Schrittes dieser schwierigen chirurgischen Methode, wodurch die Sicherheit der Anwendung deutlich verbessert wird.

Die Implantierung von Netzhautchips als neuartiges Verfahren zur Behandlung von degenerativen Netzhauterkrankungen stellt eine aufwendige Operation dar, bei der das iOCT eine wichtige Funktion einnimmt. Ein weiteres Manuskript in dieser Habilitation stellt die Nutzung der iOCT Technologie bei der Implantation eines ARGUS II Netzhautchips bei Patienten mit Retinitis pigmentosa vor (Binder and Lytvynchuk 2016). Durch die Nutzung der iOCT Methode konnten Reste von epiretinalen Membranen im Rahmen der chirurgischen Intervention zunächst erkannt und vor der eigentlichen Implantation entfernt werden, da sie ansonsten das Risiko für eine postoperative Komplikation erhöhen. Die Untersuchung des Einflusses der optischen Medien im Auge auf die Bildqualität der iOCT Methode ergab, dass sie fast keinerlei Einfluss zeigen, wodurch der Anwendungsbereich entsprechend groß ist. Allerdings war eine gute Durchführbarkeit der iOCT Methode nur bei Operationen von weniger als 3,5 Stunden Dauer und bei Abwesenheit einer kornealen Schwellung möglich. Eine Verschattung der Fovea durch die Elektroden des Arrays wurde ebenfalls in einigen Fällen mittels iOCT dokumentiert, konnte aber aufgrund der minimalen Ausdehnung und der nicht vorhandenen klinischen Beeinträchtigung der Patienten als nicht signifikant nachteilig für den Erfolg der Operationsmethode identifiziert werden.

2. *Neue chirurgische Techniken*

Die Operation der kindlichen Katarakt stellt nach wie vor einen sehr schwierigen chirurgischen Eingriff dar, bei dem häufig postoperative Komplikationen wie PCO oder Eintrübungen der visuellen Achse auftreten. Schon vor über 20 Jahren hat Dr. Tassignon aus Belgien ein völlig neuartiges Verfahren für die Behandlung einer kindlichen Katarakt entwickelt – die *bag-in-the-lens* (BIL) IOL Implantation, mit der deutlich niedrigere Komplikationsraten verbunden sind (Tassignon et al. 2002). Allerdings stellt diese Methode eine komplizierte Operation dar und die Ursachen der verbesserten Resultate sind nicht eindeutig geklärt (Tassignon et al. 2007).

In zwei Buchkapiteln, die Teil dieser Habilitationsschrift sind, hat der Autor seine Erfahrungen bei der Durchführung dieser Operationsmethode inklusive der Vorbereitung der Patienten, der Beschreibung der chirurgischen Komplikationen und der vorläufigen refraktiven und visuellen Ergebnisse veröffentlicht (Lytvynchuk und Lorenz 2019, Lytvynchuk et al. 2019). Im ersten Manuskript wurde die postoperative Refraktion und die Vorhersage des Refraktionsfehlers bei Patienten unterschiedlichen Alters nach BIL IOL Implantation untersucht. Dabei konnte zum ersten Mal dargelegt werden, dass die Präzision der BIL IOL bezüglich des postoperativen Refraktionsfehlers besser ist als bei konventioneller lens-in-the-bag oder sulcus IOL Implantation. Der Fehler bei der Vorhersage der Refraktion korrelierte zudem stark invers mit dem Alter und der Bulbuslänge.

Im zweiten Manuskript wurde die Rate der häufigsten intra- und frühen postoperativen Komplikationen unter Einbeziehung des Alters der Patienten in einer relativ großen Kohorte an der Augenklinik Gießen analysiert (Lytvynchuk et al. 2019). Dabei stellte sich heraus, dass die Erfolgsrate der Operation bei 94.4% lag und es keine Beziehung zwischen Alter der Patienten und Komplikationsrate gab.

Ein weiteres neues chirurgisches Verfahren, welches im Rahmen dieser Habilitationsschrift vorgestellt wird, betrifft die erstmalige Versorgung traumatisch bedingter Makulaforamina mittels hydraulischer zentripetaler Versetzung der Makula (Ruban, Lytvynchuk et al. 2017). Die Daten zeigen eine Erfolgsrate von 85.7% bei umgehender Operation, was leicht höher ist als bei konventionellen chirurgischen Verfahren. Durch die Versetzung der Makula, die Entfernung chorioretinaler Narben und eine leichte Massage der Makula in zentripetaler Richtung wurden sehr gute Raten bzgl. Schließung der Foramina und dadurch visuelle Verbesserungen erzielt. Die Autoren schlagen daher diese Form der Chirurgie als Erstversorgung von Makulaforamina nach Trauma vor.

