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# Glaucoma

## Intraocular Pressure and Aqueous Dynamics

*Edited by Parul Ichhpujani*

# GLAUCOMA - INTRAOCULAR PRESSURE AND AQUEOUS DYNAMICS

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# Meet the editor

Dr. Parul Ichhpujani (MS, MBA(HA)) is currently an associate professor at the Department of Ophthalmology, Government Medical College and Hospital, Chandigarh, India. She takes care of the Glaucoma and Neuro-ophthalmology Services at her center. She has done her glaucoma training from Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India, and a subsequent clinical research fellowship, under Dr. George L. Spaeth, at Wills Eye Institute, Philadelphia, USA. She is an avid researcher and an academician having coauthored a book, *Pearls in Glaucoma Therapy*; edited three books, *Expert Techniques in Ophthalmology*, *Manual of Glaucoma*, and *Glaucoma: Basic and Clinical Perspectives*; and contributed several research articles and book chapters in national as well as international books. Dr. Ichhpujani has lectured at regional, national, and international surgical meetings and serves as a reviewer for many ophthalmology journals. She was enlisted in the Power List of *Best 40 Under 40* ophthalmologists in 2014.

# Contents

# Preface

In ancient times, the aqueous humor was considered to be a "stagnant" ocular fluid that nourished the lens. In the eighteenth century, the site of aqueous production and its "circulation" were elucidated, and by the end of the nineteenth century, the dynamic principles of aqueous flow were experimentally and clinically confirmed. In the twentieth century, the discovery of the aqueous veins and advances in molecular biology outlined the aqueous dynamics even better. It was well established that the intraocular pressure is a consequence of aqueous humor inflow balanced against aqueous humor outflow. In this text, we bring together classical as well as recent discoveries on the function of the trabecular meshwork and Schlemm's canal, key to understanding the pathophysiology of glaucoma.

Despite all the advances, we still have no perfect method to measure intraocular pressure; all current methods are influenced by various ocular and non-ocular factors and can only give us an estimate of the intraocular pressure. Conventional and recent tonometry techniques are discussed in detail in a section.

Treating glaucoma is not a perfect science even till date. One of the chief problems in the current glaucoma therapy is the lack of specificity of antiglaucoma agents. Considering the aqueous humor dynamics, some pharmacological receptors such as $\alpha$-adrenergic receptors involved in aqueous humor formation are also related to aqueous humor drainage. This fact, together with the heterogeneity of the ocular tissue, creates a challenging scenario for the development of new drugs that specifically target the function of the site of outflow resistance, trabecular meshwork. Pharmacological innovations are discussed in detail in the section on management of intraocular pressure dynamics.

In recent years, surgical devices and techniques have been developed that seek to avoid the complications of traditional filtration surgery by accessing the eye's natural aqueous drainage pathways and enhancing them. The chapters on lasers and newer surgical techniques will help the readers to decide whether it's a good idea to add a new surgery to their glaucoma armamentarium.

This book provides a systematic and comprehensive compendium of topics relevant to the study of intraocular pressure and aqueous humor dynamics. Within the framework of the book, the authors had a great deal of freedom in composing their chapters. All chapters have been well reviewed.

I hope you enjoy reading this text.

Best wishes,

**Parul Ichhpujani, MS**
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Section 1

# Structural Alterations and IOP Dynamics

Chapter 1

# Schlemm's Canal: The Outflow "Vessel"

Joanna Jabłońska, Katarzyna Lewczuk and
Marek Rękas

Additional information is available at the end of the chapter

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**Abstract**

The aim of this chapter is to review the knowledge about the aqueous outflow through Schlemm's canal. Morphology of this canal and aqueous humor pathways from the anterior chamber through the trabeculum into suprascleral and conjunctival veins via connector channels are described. Additionally, the role of Schlemm's canal in the development of glaucoma and outflow resistance is discussed. Canalography as a more precise method of assessing the conventional drainage pathway and facilitating localization of an uncollapsed collector and aqueous veins is shown. Attention is also drawn to the relationship between aqueous and suprascleral veins and heartbeat.

**Keywords:** Schlemm's canal, aqueous humor, conventional drainage pathway, outflow resistance, canalography, glaucoma

## 1. Introduction

Aqueous humor (AH) is drained from the eye via two physiological pathways. The conventional path begins at the level of the irido-corneal trabecular meshwork (TM) and is responsible for approximately 83–96% of drainage. From the anterior chamber, the aqueous humor moves through the trabecular meshwork to Schlemm's canal (SC) and then to intrascleral collector channels (CCs), which lead to the intrascleral venous plexus, aqueous vessels, and venous vessels of the suprascleral space. Aqueous vessels begin as collector channels in the exterior wall of Schlemm's canal and can be seen on the surface of the eye in the corneal limbus.

Aqueous humor flows out of the anterior chamber as a mass stream regulated by a pressure gradient. In healthy human eyes, outflow facility has a value of 0.40 at 10 mmHg and is reduced with age. From a physiological perspective, the trabeculum, particularly the interior wall of

Schlemm's canal, and the trabecular meshwork near collector channels are the main sources of resistance to aqueous outflow, and the remaining part of resistance is located in the exterior wall and surrounding tissues. Elevated IOP in glaucoma is caused by an increase in aqueous outflow resistance on its drainage pathways, not by an increase in aqueous production. Many authors believe that the source of outflow resistance in correct eyes is found close to or in the area of the interior wall of Schlemm's canal. Outflow resistance is not constant but a function of IOP and rises as IOP rises.

The aqueous humor flows out of Schlemm's canal through one of 30 collector channels and aqueous veins (AVs) and then to the system of suprascleral veins, ophthalmic veins, and general circulation. According to Poiseuille's law, the resistance of aqueous veins should be insignificant if they are not collapsed or compressed. Provocative gonioscopy, during which blood reflux into Schlemm's canal is observed, is the simplest method of assessing the conventional drainage pathway and facilitating localization of an uncollapsed collector and aqueous vein. Assessment of the distribution of aqueous veins in canalography is a more precise method. Studies by Grieschaber et al. showed a relationship between postoperative intraocular pressure (IOP) level and the presence of reflux in Schlemm's canal before surgery and between the degree to which water veins were filled. Zou introduced the trabeculum bypass theory, which reduces resistance in this part of the drainage route. He observed increased flow through Schlemm's canal only in the quadrant where the implant was applied, and intraocular pressure reduction was dependent on initial pressure.

Aqueous and suprascleral veins oscillate according to heartbeat. These oscillations enable continuous lamellar flow. Pressure in aqueous veins is sufficiently high and enables reverse lamellar flow from suprascleral veins at cardiac diastole. At cardiac systole, pressure in aqueous veins increases and reverses the direction of aqueous flow with simultaneous blood reflux.

## 2. Schlemm's canal

Schlemm's canal (SC) was named in honor of the German anatomist, Friedrich Schlemm, who, in 1830, discovered the canal in the anterior chamber angle, draining aqueous humor (AH) into the bloodstream [1, 2]. It is a ring-like canal with a length of 36–40 mm encircling the cornea [3, 4] and directly adjacent to the juxtacanalicular trabecular meshwork (JCT) [5], and together with the trabecular meshwork (TM), it forms the conventional outflow pathway, which accounts for 50–90% of AH flow [6, 7]. Its cross-section has the shape of an elongated ellipse, with its longer axis measuring 150–350 μm. Three-dimensional visualizations have made it possible to take precise measurements of the canal, the cross-sectional area of which ranges from 4064 to 7164 $\mu m^2$ [8–12]. Rarely, the canal may be bi- or tripartite [13], and it may sometimes contain septa [14]. One of the primary functions of SC is to drain aqueous humor from the trabeculum to collector channels (CCs).

Due to its direct adjacency to the trabeculum, not all SC cells are identical [5, 15]. Owing to the canal's microanatomy, we can distinguish between the inner and outer wall, each built of a

continuous, single-cell layer of endothelium. The cells of both walls differ in terms of morphology [16], the presence of different marker expressions, cell organelles, and function [17]. The inner wall is more frequently analyzed because it presents the greatest resistance to drainage of AH [18–20]. Endothelial cells of the inner wall are shaped like paver stones, while the cells of the outer wall are smooth and flat [15]. Tight junctions of VE-cadherin as well as characteristic giant vacuoles and pores are the markers for cells of the inner wall. Desmin, reactivity to Factor VIII-related antigen, and the presence of Weibel-Palade bodies are the markers for cells of the outer wall [6, 21–26].

### 2.1. Embryogenesis

Schlemm's canal is a highly specialized vessel. Despite many similarities to vascular endothelium, the canal's embryonic origin and progression of its development have still not been precisely determined [5]. Earlier research suggested a vascular origin of cells [24, 27–29], but recent publications have classified them as unique endothelial cells with phenotypical traits of the endothelial cells of both blood and lymphatic vessels [30–33]. In humans, the prenatal development of SC begins with development of the trabeculum in the 17th week [15]; in the 24th week, the canal is already defined and encircles the limbus over 360°; and in the 36th week, the canal and collector channels are fully developed [34].

The organogenesis of SC was described by Kizhatil as a combination of the vascular developmental factors of angiogenesis and lymphangiogenesis. He termed this process "*canalogenesis,*" which begins from the limbal vascular plexus [30]. The development of SC can be divided into four stages, starting from differentiation of the canal's precursor cells, proliferation and migration of frontal cells, formation of the canal's lumen, and separation from the venous vascular system [5]. PROX1 and VEGFR-3 expression is required for division of frontal cells and shaping them into the canal.

### 2.2. Genetics

PROX1 (*prospero homeobox protein 1*) is the main regulator of lymphangiogenesis, and its expression is critical in transforming cells of the vascular endothelium into cells of the lymphatic endothelium [5, 30, 32]. Truong was the first to demonstrate a high level of expression of the PROX1 lymphatic transcription factor in the canal's endothelial cells, thus showing the similarity to lymphatic endothelial cells [7]. VEGFR-3 (*vascular endothelial growth factor receptor 3*), or FLT4, is a receptor belonging to the RTKs-KDR (*kinase insert domain-containing receptor*) family; it binds the VEGF-C and VEGF-D vascular endothelial growth factors, and its expression is typical of endothelium in lymphatic vessels [35]. Aspelund et al. [31] and Park et al. [32] presented the properties of the precursor cells of Schlemm's canal as well as key molecular mechanisms required for differentiation of these cells into the mature cells of the canal [31, 32]. Aspelund demonstrated that the VEGF-C vascular endothelial growth factor is necessary for activating migration of vascular endothelial cells and their further formation from transscleral venous vessels. He also demonstrated that precursor cells are, in essence, vascular endothelial cells with VEGFR-2 and TIE-2 (*tunica interna endothelial cell kinase*) expression. Precursor cells then gain PROX1 expression in order to create and form

the canal's lumen and also VEGFR-3 for later maturing of the canal's cells [31, 32]. Both aqueous humor and VEGF-C are required for proper SC development. A reduction in AH in mice resulted in the loss of elements of canal cells' lymphatic identity [32]. The direct relationship of the SC endothelium with JCT and the fact that the development of TM precedes the development of SC allow for the hypothesis that soluble factors from JCT cells may be of critical significance for obtaining phenotypical traits of SC cells. Because the inner wall of SC is in direct contact with the TM over a 360° circumference, modern canal surgery provides access to the entire inner wall of SC and the juxtacanalicular region without affecting the cornea, iris, and ciliary body. Canaloplasty may be used to deliver transgenic SC/TM vectors in glaucoma gene therapy [36].

