Assessment of the Efficacy of Microinvasive Glaucoma Surgery Techniques using an Oculopression Stress Test

Department: Klinik und Poliklinik für Augenheilkunde, Universitätsmedizin Rostock

Director: Prof. Dr. med. Dr. rer. nat. Thomas Fuchsluger, FEBO, MSc, MHBA

Title:

Assessment of the Efficacy of Microinvasive Glaucoma Surgery Techniques using an Oculopression Stress Test

Doctoral Thesis

for

the attainment of academic title

doctor medicinae (Dr. med.)

of the Faculty of Medicine

Rostock University

presented by

Dimitrios Karachalios, MUDr. born on 03. August 1990 in Rodos, Greece

from Rodos, Greece

Rostock, 09.02.2020

https://doi.org/10.18453/rosdok_id00003027

Dekan:	Prof. Dr. med. univ. Emil. C Reisinger, MBA
1. Gutachter:	Prof. Dr. med. Rudolf F. Guthoff Klinik und Poliklinik für Augenheilkunde Universitätsmedizin Rostock
2. Gutachter:	Prof. Dr. med. Maren Klemm Klinik und Poliklinik für Augenheilkunde Universitätsklinikum Hamburg-Eppendorf
3. Gutachter:	Prof. Dr. med. Robert Mlynski Klinik und Poliklinik für Hals-Nasen-Ohrenheilkunde Universitätsmedizin Rostock

Jahr der Einreichung: 2020

Jahr der Verteidigung: 2021

Contents

1. Introduction

Glaucoma is one of the leading causes of blindness worldwide. Global prevalence has been estimated to be 3.54% and the total number of people with glaucoma was 64.3 million in 2013 with a tendency to increase over the next decades. (1). In Germany, glaucoma affects approximately 972.000 people and is responsible for 15% of all blindness, second only to age related macular degeneration (2). It represents an important burden for public health, making the development of an effective treatment essential for the future (2) (3).

Glaucoma is characterized by a progressive loss of optic nerve fibres that results in visual impairment with a characteristic visual field loss. The exact mechanism in which this takes place is still not fully understood. However, increased intraocular pressure (IOP) is an important risk factor and it has been well documented that lowering the IOP is effective at preventing further progression of the disease (4).

During the last century, an enormous effort has been put into finding an effective way to control the IOP in patients with glaucoma. Important advances in medical therapy have made the use of topically applied glaucoma medication the first-line option in the majority of the cases. Laser therapy, including Argon Laser Trabeculoplasty (ALT) and Selective Laser Trabeculoplasty (SLT) represent an effective alternative in some patients. However, a considerable portion of glaucoma patients still need incisional surgery in order to reach and maintain the desired IOP. Filtration glaucoma surgery and trabeculectomy have been the most widely used procedures. Nonetheless, the potential risk for postoperative complications, some of them vision threatening, limit the wide application of these techniques that are reserved for moderate to advanced cases of glaucoma (5).

During the last years, a number of minimally invasive glaucoma surgical techniques (MIGS) have been developed in order to minimize the risk of surgery and reduce the IOP in glaucoma patients safely and effectively. MIGS share a number of key

characteristics that distinguish them from conventional glaucoma surgery. They are frequently performed *ab interno* through a clear corneal incision, thus sparing the conjunctiva. They are minimally traumatic and do not alter the ocular anatomy significantly. Recovery is generally fast and the need for postoperative care not as intense as in conventional filtration glaucoma surgery (6).

MIGS encompass a variety of surgical techniques. Some of them use micro-stents that redirect aqueous flow (6) while others achieve similar results with the help of lasers (7) or specialized cutting instruments (8) that alter the physiologic outflow pathways of aqueous humour. The basic principles for reducing the IOP remain however the same as in classical glaucoma surgery. MIGS can therefore achieve IOP reduction either by improving trabecular outflow (9) or by redirecting aqueous into the subconjunctival or suprachoroidal space (6).

Until now, the efficacy of MIGS procedures has been mainly assessed by the postoperative IOP values and the reduction in the number of IOP lowering medications that are needed postoperatively. Studies that examine the changes in aqueous dynamics in patients after MIGS surgery are limited. Given the abundance of different MIGS techniques and the lack of long-term studies, the development of an additional test that will examine the changes that occur in the outflow system of the eye after MIGS surgery will be able to better evaluate the IOP lowering potential of these procedures. It will also add to the understanding of how MIGS surgery works and will help in clinical decision making and future development of MIGS techniques. Recently, a new oculopressor device was developed in order to test the effectiveness of such MIGS procedures in a clinical setting (10).

In this study the new oculopressor device was used to examine the efficacy of different MIGS techniques. The changes of IOP that occur after oculopression were measured in glaucoma patients who underwent MIGS surgery and were compared with the results of healthy individuals and glaucoma patients without previous

surgery. To our knowledge, this is the first clinical study that tests the efficacy of MIGS surgery using the new oculopressor and one of only few studies that assess aqueous dynamics after MIGS surgery in glaucoma patients (11).

2. Principles

2.1. Anatomy and Physiology of the Eye

In order to fully understand the intraocular changes that occur after MIGS surgery and how different MIGS procedures work, it is essential to be familiar with the normal anatomy and physiology of the human eye. In the next chapters, the basic concepts of ocular anatomy and physiology are explained with particular attention to aqueous humour, its production from ciliary body and outflow pathways, as well as the characteristic changes that occur in glaucoma.

2.1.1. Gross Anatomy

The human eye is located in the anterior part of the orbit and is held in position by six extraocular muscles, the superior, inferior, medial and lateral recti and superior and inferior oblique muscles. The walls of the orbit protect the eye from external injuries and provide attachment sites for the extraocular muscles while the connective tissue of the orbit offers additional support for the eye and the vascular and neural elements that enter and exit the globe (Figure 1). A thin layer of connective tissue, the fascia bulbi (Tenon's capsule) covers the eye all the way from the optic nerve posteriorly to the corneoscleral junction anteriorly and separates it from the orbital fat (12).

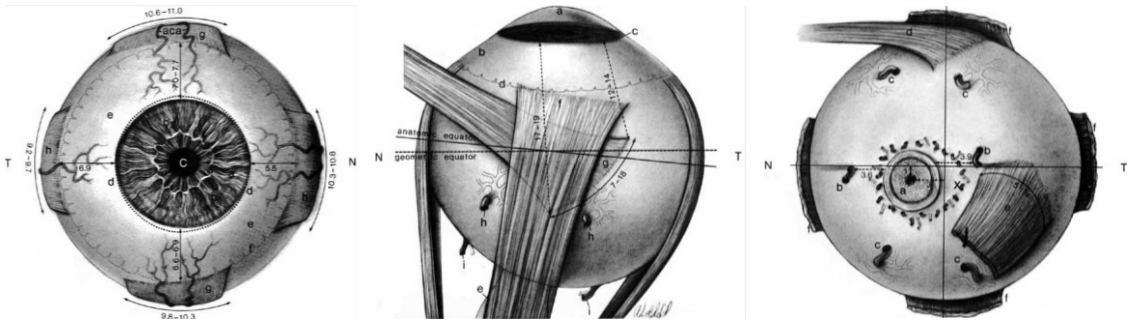


Figure 1: External anatomy of the eye and its relation with surrounding structures, the extraocular muscles and optic nerve (13)

The outer tunic of the eye consists of the sclera posteriorly and the transparent cornea anteriorly. The primary role of the sclera is to protect the intraocular structures and offer sufficient rigidity in order to maintain the shape of the eye. The cornea is part of the optical media and together with the lens offers sufficient refractive power in order to focus the light on the retina.

The uveal tract is the middle or vascular tunic of the eye and consists of the choroid posteriorly and the ciliary body and iris anteriorly. The principal role of the choroid is to provide nutrients to the underlying retina. The ciliary body is an extension of the choroid anteriorly and serves a number of important functions including production of the aqueous humour, anchoring of the lens via suspensory ligaments and accommodation for near vision. The iris can be seen as a mobile diaphragm that separates the anterior and posterior chambers of the eye and regulates the amount of light that enters the eye.

The crystalline lens of the eye is located behind the iris and is held in position by the suspensory ligaments (lens zonules) that anchor the lens to the ciliary body. Accommodation for near vision is achieved by contraction of the ciliary muscle releasing the tension of the lens zonules.

The retina lies internal to the choroid and is the primary organ of vision. Posteriorly the axons of ganglion cells exit the globe by penetrating through the sclera and form the optic nerve (Figure 2) (12) (13).

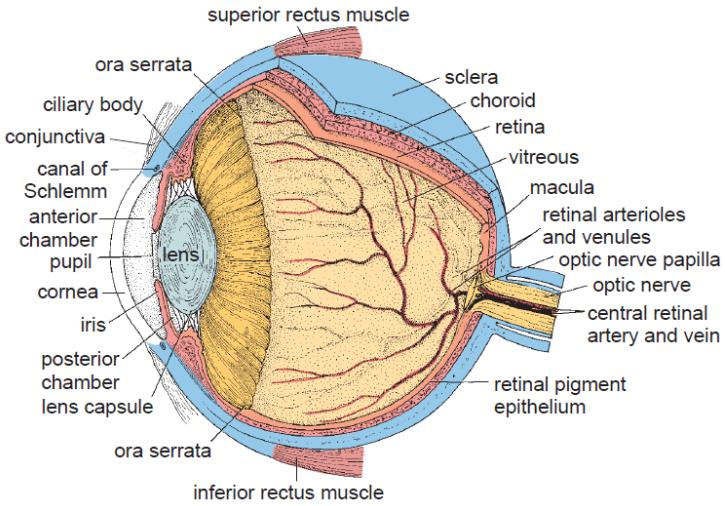


Figure 2: Illustration of the internal anatomy of the human eye (14).

The sclera is organized in three layers. The episclera is a thin superficial layer that connects the sclera to Tenon's capsule. The middle part is called sclera proper and makes up more than 95 percent of its thickness, while the suprachoroidal lamina is a thin layer that connects the sclera to the underlying choroid.

Along its surface, the sclera contains numerous openings and canals, some of them for blood vessels and nerves that enter and exit the eye. Most prominent of these are the anterior scleral foramen that is defined by the corneoscleral junction anteriorly and the posterior scleral foramen that supports the ganglion cell axons and blood vessels of the optic nerve. Several smaller openings are organized into emissary channels and vortex vein channels.

The cornea is the transparent portion of the outer tunic of the eye and has a diameter of approximately 11.7 mm in the horizontal plane and 10.6 mm in the vertical plane in adults. It is organized in five layers, the corneal epithelium, Bowman's layer, stroma, Descemet's membrane and corneal endothelium. The corneal epithelium has a thickness of 50 µm and consists of stratified nonkeratinized epithelial cells organized in approximately 5-6 layers that lie on Bowman's membrane. The corneal stroma constitutes approximately 90% of the corneal thickness. The uniform

organization of its collagen fibrils, in contrast to that of sclera, is responsible for the corneal transparency. The corneal endothelium consists of a single layer of cells that rest on Descemet's membrane. Corneal thickness measures between 520 and 670 μm, being thinnest centrally and thickest peripherally near the limbus.

The transition between cornea and sclera at the corneoscleral junction, as well as the structures of the anterior chamber angle constitute an important anatomic location. The scleral sulcus, a notch on the inner surface of the sclera near this location, forms the external wall of Schlemm's canal, the main outflow pathway for aqueous humour (12) (13) (14).

2.1.2. The Ciliary Body and the Formation of Aqueous Humour

The ciliary body was named by early anatomists after its unique resemblance to eyelashes or "cilia" and it has been a subject of research for centuries. It is part of the uveal tract and is positioned between the iris and choroid forming a slightly asymmetric girdle that encircles the eye. Its length varies, being broader temporally and inferiorly and shorter on the nasal side. In cross section it is triangular in shape with the base of the triangle facing anteriorly and the apex pointing to the opposite direction towards the choroid (Figure 3). On its anterior end the ciliary body is firmly attached to the scleral spur, while posteriorly it is only loosely attached to the sclera (13) (15). The iris inserts into the anterior surface of the ciliary body and in doing so, it leaves a small band of ciliary body tissue facing the anterior chamber that can be seen by gonioscopy between the root of the iris and scleral spur (4). The ciliary sulcus represents the anatomic region that is formed between the posterior surface of the iris and the most anterior ciliary processes. The ora serrata is the posterior end of the ciliary body. At this site the ciliary body epithelium ends abruptly and meets the retina.

The ciliary body can be divided morphologically and functionally into two parts. The anterior one third forms the pars plicata (or corona ciliaris) and is characterized by the presence of approximately 70-80 radially oriented ciliary processes with smaller ridges (minor plicae) in the valleys between them. The posterior two thirds have a smoother surface and constitute the pars plana (or orbiculus ciliaris). The pars plana and pars plicata of ciliary body are meridionally organized into ciliary process units. Each unit is made of a centrally located ciliary process that is bordered on each side by a pigmented ciliary ridge. (13) (16) (17).

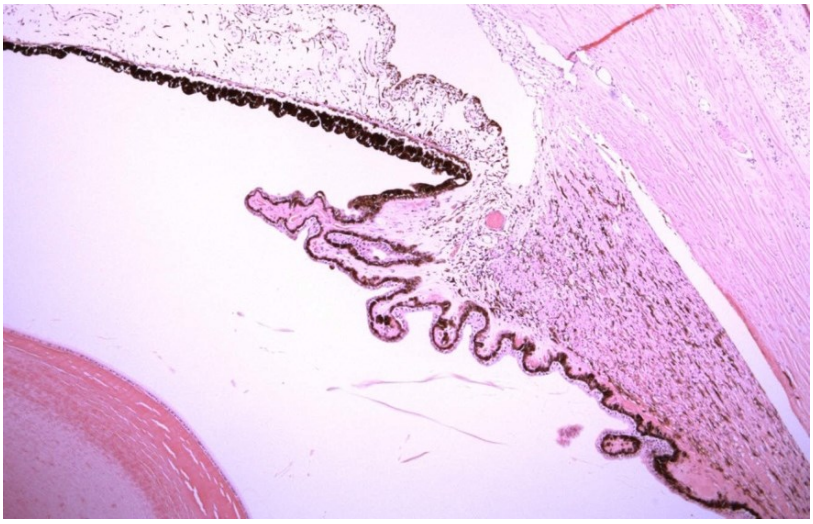


Figure 3: The ciliary body in cross section in relation to surrounding structures. Hematoxylin and Eosin (18).

The zonular apparatus of the lens consists of zonular fibres arranged in bundles that extend from the pars plana of ciliary epithelium posteriorly to the lens capsule anteriorly. Throughout their course they are closely associated with the valleys of ciliary body, the ciliary processes and minor plicae, exhibiting varying degrees of attachment with them (Figure 4) (13).

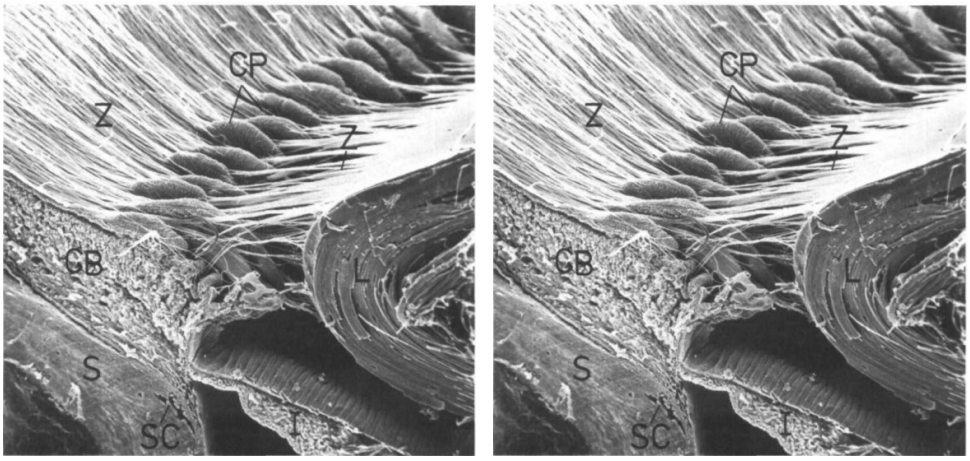


Figure 4: Scanning electron microscopy of the ciliary body (CB), ciliary processes (CP), lens zonules (Z), lens (L), sclera (S) and Schlemm's canal (SC) in cynomolgus monkey, x50 (19).

Microscopically, the ciliary body is composed of ciliary muscle, vascular tissue, stroma and an overlying double-layered ciliary epithelium (13) (15). The epithelium of ciliary body is responsible for the formation of aqueous humour and has a unique architectural configuration, in which two epithelial monolayers are in direct apical-to-apical apposition to each other (20) (21). This unique characteristic is the direct result of the infolding of optic vesicle that takes place during fetal development. The cells of ciliary body epithelium are extensively interconnected to each other with various junctional complexes suggesting that the two epithelial layers work together as a metabolic and functional unit (13) (20) (21).

The ciliary muscle is described traditionally as having three distinct parts, the outer longitudinal fibres, the middle radial or reticular fibres and the inner circular fibres. All of the muscle fibres originate from the common ciliary tendon that is located in the region of scleral spur and trabecular meshwork (13) (15) (22). The ciliary muscle serves two important functions. Firstly, it enables accommodation of the lens for near vision and secondly, it regulates aqueous outflow through its effect on Schlemm's canal, trabecular meshwork and outflow system (Figure 5) (22) (23).

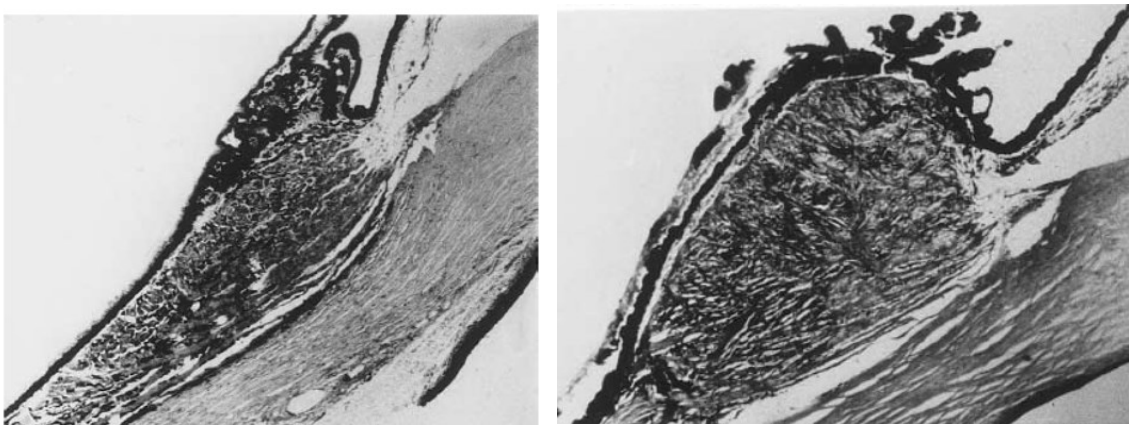


Figure 5: Ciliary muscle of monkey eyes treated with atropine (left) and pilocarpine (right). During contraction, ciliary muscle moves anterior and inward resulting in spreading of the trabecular meshwork lamellae and widening of the Schlemm's canal (24).

The ciliary body and anterior part of the uvea, including the iris derive their blood supply from the anterior and long posterior ciliary arteries. The vasculature supplying these anterior parts of the uvea forms a system of anastomoses in three levels. At first, the anterior ciliary arteries branch extensively near the limbus to form the episcleral plexus. In addition, perforating branches from the anterior ciliary arteries, as well as branches from the long posterior ciliary arteries enter the ciliary muscle and form the intramuscular plexus. Finally, branches from both the anterior and long posterior ciliary arteries reach the root of the iris and together form the major arterial circle. Ciliary processes in primates are supplied from branches of the major arterial circle (25) (26).