3. Neue chirurgische Instrumente

Die rhegmatogene Netzhautablösung stellt eine der häufigsten Notfallsituationen in der Augenheilkunde dar und die unkomplizierte Form der Erkrankung wird typischerweise durch das sogenannte *sceral buckling* therapiert. Der wichtigste Teil der Operation ist die Indentation der Sklera, um die Netzhautrisse außen an der Sklera zu markieren. Da dies mit herkömmlicher Technik nicht immer optimal funktioniert, wurde vom Autor ein neues Instrument, der sklerale *depressor-marker*, entwickelt. Durch Nutzung des Instrumentes können zwei zuvor separat durchzuführende Schritte zeitgleich durchgeführt werden, die sklerale Indentation und die sklerale Markierung. Dadurch kann dieser Teil der Operation deutlich schneller und mit höherer Präzision durchgeführt werden, was auch in einer geringeren Komplikationsrate resultiert. Die Ergebnisse der Evaluation des Instruments wurden in einem Manuskript veröffentlicht (Lytvynchuk et al. 2019).

Die Applikation von Medikamenten in den Glaskörper (IVI) stellt eine der zentralen Behandlungsmöglichkeiten für eine Vielzahl an retinalen Erkrankungen dar, da der Eingriff in vielen Fällen ambulant durchgeführt werden kann und die Komplikationsraten relativ gering sind. Aufgrund der Tatsache, dass es jedes Jahr steigende Zahlen an IVI gibt, steigen jedoch auch die Zahlen an Komplikationen unaufhörlich an. Die Ursachen für die Bildung von epiretinalen Membranen nach IVI, postoperativen Entzündungen und Netzhautablösungen sind jedoch noch nicht gut untersucht, wodurch aktive Maßnahmen zur Verringerung der Komplikationsrate nur schwer zu entwickeln sind. Ein Risiko scheint jedoch das Einbringen von Zellmaterial während der Injektion in das Innere des Auges darzustellen (Lytvynchuk et al. 2017). Die zweite Entwicklung des Autors, die im Rahmen dieser Habilitationsschrift vorgestellt wird, ist eine neuartige Injektionsnadel, welche die traumatische Verletzung bei Einstich verringern und die Einbringung von Zellmaterial signifikant reduzieren soll (Lytvynchuk et al. 2021). Zytologische Untersuchungen von Nadelaspiraten ergaben eine Verringerung des Zellmaterials von 50% gegenüber aktuell verwendeten Nadeln bei allerdings leicht erhöhter notwendiger Penetrationskraft. Da diese jedoch nicht signifikant ist und dem Chirurgen dadurch keine Nachteile entstehen, gehen die Autoren davon aus, dass die Vorteile der neuen Injektionsnadel die möglichen Nachteile überwiegen. Aktuell sind hier weitere Studien in der Vorbereitung.

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9. Acknowledgment

First of all, I would like to express my gratitude to the Dean of Medical Faculty at Justus Liebig University **Prof. Dr. med. Wolfgang Weidner** for the possibility to defend my habilitation thesis at Medical Faculty of Justus Liebig University.

I would like to thank **Prof. Dr. Dr. med. vet. Knut Stieger** for his support during accomplishing of my habilitation thesis and for giving me a valuable advises. His humanity and knowledge served me as a best example of the professional scientist, which I would like to follow in my future career. I am glad that we will continue our cooperation in the future.

I would like to thank **Prof. Dr. med. Birgit Lorenz**, the former Head of Ophthalmology Department of Justus Liebig University and former Head of the Eye Clinic of University Hospital Giessen and Marburg GmbH, for her inspiration during practicing of the newest technologies and surgical technique in the period between 2016 and 2019.

Also, I would like to thank to **Prof. Andii Sergiienko (Ukraine)**, **Prof. Dr. Susanne Binder (Austria)**, **Prof. Dr. Gisbert Richard (Germany)**, **Prof. Goran Petrovski (Finland),** who played an important role in my scientific career and supported my ideas.

My special thanks to **Dr. Andrii Ruban** and cand. Dr. med. **Maximilian Thiele** for the cooperation on our projects. With them I am honored to share first co-authorship in my publications.