### 2.3. Role of NO

Several studies have also documented the influence of cytokines (tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)1-$\alpha$, IL-$\beta$, IL-8) released by TM cells on SC cells, as well as their influence on regulation of aqueous drainage [37, 38]. Nitrogen oxide (NO) was widely studied from the perspective of its role in modulating the behavior of SC cells and regulating aqueous flow [39, 40]. Stresses in the SC endothelium trigger no production in SC cells, similarly as in other vascular endothelial cells [39]. Nitrogen oxide also mediates volume reduction in SC cells, which is linked to facilitation of AH drainage [40].

### 2.4. Biomechanics

The hydraulic conductivity of the conventional aqueous drainage pathway amounts to approximately $10^{-7}$ $cm^2$ $s^{-1}g^{-1}$, and this value also sets the lower limit for hydraulic conductivity of the SC endothelium, which is 2–5 times greater than the hydraulic conductivity of brain endothelium and the greatest in the entire human body [41]. In SC, the biomechanical conditions acting on endothelial cells resemble the microenvironment in a lymphatic vessel [30]. In SC endothelial cells, the pressure gradient is distributed from the base to the apex of a cell similarly as in lymphatic vessels, but inversely to the distribution in the case of vascular endothelium [42]. In a typical blood vessel, the basement membrane and surrounding tissue provide additional support for endothelial cells, reducing circumferential, and radial stresses acting on cells. In the case of SC cells, the inverted pressure gradient caused by AH flowing into the canal's lumen generates a force that pushes cells away from the basement membrane [43]. However, in contrast to a lymphatic vessel, SC cells are bound by tight junctions, so they maintain the pressure difference between the eyeball and episcleral veins (EPV). Forces related to the pressure drop from the base to the apex of a cell result in cell deformation and the formation of large, dome-shaped diverticula into the canal's lumen, called giant vacuoles [41, 42, 44–47]. Besides tight junctions between endothelial cells, there are extensive links between endothelial cells and cells in the JCM area. These junctions are present when SC cells form protrusions to join with JCM cells, forming parachute-like structures. These junctions, described by Johnstone, play an important role in anchoring the canal's endothelial cells in response to increases in pressure [15, 48]. The size of SC's lumen changes in response to IOP fluctuations [48]. When IOP increases, the TM widens while the canal narrows, and this is

caused by an increase in the number of vacuoles and of the area of the extracellular matrix (ECM), as well as by the fact that both walls of the canal are closer to one another. At high IOP, the probability that the canal's walls will collapse and resistance on drainage outflow pathways will grow increases significantly [48]. When IOP increases to approximately 40 mmHg, the canal collapses, with the exception of segments containing septa [20, 49], which support the walls of SC and prevent occlusion of CCs [20, 48, 49]. In eyes with glaucoma, the lumen of SC is smaller than in healthy eyes [50].

### 2.5. Microanatomy-giant vacuoles and pores

Giant vacuoles are potential spaces between extracellular matrix (ECM) and the SC's inner wall cells [15]. Giant vacuoles form dynamically and respond to changes in intraocular pressure (IOP) instantaneously [5, 51]. Their quantity and size increase as IOP increases. After enucleation, the IOP drops to zero, and vacuoles disappear within a time of <3 min [52]. The majority of giant vacuoles are found near CCs outlets [52], which suggests that a greater pressure gradient is present at CCs outlets due to the greater aqueous flow [15]. Most probably due to the specific biomechanical microenvironment, endothelial cells are characterized by contractile properties and by an elastic modulus of 1–3 kPa [41], which is slightly greater than in the case of other endothelial cells [42, 47]. SC cells owe their capability of adapting to deformations to the cytoskeleton system fortified with actin microfilaments. Cells of the outer wall have star-shaped F-actin systems that pass through most cells, in contrast to the circumferential F-actin bands observed in endothelial cells of the inner wall [53]. The position of SC cells relative to ECM allows for reception of biomechanical signals from the ECM [37], which affect the expression of cells' genes and adapt them to changes in the rigidity. The rigidity and contractility of SC cells exhibited a strong response to pharmacological stimulation. Medications increasing resistance to drainage increased the rigidity of SC cells, and inversely, medications reducing resistance to drainage reduced the rigidity of these cells [41]. In eyes with glaucoma, endothelial cells are more sensitive and exhibit an amplified response to the increase in the substrate's rigidity that occurs in glaucoma [42]. Stress caused by a rise in IOP can increase cell surfaces by up to 50% and even cause them to thin out [22]. Tight junctions between endothelial cells of the inner wall are very sensitive to increases in IOP and become less complex when IOP is elevated [37]. Endothelial deformation may initiate the formation of pores mediating aqueous transport by loosening intercellular junctions [54–56].

Pores are structures in the inner wall with sizes ranging from 0.6 to 3 μm [25, 43, 57], and they are responsible for 10% of the resistance to aqueous drainage [37]. They may be found in the walls of giant vacuoles, but they may also be unrelated to them [21]. They form the main pathway of aqueous flow through the inner wall of SC. Two pore types have been identified and characterized: type I pores (transcellular) and type B pores (paracellular) [25]. They differ in their locations, filtration ability, and formation mechanisms [43]. B pores are larger, but they are outnumbered 3–4 to 1 by I pores. Type B pores form as a result of local loosening and widening of intercellular junctions [43]. Braakman et al. [26] presented a segmentation of the aqueous drainage stream, and type B pores account for the majority of aqueous flow. Type I pores may form as a result of a combination of deformations of the cellular membrane at the

base and apex of an endothelial cell, which may occur under the influence of the aqueous filtration stream, and caveolae, vesicles, and minipores [43, 58]. Pores in Schlemm's canal are most frequently formed from minipores 60 nm in size, covered by a diaphragm containing PLVAP (plasmalemma vesicle-associated protein) [43, 58]. Molecular pore formation processes are not well known, but PLVAP is most probably involved in them, considering that pore formation is significantly impaired in mice with PLVAP deficiency [58, 59]. Pore density in the interior wall fluctuates between 1000 and 2000/mm$^2$ [55, 60]. When IOP is elevated, the number of pores in the inner wall increases [25, 51, 55]. Giant vacuoles and pores are unique features of the endothelium of SC's inner wall and of the endothelium of the arachnoid villi in the central nervous system [42, 61, 62]. Scanning electron micrograph of the inner wall of Schlemm's canal can visualize the giant vacuoles and pores at the base of a bulging structure (**Figure 1**) [56].

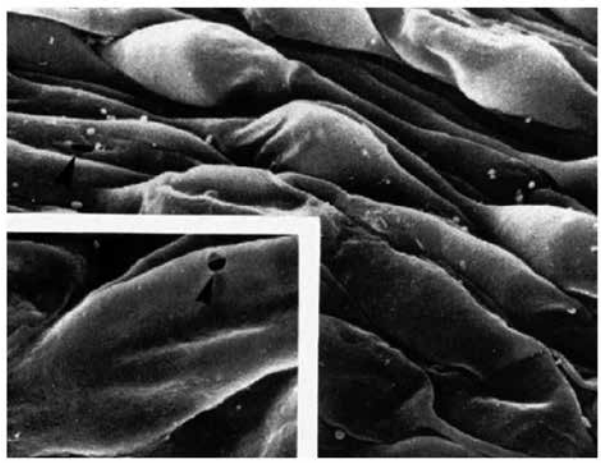

**Figure 1.** Scanning electron micrograph of the giant vacuoles and pores of the inner wall of Schlemm's canal. A pore (arrow) is observed at the base of a bulging structure (modified from Allingham et al. [56]).

The formation of giant vacuoles is directed in one direction, providing a preferential aqueous drainage pathway through the endothelium by means of a one-way valve mechanism. In the case of a pressure increase in episcleral veins and in SC that exceeds IOP, the number of vacuoles and pores decreases, preventing blood reflux from SC into the anterior chamber [42, 63, 64]. Certain medications, such as glycocorticosteroids or sphingosine-1-phosphate (S1P), which induce polymerization of the cytoskeleton's proteins [65, 66], may inhibit the formation and reduce the density of vacuoles, increasing resistance to drainage [67, 68]. Eyes with glaucoma exhibit reduced pore density, which emphasizes the critical role of the inner wall in maintaining homeostasis of AH. The aqueous flow resistance is considerably increased by the hydrodynamic interaction between pores and their basal substrate- subendothelial (basement membrane of SC cells and extracellular matrix of JCT) [69]. In particular, flow is concentrated near every pore, forming funnels that flow through the region of extracellular matrix closest to a given pore, which significantly reduces the effective area available for flow through these

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regions [42]. The goal of glaucoma therapy oriented toward SC may be to increase pore density, and thus drainage, leading to reduction in IOP [55].

### 2.6. Distribution of aqueous humor

AH in Schlemm's canal is not distributed uniformly through the canal's inner wall, but rather appears preferentially at certain locations. Drainage of AH most frequently occurs near CCs [70]. Twice as many giant vacuoles are present near collectors, which suggests that aqueous flow through the inner wall is dependent on the value of pressure [52]. Studies involving the application of fluorescent markers have also demonstrated an elevated level of markers in the pigmented part of TM adhering to CCs, suggesting that the preferred drainage outflow pathways are present near collectors [70]. Histological research on human eyes has proven that, between the 25th and 30th year of life, CCs are randomly distributed around the eye, with preferential dislocation in the inferior nasal quadrant [1, 71]. This has been confirmed by three-dimensional micro-CT tests [72]. There is high diversity in the size of CCs outlets, with values ranging between 5–50 μm and up to 70 μm depending on the type of test [1, 71, 72]. From the CCs, AH flows through a winding system of venous plexuses, from the deep scleral plexus, through the limbal plexus, to the intrascleral plexus, which ultimately leads to the episcleral veins [6].