There is sufficient evidence from microvascular casting studies of primate eyes showing that the blood supply to ciliary processes consists of two separate systems. Anterior arterioles branch from the major arterial circle and supply the anterior parts and tips of the major ciliary processes. These arterioles show focal areas of constrictions before entering into the ciliary processes that may represent arteriolar

sphincters possibly regulating the blood flow to these areas that are responsible for aqueous humour production. On the other hand, the posterior arterioles that arise from the major arterial circle lack arteriolar constrictions, enter the major ciliary processes posteriorly to the anterior arterioles and are responsible for the blood supply of their middle and basal parts. Both anterior and posterior arterioles branch laterally to form interprocess capillary networks and ultimately drain into choroidal veins (Figure 6) (26) (27).

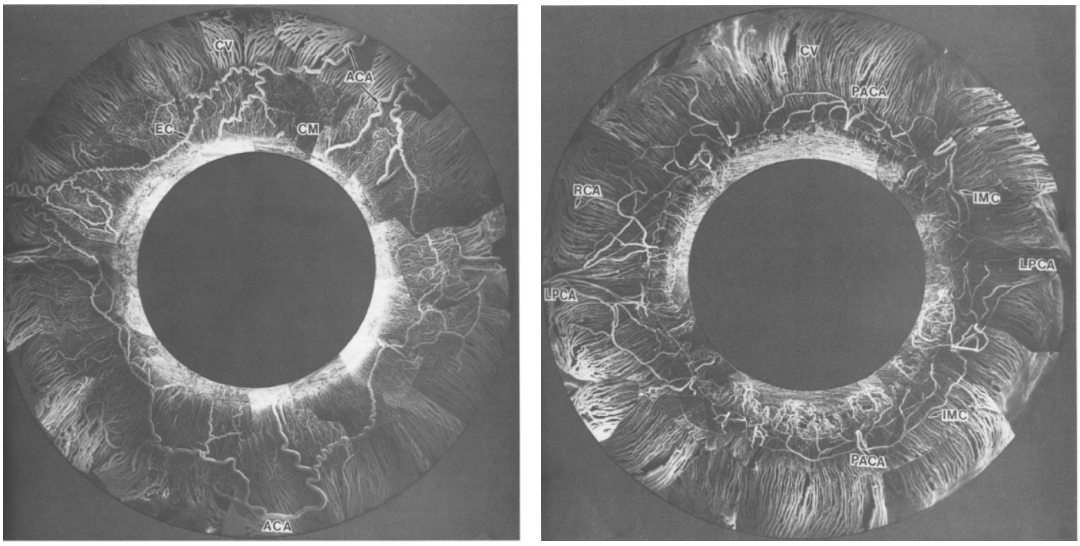


Figure 6: Montage of ocular casting technique of cynomolgus monkey. On the left side, anterior ciliary arteries (ACA) arborize at the limbus and interconnect via lateral branches to form the episcleral circle (EC). On the right side the same eye as left with anterior ciliary arteries and ciliary muscle (CM) removed. Branches of perforating anterior ciliary arteries (PACA) and long posterior ciliary arteries (LPCA) interconnect to form the intramuscular circle (IMC). RCA, recurrent ciliary artery; CV choroidal veins. Magnification 20x (25).

Until the early part of the 20th century, aqueous humour was thought to be a stagnant fluid that did not circulate. Since then, physiology of the aqueous humour production and outflow and its relationship with the development of glaucoma has

been a subject of intense research. It is now well known that aqueous humour is being continuously produced from the anterior parts of ciliary processes in the posterior chamber. It then follows a path from the posterior chamber into the anterior chamber passing through the pupil. In the anterior chamber, aqueous humour circulates under the effect of convection, flowing downwards near the cold cornea and upwards near the warmer iris. It finally exits the anterior chamber at the angle where it passes through the trabecular meshwork into Schlemm's canal and is ultimately drained into the aqueous channels and episcleral veins. A portion of aqueous humour exits the anterior chamber through a secondary "unconventional" uveoscleral pathway and it passes through the root of the iris and ciliary muscle into the suprachoroidal space (Figure 7). Aqueous humour serves a number of important functions in the eye including providing a clear fluid for optimal refraction of light, transport of nutrients and removal of waste products from avascular structures such as the cornea and lens as well as maintaining the intraocular pressure.

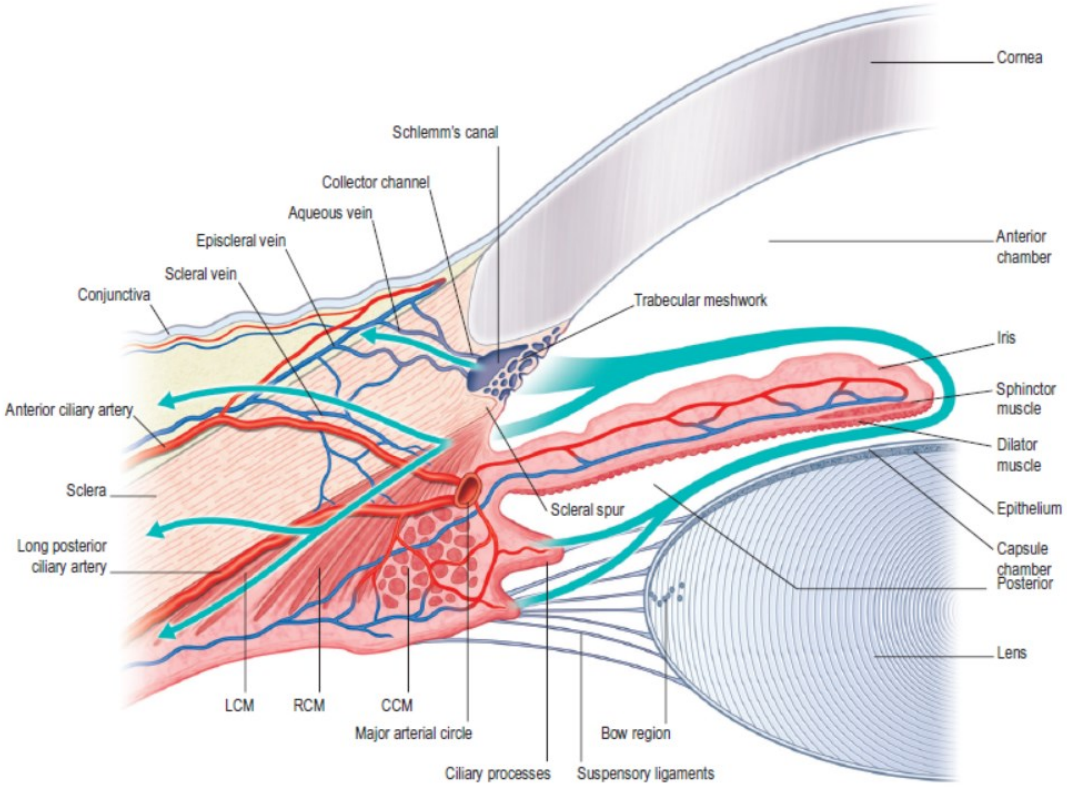


Figure 7: Schematic representation of the primate anterior ocular segment. Arrows indicate aqueous humour flow pathways. Aqueous humour is formed by the ciliary processes, enters the posterior chamber, flows through the pupil into the anterior chamber and exits at the chamber angle via the trabecular and uveoscleral routes (28).

The exact molecular mechanisms that take place during aqueous humour formation are until this day not entirely understood. The three main mechanisms that contribute to aqueous humour formation are diffusion, ultrafiltration and active secretion of ions and other molecules across the ciliary epithelium into the posterior chamber (28) (29). Ultrafiltration describes the passage of blood plasma through the highly fenestrated capillary endothelium of ciliary processes into the interstitial space between ciliary capillaries and ciliary epithelium. The main driving force of ultrafiltration is the osmotic and hydrostatic pressure gradients between capillaries and stroma. Diffusion occurs in parallel and describes the movement of molecules

down their concentration gradient. With the help of ultrafiltration and diffusion a "plasma reservoir" is accumulated in the stroma of ciliary processes between capillaries and ciliary epithelium. Further movement of this plasma reservoir into the posterior chamber is halted by the tight junctions between adjacent cells of the non-pigmented ciliary epithelium. The ciliary epithelium is able to selectively transport a number of molecules and ions across this blood-aqueous barrier in an energy dependent manner generating an osmotic gradient. Water moves into the posterior chamber through specialized water channels in the ciliary epithelium called aquaporins or through a paracellular route down the osmotic gradient that is generated from the ion transport (30) (31) (32). During this process, cells of the non-pigmented ciliary epithelium actively pump Na^+ ions into the posterior chamber with the help of Na^+/K^+ ATPase. A number of other molecules and membrane transporters also contribute to this process including Na^+/H^+ antiports, Cl^-/HCO_3^- antiports and Na-K-2Cl contransporters in the pigmented epithelium as well as the enzyme carbonic anhydrase that provides the needed HCO_3^- ions and regulates pH (Figure 8). The final composition of aqueous humour is therefore quite different from that of a simple plasma ultrafiltrate. It is characterized by a very low concentration of protein and relative higher concentration of ascorbate in relation to blood plasma. Moreover, it is slightly hypertonic and acidic with a pH of 7.2. Finally, exchange of substances between cornea, lens and neighboring structures gives aqueous humour its final composition. Lactate, for example, is found in slight excess in aqueous humour and may reflect the glycolytic activity of avascular structures such as the cornea and lens (29) (30).

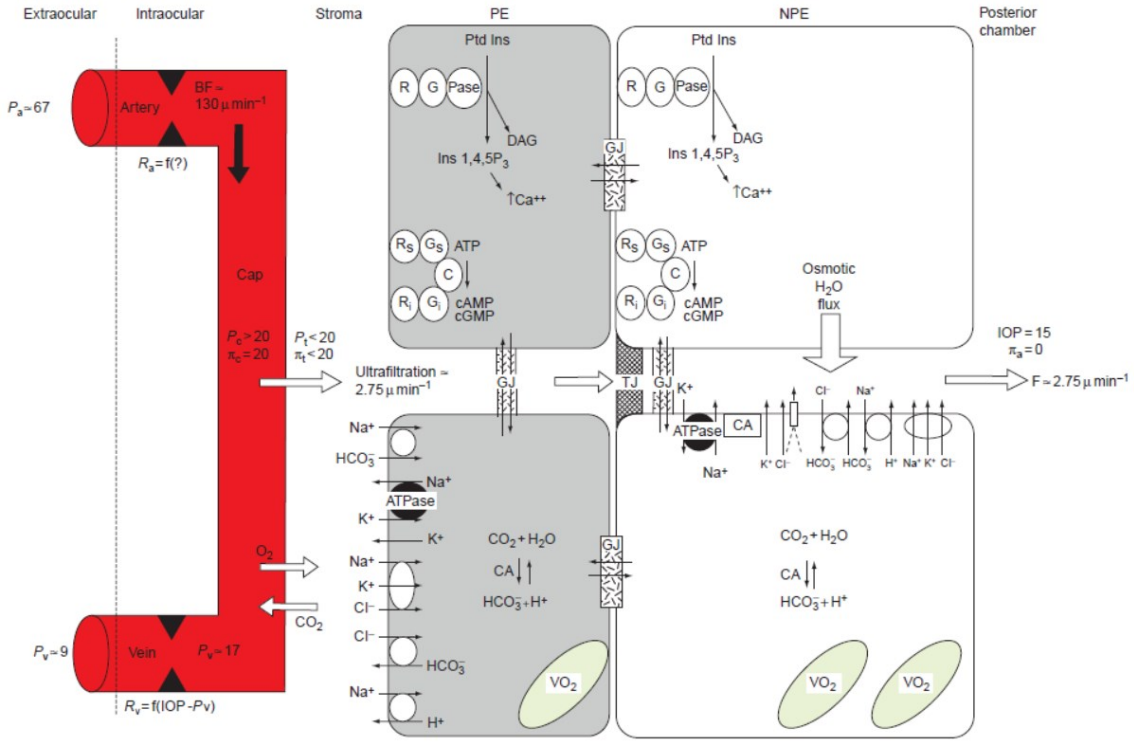


Figure 8: Overview of aqueous formation. Open circles with arrows: transporters/cotransporters/antiporters; arrows: movement via ionic channels or diffusion. P_a, extraocular arterial pressure; R_a, ciliary arterial resistance; BF, ciliary blood flow; P_c, ciliary capillary pressure; πc, capillary plasma oncotic pressure; P_t, stromal tissue hydrostatic pressure; πt, stromal tissue oncotic pressure; P_v, ciliary venous pressure; R_v, ciliary venous resistance; VO_2, mitochondrial oxygen consumption; πa, aqueous oncotic pressure; F, aqueous flow; Ptd Ins, phosphatydalinositol; G, G-protein complex; R, receptor; C, adenylate cyclase; Gs, stimulatory G-protein complex; Gi, inhibitory G-protein complex; Rs, stimulatory receptor; Ri, inhibitory receptor; GJ, gap junction; TJ, tight junction; ATPase, Na/K ATPase (33).

Ultrafiltration and diffusion are responsible for approximately 10% of the aqueous humour production. The remainder 80-90% of aqueous humor formation is dependent on the active transport mechanisms that take place across the ciliary epithelium. The active part of aqueous humour secretion is pressure-insensitive and does not depend on the actual intraocular pressure when this is in the near-normal range. On the other hand, ultrafiltration depends on the pressure gradient that is present between the capillaries and posterior chamber. The rate of aqueous humour production in the human eye is approximately 2.5 - 2.75 µl/min and the aqueous humour turnover is estimated to be 1.0 - 1.5 percent of the aqueous humour volume per minute (29) (30) (31) (33). There is a marked diurnal variation of the rate of aqueous humour formation with higher rates during the day and lower rates during the night. The exact mechanism responsible for this circadian rhythm is not fully understood but several hypotheses have been proposed. Circulating epinephrine levels may play a role in regulating this circadian rhythm. Moreover, aqueous humour production is known to decrease with age, with an approximately 2 - 2.5% reduction per decade (31) (34) (35).

2.1.3. Anterior Chamber Angle and the Outflow of Aqueous Humour

The anterior chamber angle is formed by the root of the iris, a small band of ciliary body tissue, the trabecular meshwork and Schlemm's canal near the corneoscleral junction and constitutes the major route of aqueous humour outflow of the eye. During gonioscopy, the structures of the anterior chamber angle can be directly visualized and examined (Figure 9). The inner surface of sclera near the limbus has a small indentation, the scleral sulcus with a sharp posterior border called scleral spur and a smoother anterior end that reaches the inner surface of the cornea. The trabecular meshwork is a specialized three-dimensional structure that bridges the gap of the scleral sulcus and transforms it into a canal, the Schlemm's canal. At the

anterior end of trabecular meshwork, a pigmented line represents the transition to corneal endothelium and is called Schwalbe's line. The trabecular meshwork provides the necessary resistance to aqueous outflow that is needed, in order to maintain the intraocular pressure. In addition, the anterior tendons of ciliary muscle connect directly to different parts of the trabecular meshwork at the scleral spur (4) (15) (29). Contraction of the ciliary muscle has therefore a direct effect on the three-dimensional arrangement of the trabecular meshwork lamellae and is able to change outflow resistance and facilitate aqueous humour outflow (24).

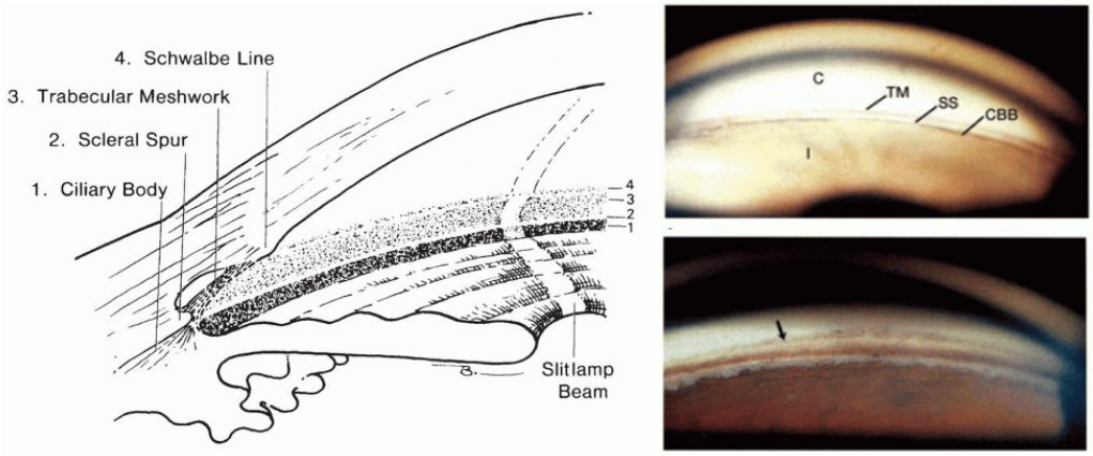


Figure 9: Anterior chamber angle and gonioscopic findings. C, cornea; TM, trabecular meshwork; SS, scleral spur; CBB, ciliary body band; I, iris (4).

The trabecular meshwork can be divided into three distinct parts based on its ultrastructural characteristics (Figure 10). The inner, lamellated part consists of the uveal and corneoscleral meshwork and the outer non-lamellated part consists of the juxtacanalicular meshwork. The uveal and corneoscleral parts of trabecular meshwork consist of irregularly arranged bands of extraceullular matrix covered by a monolayer of trabecular meshwork (TM) cells. On the other hand, the juxtacanalicular meshwork is made of a ground substance of extracellular matrix with several discontinuous layers of juxtacanalicular (JCT) cells resting on its

trabecular surface and embedded into it. The outer surface of juxtacanalicular meshwork faces the lumen of the Schlemm's canal and is covered by a continuous monolayer of endothelial cells.

In addition, the anterior part of the trabecular meshwork that is directly behind the Schwalbe's line is only lightly pigmented and contributes little to the overall filtration of aqueous humour. On the other hand, the posterior part of trabecular meshwork is more heavily pigmented and is directly associated with the Schlemm's canal, providing the main route of aqueous humour outflow.

Aqueous humour enters Schlemm's canal and is subsequently drained into a system of intrascleral aqueous channels that ultimately empty into the episcleral and conjunctival veins (Figure 11) (4) (24) (36) (37).

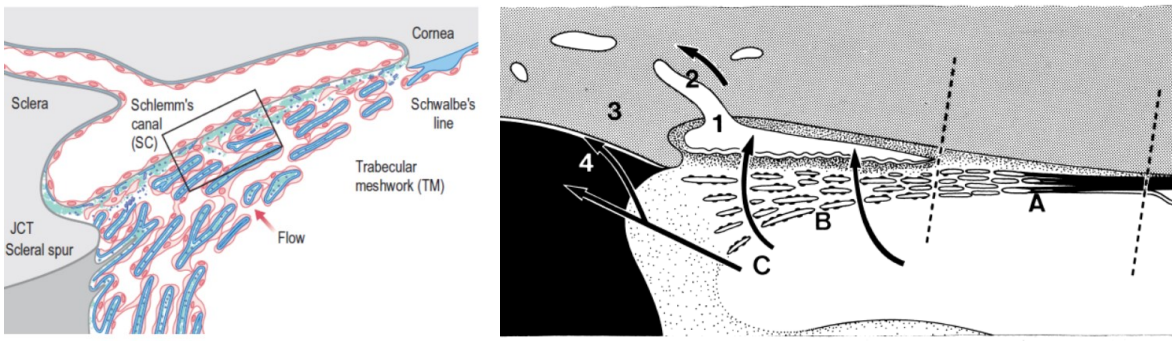


Figure 10: Trabecular meshwork (TM) and outflow of aqueous humour. TM can be subdivided into an anterior non-filtering part (A) and a posterior filtering part (B) as well as into an inner lamellated part and a non-lamellated subendothelial or juxtacanalicular part. Aqueous humour leaves through the Schlemm's canal (1) and aqueous veins (2) or through a secondary "non-conventional" unveoscleral route (C). (3) Scleral spur, (4) ciliary muscle (24) (29).