Nevertheless, I am grateful to **Dr. Carl Glittenberg (Austria)**, **Prof. Galina Lavrenchuk (Ukraine)**, **Dr. Irina Savytska (Ukraine),** who were my co-workers in previous scientific projects and co-authors in the publications.

Exceptional thanks to **Greg Russell** for correction of English, to **Stephanie Kreiling** for helping with formatting the thesis, to **Jarema Khrushch (Novorozkin) and Anke Malitte** for creating the schematic images for this thesis.

I would like to thank my father, **Dr. Mychailo Lytvynchuk**, who was the brilliant scientist, and to whom I dedicate my work, and my mother **Dr. Marta Lytvynchuk**, a well-known Ukrainian ophthalmologist, who inspires and supports me through my life.

I would like to express my thankfulness to my **Family**, my wife **Marta** and my daughter **Sophia**, for their understanding and support during my life.

10. Appendix

11. Supplemental material

Description of the videos:

1. **Video 1 – Supplemental material 1 to Section 3.1.2. iSD-OCT for retinal surgery.**
   Surgical flow of the iOCT assisted pars plana vitrectomy with inverted ILM flap technique. (Lytvynchuk LM, Falkner-Radler CI, Krepler K, Glittenberg CG, Ahmed D, Petrovski G, Lorenz B, Ansari-Shahrezaei S, Binder S.Dynamic intraoperative optical coherence tomography for inverted internal limiting membrane flap technique in large macular hole surgery. Graefes Arch Clin Exp Ophthalmol. 2019 Aug; 257(8):1649-1659. Permission granted)

2. **Video 2 – Supplemental material 2 to Section 3.1.3. Novel indications for iOCT imaging.**
   iOCT assisted imaging of the Argus II retinal prosthesis. (Lytvynchuk L, Falkner-Radler C, Grzybowski A, Glittenberg C, Shams-Mafi F, Ansari-Shahrezaei S, Binder S. Influence of optic media of the human eye on the imaging of Argus® II retinal prosthesis with intraoperative spectral-domain optical coherence tomography. Spektrum für Augenheilkunde 2020(1); 1-9. Permission granted)

3. **Video 3 – Supplemental material 3 to Section 3.2.4. Complications after pediatric cataract surgery and its management.**
   Conventional bag-in-the-lens IOL implantation technique in a case of congenital cataract operated at the age of 10 months. (Lytvynchuk L, Thiele M, Lorenz B. Analysis and management of intraoperative and early postoperative complications of bag-in-the-lens intraocular lens implantation in different age groups of paediatric cataract patients: report of the Giessen Paediatric Cataract Study Group. Acta Ophthalmol 2020; 98(2):e144-e154. Permission granted)

4. **Video 4 – Supplemental material to Section 3.2.5 New surgical treatment for traumatic macular holes.**
   Schematic representation of the hydraulic centripetal macular displacement technique. (Ruban A*, Lytvynchuk L*, Zolnikova A, Richard G. Efficiency of the Hydraulic Centripetal Macular Displacement Technique in the Treatment of Traumatic Full-Thickness Macular Holes. Retina 2017; 39 Suppl 1:S74-S83. Permission granted)

5. **Video 5 – Supplemental material to Section 3.3. New instrumentation for surgery of vitreoretinal disorders.**
   Application of new depressor-marker during chandelier assisted scleral buckling. (Lytvynchuk L, Grzybowski A, Lorenz B, Ansari-Shahrezaei S, Binder S. New Scleral Depressor-Marker for Retinal Detachment Surgery Ophthalmology. Retina 2019; 3(1):73-76. Permission granted)

12. Erklärung zur Habilitation

„Hiermit erkläre ich, dass ich die vorliegende Arbeit bzw. die mir zuzuordnenden Teile im Rahmen einer kumulativen Habilitationsschrift selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nicht veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich versichere, dass ich für die nach §2 (3) der Habilitationsordnung angeführten bereits veröffentlichten Originalarbeiten als Erst- oder Seniorautor fungiere, da ich den größten Teil der Daten selbst erhoben habe. Für alle von mir erwähnten Untersuchungen habe ich die in der „Satzung der Justus-Liebig-Universität zur Sicherung guter wissenschaftlicher Praxis“ niedergelegten Grundsätze befolgt. Ich versichere, dass alle an der Finanzierung der Arbeiten beteiligten Geldgeber in den jeweiligen Publikationen genannt worden sind. Ich versichere außerdem, dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt wurde oder Gegenstand eines anderen Prüfungsverfahrens war. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.“

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