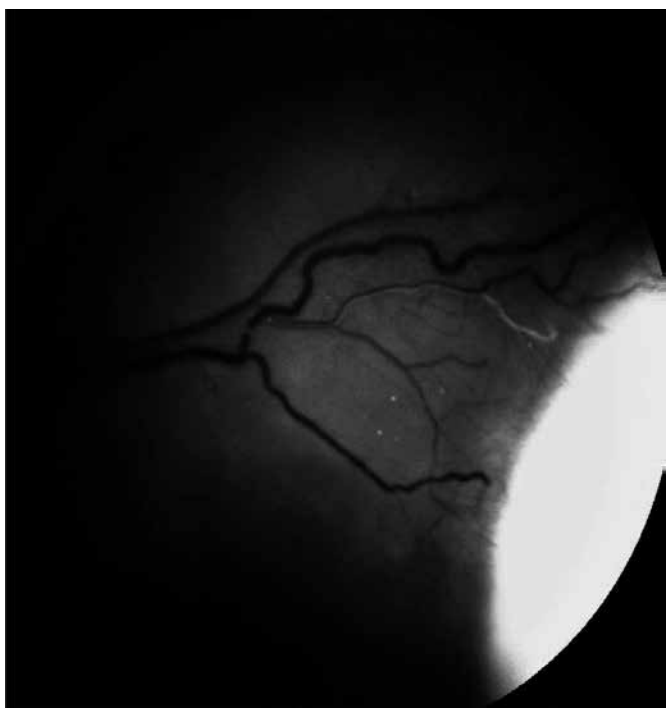

**Figure 2.** Aqueous veins.

### 2.7. Aqueous veins

Aqueous humor moves through the TM into SC, issuing forth from its lumen into CCs, aqueous veins (AVs) (**Figure 2**) and the system of episcleral veins (EPV) (**Figure 3**), ocular veins, and into the general circulation [21, 73]. AVs have lumens that are directly connected to CCs, and because of this, they are directly connected to the episcleral veins draining blood into the general circulation, bypassing the deep scleral and intrascleral venous plexuses [74, 75]. AVs containing initially clean AH are joined to episcleral veins filled with blood, which is why transition zones can be identified on the surface of the conjunctiva as large vessels with a transparent, central lumen bounded by dark blood from all sides. Linear stratification into AH and blood occurs due to the differences in these fluids' viscosity and density [76]. The composition of blood and aqueous in transition zones changes as IOP changes. Direct observation of these changes is a reliable indicator for assessment of the effectiveness of topical and surgical therapy oriented toward IOP reduction in glaucoma [77]. AVs differ in their position, size, and anatomical configuration. In a slit lamp test, 2–3 AVs are usually visible, and sporadically, up to 6 AVs may be seen [78, 79]. AVs are nonuniformly distributed and are present in the greatest number in the inferior nasal quadrants [78, 80]. Their size varies from 20 to 100 μm, 50 μm on average [78, 81, 82]. Histologically, AVs cannot be distinguished from conjunctival and EPV [80].

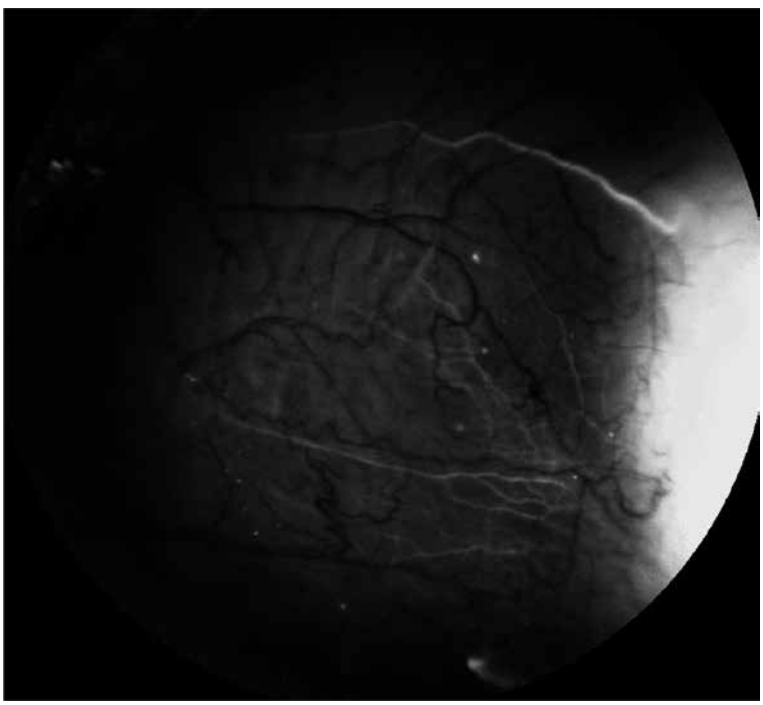

**Figure 3.** Episcleral veins.

### 2.8. Aqueous humor drainage

IOP is the primary factor affecting AH drainage. Drainage through the conventional outflow pathway is directly proportional to the IOP value within the range of physiological values [83, 84]. Drainage facility is the measure of how easily AH leaves the eye, and it is the inverse of resistance to drainage [20, 85]. In healthy human eyes, drainage facility has a value of 0.40 μl/min/mmHg at an IOP of 10 mmHg [86]. The main point of resistance to AH drainage is located at the JCM level in juxtacanalicular connective tissues, in the inner wall of SC, and its basement membrane [21, 69]. Elevated IOP in glaucoma is caused by an increase in aqueous outflow resistance on its drainage outflow pathways, not by an increase in aqueous production [87]. AH flow, defined as the movement of AH from the posterior chamber of the eye through the pupil into the anterior chamber, is lower than aqueous production because it does not include the AH that leaves the posterior chamber via other pathways [85]. The value of AH flow through the anterior chamber is not dependent on sex [88]. AH flow amounts to 2.4 ± 0.6 μl/min and decreases with age by 2% per decade [88], which may result in a reduction of up to 30% [89]. It has also been observed that flow is halved during the night (1.13–1.6 μl/min) as compared to the day (3.0–3.1 μl/min) [89, 90]. In studies with fluorescein, it was observed that flow value is also significantly lower in eyes with pseudoexfoliation syndrome than in physiologically correct eyes [88].

### 2.9. Effective filtration areas

Based on observations of the distribution of pigment and perfusion markers, it was determined that, circumferentially, drainage of AH in healthy eyes is nonuniform and segmented [91–94]. At any given time, only some AH drainage pathways are actively involved in aqueous percolation. These active areas are called effective filtration area (EFA) [50, 80, 95]. EFA is a valuable method for measuring resistance to flow and the effects of IOP changes. Segmented drainage has been described in mice [96], pigs [97], cows [91, 93], monkeys [94], and humans [70, 97, 98]. Higher marker concentration was present in the TM neighboring the outlets of CCs, and in humans, more pigment was also observed at this location, suggesting that EFA locations can be determined by using pigment distribution as a marker [80]. A sudden increase in IOP in cow eyes caused a significant reduction in EFA [91, 93]. When IOP increased suddenly, the marker was present in a greater concentration near CC outlets. When IOP was correct, the drainage patterns were more uniform, and when IOP was elevated, drainage became more segmented [91]. EFA reduction is linked to reduction in drainage facility and is reversed when pressure is reduced from high to normal level [99]. EFA reduction was also observed in an animal model, in eyes with glaucoma and chronic IOP elevation that had undergone laser therapy [100]. In this study, reduction in the marker level was determined in regions of the TM that had undergone laser therapy. It was stated that active drainage shifted from areas that had undergone laser therapy to areas not affected by therapy. In a study, where a marker was applied, significant EFA reduction was observed in eyes with glaucoma in comparison with healthy eyes [101]. In addition, the inversely proportional dependence between EFA and IOP has been documented on an animal model in the eyes of a mouse with ocular hypertension [96].

### 2.10. Pulsating flow

Drainage of AH is a complex process. Besides the traditional approach, according to which the AH moves passively in a combined stream through TM into SC, downward along the pressure gradient determined by the heart [102], a significant effect of the active process driven by means of a mechanical pump is also assumed [77]. Pulsating flow occurs as a result of oscillating compressive force caused by transitional IOP increases occurring during the cardiac cycle, blinking, and eye movements. These transitional IOP spikes cause microscopic deformations of the flexible structural elements of drainage outflow pathways. During contraction, the canal's endothelial cells move to the outside, forcing AH flow to the outlets of CCs and AVs. When the value of IOP drops, flexible elements move back to their original configuration, which leads to a relative reduction in pressure in SC inducing AH flow into the SC's lumen [11, 102, 103]. The theory that pulsating flow drives AH drainage is reflected in the dynamic equilibrium between AH and blood in AVs [104]. During contraction, the pulse wave causes flow of AH through AVs, resulting in visible widening of the aqueous layer in their lumens [78]. Eyes with glaucoma exhibit reduced pulsating flow in comparison with healthy eyes [105, 106]. In healthy eyes, the TM is susceptible to deformation under the influence of naturally occurring, dynamic changes in pressure and volume of AH flow from the anterior chamber to SC. Reduction in pulsating flow in glaucoma may be caused by changes in the TM's elasticity [75].

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Chapter 2

# Trabecular Meshwork and Intraocular Pressure Dynamics: Oxidative Stress-Induced Changes

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Additional information is available at the end of the chapter

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**Abstract**

Glaucoma is known as progressive neurodegenerative disease with irreversible loss of vision. Next to perimetric visual field defects, morphological alterations of the optic nerve and an increased intraocular pressure (IOP) occur. IOP is a fine regulated, complex homeostasis of production of aqueous humor (AH) in the non-pigmented ciliary body and its outflow. About 80% of AH is drained throughout the trabecular meshwork (TM). Any outflow resistance, with consecutive increase in IOP, can be generated by a decreased pore size or any other alterations of TM, making it more rigid. Oxidative stress, a disbalance of oxidants and antioxidants, is one mechanism, causing an altered extracellular matrix (ECM), and seems to play a key role in the pathogenesis of glaucomatous nerve atrophy. Damage of DNA, caused by oxidative stress, was shown in TM cells of glaucoma patients. This chapter gives a review about oxidative stress and its pathological alterations in the main outflow pathway—the trabecular meshwork—in glaucoma patients.

**Keywords:** glaucoma, trabecular meshwork, intraocular pressure, oxidative stress

## 1. Introduction

Glaucoma is known as a progressive neurodegenerative disease with irreversible loss of vision. Next to perimetric visual field defects, morphological alterations of the optic nerve and an increased intraocular pressure (IOP) occur. Additionally, special examinations were investigated in the last years for glaucoma diagnosis and follow-up [1–4].

IOP is a fine regulated, complex homeostasis of production of aqueous humor (AH) in the non-pigmented ciliary body and its outflow. About 80% of AH is drained throughout the trabecular meshwork (TM) [5], a sponge-like network of TM cells with glycoproteins, hyaluronic acid, elastic fibers, collagen and extracellular matrix (ECM). Any outflow resistance can be generated by a decreased pore size or any other alterations of TM, making it more rigid, resulting in an increased IOP. TM cells have the ability of different functions. Up to date it is not known, if cellular or intracellular disturbances are the origin of the altered TM in glaucoma. It is also conceivable that both mechanisms are impaired.

Oxidative stress is one mechanism, causing an altered extracellular matrix (ECM) [6] due to a disbalance of oxidants (free radicals, ROS) and antioxidants. If there is any imbalance between both with preponderance of oxidants, an irreversible cell loss is induced. Oxidative stress seems to have a key role in the pathogenesis of glaucomatous nerve atrophy [7, 8]. Damage of DNA, caused by oxidative stress, correlates significantly with IOP as well as with visual field defects [9, 10], and could be shown in TM cells in glaucoma patients [11]. Additionally, an increased lipid peroxidation, being the result of a ROS-induced cell damage, was noticed [12] as well as an impairment of metalloproteinases-2 (MMP-2) expression, resulting in an accumulation of ECM [13]. This accumulation (i.e., 'plaques') in TM could be seen several years before by electron microscopy studies [14, 15]. Additionally, actin expression can be induced by oxidative stress [16, 17], which is responsible for the rigidity of TM—the more amount of actin, the more rigid the TM [18].