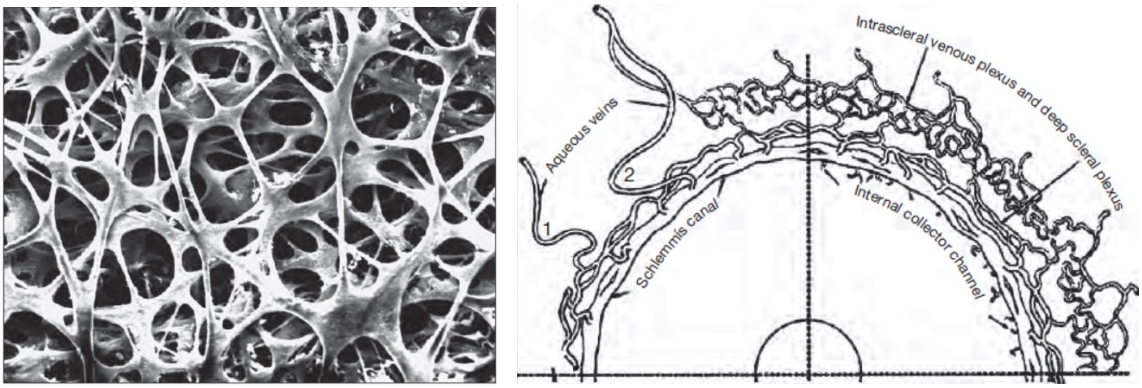


Figure 11: On the left side a scanning electron micrograph of the face of the uveal meshwork showing intersecting trabecular beams is illustrated. On the right, a schematic illustration of the aqueous outflow pathway from the Schlemm's canal to the episcleral vessels is shown (37).

The movement of aqueous across the trabecular meshwork appears to occur in a passive, pressure dependent way that is driven by the hydrostatic pressure difference between the anterior chamber and the episcleral veins. However, the exact anatomic site responsible for the outflow resistance, as well as the actual mechanism by which aqueous crosses the juxtacanalicular trabecular meshwork remain unknown.

The intertrabecular openings in the uveal and corneoscleral parts of trabecular meshwork seem to be too large to offer any resistance to outflow. According to dissection and microcapillary studies, it seems that the deepest 1/4 to 1/3 of the trabecular meshwork is the part offering the most resistance to outflow (36) (37). In particular, the extracellular matrix of juxtacanalicular meshwork appears to be responsible for a significant part of aqueous outflow resistance. A number of stimuli are able to influence outflow resistance by regulating extraceullular matrix degradation and turnover in the juxtacanalicular meshwork via enzymes of the metalloproteinase family. Finally, a number of histopathologic studies have

identified giant vacuoles and pores in the inner wall cells of Schlemm's canal suggesting a paracellular route for aqueous humour outflow (36) (38) (39).

In an effort to explain outflow resistance, some investigators proposed that flow of aqueous humour may exhibit a “funneling effect” that is the result of the anatomic relation between pores in the inner wall endothelium and juxtacanalicular tissue. In this way the “effective” resistance of the juxtacanalicular tissue would markedly increase (40).

While the main bulk of aqueous humour leaves the eye through the "trabecular" outflow pathway, a secondary "unconventional" outflow pathway exists and includes the ciliary muscle and suprachoroidal space. A portion of aqueous humour enters the ciliary body from the anterior chamber traveling along the interstitial spaces of longitudinal fibres of the ciliary muscle and reaching the supraciliary and suprachoroidal spaces. From there a number of different arguments exist regarding the fate of aqueous humour. One theory suggests that aqueous passes through the sclera and episclera into the orbital tissue from where it is absorbed by the vasculature. This route is referred as the uveoscleral pathway. A second theory suggests that aqueous is absorbed from the choroidal vasculature and then reaches the vortex veins. This this route is called uveovortex pathway. It is difficult to calculate the proportion of aqueous humour that is removed by this secondary outflow pathway but it is estimated to be less than 10% of the total flow in adults and it decreases with age (37) (41).

2.1.4. Intraocular Pressure and The Facility of Outflow

In the healthy human eye, aqueous humour production and outflow are in equilibrium and the trabecular meshwork and uveoscleral outflow pathway provide the necessary resistance to outflow in order to maintain the intraocular pressure.

This relationship between aqueous humour production, outflow and intraocular pressure can be summarized by the following formula:

$$F_{in} = F_{out} = (IOP – EVP)C + U$$

Where F_{in} the rate of aqueous humour inflow or aqueous humour production and F_{out} the rate the aqueous humour outflow in µl/min; IOP the intraocular pressure and EVP the episcleral venous pressure in mmHg; C the facility of outflow in µl/min/mmHg and U the uveoscleral outflow rate in µl/min. The facility of outflow C can also be expressed as the reciprocal value of resistance to outflow R, where:

$$C = 1/R$$

In healthy humans, aqueous humour inflow (F_{in}) is approximately 2.5 - 2.75 µl/min, episcleral venous pressure (EVP) is about 9mmHg, outflow facility (C) approximately 0.25-0.3 µl/min/mmHg and the intraocular pressure is maintained at approximately 15mmHg. While trabecular outflow increases as the IOP raises in order to maintain the balance, the uveoscleral outflow remains fairly constant in the physiologic IOP range and seems to be independent of pressure (13) (29) (33).

The distribution of intraocular pressure in the population resembles a Gaussian curve except for an elevation to the right side of the curve, possibly accounting for a subpopulation of people with an abnormally elevated intraocular pressure (Figure 12). IOP increases with increasing age and there seems to be no relation between gender and IOP. Intraocular pressure follows a circadian rhythm. Most commonly, IOP is higher in the morning and drops to lower values in the evening. Other patterns of this diurnal rhythm of IOP can be encountered however in some individuals with peak IOP values in the afternoon or during the night. Fluctuations of the IOP of more

than 5mmHg are not common and wider oscillations may actually suggest the presence of glaucoma. Intraocular pressure is pulsatile following the arterial pulse and the cardiac cycle (4) (13) (28). Other factors influencing the IOP are postural changes and respiration, with an increase of IOP in the supine position and during a Valsalva maneuver (4) (42).

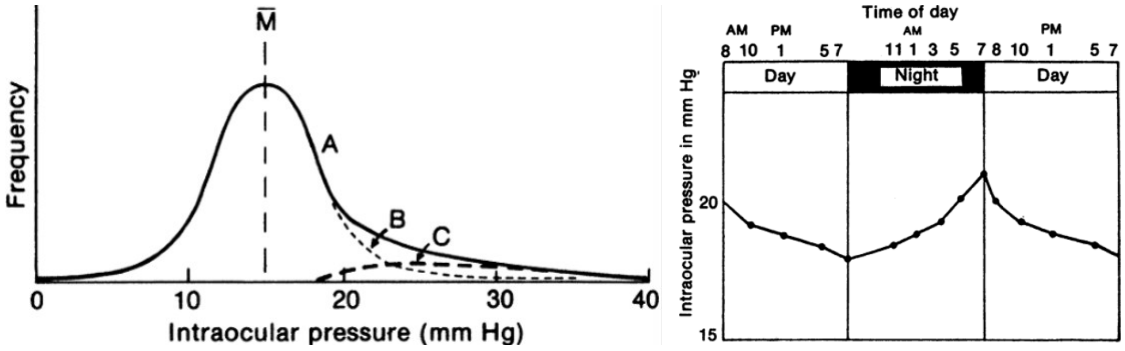


Figure 12: On the left side a theoretical distribution of intraocular pressure in the population is shown. Note that the curve is slightly skewed to the right. This could be explained by two subpopulations. Group B would make up the normal population following the Gaussian curve and group C could represent the subpopulation with abnormally elevated IOP. On the right side a graphical representation of the normal diurnal variation of IOP (13).

Measurement of IOP can be achieved with a variety of methods. Direct measurement is invasive, requires a manometer placed inside the eye and is possible to perform only in cadaver eyes or in animal studies. On the other hand, a number of techniques have been developed that can calculate the IOP by measuring the response of the eye to various types of mechanical deformation. The method that is used by these techniques is called tonometry and it can be further divided into applanation and indentation tonometry. With applanation tonometry a force is applied on the corneal surface until it is flattened. With knowing the force that is required to flatten or "applanate" a specific surface area of the cornea the

IOP can then be calculated. Applanation tonometers can be further subdivided into tonometers that use a fixed force and those that flatten a fixed area of the cornea with variable forces. One of the first applanation tonometers that were developed was the Maklakoff tonometer in 1855 that uses a fixed force technique. It was made of a metalic cylinder of known weight and a flat plate on its bottom that rested on the cornea. A special dye and anesthetic agent were applied on the eye and the tonometer was positioned on the cornea. The applanated area could then be measured from the bottom of the tonometer plate (13) (4). Fick developed a fixed area applanation tonometer in the late 19th century that was later improved by Goldmann and this has been the “gold standard” for IOP measurement since then (Figure 13, left). More recently, a non-contact tonometer using the same principle as the Goldmann applanation tonometer was introduced by Grolman in 1972 and uses an air column to applanate the corneal surface (13) (43) (44).

The standard indentation tonometer was developed by Schiotz in 1905 and was widely used before the modernization of applanation tonometry by Goldmann. While applanation tonometers only flattens the corneal surface, indentation tonometers indent the cornea resulting in a considerable deformation of the eye and subsequent displacement of aqueous that raises the IOP to a new, higher value. With Schiotz tonometer the degree of indentation can be read on a scale on the tonometer and the IOP can be derived using conversion tables (Figure 13, right). Other types of tonometers that use both applanation and indentation principles include the Mackay-Marg tonometer, the pneumatic tonometer and Tono-Pen (4) (13) (45).

An induction-based, impact tonometer was developed by Kontiola in 2000 that is able to measure the IOP from calculating the rebound motion of a small probe that is propelled towards the corneal surface using magnets. The advantage of this technique is that it is fast, it requires no local anesthetic agent and it can be performed with the help of a small, handheld instrument with minimal patient

discomfort (46) (47). The overall reliability of rebound tonometry and its correlation with Goldman applanation tonometry has been found to be good making the new IOP measuring technique a good alternative to standard tonometry. Nonetheless, rebound tonometry tends to slightly overestimate IOP compared to standard applanation tonometry (48) (49) (50) (51).

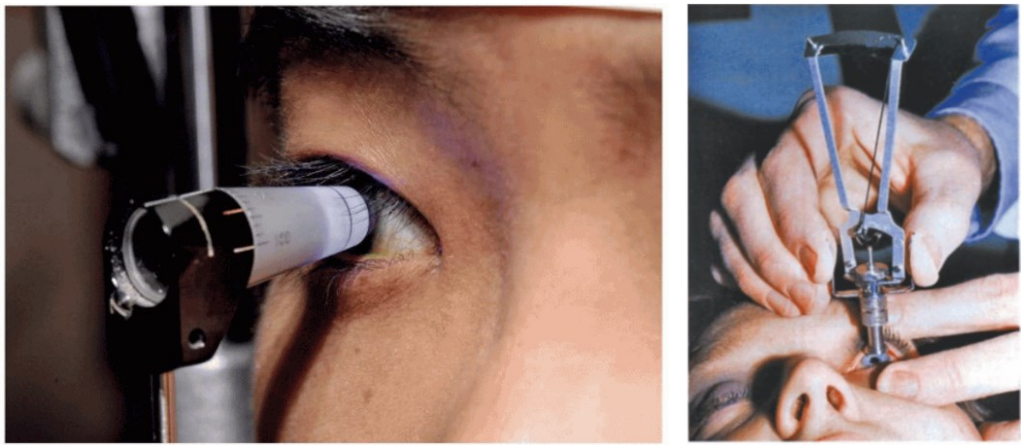


Figure 13: On the left photograph the technique of applanation tonometry using the Goldman tonometer and, on the right photograph the technique of indentation tonometry using the Schiotz tonometer (4).

Tonometry, despite its importance in the everyday clinical practice and in the study of glaucoma, has its limitations. In indentation tonometry with the Schiotz tonometer, the degree of corneal indentation depends not only on the actual intraocular pressure, but also on the ocular rigidity and the distensibility of the ocular structures. For routine measurements, a normal ocular rigidity is assumed. This introduces however a substantial source of error in eyes with an abnormally high ocular rigidity (e.g. hyperopic eyes) or low ocular rigidity (e.g. myopic eyes), giving falsely high or low readings respectively. In Applanation tonometry, on the other hand, measurements are influenced by the corneal thickness (28). In rebound tonometry, IOP measurement seems to depend on the corneal thickness and biomechanical

properties of the cornea such as corneal hysteresis and corneal resistance factor (47) (50) (51).

Clinically, the facility of outflow can be determined with the help of tonography. The tonographic principle was introduced by Grant in 1950 and was based on the observation that repeated Schiotz tonometry resulted in a decrease of the IOP. After placing the Schiotz tonometer on the patient's eye, the IOP is raised resulting in an increase of trabecular outflow. If the Schiotz tonometer is left resting on the eye, an increasing amount of intraocular fluid will be forced out of the eye and the IOP will start to decline. Using an electronic Schiotz tonometer, Grant recorded the slope of falling IOP with the tonometer resting on the patient's cornea (Figure 14) and with the help of Friedenwald's observations on the volume and pressure relationships of the eye he calculated the outflow facility from the rate of IOP decline on the tonographic curve (52) (53).

It was shown that glaucomatous eyes have a decreased facility of outflow and that the slope of the declining IOP during tonography was not as ''steep '' as the one derived from healthy individuals. It was also shown that the primary reason of increased IOP in glaucomatous eyes was an increased resistance to aqueous outflow and not a hypersecretion of aqueous humour as it was previously falsely believed. As in indentation tonometry, the tonographic measurements are influenced by the ocular rigidity. Grant used for his mathematic formulas an average of ''normal'' ocular rigidity. While quite accurate in most eyes, tonography should be performed with care in eyes with an abnormal rigidity as is the case in patients with high myopia. In addition, a number of ocular parameters change upon placing the tonometer on the eye, including ocular blood flow, the episcleral venous pressure and the rate of aqueous humour production, that are not taken into account in Grant's mathematical formulations for calculating outflow facility (53) (54).

Another method that examines aqueous dynamics and the aqueous outflow system is Ulrich's oculopression tonometry. Ulrich *et al* developed a new technique in 1987 that used a suction cup placed on the conjunctiva that was able to raise the IOP to a predetermined level independent of the baseline IOP. The device was coupled to a slit lamp, so that the IOP could be directly measured using an applanation tonometer at any time during the oculopression (Figure 15). In his protocol, the IOP was raised to 45 mmHg and was maintained at this level for 8 minutes. He showed that the IOP after oculopression was significantly higher in glaucoma a patients in comparison to healthy individuals and proposed this new technique as an additional diagnostic test for assessing glaucoma suspects (55) (56).

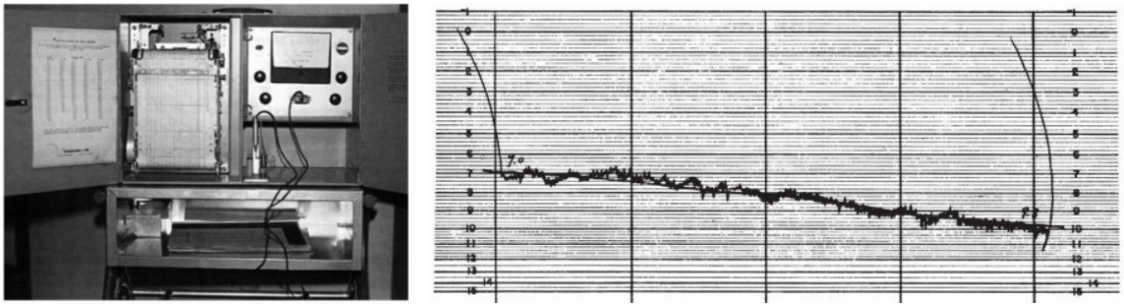


Figure 14: On the left side a tonographic unit and on the right side a tonographic curve showing the steady decline of IOP during tonography. Fine oscillations are due to IOP variations following the cardiac cycle while larger waves are the result of respiration and periodic variations of systemic blood pressure (Traube-Hering waves) (4).

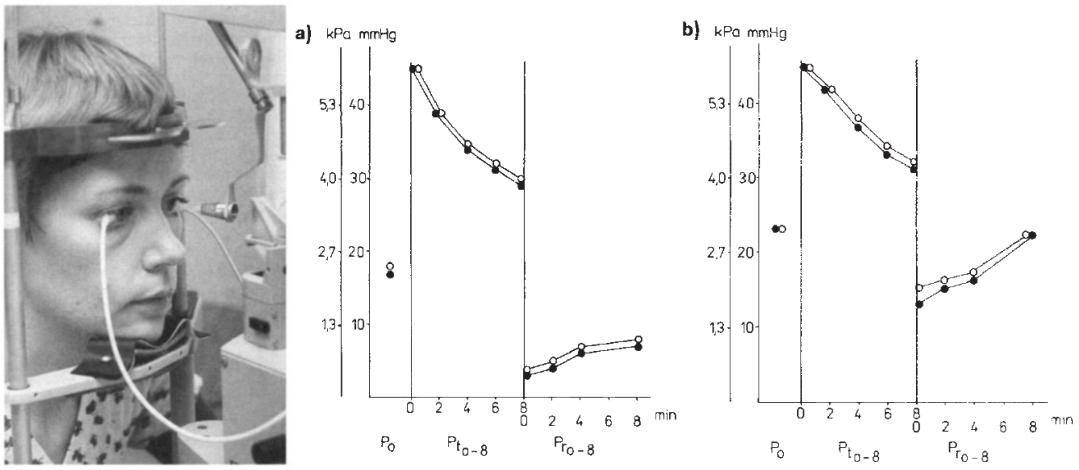


Figure 15: Ulrich's oculopression tonometry with the two suction cups coupled to a slit lamp and an applanation tonometer. The graph in the middle (a) is that of a healthy individual and the graph on the right side (b) that of a patient with open-angle glaucoma. Note the difference in the IOP after oculopression (PR0) between the two subjects (55).

2.2. Glaucoma: Basic Concepts in Diagnosis and Treatment

2.2.1. Etiology and Classification of Glaucoma

Glaucoma does not refer to a single disease entity. It rather comprises a larger group of ocular disorders sharing a set of characteristic abnormalities including cupping and atrophy of the optic nerve head that leads to progressive deterioration and loss of the visual field. In most but not all the cases there is a direct relation to an abnormally increased IOP. Classically, glaucoma has been divided into open-angle and angle-closure types. A third group of “developmental glaucoma” is associated with abnormal development of the anterior segment and aqueous outflow system and tends to appear earlier in life. Open-angle glaucoma can be further subdivided into a primary type or be caused by a secondary mechanism due to an underlying disorder. Angle-closure glaucoma can also be further characterized according to its clinical presentation as acute, subacute or chronic. The following table (Table 1) summarizes the current classification scheme for glaucoma (28).

Open-angle glaucoma	*Primary open angle glaucoma (associated with high intraocular pressure)* *Low tension glaucoma (intraocular pressure within normal range)* *Secondary open angle glaucomas* • Pseudoexfoliation glaucoma • Pigmentary dispersion glaucoma • Steroid induced glaucoma • Lens-induced glaucoma a. Phacolytic glaucoma b. Lens-particle glaucoma c. Phacoanaphylaxis • Glaucoma after cataract surgery a. α-Chymotrypsin glaucoma b. Glaucoma associated with viscoelastics c. Glaucoma associated with pigment dispersion and intraocular lens d. UGH syndrome (uveitis, glaucoma, hyphema) e. Glaucoma after Nd:YAG posterior capsulotomy • Posttraumatic glaucoma

	• Glaucoma associated with intraocular hemorrhage a. Ghost cell glaucoma b. Hemolytic glaucoma c. Hemosiderosis • Glaucoma associated with retinal detachment • Glaucoma associated with uveitis a. Fuch's heterochrmomic iridocyclitis b. Posner-Schlossman syndrome c. Uveitis associated with Herpes simplex or Herpes zoster • Glaucoma after vitreoretinal surgery (intraocular gas or silicone oil) • Glaucoma associated with an intraocular tumor • Amyloidosis • Glaucoma associated with increased episcleral venous pressure a. Superior vena cava obstruction b. Arteriovenous fistula
Angle-closure glaucoma	*Primary angle-closure* • Pupillary block • Plateau iris • Phacomorphic block *Secondary angle-closure* • Neovascular glaucoma • Iridocorneal endothelial syndrome • Epithelial downgrowth • Fibrous ingrowth • Ciliary block • Suprachoroidal hemorrhage • Choroidal effusion
Developmental glaucoma	*Primary glaucoma* • Congenital glaucoma • Autosomal dominant juvenile glaucoma • Glaucoma associated with systemic abnormalities a. Chromosomal disorders b. Neurofibromatosis c. Oculocerebrorenal or hepatocerebrorenal syndrome d. Sturge-Weber syndrome e. Mucopolysachcharidosis • Glaucoma associated with ocular abnormaligies a. Axenfeld-Rieger syndrome b. Peters syndrome c. Aniridia d. Microcornea syndromes e. Sclerocornea

	Secondary glaucoma • Posttraumatic glaucoma • Glaucoma associated with an intraocular neoplasm a. Retinoblastoma b. Leukemia • Glaucoma associated with uveitis • Lens-induced glaucoma a. Subluxation with pupillary block (Marfan syndrome, Homocysteinuria) b. Spherophakia with pupillary block • Glaucoma associated with congenital cataract surgery • Steroid induced glaucoma • Neovascular glaucoma a. Coat's disease b. Familial exsudative vitreoretinopathy c. Retinoblastoma • Secondary angle-closure glaucoma a. Microphthalmos b. Nanophthalmos c. Retinopathy of prematurity d. Persistent hyperplastic primary vitreous e. Aniridia f. Iridoschisis g. Cornea plana • Glaucoma associated with increased episcleral venous pressure a. Idiopathic elevated episcleral venous pressure b. Orbital vascular malformations • Glaucoma secondary to intraocular infections a. Toxoplasmosis b. Herpetic iritis c. Congenital rubella

Table 1: Classification of glaucoma (4) (28).

Regardless of the type of glaucoma, the final common pathway is that of progressive loss of optic nerve fibres and resulting atrophy of the optic nerve head. This is clinically manifested with a characteristic pattern of visual field loss. The single most strongly associated risk factor with the presence of glaucoma is an increased IOP and it has been shown that lowering the IOP can substantially decrease the risk of disease progression. Other risk factors have also been identified. These include a positive family history, increasing age, myopia, diabetes mellitus and migraine. A

strong association between a glaucoma and a low diastolic ocular perfusion pressure (i.e. the difference between diastolic arterial blood pressure and intraocular pressure) has also been identified (4).

2.2.2. Diagnosis of Glaucoma

A wide variety of diagnostic tools have been developed in order for the ophthalmologist to be able to detect glaucomatous changes in their earliest stages, before advanced visual field loss has already taken place and when intervention with IOP lowering regimens would be most beneficial.

The most basic of the examinations is the appearance of the optic nerve head during fundus examination with a dilated pupil (Figure 16). Characteristic glaucomatous changes of the optic nerve head include thinning and notching of the neural rim, deepening of the optic cup, exposure of the lamina cribrosa, splinter hemorrhages near the margin of the optic nerve head, appearance of vessels that bridge an enlarged optic cup, baring of the circumlinear vessels and nerve fibre layer defects. Special investigations with the help of confocal scanning laser tomography (HRT-III Heidelberg Engineering), confocal scanning laser polarimetry (Nerve Fiber Analyzer NFA-I) and spectral domain optical coherence tomography (SD-OCT) can deliver substantially more information regarding the anatomy of the optic nerve head, the thickness of the retinal nerve fibre layer (RNFL) and the configuration of optic cupping in relation to the neural rim (4).

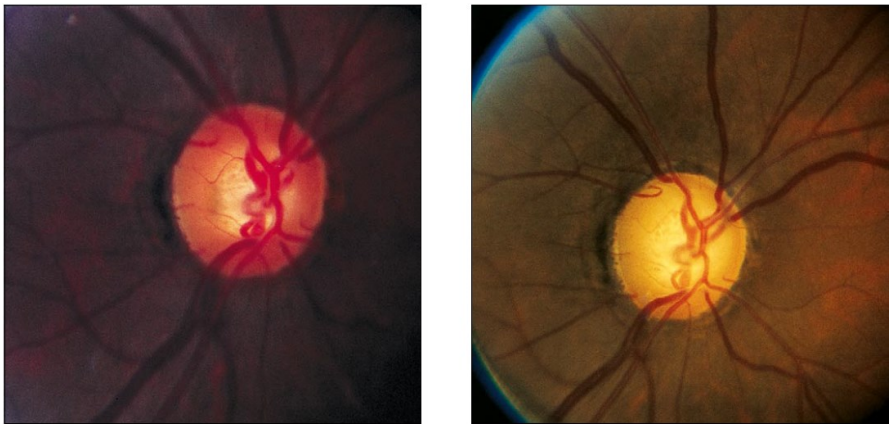


Figure 16: On the left side a photograph of the optic disc of a patient with primary open-angle glaucoma and on the right side the same eye after a 12-year interval showing progression of the glaucomatous cupping and atrophy with concentric enlargement of the cup and focal thinning of the neural rim in the superotemporal quadrant (28).

Functional examinations include visual acuity, visual field testing, color vision and contrast sensitivity. Visual field is a technique used to assess the central as well as the peripheral vision and measures the ability of the retina to distinguish a bright stimulus against a less illuminated background. Typical visual field defects for glaucoma include a generalized depression of the visual field, nasal step or depression, Seidel's scotoma (i.e. enlargement of the blind spot in an arcuate manner) and isolated paracentral scotomata that may progressively enlarge and coalesce to form classic arcuate defects (Bjerrum scotomata). Advanced glaucomatous visual field defects can take the form of small central islands with or without sparing of the temporal visual field (28).

2.2.3. Treatment of Glaucoma

At present, the only proven method for delaying the progression of glaucomatous optic atrophy in patients with glaucoma is lowering the IOP.

Topically administered IOP-lowering agents can decrease the intraocular pressure by decreasing aqueous humour production or by increasing the rate of aqueous humour outflow. Currently there are five groups of locally administered antiglaucoma medications in clinical use. These include prostaglandin analogues, beta-receptor antagonists, carbonic anhydrase inhibitors, alpha-2 selective adrenergic agonists and parasympathomimetics. Systemically administered agents (carbonic anhydrase inhibitors and osmotics) are usually given only for a limited period of time when the IOP is very high and cannot be otherwise controlled and until a more definitive treatment can be planned, usually that being some kind of surgical intervention. Often the first line of therapy is a monotherapy involving a single topically administered IOP lowering medication. The IOP should be sufficiently reduced to a level in which the progression of glaucomatous visual field loss is kept to a minimum (4) (5).

Although topical IOP-lowering medications are able to decrease the IOP substantially and in most cases sufficiently enough in order to halt the progression of the disease, an additional factor that must be taken into account is that of patient compliance and adherence to the treatment plan. In a systematic review of the literature, Reardon *et al* found that according to electronic monitoring more that 20% of the patients met criteria for poor compliance and according to prescription records only 31% of the patients had not discontinued their treatment at 12 months (57). In a more recent study, Rajurkar K *et al* found that among 151 glaucoma patients that were interviewed, 49% of them reported problems in using glaucoma medication, 16% reported total non-compliance and 35% had an improper technique for administering the eye drops (58). The most common reasons for poor compliance and adherence to the treatment are complexity of the medication regimen, side effects, poor manual coordination, forgetfulness and cost of medication (59). In a recent study from Germany, Frech S *et al* found that the mean level of adherence

in terms of prescriptions filled was 66.5%. Risk groups for non-adherence were patients between the ages of 50 and 59, as well as patients older than 80 years, patients with a longer duration of glaucoma and patients with considerable comorbidity (60).

Besides medical therapy, there are a number of alternative treatment modalities for glaucoma patients who need further IOP reduction or patients with poor compliance. Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) are both effective and safe treatment options for lowering the IOP. Both ALT and SLT are performed at the slit lamp with the help of an argon or Nd:YAG laser and a Gonio-lens. (5). ALT and SLT reduce the IOP by increasing trabecular outflow facility (61) (62) (63). Nonetheless, several studies showed that the IOP-lowering effect of both ALT and SLT wears off with time and that approximately half of the patients treated with either technique will have lost the IOP-lowering effect after 5 years (4) (5).

Traditional glaucoma filtration surgery has the advantage of being able to decrease the IOP substantially for a long time in most patients and is being used in moderate to advanced glaucoma for optimal IOP control. However, the risk of postoperative complications, in some cases vision-threatening, has urged clinicians into searching for a better alternative. Non-penetrating glaucoma surgery techniques, including deep sclerectomy, viscocanalostomy and canaloplasty have the advantage of not entering the anterior chamber directly during surgery and thus minimizing the risk of postoperative complications such as hypotony, shallow anterior chamber, hyphema and choroidal effusions (4) (5) (64).

During the last years a number of minimally invasive glaucoma surgical procedures have been developed that use small intraocular implants or laser energy in order to reduce the IOP to the desired level (6) (7). During the next paragraphs a number of these surgical procedures will be discussed. Finally, a new test based on a simplified

oculopression technique will be introduced for assessing the effectiveness of these new surgical techniques in glaucoma patients postoperatively.

2.3. Microinvasive Glaucoma Surgery

2.3.1. The iStent Inject System: A Trabecular Micro-Bypass Device

The iStent inject (model GTS400) is a second-generation trabecular micro-bypass device that is implanted into the Schlemm's canal in the nasal portion of the anterior chamber angle using an *ab interno* approach, clear corneal incision and a specialized injector system for the treatment of glaucoma. The implant is 360 µm in length, with a maximum width of 230 µm. It is cone-shaped and is made of heparin coated, gamma-sterilized titanium. The injector system is preloaded with two stents, so that it can deliver both of them without exiting the eye between the first and second implantation (Figure 17). After a successful implantation the stent is positioned with its flange residing in the anterior chamber, the thorax embedded in the trabecular meshwork and its head inside Schlemm's canal (Figures 18 and 19). It has an inlet orifice on its one end facing the anterior chamber and four outflow openings on the opposite end that resides inside Schlemm's canal. The device bypasses the trabecular meshwork and works by improving the aqueous outflow facility (9).

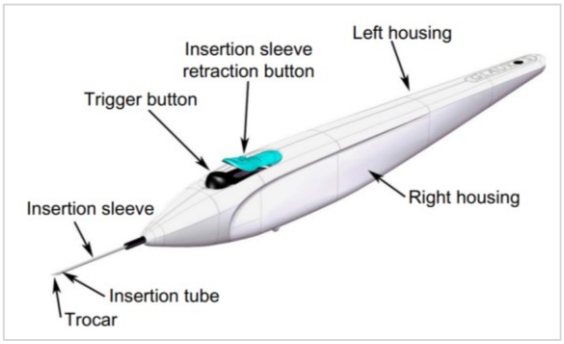


Figure 17: The G2-M-IS injector system is preloaded two GTS400 stents. The injector enters the eye with an anteriorly placed 23-gauge stainless steel insertion tube and delivers the stents into Schlemm's canal after activation of the trigger mechanism by the surgeon. Normally two iStent inject devices are implanted into Schlemm's canal at the nasal portion of anterior chamber angle, separated by 2-3 clock hours (65).

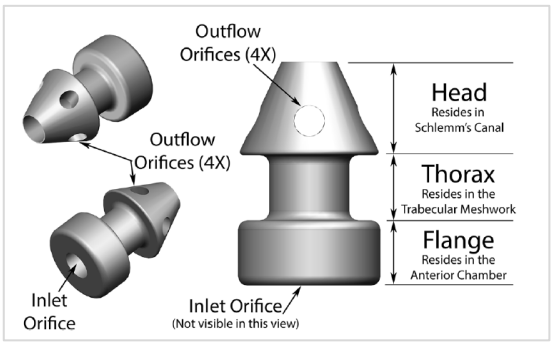


Figure 18: The GTS400 iStent inject device is a cone-shaped, heparin-coated, titanium micro-stent. It consists of a flange, thorax and a conical head. After implantation of the stent with the automated injector system the iStent inject is positioned with its flange facing the anterior chamber and the head residing inside Schlemm's canal (66).

Several studies have examined the efficacy and safety profile of iStent inject. Implantation can be performed either as a stand-alone operation or in combination with cataract surgery. The procedure has been shown to be safe with only few

postoperative adverse events, most of which are minor and not vision-threatening (6). In a large meta-analysis of 1767 eyes, the most common postoperative complications were elevation of the intraocular pressure, stent blockage or obstruction, stent malposition and hyphema (67).

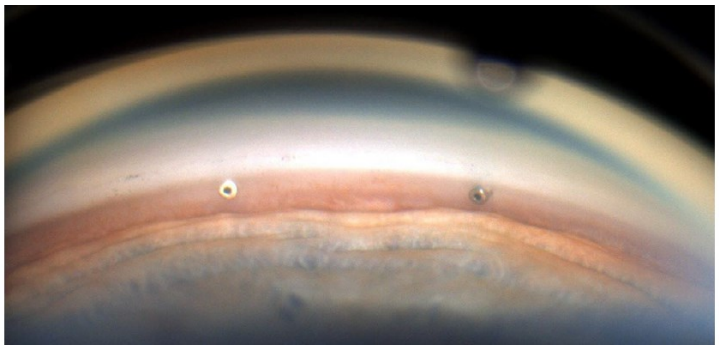


Figure 19: Two GTS400 stents gonioscopically visible after successful implantation in the anterior chamber angle (68).

2.3.2. The XEN45 Gel Stent System: A Subconjunctival Micro-Stent

XEN gel stent is a subconjunctival micro-stent designed for the treatment of glaucoma. It is a 6 mm long tube made of porcine collagen cross-linked with glutaraldehyde with a lumen diameter of 45 µm. The material of the stent has the distinctive ability to remain stiff when dehydrated while it softens upon contact with aqueous humour. The XEN gel stent is implanted into the subconjunctival space on the upper nasal part of the conjunctiva through an *ab interno* approach with clear corneal incision and the help of a specialized inserter device (Figure 20). The procedure can be performed as a stand-alone operation or in combination with cataract surgery. After the implantation a conjunctival filtering bleb is formed at the site of the stent that results from subconjunctival filtration of aqueous humour. The use of an antifibrotic agent is thus generally recommended to avoid scarring (6). Most commonly 0.1 ml of mitomycin C (MMC) 0.1 mg/ml is used, it is administered under the conjunctiva prior to stent implantation and not washed out (69) (70). After

correct placement of XEN gel stent, a small portion of it, approximately 1 mm, is visible in the anterior chamber, 2 mm are inside the scleral tunnel that is formed and 3 mm are visible under the conjunctiva (71).

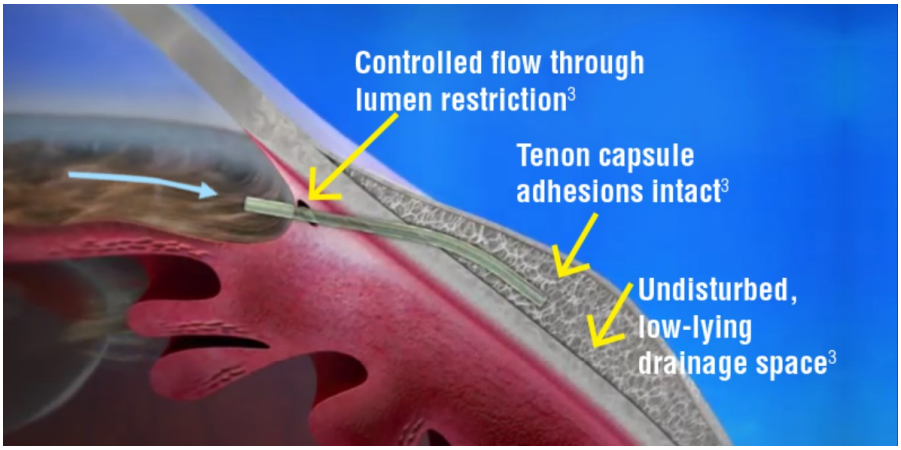


Figure 20: Schematic representation of the XEN gel stent after successful implantation. A fistula is created connecting the anterior chamber with the subconjunctival space allowing for the filtration of aqueous humour through the stent lumen (72).

2.3.3. Excimer Laser Trabculostomy

Krasnov, in his original 1973 paper, was the first to describe the use of a Q-switched laser to produce “micropunctures” in the outflow region of anterior chamber angle for the treatment of open-angle glaucoma (Figure 21). In contrast to previous types of lasers, the Q-switched, modulated laser used by Krasnov was able to deliver a very large amount of energy in a short burst, thus eliminating the thermal and coagulative effects on tissues that were observed with previous types of lasers. The result was the formation of microscopic holes on the outflow region of anterior chamber angle with an improvement of outflow facility and drop of IOP. The new technique was named laseropuncture (73). While the technique described by Krasnov did not find widespread clinical use, it did open the way into the

development of other laser techniques that targeted the anterior chamber angle and the trabecular outflow pathway of the eye.

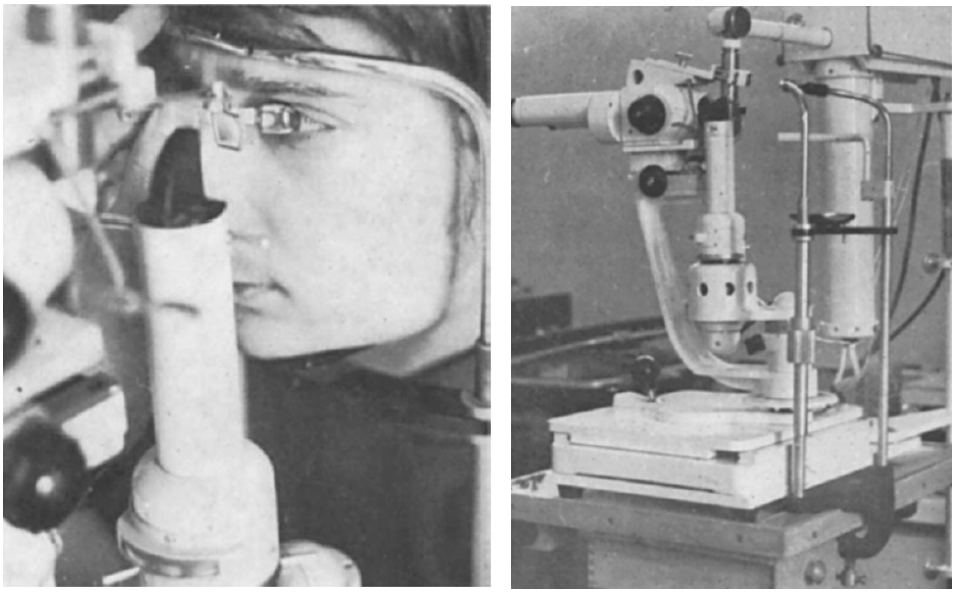


Figure 21: Photograph of the Krasnov goniolens used in laseropuncture (left) and the original Q-switched laser unit adapted to a slit lamp (right) (73).

Vogel *et al* developed a new surgical technique with the help of an excimer laser and published their first clinical findings in 1996 and 1997. The new laser could ablate the trabecular meshwork and remove the target tissue with only minimal thermal and coagulative damage. As a result, a new direct communication between the anterior chamber and Schlemm's canal is achieved. The procedure is performed with an *ab interno* approach, small corneal incision and the help of a laser probe under gonioscopy (Figure 22). They documented an IOP lowering effect in 30 out of 35 treated eyes with the new, minimally invasive technique (74) (75). Since then, other studies have also documented the IOP lowering effect of ELT either as stand-alone operation or combined with cataract surgery and the procedure has been shown to be safe with minimal perioperative and postoperative complications (76).