In which way is oxidative stress induced, especially in glaucoma patients? Certainly, endogenous and exogenous factors contribute together. For example, daylight (especially ultraviolet light) can induce ROS in AH [19, 20]. Further on a vascular dysregulation [21] is discussed in glaucoma pathogenesis. An impaired blood flow with decreased nutritive supply can result in hypoxia, the main factor of inducing oxidative stress [22]. This hypothesis is supported by an increased concentration of vascular endothelial growth factor (VEGF) and erythropoietin in samples of AH in glaucoma patients [23, 24].

## 2. Oxidative stress and glaucoma

### 2.1. Oxidative stress: ROS and RNS

Oxidative stress was first described by Sies [25]. It is the result of an imbalance between oxidant (free radicals, reactive oxygen species and ROS) and antioxidant agents. Commonly, it is assumed that an excess of ROS, which follows from an increased production or decreased depletion, is the main reason for oxidative stress. Furthermore, a reduced antioxidant level can cause elevated ROS levels [26]. This imbalance with a preponderance of ROS results in a cytotoxicity with an irreversible cell loss.

The molecular basic for this damage can be found the reactivity of ROS. Free radicals are very aggressive molecules due to their unpaired electron [27]. They are generated under aerobic conditions. Excessive physical activities, infections or toxicity (e.g. cigarette smoke, UV

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radiation), are only some of the ROS causing agents. Even microwave radiation was found to induce oxidative stress [28]. ROS production can be found mainly in mitochondria [29]. Electrons ($e^-$) and protons ($H^+$), which were released by oxidation of fats and carbohydrates, enter the 'electron transfer chain.' In this chain, several consecutive reactions transfer electrons from NAPH to $O_2$ (oxygen) via respiratory enzyme complexes [30]. 'NADH dehydrogenase complex' transfers the electrons from NADH via flavin and iron-sulfur centers to ubiquinone. At this point, the second complex 'cytochrome b-c1' passes the electrons to cytochrome c, containing the 'cytochrome oxidase complex'. This step forwards the electrons to react with $O_2$ [30]. Almost 98% of $O_2$ is reduced to $H_2O$. The remaining 2% were reduced only incompletely, resulting in the production of ROS [31]. Considering this fact, it is of interest that not only the biochemical alterations of free radicals, but also the cellular energy level (redox status) is important, when talking about oxidative stress [32].

Several molecules are subsumed in the ROS group, which are all intermediate products, originated from $O_2$: hydrogen peroxide ($H_2O_2$), singlet oxygen (½ $O_2$), hydroxyl radical (HO) and superoxide ($O_2^-$). Molecular $O_2$ reacts with a single electron, followed by the uptake of several protons. This reaction produces the reactive oxygen species [33]:

$$O_2 + e^- \rightarrow \mathbf{O_2}\cdot^- \tag{1}$$

$$O_2\cdot^- + H^+ \rightarrow HO_2 \tag{2}$$

$$HO_2\cdot + e^- + H^+ \rightarrow \mathbf{H_2O_2} \tag{3}$$

$$H_2O_2 + e^- + H^+ \rightarrow \mathbf{HO}\cdot + H_2O \tag{4}$$

$$HO\cdot + e^- + H^+ \rightarrow H_2O \tag{5}$$

If iron reacts with ROS, the production of further ROS is catalyzed (Fenton reaction, [33]).

$$H_2O_2 + Fe^{2+} \rightarrow OH^- + FeO^{2+} + H^+ \rightarrow \mathbf{HO}\cdot + HO^- + Fe^{3+} \tag{6}$$

The hydroxyl radical is the most powerful radical, which is known up to now. It can cause membrane peroxidation and protein carbonylation [33], dectract or add electrons and hydrogen to the DNA, resulting in further radicals [34–36].

Organisms show diverse cellular escape mechanisms against ROS, which eliminates superoxide under normal conditions [29, 33, 37–39]:

$$2\mathbf{O_2}\cdot^- \rightarrow \text{½ } O_2 \tag{7}$$

$$2\mathbf{O_2}\cdot^- + \text{SOD} \rightarrow H_2O_2 + \ O_2 \tag{8}$$

$$\mathbf{H_2O_2} + \mathbf{O_2}^- \rightarrow O_2 + \text{HO}\cdot + \text{HO}^- \tag{9}$$

$$\mathbf{H_2O_2} + \text{Katalase} \rightarrow H_2O + \text{½ } O_2 \tag{10}$$

$$\mathbf{H_2O_2} + 2\ \text{GSH} + \text{GSH} - \text{Peroxidase} \rightarrow \text{GSSG} + 2\ H_2O \tag{11}$$

SOD superoxide dismutase

GSH glutathione

GSSG glutathione disulfide

At 'normal' ROS levels, these free radicals are interacting with other cellular molecules in cell regulation, transcription and cell proliferation. Additionally, they are very important as protective mechanism against distinct bacteria or fungi [26, 29, 33]. However with increasing amounts, ROS changes its function from defensive to aggressive.

Next to ROS, N-containing radical molecules were known to have oxidative power [40, 41]. Reactive nitrogen species (RNS) are derived from the nitric oxide (NO). Free radicals react rapidly with NO, forming RNS [42, 43]:

$$O_2\cdot^- + \text{NO}\cdot \rightarrow \mathbf{ONOO}^- \tag{12}$$

$ONOO^-$ peroxynitrite

Superoxide can be built by diverse reactions (see above) under different conditions. High concentrations of lipoproteins disturb the NOS pathway, which cause an increased amount of superoxide [25]. Peroxynitrite is not a stable molecule. It reacts very fast with almost all classes of biomolecules, thus being a potential cytotoxic agent [42]. It works similar to hydroxyl radicals, thus inducing DNA damages with breaks, nitrations and oxidations [36]. Unlike $H_2O_2$ peroxynitrite can be degraded without metal ions by inducing radicals [44, 45]:

$$\text{ONOO}^- + \text{H}^+ \rightarrow \text{OH}\cdot + \cdot\text{NO}_2 \tag{13}$$

Peroxynitrite can react with several molecules. Next to molecules with aromatic structures (e.g. alpha-tocopherol [46]), thiols [47] can be modified. These reactions generate further radicals, which can induce themselves peroxidation in lipids [48].

In which way does ROS or RNS accumulate? Is there an alteration at the protein or even gene level, which results in this imbalance? Which external factors induce this 'program?' The final answer to all these questions is open up to now. There are evident hints that several transcription factors are involved in this complex network (e.g. p53, [49]).

### 2.2. Oxidative stress: molecular interactions

ROS and RNS can react with even each biochemical molecule (e.g. lipids, proteins). Cell membranes, containing a high amount of phospholipids and triglycerides, are one of the targets [50, 51]. After peroxidation of the lipids, bond arrangement and nonenzymatic Hock cleavage start. The produced $\alpha$, $\beta$ polyunsaturated lipid aldehydes act as radicals in turn [52]. Thus, a reaction chain is triggered. Additionally, the membrane structure and integrity are disturbed [53]. In particular, nerve structures are even more sensitive for oxidative stress as showing a large amount of lipids and high energy requirement [54].

Additionally, free radicals attack the ion channels within the cellular [55] as well as intracellular membranes [56]. The conductance is significantly altered, resulting in an altered excitability of the membranes. After free radical attacks proteins change their backbone and/or side chain structure in that way, that it reacts itself with other amino acid side chains to build carbonyl chains. Unfolding, misfolding and consecutive loss of activity remains [57].

As third target, ROS/RNS attack DNA by purine or pyridine bases structure changes. Yet, protein cross-linking and breaks in the DNA string were detected [39, 58]. These mutations can concern nuclear as well as mitochondrial DNA (mtDNA). However, in particular, mitochondrial DNA is affected, resulting in an impaired energy production [59, 60].

Why are mutations more dangerous, when affecting mitochondrial than nuclear DNA? Several hypotheses were discussed in this context. It is assumed that because of the local closeness of the enzyme complexes, which are involved in the electron transfer chain, next to the mitochondrial DNA, the produced ROS can attack the mtDNA more severe [61–63]. Additionally, mtDNA can replicate independently of the S-Phase, thus being more sensitive for oxidative agents, when the redox level is more oxidative [64], and free nucleotides are low [65]. Recent reports even suggest that hPrimpol1/CCDC111 (human primase-polymerase 1) is involved in DNA reparation due to its primase and DNA polymerase activity [66].

### 2.3. Oxidative stress: glaucoma

The influence of oxidative stress is discussed in the pathogenesis of several neurodegenerative diseases, like Morbus Parkinson or Morbus Alzheimer, as well as ophthalmic disorders, for example, glaucoma. The pathogenesis of glaucoma, being the second cause for blindness [67], is unknown up to now.

Glaucoma seems to be a multifactorial disorder. The most important risk factor for converting to glaucoma or glaucoma progression can be seen in the IOP [68, 69]. However, not all patients show a stable glaucoma disease after IOP regulation, and thus, several other factors seem to be involved. 'Vascular dysregulation' [21], glutamate exotoxicity [70], an interrupted retrograde transport of neutrophins [71] as well as ocular ischemia [72–74] and oxidative stress [7, 8, 75–77] are established in this discussion.

Glaucoma is characterized by an altered optic disc, visual field defects and an elevated intraocular pressure (IOP). As consequence of the increased IOP, retinal ganglion cells (RGC) and axons will die and cause the typical optic nerve appearance with glaucomatous excavation. Free radicals are known to induce oxidative stress in retinal ganglion cells, resulting in apoptosis of these cells [78]. Trapping ROS/RNS with NF-E2 related factor 2 (Nrf2), the death of RGC, seems to be prevented [79]. Several studies have been performed to investigate the potential influence of oxidative stress in glaucoma patients. It was shown that the L-arginine/nitric oxide system is altered in patients with glaucoma [80]. Increased concentrations of superoxide dismutase, malondialdehyde and glutathione peroxidase could be detected in aqueous humor of patients with primary open-angle glaucoma (POAG) [81, 82]. Additionally, antioxidant activity was shown to be decreased in POAG [82]. If systemic antioxidant reserve is low, more severe perimetric defects occurred [83, 84]. Further on the DNA damage, caused by oxidative stress, correlates significantly with glaucomatous visual field defects and IOP [9, 10].

Up to now, there are evident hints for a critical role of oxidative stress in the pathogenesis of glaucoma, yet there are several questions unanswered. However, oxidative stress induces change within different ocular structures, whereas alterations in tissues, influencing IOP, are of special interest.