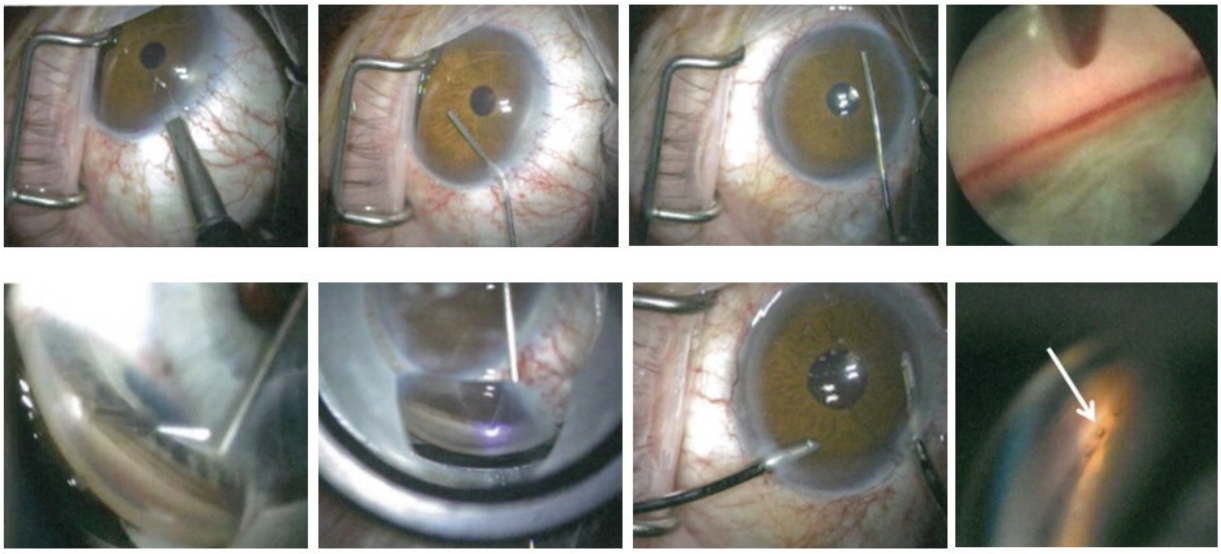


Figure 22: Surgical steps of an *ab interno* excimer laser trabeculostomy (ELT). First a paracentesis is performed in the superotemporal quadrant in peripheral cornea (upper left) and the anterior chamber is stabilized using a viscoelastic agent. The fibre-optic probe enters the anterior chamber and is advanced to contact the trabecular meshwork on the opposite side. The position of the laser probe is controlled endoscopically (upper right) or using a goniolens (lower left). Four to ten channels are created using the excimer laser. The laser probe is removed and the viscoelastic agent is washed out and replaced by balanced salt solution. Patent trabeculostomy channels are seen gonioscopically after the operation (bottom right) (76).

3. Materials and Methods

In previous studies, success and failure of IOP lowering procedures, including minimally invasive glaucoma surgical techniques, has been mainly judged according to the postoperative IOP, change of IOP from preoperative baseline values or the number of glaucoma medications needed in order maintain the IOP at the desired level (6). However, IOP is only one of many parameters that define intraocular physiology and aqueous humour dynamics in the human eye. Tonography, first introduced by Grant and later further developed by Leydhecker, has been used to estimate the facility of aqueous outflow and distinguish between healthy individuals and patients with glaucoma in the past (52) (53) (54). Ulrich *et al* developed another technique for evaluating aqueous dynamics that eliminated several of the limitations encountered in classic tonography. They measured the fall of IOP that occurred after a period of oculopression using a suction cup coupled to an applanation tonometer in order to identify patients with glaucoma and named the technique oculopression tonometry (55) (56). With the development of newer techniques that are able to measure the IOP accurately and fast in the sitting position with minimal patient discomfort (43) (44) (46), as well as new high resolution imaging studies of the optic nerve head that can detect early glaucomatous changes (77) (78) (79), tonography and oculopression tonometry have become nowadays obsolete in the everyday clinical practice.

This study attempts to investigate the changes of aqueous dynamics that occur after minimally invasive glaucoma surgery in order to better evaluate the efficacy and IOP lowering potential of different MIGS procedures. For this purpose, a newly developed oculopressor device was used (10). This device is a modification of the Taylor oculopressor and consists of a metallic cylinder weighing 60 g that moves freely inside a barrel-shaped plastic tube (Figure 23). During the oculopression, the foot of the metallic cylinder rests on the closed eyelid and exerts pressure on the

eye, raising the IOP at approximately 43mmHg (10). The examiner holds the device upright from its plastic part and the patient is asked to fixate at an object on the ceiling directly above him (Figure 24).

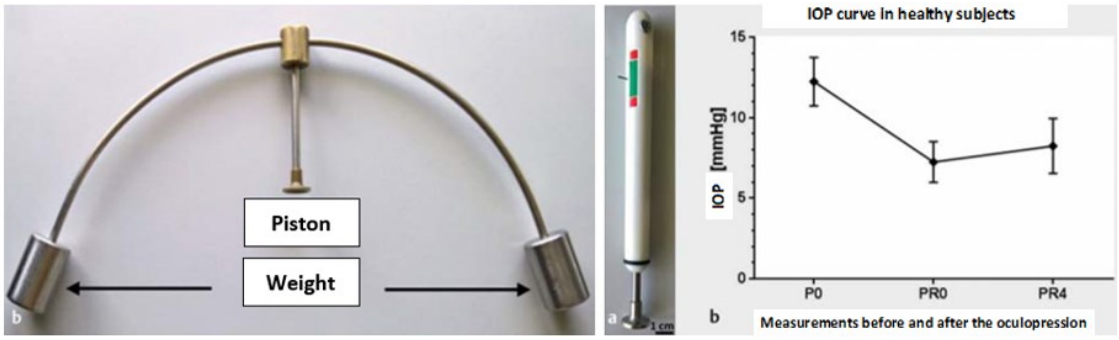


Figure 23: The Taylor oculopressor (left) uses a metallic piston connected to two weights on each side. The new modified version (right) uses a similar metallic cylinder that is held upright inside a barrel shaped plastic tube. The IOP is measured using the iCare Tonometer. The result is a curve of IOP. P0 is the IOP at baseline before oculopression, PR0 the IOP directly after removal of the oculopressor from the eye and PR4 the IOP after a recovery period of 4 minutes (10).

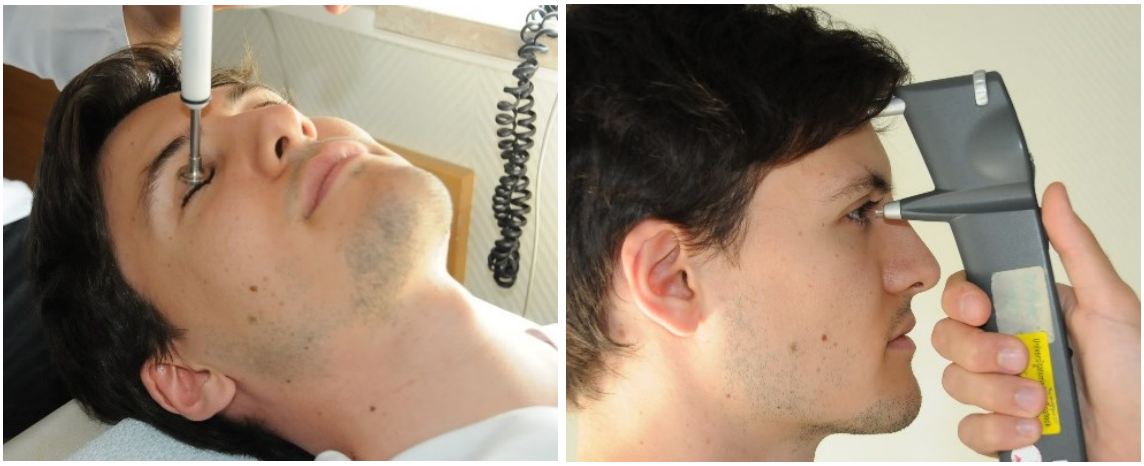


Figure 24: Measurement of the IOP with the iCare tonometer is followed by a 4-minute long oculopression in the supine position. IOP is measured immediately after removal of the oculopressor and again 4 minutes later.

Even though it is a new technique, the underlying theory is well established from previous works on tonography and oculopression tonometry (52) (53) (55). It is known, that upon placing the oculopressor on the eye the rate of aqueous outflow is artificially increased resulting in the displacement of a set amount of intraocular fluid. As a result, after removal of the oculopressor from the eye the IOP has fallen into a new, lower level. Eventually the IOP starts to rise again slowly until a steady state of aqueous humour production and outflow is achieved once again. The modified oculopression technique can therefore be regarded as a kind of “stress test” and the IOP reduction that occurs after oculopression reflects the overall outflow facility of the eye.

In the study protocol IOP was first measured in the sitting position using the iCare tonometer. Oculopression was then performed on the study eye in the supine position for 4 minutes. The IOP was measured immediately after removal of the oculopressor from the eye and again 4 minutes later. The results can be outlined in a graph where *P0* is the IOP at baseline, *PR0* the IOP directly after removal of the oculopressor and *PR4* the IOP after a recovery period of 4 minutes (Figure 23).

A 4-minute long oculopression has the advantage of being short enough in duration, in order to be able to examine patients routinely during consultation hours. It is also of sufficiently long duration, so that the IOP reduction that occurs can generate an IOP curve that can be measured accurately.

In comparison to Ulrich's oculopression tonometry, in which a repeated IOP measurement with the Goldmann applanation tonometer and the use of a suction cup placed on the conjunctiva is necessary for the measurements, the modified technique that we propose has the additional advantage of being more comfortable for the patients as no parts of the oculopession device come in direct contact with the cornea or conjunctiva during the test.

Moreover, measurement of the IOP with the iCare tonometer is sufficiently fast and accurate and it can be easily performed immediately after the patient stands up from the supine position.

Selection of patients was performed retrospectively after careful examination of patient files, diagnoses, previous surgeries and other ocular diseases from patient records. Exclusion criteria were extensive corneal scarring or previous corneal surgery that could otherwise influence an accurate IOP measurement with the iCare tonometer, ALT or SLT during the previous 3 years as well as previous filtration glaucoma surgery, as these procedures could have an impact on the oculopression curve that we measure and finally advanced glaucoma with considerable visual field loss. Most of the glaucoma patients that received a MIGS surgery between the years 2015 and 2018 in the department of ophthalmology (Rostock University Medical Center) and were available for further screening were recruited in the study. An additional group of healthy individuals and a group of patients with glaucoma but without previous ocular surgery were examined with the same protocol for comparison.

All patients and healthy subjects underwent a thorough ophthalmological examination including examination of the anterior segment at the slit-lamp, fundus examination, gonioscopy (only in glaucoma patients) and documentation of local medication before and after the surgery, as well as documentation of any adverse events. Diagnosis and assessment of glaucoma was based on the funduscopic appearance of the optic nerve head and changes in the visual field, as well as findings in HRT (Heidelberg Retina Tomograph) and OCT (Optical Coherence Tomography) of the optic nerve head. All participants were asked to sign an informed consent before their participation in the study.

Finally, a thorough statistical analysis of the results was performed using standard tests with SPSS software (Statistical Package for the Social Sciences) including descriptive statistics, one-sample Kolmogorov-Smirnov test for assessing test distribution, Kruskal-Wallis, Mann-Whitney and one-way ANOVA tests for further evaluation of the test variables.

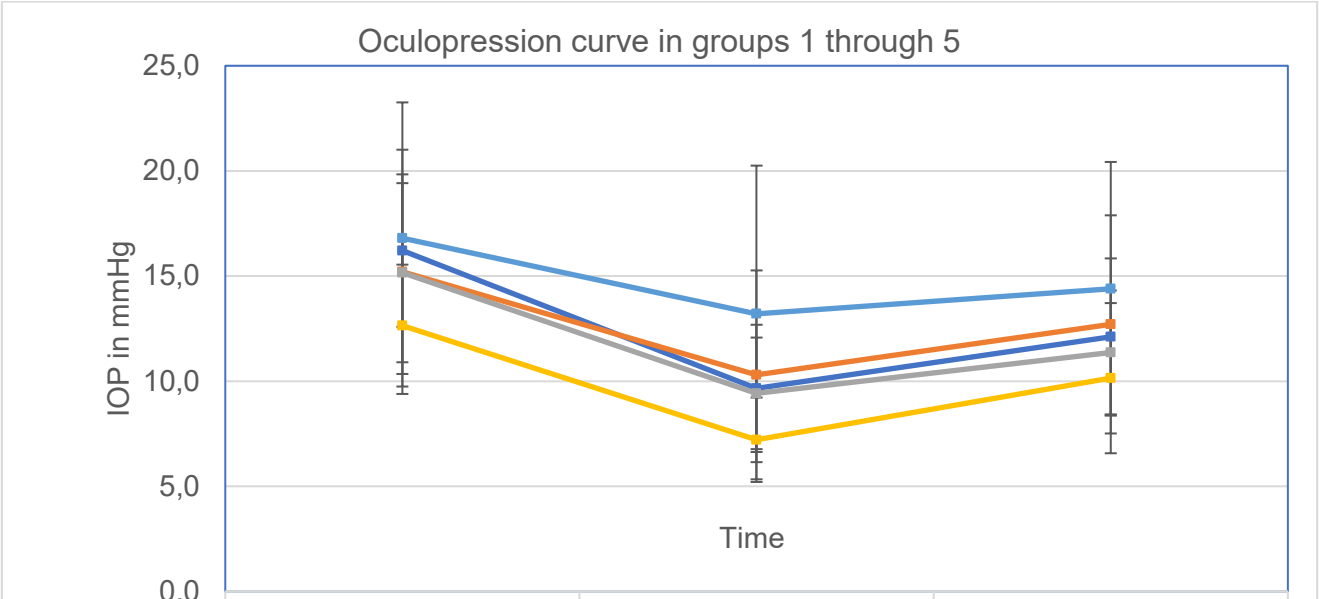
4. Results

Overall, 86 individuals were examined and divided into 5 different groups. All study subjects underwent IOP measurements and oculopression of the study eye according to the aforementioned protocol. The first group consisted of 38 healthy individuals between the ages of 23 and 81 (mean age was 36.9 ± 16.6 years) that had no history of previous ocular surgery or other eye disease. The second group consisted of 10 patients between the ages of 54 and 82 (mean age was 72.7 ± 8.8 years) that were diagnosed with glaucoma and had no history of previous ocular surgery. Eight patients from the second group had a primary open-angle glaucoma, one patient had open-angle glaucoma secondary to pseudoexfoliation syndrome (PEX) and one patient had open-angle glaucoma secondary to pigment-dispersion. Groups 3, 4 and 5 consisted of 38 patients between the ages of 33 and 91 years (mean age was 70.4 ± 10.9 years) with different types of glaucoma and had previously undergone one of three different MIGS procedures (iStent inject implantation, XEN stent implantation and ELT). The procedures were performed either as stand-alone operations or combined with a cataract surgery. In group 3, 19 patients with glaucoma had previously received an iStent inject implantation. In group 4, 14 patients had previously received a XEN stent implantation and in group 5, 5 patients had undergone ELT (see Table 2). The average time interval between surgery and oculopression was 7.3 ± 5.9 months in group 3, 10.5 ± 11.0 months in group 4 and 4.8 ± 5.3 months in group 5.

Group	Definition	Number of individuals	Age (range, mean ± SD) in years
1	Healthy individuals without previous ocular surgery or eye disease	38	23-81, 36.9 ± 16.6
2	Patients with diagnosed glaucoma without previous surgery	10	54-82, 72.7 ± 8.8
3	Patients with diagnosed glaucoma and previously performed iStent inject implantation (stand-alone or in combination with cataract surgery)	19	57-85, 74.3 ± 7.1
4	Patients with diagnosed glaucoma and previously performed XEN gel stent implantation (stand-alone or in combination with cataract surgery)	14	55-91, 70.4 ± 9.3
5	Patients with diagnosed glaucoma and previously performed ELT	5	33-76, 55.6 ± 15.4

Table 2: Definition of groups, number of individuals in each study group and corresponding range, mean and standard deviation (SD) of age in each of the groups.

In most test subjects, the IOP curve that was obtained followed the same trend with an initial reduction of IOP after the 4-minute long oculopression and a gradual rise of IOP during the recovery phase (Figure 25, Figure 28).



	P0	PR0	PR4
Group 1	16,2	9,7	12,1
Group 2	15,2	10,3	12,7
Group 3	15,2	9,4	11,4
Group 4	12,6	7,2	10,1
Group 5	16,8	13,2	14,4

Figure 25: Oculopression curve in groups 1 through 5. Group 1 (Healthy individuals), Group 2 (Patients with diagnosed glaucoma without previous surgery), Group 3 (Patients after iStent inject implantation), Group 4 (Patients after XEN gel stent implantation), Group 5 (Patients after ELT).

By calculating the Spearman's rank correlation coefficient, a statistically significant correlation ($p<0.05$) between the baseline IOP (P0) and the degree of IOP reduction that occurred after oculopression (PR0-P0) was found in groups 1 through 4. Generally, patients with higher baseline IOP had a more pronounced reduction of IOP after oculopression. In order to eliminate this problem and be able to assess the "oculopressive" effect independently, we introduced an additional parameter and calculated the percentage of IOP reduction in relation to baseline IOP with the following formula:

$$\text{IOP Reduction (percentage)} = [(PR0-P0)/P0]x100\ \%$$

Mean baseline IOP was 16.2 ± 3.6mmHg in group 1 (healthy individuals) and decreased to 9.7 ± 3.0mmHg after oculopression representing a 40.7 ± 11.8% drop from baseline. In the recovery phase IOP increased to 12.1 ± 3.7mmHg. In group 2 (patients with glaucoma and without previous surgery) mean IOP at baseline was 15.2 ± 5.8mmHg under local medication, it decreased to 10.3 ± 5.0mmHg after oculopression, representing a 34.3 ± 9.5% drop and increased again after the recovery period to 12.7 ± 5.2mmHg. Patients after implantation of iStent inject (group 3) had postoperatively a mean IOP of 15.2 ± 4.3mmHg at baseline. IOP dropped to 9.4 ± 2.7mmHg after oculopression, representing a 36.5 ± 14.0% decrease from baseline and rose again to 11.4 ± 2.9mmHg after the recovery phase. Patients after implantation of XEN stent (group 4) had the lowest mean IOP at baseline with 12.6 ± 2.9mmHg. IOP decreased after oculopression to 7.2 ± 2.0mmHg, the lowest IOP after oculopression in all of the groups, representing a 42.8 ± 10.2% drop from baseline and increased again after the recovery phase to 10.1 ± 3.6mmHg. Group 5 (glaucoma patients after ELT) had a mean IOP of 16.8 ± 6.5mmHg at baseline, the highest among all groups. It decreased after oculopression to 13.2 ± 7.0mmHg representing only a 25.7 ± 13.9% drop. It then rose again to 14.4 ± 6.0mmHg after the recovery period (Figures 25, 26 and 27).

The change of IOP in respect to baseline values is graphically depicted in Figure 28. During the recovery phase mean IOP increased in all groups but did not reach the initial IOP values in any of the studied groups.

The IOP reduction after oculopression (PR0-P0) was statistically significantly lower ($p=0.021$) in group 2 (patients with glaucoma and without previous surgery) in comparison to group 1 (healthy individuals). PR0-P0 did not differ significantly in patients after iStent implantation (group 3) or XEN Stent implantation (group 4) in comparison to healthy probands ($p=0.142$ and $p=0.058$ respectively).

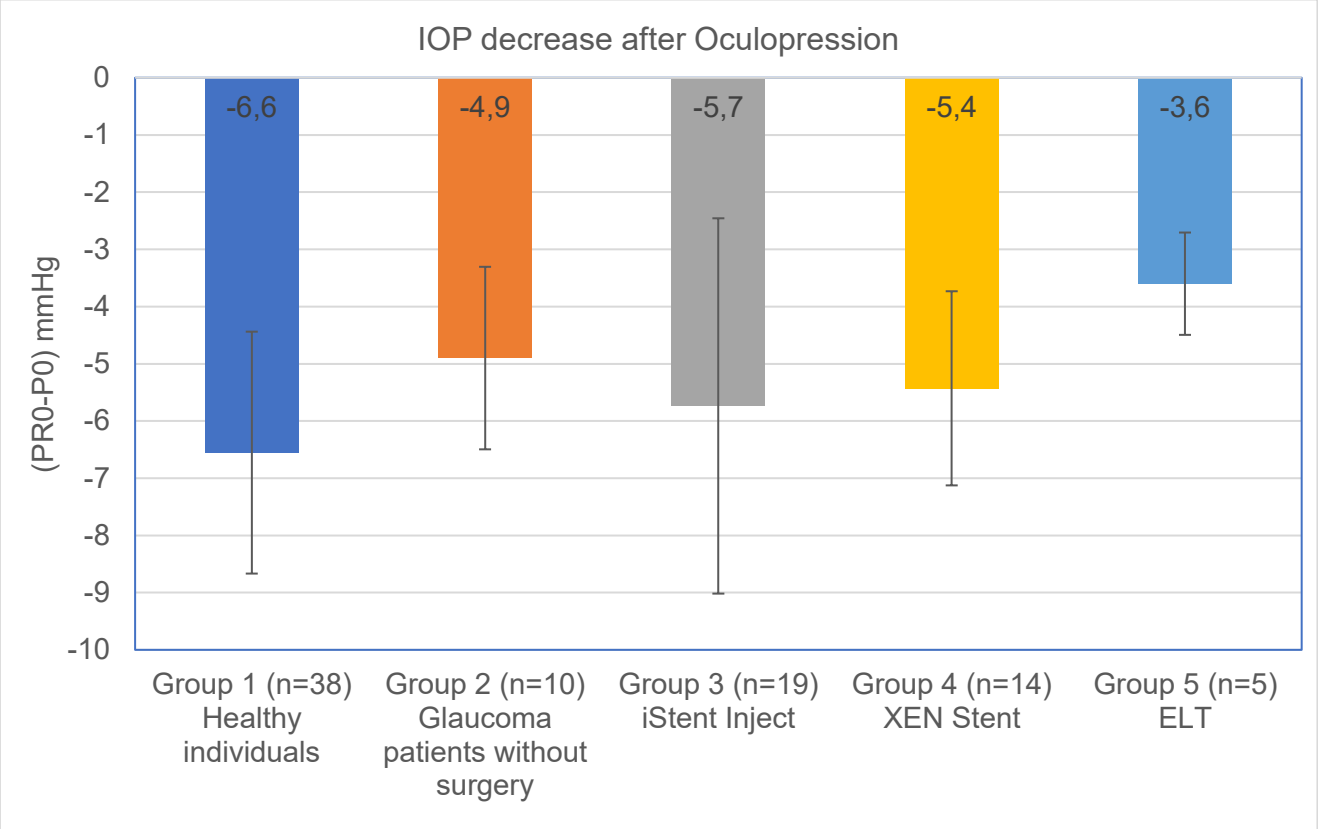


Figure 26: The fall of IOP immediately after oculopression (PR0-P0) in absolute values in groups 1 through 5.

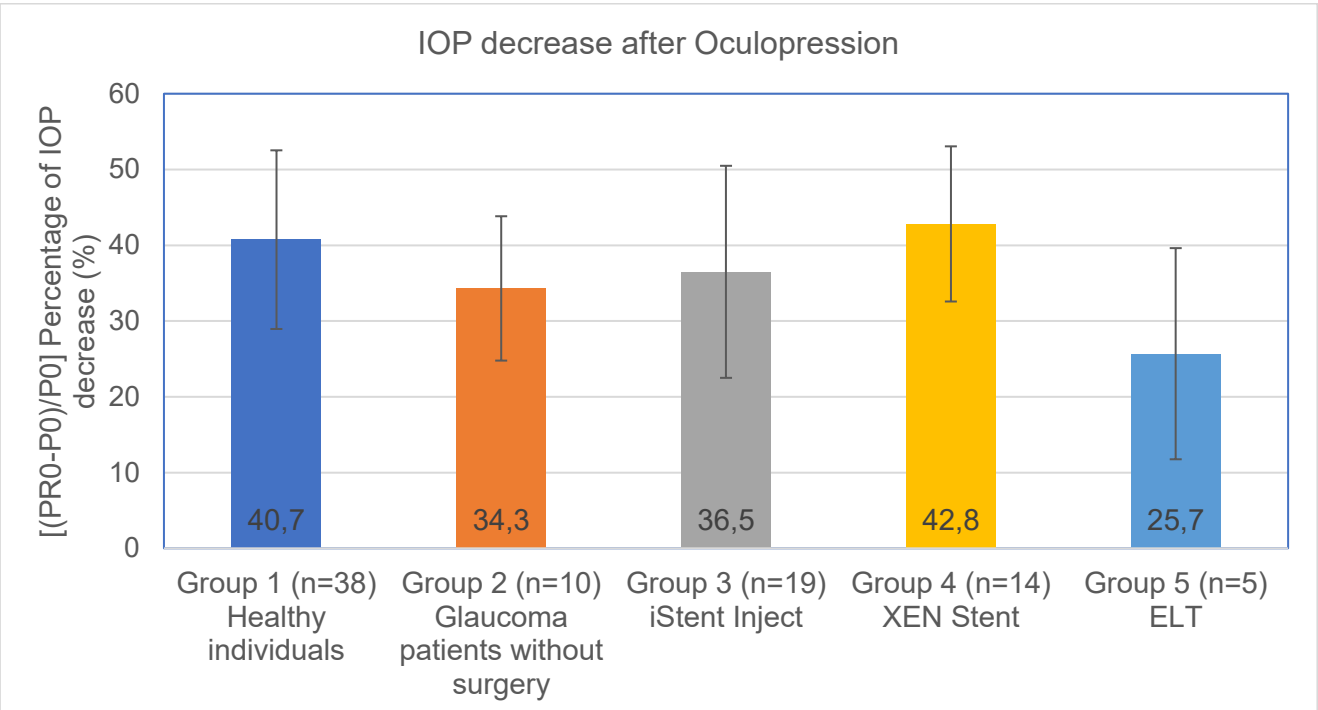


Figure 27: The fall of IOP immediately after oculopression [(PR0-P0)/P0] in percentage in groups 1 through 5.

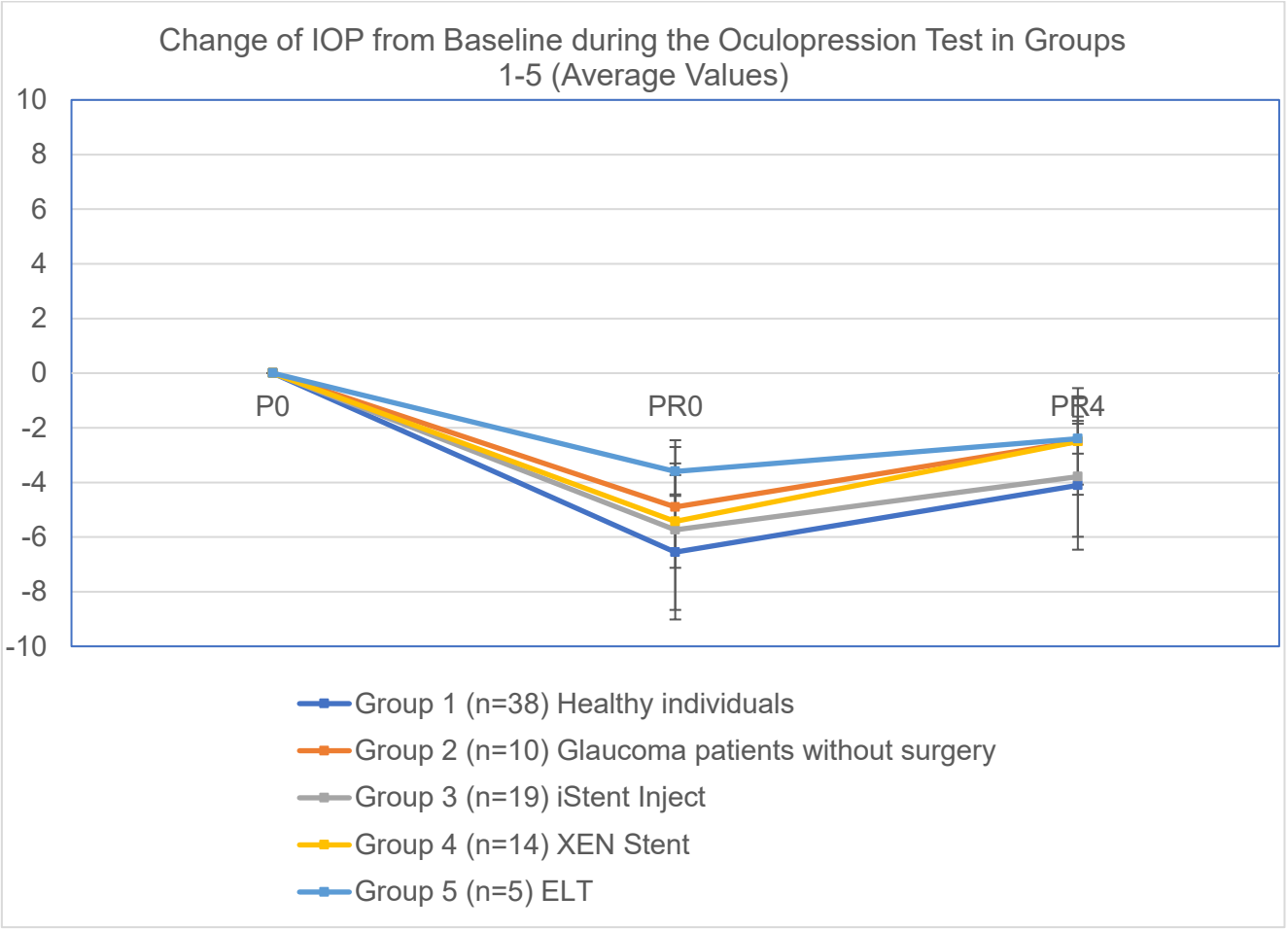


Figure 28: The change of IOP in relation to baseline IOP during the oculopression test in groups 1 through 5 (Average values).

The mean number of different IOP lowering medications was 2.5 ± 1.3 in the group of glaucoma patients without previous operations (group 2). In glaucoma patients after XEN stent or iStent inject implantation (groups 3 and 4) the number of IOP lowering medications that were needed was statistically significantly lower in comparison to group 2 (p=0.006 and p=0.01 respectively) (Figure 29). Patients after implantation of XEN gel stent (group 4) needed the least amount of medications (n=0.4 ± 0.9), followed by patients after iStent inject implantation (n=0.8 ± 1.4) and patients after ELT (n=1.6 ± 0.9). Only 6 out of 19 patients after iStent inject and 2 out of 14 patients after XEN stent implantation needed further IOP reduction using locally administered eye drops. In contrast, only 1 out of the 5 individuals who

received an ELT could discontinue the antiglaucoma medication postoperatively (Figure 30). It is important to notice that what was documented here was the number of different medication classes that the patient was using and not the number of daily applications. For example, if a patient had a beta-blocker agent in his medication plan that was applied two times per day, the number of IOP lowering medications was 1, even though he had to take the same eye drops twice, in the morning and in the evening.

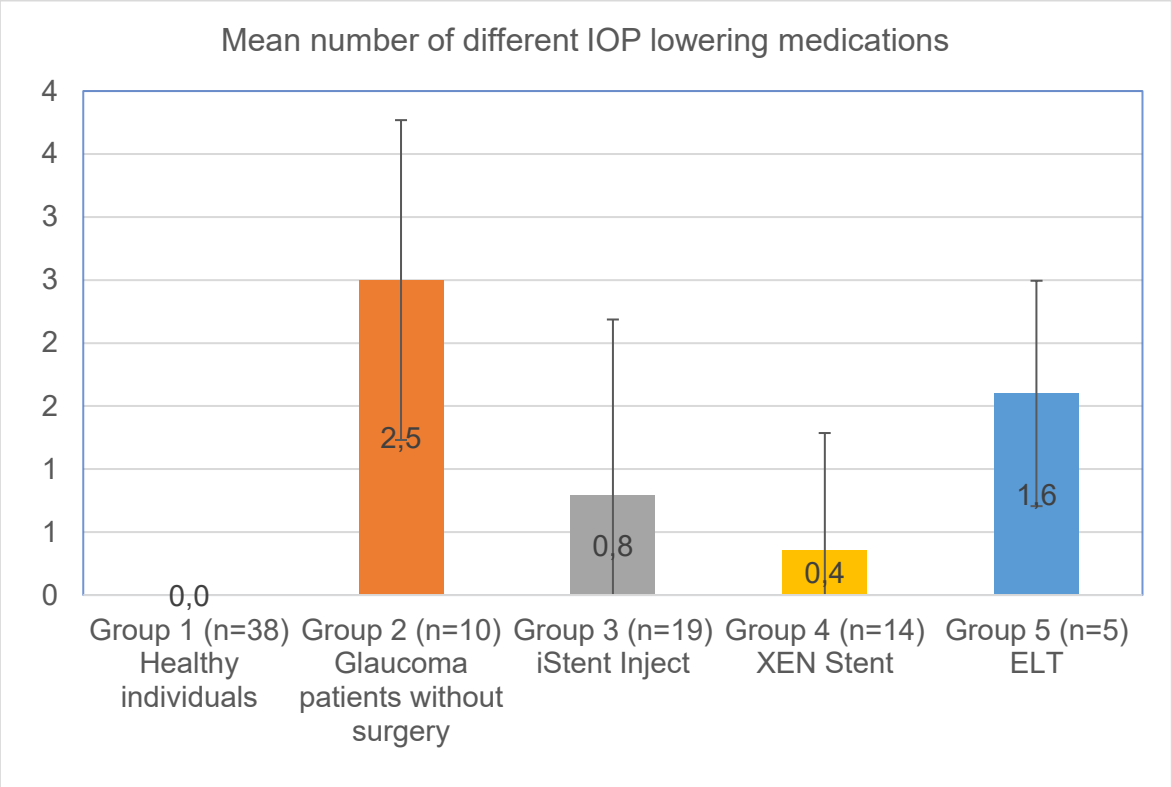


Figure 29: Mean number of antiglaucoma medications used at the time of the study in groups 1-5.

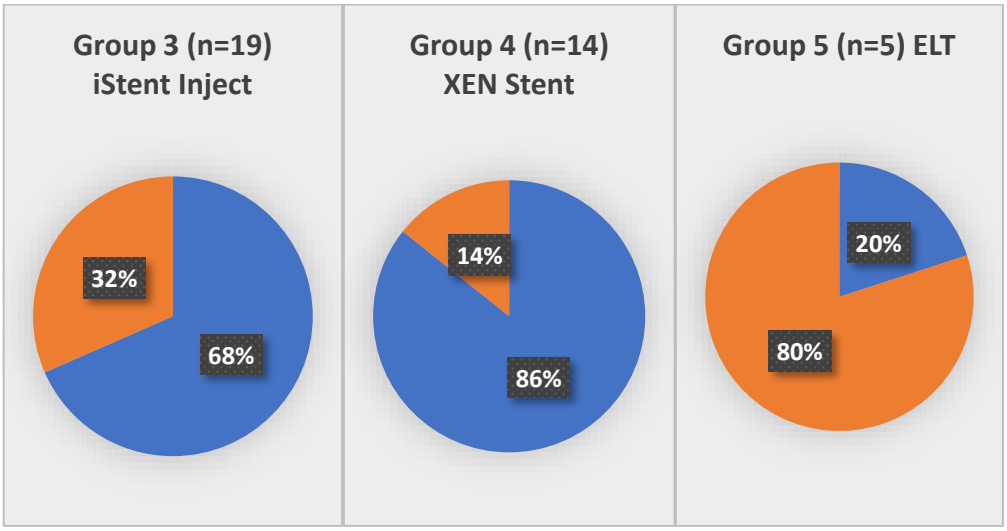


Figure 30: Number of patients that needed further IOP reduction with topical medication (orange) and medication free patients (blue) after MIGS surgery.

The age of test subjects did not show any consistent correlations neither with baseline IOP nor with the IOP decrease after oculopression in the examined population.

Due to the nature of the operation, a considerable portion of patients after implantation of XEN stent had to come for surgical revision and needling of the filtering bleb due to conjunctival scarring in our clinic. Five out of the 14 patients that were included in the study had at some point received a surgical revision with needling of the filtering bleb and one of these 5 patients had undergone needling three times by the time of the study. The needling rate was thus calculated to be 35% in the selected population.

5. Discussion

Several studies have assessed the IOP lowering effect of MIGS surgical techniques in the past. In this chapter we will first discuss some of the similarities between those studies and our findings. We will then describe in which way our approach differs from that of previous studies and how our findings contribute to the overall understanding of how MIGS surgery works. Finally, we will try to explain the advantages that microinvasive surgical techniques offer in modern glaucoma surgery but at the same time define their limitations as well.

With some exceptions, our results generally follow the same trend seen in published literature. Regarding the older techniques, the oculopression curves that were obtained in our study were similar to that of tonography and oculopression tonometry, which also produce a gradual IOP reduction after a force is applied on the eye surface (in the case of tonography) or when the IOP is artificially increased using suction cups placed on the conjunctiva (in the case of oculopression tonometry) (52) (55). This finding supports the theoretical basis of our study and confirms our hypothesis, that our technique can be regarded as a kind of “stress test” that reflects the outflow facility of the eye (IOP reduction in the first part of the oculopression curve) and the physiologic return to the steady state (rise of IOP in the second part of the oculopression curve during the recovery period).

As far as baseline IOP after MIGS surgery is concerned, our measurements agree with the results of previous studies in several instances. We found a mean IOP of 15.2 ± 4.3mmHg after iStent inject implantation. In several studies mean IOP after implantation of iStent inject has been documented to be in the range between 13.0 and 16.25mmHg (6) (66) (80) (81).

Arriola-Villalobos *et al* evaluated the efficacy and safety of iStent inject combined with phacoemulsification in 20 patients with a mean follow up of 47.40 ± 18.46 months. Mean IOP at baseline was 19.95 ± 3.71mmHg under medication and 26.0

± 3.11mmHg after medication washout. At the end of the follow up period mean IOP was 16.25 ± 1.99mmHg with a 36.92% decrease from baseline IOP (80). Voskanyan *et al* examined 99 patients with open-angle glaucoma that underwent implantation of two GTS400 stents over a period of 12 months. Mean IOP at screening was 22.1 ± 3.3mmHg under medication and 26.3 ± 3.5mmHg after medication washout. At month 12, mean IOP was 15.7 ± 3.7mmHg representing a 39.7% decline from baseline IOP (66). In a more recent study, Clement *et al* evaluated the safety and efficacy of iStent inject combined with cataract surgery in a retrospective study of 165 eyes of patients with various types of glaucoma or ocular hypertension. They found that mean IOP decreased significantly from 18.27 ± 5.41mmHg at baseline to 14.04 ± 2.98mmHg at month 12, which equals a 23.2% reduction (81). Best *et al* investigated the efficacy of iStent inject in combination with cataract surgery in a prospective, randomized, simple-blind study. They examined 65 eyes from 56 patients with primary open-angle glaucoma, 31 of which underwent a combined cataract surgery with implantation of two GTS400 stents and 34 of which underwent cataract surgery without stent implantation. Mean follow-up time was 14 months. Patients that received the combined surgery showed a mean IOP reduction of 5.9mmHg or 23.5% from baseline while patients that received cataract surgery alone showed a mean IOP reduction of 2.1mmHg or 9.5% from baseline (68). In another study, Klamann *et al* evaluated 35 patients with open-angle glaucoma that received two GTS400 stents. They found an average IOP decrease of 33% from baseline at 6 months (82). All studies found a significant reduction of antiglaucoma medication postoperatively (66) (68) (80) (81) (82).