## 3. Intraocular pressure

Intraocular pressure is the result of aqueous humor (AH) production and outflow through trabecular meshwork and uveoscleral. This circular flow is regulated until a steady state arises. The production of AH starts at the non-pigmented ciliary body. Plasma of the vascular plexus is filtrated by diffusion, ultrafiltration and active secretion to build the AH. First of all, lipid-soluble molecules diffuse according to a gradient. Second, water and water-soluble molecules are ultrafiltrated because of an osmotic gradient and hydrostatic pressure [85]. Active secretion completes the process of AH production [86]. Electrolytes flow due to an electrochemical gradient [87] into the interstitial space, whereas protein transporters, ion channels, aquaporins and enzymes work together to pass molecules, ions or ascorbic acid through the blood-aqueous barrier [88–91]. Liquid diffusion is a consecutive result of the movement of electric charge [92], which is completed by the work of aquaporins.

The produced AH is similar to plasma, yet proteins are 200× less and ascorbic acid 20× higher than in plasma [93]. Additionally, endothelin-1 [94], several growth factors [95], enzymes

(collagenase) [96] or Immunoglobulin G [97], intrinsic glycoproteins [98] and transferrin [99] can be detected.

After production in the posterior part of the eye, AH flows through the pupil. Convection effectuates the movement of AH in the anterior chamber. AH circulates with an upward trend at the cornea and downstream flow at the iris [100]. The outflow of AH is provided by two pathways: The trabecular meshwork in the anterior chamber angle drains off the AH into the Schlemm's canal. The fluid passes multiple intrascleral collector canals until drainage into episcleral veins, ciliary veins and veins of the extraocular muscles [101, 102]. The second draining pathway is the uveoscleral outflow. Through the uveal meshwork and the anterior parts of the ciliary muscle, AH flows toward suprachoroidal space and sclera, where it is resorbed by several veins [103–105].

To generate the IOP distinct, resistance factors have to be considered: the conventional outflow pathway via trabecular meshwork with resistance of 3–4 mmHg/μl/min and the episcleral vein pressure of 8–10 mmHg [106–108] results in IOP of about 15.5 ± 2.57 mmHg in normals [109–111].

Because the outflow through the trabecular meshwork (TM) is dependent on resistance of the trabecular meshwork, the factors, influencing resistance in TM, are of special interest in IOP.

## 4. Trabecular meshwork

In patients with POAG, the trabecular meshwork is characterized by an increased outflow resistance leading to an elevated IOP. It is assumed that the increased outflow resistance is attributed to various morphological and biochemical alterations of the TM of glaucomatous eyes. So have electron microscopic and immunohistochemical studies of TM cells demonstrated an increased accumulation of extracellular matrix, the so-called plaque material, in the juxtacanalicular region of the TM [112, 113]. An increased accumulation of fibronectin was found in the TM of glaucomatous donor eyes as compared to the TM of control eyes [114]. In addition, TM cells showed an increased cell loss as compared to age-matched control TM cells [115]. Later, Liton et al. have also demonstrated an accelerated senescence of TM in comparison with age-matched control donors [116].

The reasons for these changes are still not clear. One factor, which may play an important role in the pathogenesis of POAG, is oxidative stress [117]. Patients with POAG showed mutations in the mitochondrial genome and a reduced mitochondrial respiratory activity compared to control groups [118]. Also the antioxidative capacity in the aqueous humor of patients with POAG was found to be reduced by more than 50% compared to non-glaucomatous eyes [119]. Furthermore, an increased level of 8-hydroxy-2′-deoxyguanosine, a molecular biomarker for oxidative damage, was detected in TM samples collected from glaucoma patients undergoing standard filtration surgery [10]. The oxidative damage in these cells correlated with the visual field defects of these operated glaucoma patients [10]. Besides that, oxidative stress can also

induce inflammation of the TM cells [8] and alter their mobility [120], which leads to contractile dysfunction and damage of the TM cells. Thus, these studies suggest that oxidative stress may be involved in the pathogenesis of POAG.

The human TM is a highly sensitive tissue to oxidative stress, since it is equipped with few antioxidant defense mechanisms [121, 122]. *In vitro* studies showed that increased levels of hydrogen peroxide stimulated the migration of TM cells, which lead to trabecular thickening and enlargement or collapse [123]. Furthermore, hydrogen peroxide could also cause endothelial cell loss and thus a disruption and collapse of the TM [124]. It is assumed that TM cell loss is caused by oxidative stress-induced apoptosis via inflammation, mitochondrial damage, hypoxia and endothelial dysfunction [125]. We could demonstrate that oxidative stress in form of hydrogen peroxide was able to induce cell death, extracellular matrix production, and accelerated senescence in cultured human TM cells. Based on these studies, it was postulated that oxidative stress may play a role in cell death, release of inflammatory markers, extracellular matrix accumulation, advanced senescence and disarrangement of the cytoskeleton of TM cells. These oxidative stress-induced TM changes may be responsible for a reduced outflow facility and thus an increased IOP.

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# Measuring Intraocular Pressure

Chapter 3

# Conventional Intraocular Pressure Measurement Techniques

Umit Yolcu, Abdullah Ilhan and Ahmet Tas

Additional information is available at the end of the chapter

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**Abstract**

Determining the intraocular pressure (IOP) is a part of routine ophthalmic examination. Elevated IOP is a risk factor for glaucoma, and reducing the IOP is the only way to halt or dampen glaucoma progression. Therefore, precise measurement of IOP is critical in glaucoma management. Tonometry is the procedure of determining IOP using various techniques. Various devices are available in the market for determining IOP. Each one works with different principles. Different methods have been introduced and some of them in development, but there is still no perfect clinical method for exact measurement of IOP. This chapter aims to explore various tonometry devices available in the market while explaining their working principles, features, advantages, and disadvantages. Clinicians must choose proper technique balancing the accuracy, convenience, and cost of the tonometers. Estimation values of tonometers should be used with clinical aspects of patients.

**Keywords:** tonometer, intraocular pressure, Goldmann applanation tonometer, Tono-Pen, Schiotz, rebound tonometer, pneumotonometer, manometry, noncontact tonometer

## 1. Introduction

Fluid pressure inside the eyeis responsible for maintaining the shape of the globe as known as intraocular pressure (IOP). Since Bannister described the relation between blindness and firmness of the eye in the sixteenth century, IOP has been regarded as a vital parameter of the eye. Accurate measurement of IOP with proper technique is crucial in diagnosis and management of glaucoma and related conditions. Increased IOP is known to be associated with progressive optic nerve damage [1]. Currently, lowering IOP is the only way to control glaucoma and prevent optic nerve damage. Secretion of aqueous humor and regulation of outflow are critical in maintaining the normal IOP. Aqueous humor is produced in posterior chamber,

passes through the pupil into the anterior chamber, and leaves the eye via trabecular meshwork and uveo-scleral pathway. The balance between production and outflow determines the level of IOP, which is approximately 16 mmHg [2]. Age, surgery, trauma, medication, and various diseases may affect production or outflow of the aqueous humor and result in changes in IOP [3].

Tonometers are the instruments used for obtaining IOP. Measurements of an ideal tonometer should be accurate, reproducible, and repeatable. It should be portable, easy to use, simply calibrated, and standardized. Despite all the technological advances since sixteenth century, we still do not have a perfect method to measure IOP in clinical practice. Most of the currently available tonometers are used over cornea, which is only available and accessible structure for estimating IOP. All current clinical measurement techniques are affected by ocular and non-ocular factors and provide us with an estimate of the IOP [4].

Perceiving the working principles of tonometers and the factors affecting their measurement results would help examiners to choose the most proper technique.

The "conventional" tonometers covered in this chapter include:

1. Indentation tonometry: Schiotz tonometer
2. Applanation tonometry: Goldmann applanation tonometer
3. Noncontact tonometer
4. Pneumotonometer
5. Mackay-Marg tonometer and Tono-Pen tonometry
6. Transpalpebral tonometry
7. Manometry

## 2. Indentation tonometry: Schiotz tonometer

Schiotz tonometer works with *"indentation"* principle, which implies that higher IOP requires higher weight or force to indent. It measures the depth of corneal indentation by a plunger carrying a known weight. The body of the tonometer consists of a curved footplate that rests on the cornea and a known weighted plunger moving freely within a shaft in the footplate. When measuring the IOP, the subject must be positioned in supine position and topical anesthetic drops should be applied. After placing the footplate on the cornea perpendicularly, the plunger moves in an amount depending on the IOP. Movement of the plunger is indirectly proportional to the IOP. A scale on the plunger gives a reading of the movement amount (**Figure 1**). The reading is converted to IOP in mmHg using a conversion table.

This is a mechanical method hence not very reliable in all cases. Conversion Table assumes an average coefficient of ocular rigidity. Therefore, in case of a change in ocular rigidity, blood volume alteration during the measurement and alterations in corneal properties such as steep

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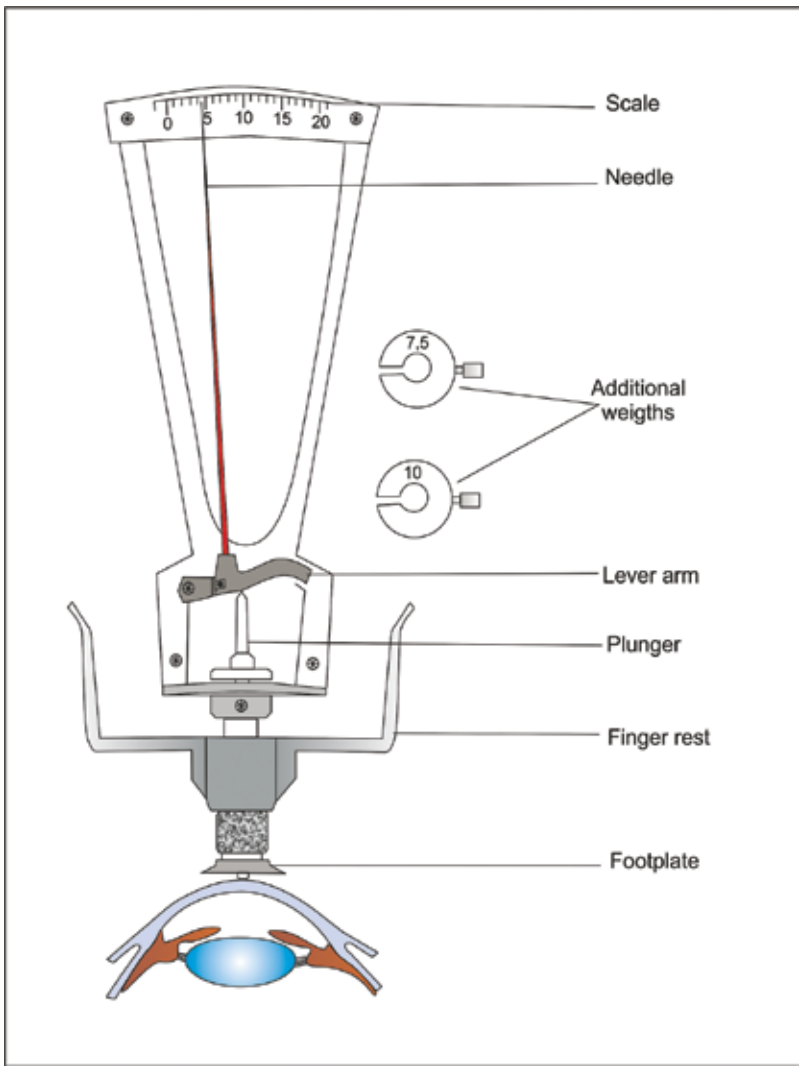


**Figure 1.** A schematic representation of Schiotz tonometer.

and thicker cornea can cause faulty IOP measurement results. Footplate must be sterilized either with alcohol swap or soaking with 1:1000 merthiolate solution. Schiotz tonometer is considered obsolete in many centers in the developed world but still is an important tool on peripheral centers across the developing nations.