Nevertheless, in our test we do not simply measure the IOP postoperatively. The oculopression test in our study is a dynamic measurement and the IOP reduction that occurs (PR0-P0) in the first part of the test reflects the outflow facility of the eye. In patients after iStent inject implantation (group 3) we found a more pronounced

IOP reduction after oculopression in relation to non-operated glaucoma patients (group 2). it can therefore be suggested that iStent inject implantation had a positive effect on aqueous outflow facility.

Currently there are only few studies that measure aqueous dynamics in patients after MIGS surgery. A study from Fernández-Barrientos *et al* measured the changes in aqueous humour dynamics using fluorophotometry in a group of 33 patients with open-angle glaucoma or ocular hypertension scheduled to receive cataract surgery with or without implantation of iStent (first generation implant). In both groups aqueous flow (F) was similar before surgery and did not change postoperatively. Trabecular outflow facility (Ct) however increased in both groups. In the first group that received cataract surgery with iStent, Ct increased by 275% to 0.45 ± 0.27 µl/min/mmHg while in the second group that received cataract surgery alone Ct increased by 46% to 0.19 ± 0.05 µl/min/mmHg (11).

The results from Fernández-Barrientos *et al* agree in this regard with the findings in our study. Though not measuring the outflow facility directly, our test also assesses the aqueous outflow system.

Nonetheless, fluorophotometry and oculopression tonometry are inherently different methods for assessing aqueous humour dynamics. The main difference lies in the fact that in oculopression techniques an external force is applied on the surface of the eye. The intraocular changes that occur in response to this external force are then measured using tonometry. On the other hand, studies of aqueous dynamics that use the principle of fluorophotometry measure aqueous flow without altering the physiologic steady state of the eye.

Patients after XEN stent implantation had a considerably lower IOP at baseline in our study compared to previous studies in the published literature. Baseline mean IOP was 12.6 ± 2.9mmHg in our study and it has been documented to be between 14.8 and 17.1mmHg in several other studies (6) (69) (71) (83). This could be in part

explained by the low target IOP in the selected patients and the tendency of relatively prompt intervention (e.g. Needling or surgical revision of the filtering bleb) in patients where the IOP increased above the desired level in our clinic.

In our study, patients after XEN stent implantation demonstrated a large reduction of IOP after oculopression (PR0-P0) and in percentage values, they had the largest IOP reduction among all groups, even in comparison to healthy individuals (IOP reduction after oculopression was -40.7 ± 11.8% in healthy individuals and -42.8 ± 10.2% in the XEN stent group). In addition, the lowest value among all IOP measurements was 7.2 ± 2.0mmHg, the mean IOP directly after oculopression in the XEN stent group.

Previous studies have documented the IOP lowering efficacy of XEN get stent. Reitsamer *et al* evaluated 218 eyes of 199 patients with moderate primary open-angle glaucoma that received a XEN gel stent with or without concomitant cataract surgery. The follow up time was 24 months. Mean IOP was reduced from 21.4 ± 3.6mmHg at baseline to 14.9 ± 4.5mmHg at month 12 (representing a -29.3% reduction) and 15.2 ± 4.2mmHg at month 24 (representing a -27.8% reduction), while the number of IOP lowering medications was decreased from 2.7 ± 0.9 at baseline to 0.9 ± 1.1 and 1.1 ± 1.2 at month 12 and 24 respectively. Needling rate was documented to be 41.1% and mean number of needling procedures was 1.6 ± 1.1 at 24 months (71). In another study from Smith *et al*, 1-year outcomes after XEN gel stent implantation in 68 patients with glaucoma were evaluated. Mean IOP decreased from 22.1mmHg at baseline to 14.8mmHg at 12 months, representing a 33% reduction. Mean number of IOP lowering medications reduced from 2.9 at baseline to 1.1 at 12 months. Revision or needling of the subconjunctival bleb was necessary in 30 patients (44.1%) and 15 patients (22.1%) developed a significant perioperative or postoperative complication, including hyphema (n=6), iris prolapse (n=1), hypotony (n=5), choroidal effusions (n=1), tube exposure requiring surgical

revision (n=1) and hypotony with severe choroidal effusion (n=1) (83). In a retrospective study, Heidinger *et al* evaluated 199 eyes from 160 patients that received a XEN gel stent from 2014 to 2016. They found that mean IOP decreased from 22.8 ± 6.9mmHg at baseline to 17.1 ± 6.1 mmHg, 17.1 ± 5.9mmHg and 16.4 ± 3.8mmHg after 1, 12 and 18 months. Mean number of medications was also reduced from 2.9 ± 1.0 at baseline to 1.8 ± 1.4 after one year (69).

Our findings, as well as the results from previously published studies that investigated the efficacy of XEN gel stent indicate that the subconjunctival filtering pathway can be very effective at lowering the IOP, and possibly more effective than interventions that target the trabecular outflow (i.e. iStent inject or ELT).

The subconjunctival filtering pathway that is created during XEN gel stent surgery is however a “non-physiologic” state for the human eye, in that normally the aqueous humour does not reach the subconjunctival spaces. Subconjunctival filtration is the principle that is also used in some of the more invasive glaucoma surgeries, such as trabeculectomy (4). The drawback in all of these surgical techniques is the possibility of conjunctival scarring and resulting bleb failure. Patients must therefore be informed of the potential risks that are associated with every filtering procedure that result in the formation of a subconjunctival bleb, including that of XEN gel stent as well as the necessity of an intensive postoperative care and the relatively high probability of needling or surgical revision (69) (4).

As mentioned above, we found a needling rate of 35% in our patients after XEN gel stent implantation. The results are comparable to the aforementioned studies from Reitsamer *et al* (41.1% needling rate) and Smith *et al* (44.1% needling rate). However, due to the exclusion criteria that we used; patients that had to undergo a different kind of surgery due to stent failure (e.g. trabeculectomy) were not included into our calculations. It is therefore safe to assume that the complication and revision rate were actually higher than the numbers our data show.

Interestingly, ELT has not been able to achieve the same level of IOP reduction as iStent inject or XEN stent in our study. We found a baseline mean IOP after ELT of 16.8 ± 6.5mmHg. This agrees in part with observations in previous studies, where IOP was between 16.5mmHg and 19.6mmHg after ELT, considerably higher than the IOP after iStent inject or XEN stent (7) (84) (85).

ELT patients also exhibited the lowest IOP reduction after oculopression in our study with -3.6 ± 0.9mmHg in absolute values and -25.7 ± 13.9% reduction in regard to baseline IOP. However, with only 5 patients in the ELT group, further conclusions are difficult to be made at this point due to the low number of participants.

Current literature regarding ELT is limited. A number of studies have examined however the IOP lowering effect after ELT. Pache *et al* examined 135 patients with open-angle glaucoma or ocular hypertension that received ELT as stand-alone procedure or combined with cataract surgery. The two groups were further subdivided according to baseline IOP (group 1 when IOP was ≥ 22mmHg and group 2 when IOP was ≤ 22mmHg). In the group that received ELT without cataract surgery, mean IOP decreased from 27.9 ± 3.9mmHg to 19.3 ± 5.5mmHg after 1 year when baseline IOP was ≥ 22mmHg and from 20.2 ± 1.1mmHg to 17.6 ± 3.3mmHg when baseline IOP was ≤ 22mmHg. In the second group that received ELT combined with cataract surgery, mean IOP decreased from 26.4 ± 2.75mmHg to 16.7 ± 2.75mmHg after 1 year when baseline IOP was ≥ 22mmHg and from 19.6 ± 1.1mmHg to 16.3 ± 2.2mmHg when baseline IOP was ≤ 22mmHg (7). Töteberg *et al* evaluated 24 eyes of 24 patients with cataract and open-angle glaucoma or ocular hypertension that received a combined operation of ELT with phacoemulsification and intracapsular lens implantation. The follow up time was 12 months. Mean best corrected visual acuity (BVCA) increased from 0.45 ± 0.25 at baseline to 0.78 ± 0.30 at 12 months while mean IOP decreased from 25.33 ± 2.85mmHg to 16.54 ± 4.95mmHg representing a 34.70% reduction. Mean number of IOP lowering

medications decreased from 2.25 ± 1.26 to 1.46 ± 1.38 at 12 months (84). Another study from Babighian *et al* examined the efficacy and safety of ELT in 21 eyes from 21 patients with primary open-angle glaucoma. They found that mean IOP decreased from 24.8 ± 2.0mmHg at baseline to 16.9 ± 2.1mmHg after a mean follow-up of 25.3 ± 1.3 months corresponding to a 31.8% reduction. Mean number of IOP lowering medications also decreased from 2.24 ± 0.6 to 0.71 ± 0.8 (85).

In our study, we documented a significant reduction in the amount of IOP lowering medications in patients after iStent and XEN stent surgery. Mean number of antiglaucoma medications was 0.8 ± 1.4 after iStent inject and 0.4 ± 0.9 after XEN stent implantation. Patients after ELT still needed fewer medications compared to non-operated glaucoma patients (1.6 ± 0.9 versus 2.5 ± 1.3) but the number of antiglaucoma medications that they needed was considerably higher than iStent and XEN stent patients. Our results agree with the results of previous studies that have examined MIGS techniques and have also found a significant decrease of antiglaucoma medications postoperatively (6) (7) (66) (69).

To conclude, it is important to keep in consideration that, compared to the aforementioned studies in most cases of which the preoperative – postoperative IOP reduction after MIGS surgery was simply calculated, we measured the IOP reduction that occurred after oculopression postoperatively. In this regard, our test measures something fundamentally different from that in previous studies and therefore it cannot be directly compared with them. In our opinion, our test introduces an important new parameter that describes not only the current IOP but offers some additional information regarding the status of aqueous outflow system and intraocular physiology. Many researchers have been examining these physiological events since decades. It is however the simplicity of the modified oculopressor technique and the ease of use of rebound tonometry that enabled us to carry out such an examination in a clinical setting in patients after MIGS surgery.

In our study, the most important parameters were the IOP reduction that occurred after oculopression (calculated in absolute values, PR0-P0 and also in relation to the baseline IOP, [PR0-P0]/P0x100%). Both measurements differed among the studied groups as seen in figures 26 and 27 and in regard to PR0-P0, healthy individuals showed a significantly larger reduction of IOP after oculopression compared to non-operated patients with glaucoma (-6.6 ± 2.1mmHg reduction in healthy individuals versus -4.9 ± 1.6mmHg reduction in non-operated glaucoma patients). This agrees with older observations with tonography and oculopression tonometry that also show a distinctive difference in outflow facility between healthy individuals and patients with glaucoma (53) (54) (55). The oculopression curves of patients after XEN stent and iStent inject implantation were different compared to non-operated glaucoma patients and their results approximated those of healthy individuals. This suggests that the intraocular implants positively influenced aqueous outflow and that they had a “corrective” effect on the oculopression curve in the selected patients. However, a direct comparison between the different MIGS procedures is not possible at this point, as the number of the examined patients is limited. Moreover, in future studies preoperative as well as postoperative measurements with the oculopression test in patients that are scheduled to receive a MIGS surgery should be carried out in order to better examine the effect that these procedures have on aqueous outflow.

Nonetheless, based on our findings we can still make some additional observations regarding MIGS techniques. In our study, the trabecular approaches that we examined (ELT and iStent inject implantation) were considerably simpler, safer and less invasive compared to the subconjunctival approach used during XEN stent implantation. This is also evident in the number of postoperative complications and number of surgical revisions needed (35% needling rate after XEN Stent implantation). However, patients after XEN stent implantation benefitted from lower

IOP values postoperatively. Apparently, there is a kind of trade-off between the “invasiveness” of a glaucoma surgery and its IOP lowering effect that needs to be considered during clinical decision making. In general, we could say that the more invasive an operation is, the greater its IOP lowering effect. With MIGS, the glaucoma surgeon tries to achieve the best postoperative IOP, while keeping a low complication profile. During the last years, MIGS surgery has revolutionized the way decision making is being made when considering IOP reduction in glaucoma patients. More patients are operated early in the disease course in order to prevent side effects of local medication or reduce the amount of eye drops a patient may need. More invasive glaucoma surgeries like trabeculectomy and other incisional techniques are nowadays reserved for more advanced cases of glaucoma, where other approaches have failed. A substantial number of patients could thus benefit from such microinvasive glaucoma surgeries, postponing or even avoiding some of the more invasive procedures.

The best surgical technique that will achieve a substantial and long-lasting IOP reduction with minimal complications is still to be found. It is our belief, that the newly introduced oculopression technique will have an important place in the assessment of current glaucoma surgical techniques and in the development of new MIGS surgical techniques in the future. As more intraocular implants and MIGS techniques are being developed, more reliable parameters that can assess the IOP lowering potential of these procedures are needed, and the new oculopression technique could be one of them. However, a larger number of patients will have to be examined, in order to detect differences between individual surgical techniques.

We hope, that the oculopression technique that we introduced, will be able to help in clinical decision making and the evolution of glaucoma surgery in the future.

6. Summary

Glaucoma is one of the most common causes of blindness worldwide. The only evidence-based treatment to slow down the progression of glaucoma is the reduction of intraocular pressure (IOP) using local medication or through surgery. During the last years, a large number of microinvasive glaucoma surgery techniques (MIGS) have been developed, in order to reduce the IOP in glaucoma patients safely and effectively. Until now, efficacy of MIGS has been assessed mainly according to the postoperative IOP and the number of medications used. Results from long-term studies are rare or currently not available in the majority of the cases. In order to better evaluate the functionality of MIGS, a new examination method has been developed with the help of a new oculopressor device. In this study the efficacy of different MIGS techniques was examined using the new oculopressor.

At first, glaucoma patients that had previously received a MIGS surgery (iStent inject, XEN Stent, ELT) were examined with the new oculopression test. Their results were compared with those of non-operated patients and healthy individuals. Overall, 38 healthy subjects (group 1), 10 non-operated patients (group 2), 19 patients after iStent inject implantation (group 3), 14 patients after XEN Stent implantation (group 4) and 5 patients after ELT (group 5) were examined. The new examination measures the reduction of IOP that occurs after oculopression and can be seen as an indirect measurement of the outflow facility of the eye.

The IOP-reduction after oculopression differed among the study groups. Non-operated patients showed a significantly lower IOP-reduction compared to healthy individuals. Patients after iStent inject and XEN stent implantation showed a larger reduction of IOP after oculopression in relation to non-operated patients and their results approximated those of healthy individuals. These patients needed fewer medications postoperatively in relation to non-operated patients. Patients after ELT

showed postoperatively a smaller reduction of IOP after oculopression compared to iStent inject and XEN stent patients.

MIGS can increase the outflow facility of the eye in patients with glaucoma. Though ELT had the lowest impact on the aqueous outflow among the studied procedures in this study. The new test can help in the evaluation of current and further development of new MIGS in the future.

.

Bibliography

1. Tham YC, Li X, Wong TY et al. Global Prevalance of Glaucoma and Projections of Glaucoma Burden through 2040: A Systematic Review and Meta-Analysis. Ophthalmology 2014; 121(11): 2081-2090.

2. Deutsche Ophthalmologische Gesellschaft. Weißbuch zur Situation der Ophthalmologischen Versorgung in Detuschland. München: Deutsche Ophthalmologische Gesellschaft; 2012

3. Wang W, He M, Li Z et al. Epidemiological Variations and Trends in Health Burden of Glaucoma Worldwide. Acta Ophthalmologica 2019; 97(3): e349-e355.

4. Allingham RR. Shields Textbook of Glaucoma. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011

5. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 3: Treatment principles and options. British Journal of Ophthalmology 2017; 101: 130-195.

6. Pillunat LE, Erb C, Jünemann AGM et al. Micro-Invasive Glaucoma Surgery (MIGS): A Review of Surgical Procedures Using Stents. Clinical Ophthalmology 2017; 11: 1583-1600.

7. Pache M, Wilsmeyer S, Funk J. Laserchirurgie und Glaukom: Excimer-Laser-Trabekulotomie. Klinische Monatsblätter für Augenheilkunde 2006; 223(4): 303-307.

8. Minckler D, Baerveldt G, Ramirez MA et al. Clinical resulsts with the Trabectome, a novel surgical device for treatment of open-angle glaucoma. Transactions of the American Ophthalmological Society 2006; 104: 40-50

9. Bahler CK, Hann CR, Fjield T et al. Second-Generation Trabecular Meshwork Bypass Stent (iStent Inject) Increases Outflow Facility in Cultured Human Anterior Segments. American Journal Of Ophthalmology 2012; 153(6): 1206-1213.

10. Kopp F, Koschmieder A, Stahnke T et al. Entwicklung eines Okulopressors zur Evaluation der Funktionalität von Glaukomdrainage-Implantaten. Klinische Monatsblätter für Augenheilkunde 2018; 235(12): 1360-1365.

11. Fernández-Barrientos Y, García-Feijoó J, Martinez-de-la-Casa JM et al. Fluorophotometric Study of The Effect of The Glaukos Trabecular Microbypass Stent on Aqueous Humor Dynamics. Investigative Ophthalmology & Visual Science 2010; 51(7): 3327-3332.

12. Standring S, Borley NR, Gray H. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 40th ed. Edinburgh: Churchill Livingstone Elsevier, 2008

13. Tasman W, Jaeger EA. Duane's Ophthalmology. Lippincott Williams & Wilkins, 2007

14. Ross MH, Pawlina W. Histology: A Text and Atlas. 6th ed. Philadelphia: Lippincot Williams & Wilkins, 2011

15. Duke-Elder S, Wybar KC. The Anatomy of The Visual System. In: Duke-Elder S, Wybar KC. System of Ophthalmology, Volume II. London: Henry Kimpton; 1961

16. Straatsma BR, Landers MB, Kreiger AE. The Ora Serrata in The Adult Human Eye. Archives of Ophthalmology 1968; 80(1): 3-20.

17. Fine BS, Zimmerman LE. Light and Electron Microscopic Observations on The Ciliary Epithelium in Man and Rhesus Monkey. Investigative Ophthalmology 1963; 2(2): 105-137

18. Borges-Giampani AS, Giampani J Jr. Anatomy of Ciliary Body, Ciliary Processes, Anterior Chamber Angle and Collector Vessels. In: Rumelt S. Glaucoma - Basic and Clinical Aspects. IntechOpen, 2013. Available from: https://www.intechopen.com/books/glaucoma-basic-and-clinical-aspects/anatomy-of-ciliary-body-ciliary-processes-anterior-chamber-angle-and-collector-vessels

19. Rohen JW. Scanning Electron Microscopic Studies of the Zonular Apparatus in Human and Monkey Eyes. Investigative Ophthalmology & Visual Science 1979; 18(2): 133-144.

20. Bairati A, Orzalesi N. The Ultrastructure of The Epithelium of The Ciliary Body: A Study of The Junctional Complexes and of The Changes Associated with The Production of Plasmoid Aqueous Humour. Zeitschrift für Zellforschung 1966; 69: 635-658.

21. Raviola G, Raviola E. Intercellular Junctions in The Ciliary Epithelium. Investigative Ophthalmology & Visual Science 1978; 17(10): 958-981

22. Tamm ER, Lütjen-Drecoll E. Ciliary Body. Microscopy Research and Technique 1996; 33(5): 390-439.

23. Ebersberger A, Flügel C, Lütjen-Drecoll E. Ultrastrukturelle und enzymhistochemische Untersuchungen über regionale Strukturunterschiede innerhalb des Ziliarmuskels bei verschiedenen Spezies. Klinische Monatsblätter für Augenheilkunde 1993; 203(7): 53-58.

24. Lütjen-Drecoll E. Functional Morphology of The Trabecular Meshwork in Primate Eyes. Progress in Retinal and Eye Research 1998; 18(1): 91-119.

25. Morrison JC, Van Buskirk EM. Anterior Collateral Circulation in the Primate Eye. Ophthalmology 1983; 90(6): 707-715.

26. Morrison JC, Van Buskirk EM. Ciliary Process Microvasculature of the Primate Eye. American Journal of Ophthalmology 1984; 97(3): 372-383.

27. Morrison JC, DeFrank MP, Van Buskirk EM. Comparative Microvascular Anatomy of Mammalian Ciliary Processes. Investigative Ophthalmology & Visual Science 1987; 28(8): 1325-1340

28. Stamper R, Lieberman M, Drake M. Becker-Shaffer's Diagnosis and Therapy of The Glaucomas. 8th ed. Edinburgh: Mosby Elsevier; 2009.

29. Levin LA, Nilsson SFE, Ver Hoeve J et al. Adler's Physiology of The Eye. 11th ed. Edinburgh: Saunders Elsevier; 2011.

30. Macknight ADC, McLaughlin CW, Peart D et al. Formation of The Aqueous Humor. Clinical and Experimental Pharmacology and Physiology 2000; 27(1-2): 100-106.

31. Goel M, Picciani RG, Lee RK et al. Aqueous Humor Dynamics: A Review. The Open Ophthalmology Journal 2010; 4: 52-59.

32. Yamaguchi Y, Watanabe T, Hirakata A et al. Localization and Ontogeny of Aquaporin-1 and -4 Expression in Iris and Ciliary Epithelial Cells in Rats. Cell and Tissue Research 2006; 325(1): 101-109.

33. Kiel JW, Hollingsworth M, Rao R et al. Ciliary Blood Flow and Aqueous Humor Production. Progress in Retinal and Eye Research 2011; 30(1): 1-17.

34. Toris CB, Yablonski ME, Wang YL et al. Aqueous Humor Dynamics in The Aging Human Eye. American Journal of Ophthalmology 1999; 127(4): 407-412.

35. Nau CB, Malihi M, McLaren JW et al. Circadian Variation of Aqueous Humor Dynamics in Older Healthy Adults. Investigative Ophthalmology & Visual Science 2013; 54(12): 7623-7629.

36. Acott TS, Kelley MJ. Extracellular Matrix in The Trabecular Meshwork. Experimental Eye Research 2008; 86(4): 543-561.

37. Freddo TF, Mortimer C, Gong H. Aqueous Humor and The Dynamics of its Flow: Mechanisms and Routes of Aqueous Humor Drainage. In: Albert DM, Miller JW, Azar DT. Albert & Jakobiec's Principles & Practice of Ophthalmology, Volume II. 3rd ed. Philadelphia: Saunders Elsevier; 2008.

38. Ethier CR, Coloma FM, Sit AJ et al. Two Pore Types in The Inner-Wall Endothelium of Schlemm's Canal. Investigative Ophthalmology and Visual Science 1998; 39(11): 2041-2048.

39. Epstein DL, Rohen JW. Morphology of The Trabecular Meshwork and Inner-Wall Endothelium after Cationized Ferritin Perfusion in The Monkey Eye. Investigative Ophthalmology and Visual Science 1991; 32(1): 160-171.

40. Johnson M, Shapiro A, Ethier CR et al. Modulation of Outflow Resistance by The Pores of The Inner-Wall Endothelium. Investigative Ophthalmology and Visual Science 1992; 33(5): 1670-1675.

41. Johnson M, McLaren JW, Overby DR. Unconventional Aqueous Humor Outflow: A Review. Experimental Eye Research 2017; 158: 94-111.

42. Krieglstein GK, Langham ME et al. Influence of Body Position in The Intraocular Pressure of Normal and Glaucomatous Eyes. Ophthalmologica 1975; 171: 132-145.

43. Goldmann H, Schmidt TH. Über Applanationstonometrie. Ophthalmologica 1957; 134(4): 221-242.

44. Grolman B. A New Tonometer System. Optometry and Vision 1972; 49(8): 646-660.

45. Friedenwald JS. Contribution to The Theory and Practice of Tonometry. American Journal of Ophthalmology 1937; 20(10): 985-1024.

46. Kontiola AI. A New Induction-Based Impact Method for Measuring Intraocular Pressure. Acta Ophthalmologica Scandinavica 2000; 78(2): 142-145.

47. Iliev ME, Goldblum D, Amstutz C et al. Comparison of Rebound Tonometry with Goldmann Applanation Tonometry and Correlation with Central Corneal Thickness. British Journal of Ophthalmology 2006; 90(7): 833-835.

48. Nakamura M, Darhad U, Tatsumi Y et al. Agreement of Rebound Tonometer in Measuring Intraocular Pressure with Three Types of Applanation Tonometers. American Journal of Ophthalmology 2006; 142(2): 332-334.

49. García-Resúa C, González-Meijome JM, Gilino J et al. Accuracy of The New iCare Rebound Tonometer Vs. Other Portable Tonometers in Healthy Eyes. Optometry and Vision Science 2006; 83(2): 102-107.

50. Rao A, Kumar M, Prakash B et al. Relationship of Central Corneal Thickness and Intraocular Pressure by iCare Rebound Tonometer. Journal of Glaucoma 2014; 23(6): 380-384.

51. Chui WS, Lam A, Chen D et al. The Influence of Corneal Properties on Rebound Tonometry. Ophthalmology 2008; 115(1): 80-84.

52. Grant WM. Tonographic Method for Measuring The Facility and Rate of Aqueous Flow in Human Eyes. Archives of Ophthalmology 1950; 44(2): 204-214.

53. Grant WM. Clinical Measurements of Aqueous Outflow. Archives of Ophthalmology 1951; 46(2): 113-131.

54. Leydhecker W. Klinische Bedeutung der Tonographie und des Tonographietests. Documenta Ophthalmologica 1968; 25(1): 100-112.

55. Ulrich WD, Ulrich Ch, Neuhöffer E et al. Okulo-Pressions-Tonometrie (OPT) - Ein Neues Tonographisches Verfahren zur Glaukomdiagnostik. Klinische Monatsblätter für Augenheilkunde 1987; 190(2): 109-113.

56. Stodtmeister R, Pillunat LE, Brenner F. Beurteilung der Kammerwasserdynamik mit der Okulopressionstonometrie nach Ulrich. Ophthalmologica 1988; 196(2): 57-66.

57. Reardon G, Kotak S, Schwartz GF. Objective Assessment of Compliance and Persistence Among Patients Treated for Glaucoma and Ocular Hypertension: A Systematic Review. Patient Preference and Adherence 2011; 5: 441-463.

58. Rajurkar K, Dubey S, Gupta PP et al. Compliance to Topical Anti-Glaucoma Medications Among Patients at A Tertiary Hospital in North India. Journal of Current Ophthalmology 2017; 30(2): 125-129.

59. Stryker JE, Beck AD, Primo SA et al. An Exploratory Study of Factors Influencing Glaucoma Treatment Adherence. Journal of Glaucoma 2010; 19(1): 66-72.

60. Frech S, Kreft D, Guthoff RF et al. Pharmacoepidemiological Assessment of Adherence and Influencing Co-Factors among Primary Open-Angle Glaucoma Patients-An Observational Cohort Study. PLoS One 2018; 13(1).

61. Brubaker RF, Liesegang TJ. Effect of Trabecular Photocoagulation on The Aqueous Humor Dynamics of The Human Eye. American Journal of Ophthalmology 1983; 96(2): 139-147.

62. Beltran-Agullo L, Alaghband P, Obi A et al. The Effect of Selective Laser Trabeculoplasty on Aqueous Humor Dynamics in Patients With Ocular Hypertension and Primary Open-Angle Glaucoma. Journal of Glaucoma 2013; 22(9): 746-749.

63. Stein JD, Challa P. Mechanisms of Action and Efficacy of Argon Laser Trabeculoplasty and Selective Laser Trabeculoplasty. Current Opinion in Ophthalmology 2007; 18(2): 140-145.

64. Mendrinos E, Shaarawy T. Nonpenetrating Glaucoma Surgery: Indications, Techniques, Complications and Results. In: Albert DM, Miller JW, Azar DT. Albert & Jakobiec's Principles & Practice of Ophthalmology, Volume II. 3rd ed. Philadelphia: Saunders Elsevier; 2008.

65. Fea AM, Belda JI, Rękas M et al. Prospective Unmasked Randomized Evaluation of The iStent Inject Versus Two Ocular Hypotensive Agents in Patients with Primary Open-Angle Glaucoma. Clinical Ophthalmology 2014; 8: 875-882.

66. Voskanyan L, Garcia-Feijoó J, Belda JI et al. Prospective, Unmasked Evaluation of The iStent Inject System for Open-Agnle Glaucoma: Synergy Trial. Advances in Therapy 2014; 31(2): 189-201.

67. Popovic M, Campos-Möller X, Saheb H et al. Efficacy and Adverse Event Profile of The iStent and iStent Inject Trabecular Mydro-Bypass for Open-Angle Glaucoma: A Meta-Analysis. Journal of Current Glaucoma Practice 2018; 12(2): 67-84.

68. Best UP, Domack H, Schmidt V et al. Mikroinvasive Glaukomchirurgie - Wirksamkeit von Trabekulären Stents bei Kombinierten Eingriffen. Der Ophthalmologe 2018; 116(8):771-779.

69. Heidinger A, Christoph S, Lindner E et al. A Retrospective Study of 199 Xen45 Stent Implantations from 2014 to 2016. Journal of Glaucoma 2019; 28(1): 75-79.

70. Hohberger B, Welge-Lüßen UC, Lämmer R. MIGS: Therapeutic Success of Combined Xen Gel Stent Implantation with Cataract Surgery. Graefe's Archive of Clinical and Experimental Ophthalmology 2018; 256(3): 621-625.

71. Reitsamer H, Sng C, Vera V et al. Two-Year Results of A Multicenter Study of The Ab Interno Gelatin Implant in Medically Uncontrolled Primary Open-Angle Glaucoma. Graefe's Archive for Clinical and Expirimental Ophthalmology 2019; 257(5): 983-996.

72. Allergan. xengelstent. online: hcp.xengelstent.com/ab-interno-approach. 13 May 2019.

73. Krasnov MM. Laseropuncture of Anterior Chamber Angle in Glaucoma. American Journal of Ophthalmology 1973; 75(4): 674-678.

74. Vogel MG, Lauritzen K, Quentin CT. Punktuelle Ablation des Trabekelwerks mit dem Exzimerlaser beim Primären Offenwinkelglaukom. Der Ophthalmologe 1996; 93(5): 565-568.

75. Vogel M, Lauritzen K. Punktuelle Excimerlaserablation des Trabekelwerks Klinische Ergebnisse. Der Ophthalmologe 1997; 94(9): 665-667.

76. Berlin MS, Töteberg-Harms M, Kim E et al. Excimer Laser Trabeculostomy (ELT): An Effective MIGS Procedure for Open-Angle Glaucoma. In: Samples JR, Ahmed IIK. Surgical Innovations in Glaucoma. New York: Springer; 2014.

77. Mikelberg FS, Parfitt CM, Swindale NV et al. Ability of The Heidelberg Retina Tomograph to Detect Early Glaucomatous Visual Field Loss. Journal of Glaucoma 1995; 4(4): 242-247.

78. Weinreb RN, Shakiba S, Zangwill L. Scanning Laser Polarimetry to Measure The Nerve Fiber Layer of Normal and Glaucomatous Eyes. American Journal of Ophthalmology 1995; 119(5): 627-636.

79. Wollstein G, Schuman JS, Price L et al. Optical Coherence Tomography Longitudinal Evaluation of Retinal Nerve Fiber Layer Thickness in Glaucoma. Archives of Ophthalmology 2005; 123(4): 464-470.

80. Arriola-Villalobos P, Martinez-de-la-Casa JM, Diaz-Valle D et al. Glaukos iStent Inject Trabecular Micro-Bypass Implantation Associated with Cataract Surgery in Patients with Coexisting Cataract and Open-Angle Glaucoma or Ocular Hypertension: A Long-Term Study. Journal of Ophthalmology 2016.

81. Clement CI, Howes F, Ioannidis AS et al. One-Year Outcomes Following Implantation of Second-Generation Trabecular Micro-Bypass Stents in Conjunction with Cataract Surgery for Various Types of Glaucoma or Ocular Hypertension: Multicenter, Multi-Surgeon Study. Clinical ophthalmology 2019; 13: 491-499.

82. Klamann MKJ, Gonnermann J, Pahlitzsch M et al. iStent Inject in Phakic Open Angle Glaucoma. Graefe's Archive for Clinical and Expirimental Ophthalmology 2015; 253(6): 941-947.

83. Smith M, Charles R, Abdel-Hay A et al. 1-Year Outcomes of The Xen45 Glaucoma Implant. Eye 2019; 33(5): 761-766.

84. Töteberg-Harms M, Ciechanowski PP, Hirn C et al. 1-Jahres-Ergebnisse nach Kombinierter Kataraktoperation und Excimer-Laser-Trabekulotomie bei Erhöhtem Intraokulardruck. Der Ophthalmologe 2011; 108(8): 733-738.

85. Babighian S, Rapizzi E, Galan A. Efficacy and Safety of Ab Interno Excimer Laser Trabeculotomy in Primary Open-Angle Glaucoma: Two Years of Follow-Up. Ophthalmologica 2006; 220(5): 285-290.

List of Figures

List of Tables

Abbreviations

ACA	Anterior Ciliary Arteries
ALT	Argon Laser Trabeculoplasty
BVCA	Best Corrected Visual Acuity
CB	Ciliary Body
CBB	Ciliary Body Band
CM	Ciliary Muscle
CP	Ciliary Processes
CV	Choroidal Veins
EC	Episcleral Circle
ELT	Excimer Laser Trabeculostomy
EVP	Episcleral Venous Pressure
GJ	Gap Junctions
HRT	Heidelberg Retinal Tomograph
IMC	Intramuscular Circle
IOP	Intraocular Pressure
JCT	Juxtacanalicular Trabecular Meshwork
LPCA	Long Posterior Ciliary Arteries
MIGS	Microinvasive Glaucoma Surgery
MMC	Mitomycin C
NFA	Nerve Fiber Analyzer
OCT	Ocular Coherence Tomography
PACA	Perforating Anterior Ciliary Arteries
PEX	Pseudoexfoliation Syndrome
RCA	Recurrent Ciliary Artery
RNFL	Retinal Nerve Fiber Layer
SC	Schlemm's Canal
SD-OCT	Spectral Domain Optical Coherence Tomography
SLT	Selective Laser Trabeculoplasty
SPSS	Statistical Package for the Social Sciences
SS	Scleral Spur
SD	Standard Deviation

TJ	Tight Junctions
TM	Trabecular Meshwork

Symbols

F_{in}	Rate of aqueous humour inflow
F_{out}	Rate of aqueous humour outflow
C	Facility of outflow
U	Uveoscleral outflow rate
R	Resistance to ouflow
F	Aqueous flow
Ct	Trabecular outflow facility
P0	Baseline intraocular pressure
PR0	Intraocular pressure after the 4-minute long oculopression
PR4	Intraocular pressure after the 4-minute long recovery phase

Declaration of Authorship

I hereby declare that the doctoral thesis that I am submitting was written entirely by me with no help from second parties. I did not use any sources other than those listed in the bibliography section and the passages of the works that were adopted were correctly cited.

I also declare that I have not applied for doctoral title in any other institution and that the present thesis has not been submitted to another examining committee in Germany or abroad in this or any other form.

Dimitrios Karachalios, MUDr.

Rostock, 09. February 2020

Acknowledgments

First and foremost, I would like to thank my supervisor, Prof. Rudolf F. Guthoff for his invaluable advice and constant support during this study. His methodology, scientific work and mentorship has been an inspiration for me through the last years. With his enthusiasm and dedication to scientific excellence he showed me the way and introduced me into clinical research. For this I will be forever gratefull.

Moreover, I would like to thank Dr. Thomas Stahnke, Prof. Günther Kundt and the rest of the research team, Dr. Anita Koschmieder and Dr. Franziska Kopp for their invaluable help throughout this project.

I would also like to express my gratitude to my dearest friend, Rüdiger. Without his continuous guidance and support, none of this would be possible. Thank you for always being there for me.

Finally, I would like thank my family and girlfriend for their endless love and support.

Doctoral Theses

- A new oculopression technique was successfully used in a clinical setting for assessing the efficacy of microinvasive glaucoma surgery.

- Most of the examined subjects showed an initial decrease of IOP after the 4-minute long oculopression with a subsequent rise of IOP during the recovery period. This finding supports our hypothesis, that the new oculopression technique could be used as an indirect measurement of aqueous outflow facility.

- The extent of the initial IOP reduction after oculopression (PR0-P0) varied among the studied groups.

- Healthy subjects showed the largest IOP reduction after oculopression (PR0-P0) and their results were statistically significantly different in comparison to non-operated glaucoma patients.

- The IOP curve of glaucoma patients after XEN Stent or iStent inject implantation approximated that one of healthy subjects, suggesting that these intraocular implants had positively influenced aqueous outflow and “corrected” the IOP curve of glaucoma patients.

- Patients after MIGS surgery benefited from a relatively low complication profile and a significant reduction in the topically applied antiglaucoma medication.

- In future studies, the new oculopression technique can be used to reveal differences between individual MIGS techniques. In order to do that, a larger number of patients must be examined, with preoperative and postoperative measurements of the same individuals.

Lebenslauf

PERSÖNLICHE DATEN

Name	Dimitrios Karachalios
Geburtsdatum	03.08.1990
Geburtsort	Rhodos, Griechenland
Anschrift	Barnstorfer Weg 26 18057 Rostock, DE
Telefon	+49 176 752 777 91
E-Mail	karajim90@gmail.com

STUDIUM

2016 bis jetzt	**Facharztausbildung** Universitätsmedizin Rostock, Augenklinik		
2015-2016	St. Vincentius Kliniken Karlsruhe Abteilung der Ophthalmologie		
2008-2014	**Medizinstudium** Universität Comenius in Bratislava, Slowakei Medizinische Fakultät		
	Staatliche Prüfungen	*Innere Medizin*	*A*
		Pädiatrie	*B*
		Gynäkologie und Geburtshilfe	*A*
		Chirurgie	*D*
		Diplomarbeit	*A*
2013-2014	**Praktisches Jahr**		
Pädiatrie	Universität Krankenhaus für Pädiatrie DFNsP in Bratislava, Slowakei		
Gynäkologie	Universität Krankenhaus Cyril a Metod in Bratislava, Slowakei		
Chirurgie	Universität Krankenhaus AXEPA in Thessaloniki, Griechenland		
Innere Medizin	Universität Krankenhaus IPPOKRATIO in Thessaloniki, Griechenland		
2014	**Diplomarbeit** Autoimmune Liver Diseases		

PRAKTIKA

2015	**Augenheilkunde** Gemeinschaftspraxis Augenärzte in Müllheim im Markgräferland, Deutschland
2015 Mai	**Augenoptik** Albrecht Optik in Freiburg im Breisgau, Deutschland
2013 August	**Pädiatrie** (2 Wochen) Rhodos Allgemeines Krankenhaus
2013 Juni	**Gynäkologie und Geburtshilfe** (2 Wochen) Alexandroupoli Allgemeines Krankenhaus

2012 Juli	**Innere Medizin** (2 Wochen) Thessaloniki Allgemeines Krankenhaus „G. Gennimatas“ **Chirurgie** (2 Wochen) Thessaloniki Allgemeines Krankenhaus „G. Gennimatas“
2011 Juli	**Innere Medizin** (1 Woche) Rhodos Allgemeines Krankenhaus **Chirurgie** (1 Woche) Rhodos Allgemeines Krankenhaus

SCHULBILDUNG

2005-2008	**Schulausbildung** Rhodos College, Griechenland *Abitur (Note 19,4/20)*

SPRACHKENNTNISSE

Deutsch	Kompetente Sprachverwendung Goethe Institut Zertifikat C1
Englisch	Kompetente Sprachverwendung University of Michigan USA, Certificate of Proficiency in English
Slowakisch	Elementare Sprachverwendung
Griechisch	Muttersprache

Unterschrift
MUDr. Dimitrios Karachalios