## 3. Applanation tonometry: Goldmann applanation tonometer

Goldmann applanation tonometer (GAT) is the most widely used method and regarded as the reference standard. It was introduced in the mid-1950s and works based on the "*Imbert-Fick*

*principle,*" which states that the pressure (P) inside a sphere equals the force (F) necessary to flatten its surface divided by the area (A) of flattening, P = F/A [5]. According to Imbert-Fick principle, eye must be perfectly sphere, dry, perfectly flexible, and indefinitely thin. But cornea is aspheric, wet with tear film, not perfectly flexible or thin. To overcome these limitations, Imbert-Fick law was modified. The tip to flatten the cornea was calculated, and a tip with a fixed area with a diameter of 3.06 mm (7.35 $mm^2$) to minimize the impact of ocular rigidity and surface tension of the tear film was chosen. GAT measures the required force to flatten an area of the cornea of 3.06 mm diameter (**Figure 2**). The force in grams required for applanating this specific area multiplied by 10 equals the IOP in mmHg.

In this method, the instrument is mounted on a slit lamp and the examiner looks at the center of the plastic prism tip, through the slit lamp microscope (**Figure 3**). Then, with the forward movement of the microscope, the tip is contacted slightly to the cornea. Local anesthetic and fluorescein drops are applied before the measurement. Fluorescein dye highlights the tear film when a cobalt blue light is used. Internal prisms of the tip divide the fluorescein meniscus into the superior and inferior arc. When the internal edges of arcs are aligned properly by adjusting the tension knob, a circular area of cornea in 3.06 mm diameter has been flattened at the apex, and examiner can read the IOP from the scale on the adjusting knob directly in mmHg by multiplying 10. After the procedure, it must be disinfected properly. Tip of the tonometer can be disinfected by 70% isopropyl alcohol wipes or soaking 3% hydrogen peroxide solution. The GAT provides an average of IOP between diastolic and systolic pressure.

According to the inventors, optimal IOP measurement can be achieved if the central corneal thickness is approximately 0.5 mm with a well-calibrated GAT [6]. Ehlers et al. reported that GAT most accurately measures intracameral IOP if the central corneal thickness was 520 μm. Variations in corneal thickness and elastic properties have a significant effect on applanation readings of GAT [7, 8]. Thicker corneas can cause overestimation of IOP, and thinner corneas

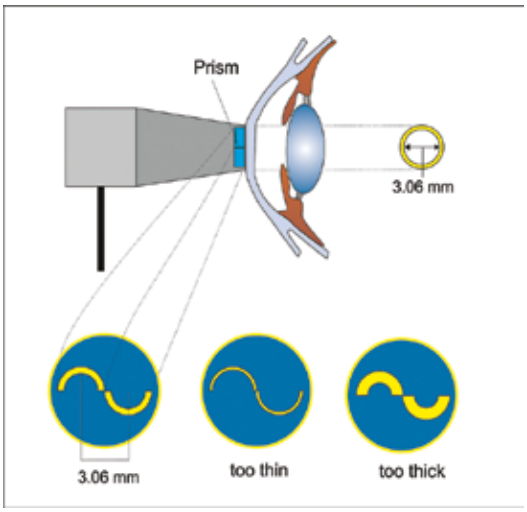


**Figure 2.** A schematic representation of IOP measurement with Goldman applanation tonometer.

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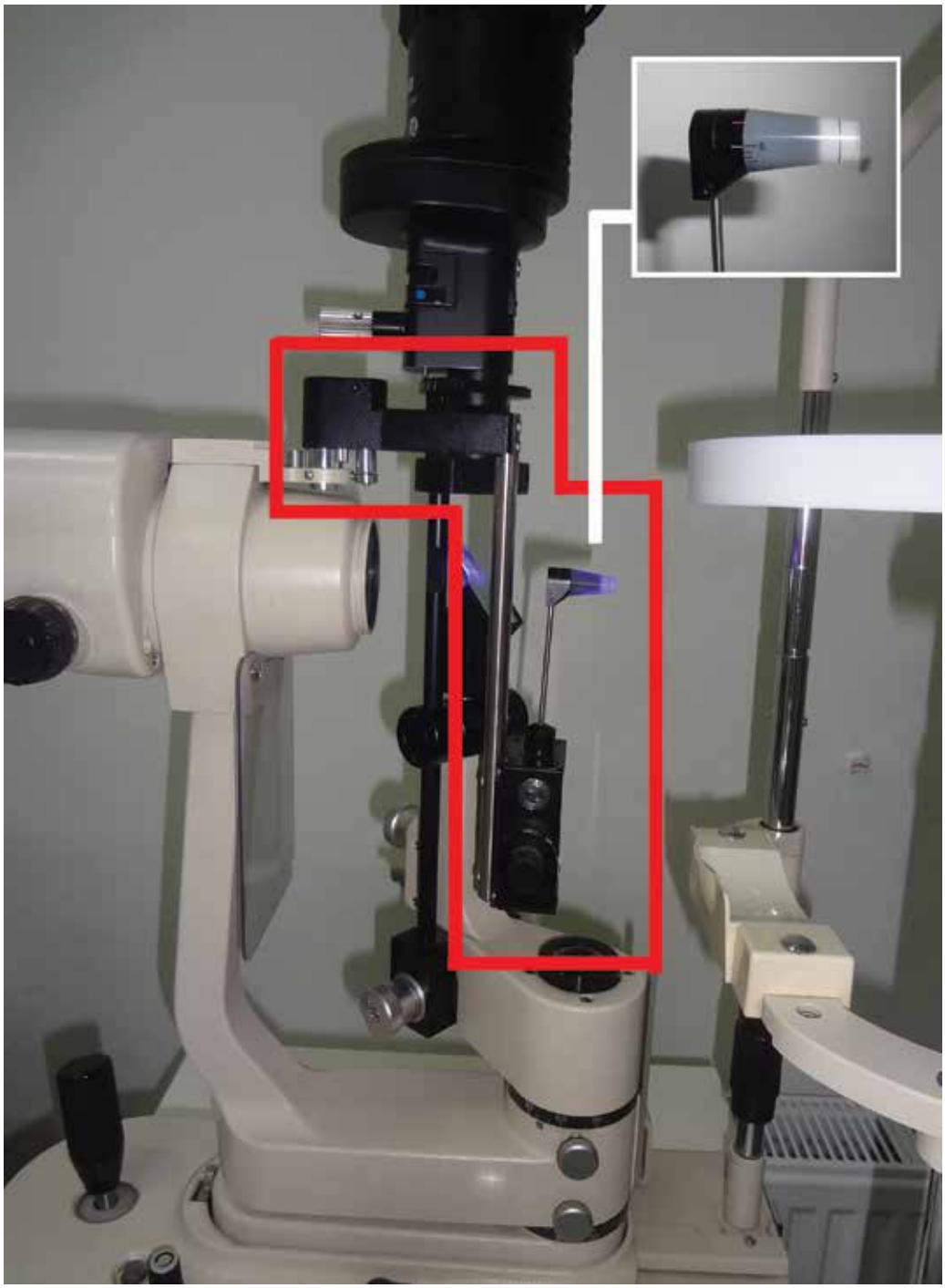

**Figure 3.** Goldman applanation tonometer, red line outlines tonometer mounted on a slit lamp, and white line magnifies tip of the tonometer.

can cause underestimation of IOP with GAT. Central corneal thickness greatly varies among the general population, and it should be corrected according to the thickness of the cornea [9]. Measurement of GAT may be affected by using excessive or insufficient amount of fluorescein, Valsalva's maneuver, corneal curvature, astigmatism, corneal scarring, eyelid squeezing, prior refractive surgery and indirect pressure on the globe [10]. High corneal curvature can be compensated by rotating tip to the axis of astigmatism. GAT must be calibrated by the user on a regular basis to maintain its accuracy. Despite these limitations, it is still popular and widely used due to low cost, simplicity and lack of consumables.

Goldman tonometry is not portable, and the subject must be in upright position. Handheld, portable version of GAT is called as Perkins tonometer. It is battery powered, uses GAT tip, and requires fluorescein dye. It has an internal mechanism and allows using either in supine or in upright position. Disinfection of the tip for both tonometers must be done properly. Wiping with alcohol solution does not kill all pathogens, and tip should be soaked in hydrogen peroxide or bleach solution at least 10 min and then should be washed.

## 4. Noncontact tonometer

Noncontact tonometry (NCT) also known as air puff tonometer works in a similar fashion as applanation tonometry, but it uses compressed air to flatten the corneal apex. It does not require direct contact with the cornea or topical anesthesia and can be used in uncooperative patients and children (**Figure 4**). No disinfection procedure is also required.

During the procedure, the device emits a column of air with gradually increasing intensity to the subject's cornea. Highly sensitive electro-optical sensors scan and detect the exact time of the corneal flattening and shut off the air pulse. Thereafter, the device records the value of force information at the moment of corneal flatting and calculates the IOP in mmHg.

Similar with GAT, NCT is also affected by corneal biomechanical factors such as ocular rigidity and central corneal thickness [11]. NCT measures IOP in a few milliseconds, and therefore, it may be affected by ocular pulse amplitude. A minimum of three measurements should be averaged to estimate the mean IOP. Modern NCT devices are advanced greatly than previous models and are well correlated with GAT measurements [12].

## 5. Pneumotonometer

The pneumotonometer was first invented by Durham et al. and modified by Langham and McCarthy [13]. It basically works like applanation tonometer; however, sensor of the device is air pressure. A slightly convex plunger with a 5-mm tip moves on a cushion of an air stream. The anesthetized cornea is intended by the tip and air pressure. When the tip and cornea are flat, pushing pressure equals the pressure in the eye. After measurement of IOP, the tip keeps indentation for 5–10 s more and provides real-time pressure monitoring of the eye during this period. The device measures the pressure in the system and displays or writes on graph paper for about 5 or 10 s.

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**Figure 4.** External view of a noncontact tonometer.

Unit of the pneumotonometer is portable and does not need to be mounted on a slit lamp. Measurement procedure is easy to learn and requires less skill than GAT. On the other hand, the tip must be sanitized for each patient. Tip can be cleaned in 70% isopropyl alcohol for 5 min and disinfected in 3% hydrogen peroxide solution.

The pneumotonometer gives 1–3 mmHg higher reading in normal IOP range than GAT, but readings tend to be similar in glaucomatous eyes [14]. A manometry study showed that pneumotonometer overestimates IOP at 10, 20, and 30 mmHg set points [15]. However, another study showed that pneumotonometer consistently underestimated IOP in the range of 5–58 mmHg. Like other applanation tonometers, pneumotonometer is susceptible to corneal thickness changes and measurements are positively correlated with increasing thickness [16, 17].

## 6. Mackay-Marg tonometer and Tono-Pen tonometry

Mackay-Marg tonometer was first described in the 1950s by Mackay et al., which is an electronic applanation tonometry working with Imbert-Fick principle. It uses a free plunger and a strain gauge for measuring the force necessary to flatten the cornea. A newer version of the Mackay-Marg tonometer is Tono-Pen, which was introduced in the 1980s as a small handheld device. The device is portable, easy to use, and powered by a battery. Tip of the tonometer has an applanating surface and a microscopically small plunger protruding from the center of the applanating surface. When applanating surface contacted with the cornea, plunger takes the corneal resistance and IOP shows an increasing record. Strain gauge linked to the plunger measures the force change and converts to mmHg electronically (**Figure 5**).

**Figure 5.** A schematic representation describing the working principle of Tono-Pen.

Tono-Pen tonometry uses a very small area of the cornea, and IOP measurement can be achieved from any normal portion of the cornea. Therefore, it is especially handy in the presence of corneal scarring, corneal grafts, band keratopathy, or similar cases. As Tono-Pen is designed to estimate IOP from especially center part of the cornea, it is affected by changes in corneal thickness and tends to overestimate IOP compared to GAT [18]. Moreover, in case of measurement from the peripheral portion of the cornea, the device may estimate IOP higher than normal [19]. Excessive pressure application on the globe during the measurement procedure may cause higher IOP estimation than normal. In optimal conditions, Tono-Pen readings are well correlated with GAT measurements within normal IOP ranges [20]. Single-use disposable covers are available for the tip of the Tono-Pen. Tip should not be disinfected with solvent and cleaning solutions.

## 7. Transpalpebral tonometry

Several centuries ago, IOP was first evaluated by eye palpation through the eyelids. However, this method is subjective and uncertain. This device aims to perform this evaluation method (ballistic) by sensors in an automated fashion. It applies pressure on an area of 1.5 mm in diameter by a rod through the eyelid, and the eyelid acts as a transmissive part. The device can be used in supine or upward position and does not require corneal anesthesia. In supine position, patient is instructed to look up 45° superiorly and the device is placed appropriately on the cartilaginous part of the lid while keeping the tonometer vertically. Rod of the device falls automatically with gravity and after analyzing the momentary change of the rebound; IOP is estimated and displayed in mmHg. Sterilization is not required. The device does not have a guiding feature for proper placement, stabilization, and orientation. It has been reported that results seem to be affected by corneal thickness, especially thinner corneas [21]. Results of Diaton were showed high variability and poor agreement with GAT results. Hereby, the authors recommend this device only for screening purposes (**Figure 6** and **Table 1**) [22, 23].

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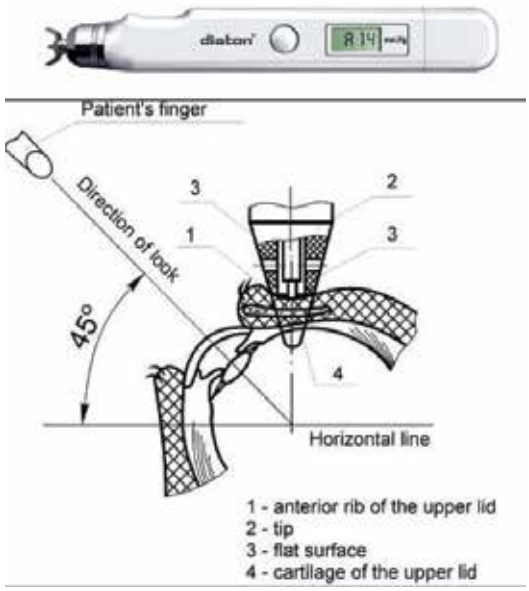


**Figure 6.** Diaton transpalpebral tonometer.

| | **Working principle** | **Brand name** | **Contact/noncontact** |
|---|---|---|---|
| Conventional tonometers | | | |
| Goldmann applanation tonometer | Fixed area applanation | Goldman tonometer/perkins tonometer in various brands | Contact |
| Electronic applanation tonometer | Mackay-Marg applanation | Tono-Pen, Accupen | Contact |
| Noncontact tonometry | Air puff applanation | Various brands | Noncontact |
| Pneumatic tonometer | Fixed area applanation with air pressure | Reichert Model 30 | Contact |
| Newer tonometers | | | |
| Ocular response analyzer | Bidirectional air puff | Reichert ocular response analyzer | Noncontact |
| Scheimpflug noncontact tonometer | Air puff; corneal analysis with Scheimpflug imaging | Oculus Corvis ST | Noncontact |
| Dynamic contour tonometer | Contour-matched piezoresistive sensor | Pascal DCT | Contact |
| Rebound tonometer | Ballistic probe | iCare Rebound tonometer | Contact |
| Transpalpebral tonometer | Ballistic probe through eyelid | Diaton | Contact (eyelid) |

**Table 1.** Currently available tonometers in the market.

## 8. Manometry

Manometry is an invasive technique that precisely measures the real pressure inside the eye. Results of the manometry are the reference pressure for all other tonometers. It is especially used in laboratory conditions for continuous IOP measurement. It evaluates the effects of pharmacologic of physiologic manipulators and useful in exploring the aqueous humor dynamics. It is also used for calibrating and validating the results of various types of tonometers on postmortem human eyes.

The ideal tonometer would be easy to use, portable, reliable, and comfortable for both the patient and physician. It should have low inter- and intraoperator variability and provide an IOP reading that is close to the manometric IOP of the individual. To date, no such tonometer exists. Till date, the gold standard for IOP measurements is Goldmann applanation tonometer.

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Chapter 4

# Newer Intraocular Pressure Measurement Techniques

Maria Letizia Salvetat, Marco Zeppieri and
Paolo Brusini

Additional information is available at the end of the chapter

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**Abstract**

An elevated intraocular pressure (IOP) has been shown to be one of the major risk factors for glaucoma. It is of utmost importance to obtain accurate and precise IOP when dealing with patients with ocular hypertension and glaucoma, especially patients who have undergone ocular surgery. Goldmann applanation tonometer (GAT) was first introduced in the 1950s and is still currently considered as the gold standard to measure IOP. Although the reproducibility of GAT has shown to be quite good, its accuracy provides several limitations. In particular, IOP measurements taken with GAT have been demonstrated to be influenced by many corneal parameters, including central thickness, curvature, astigmatism and biomechanics. Other disadvantages of GAT include the need for local anesthetic drops, for fluorescein and for a slitlamp. Several different methods have been proposed to overcome the disadvantages found in GAT. The newer devices used as alternative tonometric methods include the iCare rebound tonometer, the BioResonator applanation resonance tonometer, the Pascal dynamic contour tonometer, the ocular response analyzer, the Corvis ST pachy-tonometer and Ocuton S. The precision and accuracy of these alternative tonometric methods in comparison with GAT have been reported and discussed.

**Keywords:** tonometry, intraocular pressure, precision, accuracy, central corneal thickness, corneal biomechanical properties

# 1. Introduction

## 1.1. Importance of the intraocular pressure (IOP) measurement

Accurate and reproducible IOP evaluation is crucial with regard to the classification, management and follow-up of patients with ocular hypertension and glaucoma, and in patients that have undergone ocular surgical procedures.

Elevated intraocular pressure (IOP) has been shown to be one of the major risk factors for glaucoma [1]. Although the vulnerability of the optic nerve can vary among patients, longitudinal randomized controlled population-based trials have provided strong evidence that the reduction in the mean IOP of only 1 mmHg is significantly effective in preventing the development [2] and in delaying the progression [3] of the glaucomatous damage. Goldmann applanation tonometer (GAT) has been considered as the clinical gold standard for IOP measurement since it was introduced in the 1950s [4]. Although the reproducibility of GAT has shown to be quite good, its accuracy provides several limitations. In particular, IOP measurements taken with GAT have been shown to be influenced by many corneal parameters, including central thickness, curvature, astigmatism and biomechanics. Other disadvantages of GAT include need for local anesthetic drops, fluorescein and a slitlamp. Several different methods have been proposed to overcome the disadvantages found in GAT. The newer alternative tonometric methods include the iCare rebound tonometer, the BioResonator applanation resonance tonometer, the Pascal dynamic contour tonometer, the ocular response analyzer and the Corvis ST pachy-tonometer.

The purpose of this chapter is to discuss the advantages, disadvantages, precision and accuracy of the "newer" alternative tonometric methods.

Newer tonometers covered in this chapter include the following:

**i.** ***Rebound tonometry***

**ii.** ***BioResonator applanation resonance tonometer (ART)***

**iii.** ***Pascal dynamic contour tonometer (DCT)***

**iv.** ***Ocular response analyzer (ORA)***

**v.** ***Corvis ST pachy-tonometer***

**vi.** ***Ocuton S***

*I. Rebound tonometry*

Rebound tonometry, also known as "impact" or "dynamic tonometry," was first introduced by Obbink about 60 years ago [5]. In 1997, Kontiola introduced an improved and simpler new rebound tonometer, better known as an induction-based impact tonometer [6], that became commercially available as the iCare tonometer in 2003 (**Figure 1**). The method is based on the use of a moving probe that collides with the eye: the motion parameters of the probe, which vary according to eye pressure, are monitored and used in the calculation of IOP [6].

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**Figure 1.** The iCare rebound tonometer.

The iCare (Tiolat Oy, Helsinki, Finland) is routinely used in clinical practice in several clinics nowadays. The device is handy and light-weighed (250 g) [7]. It is composed of a small disposable thin metal probe (about 5 cm in length and 1 mm in diameter) and a solenoid and magnet housed in a metal case. The tonometer is placed in front of the eye, using the forehead to properly position the tip of the probe about 5 mm from the central cornea. The button is pressed in taking IOP measurements, which activates an electric signal that is sent to the solenoid and magnet to move the probe forward. The tip of the probe hits the cornea, rebounds and induces a voltage in the solenoid, which amplifies the signal to a microprocessor. It is advisable to take at least six readings, so that a mean IOP can be calculated by the built-in software [7].

The iCare PRO is a new version, which provides advantages not offered in the previous model, such as measuring IOP also in a supine position, thus useful in bedridden and surgical patients. The iCare one is a simplified version, which has recently been introduced. It can be used independently by patients for at-home autotonometry [8].

The iCare tonometer has shown good reproducibility [9] and correlation with GAT and other tonometers in healthy and glaucomatous eyes [9], and in eyes after keratoplasty [10]. A tendency of the iCare to overestimate the IOP measurements taken with GAT, with a similar trend at different IOP levels, has been reported by several authors [11, 12].

Although iCare was designed not to be influenced by corneal properties, studies have shown that CCT and other corneal structural characteristics affect IOP readings [9, 10, 13]. The iCare tonometer appeared less influenced by corneal edema when compared to GAT [10, 14].

The main advantages of this tonometric method are that the instrument is small, lightweight and portable, easy to use; slitlamp, local anesthesia and fluorescein are not required; IOP is taken in a comfortable sitting position and with the iCare PRO also in the supine position; the rapid measurement enables monitoring in noncompliant subjects. The probes are disposable, and thus, the risk of microbiological contaminations is avoided.

*II. BioResonator applanation resonance tonometer (ART)*

The applanation resonance tonometer (ART) is a new tonometer based on the resonance technique (**Figure 2**) proposed by Eklund et al. in 2003 [15]. The ART estimates IOP by combining simultaneous continuous sampling of both parameters considered in the applanation principle, which include the force needed to applanate the cornea and the corresponding contact area [15]. The current commercial version of ART, known as the BioResonator ART (Medical sensors and Instruments, BioResonator AB, Sweden), has been recently released and is available in a manual and automatic servo-controlled version [16]. The instrument is made up of a sensor and transducer that can measure the contact force in a continuous manner. The resonance sensor is made up of a cylindrical piezoelectric element that has a known resonance frequency. When the sensor is brought in contact with the cornea, the acoustic impedance of the cornea mechanically loads the sensor and modifies the resonance frequency, with a frequency shift, which is proportional to the contact area between sensor and cornea [15]. IOP is calculated from the slope of the relationship between force and frequency evaluated in a specific frequency shift interval corresponding to an interval applanation area between 4.9 and 11.0 $mm^2$ [15]. The sensor module of the ART is attached to a standard slitlamp in a similar position as the GAT probe. The ART probe is disinfected with 70% ethanol before each subject, and local anesthetic drop (0.4% benoxinate hydrochloride) is required before IOP measurements. ART is available in two versions: the manual one (BioResonator ART manual), in which the sensor is manually pushed toward the cornea, and the automatic servo-controlled version (BioResonator ART servo), in which a small motor provides the sensor movement. The device provides the median of repeated IOP values, in addition to a Quality Index (QI >2 should be excluded) that reflects the standard deviation of the data. The ART is self-calibrated.


**Figure 2.** The bioresonator applanation resonance tonometer (ART).

BioResonator ART IOP measurements have been demonstrated to be affected by CCT [15, 17]. The overestimation of the IOP measurements obtained with ART relative to GAT has been demonstrated in previous studies [17].

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*III. Pascal dynamic contour tonometer (DCT)*

The pascal dynamic contour tonometer (DCT) (**Figure 3**), developed by Kaufmann et al. [18], is not based on corneal applanation. It has a concave measuring tip, which is applied on the corneal surface to provide a "contour matching" with the aid of a built-in sensor, which is representative of the pressure inside the eye. The Pascal DCT should be therefore less influenced by corneal properties. Previous studies have shown that there is a good concordance between Pascal DCT and GAT in eyes with normal corneas [19]. In eyes that have undergone laser *in situ* keratomileusis (LASIK), the Pascal DCT appears to provide a more reliable measurement of IOP than GAT, which tends to measure artificially lower IOP values [20].

**Figure 3.** The pascal dynamic contour tonometer (DCT).

The Pascal DCT (SMT Swiss Microtechnology AG, Zurich, Switzerland) [18] is slitlamp mounted and is calibrated automatically. The tonometer has a 10 mm concave radius tip and a built-in 1 mm sensor. The device beeps when the correct position on the corneal surface is obtained. The instrument measures IOP with the use of anesthetic drops in about 5 s and provides digital outcomes in addition to ocular pulse amplitude and quality score (Q that ranges from 1 to 6) data. Acceptable data are defined as $Q < 4$.

The Pascal DCT has shown high reproducibility [21]. As reported by several authors, the Pascal DCT measurements tend to be higher than GAT readings [22].

The Pascal DCT measurement seems to be not significantly affected by CCT [19]. Moreover, studies conducted on cadaver eyes and in patients who had undergone LASIK showed a significantly lower correlation of CCT with measured IOP values with Pascal DCT than with GAT [18].

*IV. Ocular response analyzer (ORA)*

The ocular response analyzer (ORA) (**Figure 4**) was introduced by Luce in 2005 [23]. It is an air-puff tonometer that, in addition to the traditional IOP measurement supplied, further indents the cornea with air pressure and measures the point at which the cornea recovers from

applanation. This device is based on the principle that information on corneal biomechanics can be obtained by measuring the corneal deformation in response to an air impulse. The ORA uses an electro-optical infrared system to monitor the 3-mm central cornea [23]. The puff of air moves the cornea in an inward fashion, which is considered as the first inward applanation creating a mild concave form. As the force generated by the air decreases, the surface of the cornea takes on the normal convex form in this second outward applanation phase.

**Figure 4.** The ocular response analyzer (ORA).

The ORA provides interesting information on the biomechanical characteristics of the cornea. The rapid deformation of the cornea during the air impulse absorbs energy that causes a time delay in the occurrence of the applanation events that are the result of viscous damping in the corneal tissue. The difference between two independent pressure values derived from the two applanation events is defined as "hysteresis" (CH). The instruments provide the corneal compensated IOP (IOPcc) that utilizes information of individual corneal biomechanics, and it is reported to be less affected by corneal properties, such as CCT, in comparison with GAT [23].

Previous authors demonstrated that the ORA significantly overestimated IOP compared with GAT, especially at high IOP levels. Moreover, ORA IOP readings have been demonstrated to be affected by CCT [24].

*V. Corvis ST*

The Corvis ST (Oculus, Wetzlar, Germany) (**Figure 5**) [25] is a current used instrument that utilizes air-puff noncontact technology with built-in ultra-high-speed Scheimpflug technology. This instrument provides IOP measurements in addition to optical pachymetry data and *in vivo* corneal biomechanical parameters. The device measures corneal biomechanics data based on corneal deformation due to an applied force of air.

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**Figure 5.** The Corvis ST pachy-tonometer.

The Corvis ST (Oculus, Wetzlar, Germany) released in 2013 [25] uses a quick burst of air (with a Gaussian distributed intensity and duration of 25 ms) on the center of the cornea that causes the initial inward applanation. The cornea then returns to a normal convex shape as the force of the air decreases to provide outward applanation. The Scheimpflug camera precisely records the corneal movements and records more than 100 images in about a half of a second with a resolution >600 × 400 pixels, for a central corneal surface of about 8.5 mm. The numerous corneal scans without the influence of the air puff are used to provide pachymetry readings. The first applanation phase is used to determine IOP measurements, which is not corrected for CCT and corneal deformation parameters (CDPs). The Corvis ST printout provides IOP and CCT measurements and 10 numerical corneal deformation parameters (CDPs), whose importance remains to be fully elucidated. They have been demonstrated to be highly sensitive to IOP that suggests their variation in relation to normal and pathological short- and long-term IOP fluctuations [26]. On the other hand, they are also known to be affected by IOP-independent variables, including patient age, CCT, corneal hydration, corneal stiffness and boundary conditions related to the sclera and the ocular muscles [26].

The precision of Corvis ST has been demonstrated to be excellent for the IOP and CCT values, but decreased for the CDPs [26]. The Corvis ST showed a tendency to underestimate IOP readings compared to GAT in some studies [25, 26]. IOP readings taken with Corvis ST seem to be significantly affected by CCT [25, 26].

*VI. Ocuton S*

The Ocuton S (EPSa GmbH, Saalfeld, Germany) (**Figure 6**) [27] is a handheld self-tonometer that works according to the principle of applanation tonometry established by Goldmann.


**Figure 6.** The Ocuton S self-tonometer.

After applying topical anesthesia, the patient holds the tonometer and applies the measuring prism directly to his cornea. The device provides a digital display of his IOP. Considering that the Ocuton S is based on the applanation principle, it should thus be influenced by the corneal thickness, although it is still unclear whether this influence is of a similar extent to that in Goldmann applanation tonometry [28].

The newer version Ocuton S*TT-MV automatically verifies the applanated area. Lanfermann and coworkers showed that the Ocuton S*TT-MV improves measuring accuracy significantly and approaches the accuracy achieved using GAT [29].

There is no "perfect" tonometer till date, and the clinicians must choose a tonometer wisely, balancing precision, accuracy, convenience and cost. IOP is a widely varying physiologic parameter; therefore, a series of IOP measurements should be taken, and the IOP data should only be used in the context of the overall clinical picture.

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None.

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Chapter 5

# FM Continuous Monitoring of Intraocular Pressure, an Engineering Perspective

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Additional information is available at the end of the chapter

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**Abstract**

This chapter discusses the problem of continuously monitoring intraocular pressure (IOP) from an engineering perspective. It is aimed to all public in general although we think that medical staff and engineers may benefit the most from it. Although equations are included for engineers to get a glimpse of how the system works, this chapter does not go into great detail in mathematics and physics to make it understandable to medical staff. It provides though references for engineers who wish to get a better understanding of key subjects tackled in this chapter. The chapter is organized as follows: Section 1 introduces intraocular pressure (IOP) and need for its continuous monitoring. Section 2 describes the most recent efforts to develop a continuous IOP monitoring system. Section 3 shows what medical and engineering considerations must be taken into account to effectively measure IOP. Section 4 deals with health issues due to tissue warming and how to prevent them. Section 5 explains how an implant can be fabricated using either passive electronic components or active ones. Finally, Section 6 explains how the pressure sensor and the electronic circuits can be integrated.

**Keywords:** biomedical implants, IOP monitoring, magnetic coupling, wireless coupling, wireless power transmission

## 1. Introduction

Before we can begin to talk about intraocular pressure (IOP) continuous monitoring, let us have a look at some key facts according to the World Health Organization (WHO) [1]:

- There are 285 million people estimated to be visually impaired worldwide, of which 246 million have low vision.
- About 90% of the visually impaired people globally live in low-income environments.
- Eighty per cent of all visual impairment can be prevented or cured.

Among the three major causes globally that cause visual impairment is glaucoma. Glaucoma can be understood as a group of ocular diseases mainly associated with a rise in intraocular pressure. All these groups of diseases have in common the progressive injury to the optic nerve [2]. If glaucoma is left untreated, it can cause total blindness.

The problem with diseases such as glaucoma is that they present no symptoms, so trying to diagnose it without previously measuring the IOP becomes a real challenge. Actual methods for IOP measurement involve the use of medical equipment called tonometers. Tonometers measure IOP over the cornea but in some cases, where the hardness of the cornea is above normal standards, important measurement errors can be produced which do not allow a correct IOP estimation.

There are nowadays other indirect methods that have been under research in the last years such as multifocal electroretinography to know the effects of IOP rising [3]. Nevertheless, with available tonometry and electroretinography techniques, it is not possible to take measurements during normal activities of the patient such as the sleep cycle, stage where IOP can be increased in a significant manner. In order to take an IOP measurement with tonometry or multifocal electroretinography methods, the measurement must be taken by qualified personnel which implies that the patient has to be in the hospital facilities.

The development of sensors with the capacity of measuring IOP inside the eyeball is of paramount importance in order to know with all precision not only intraocular pressure values but also IOP variations in daily activities of the patients.

A new measurement instrument is needed that allows medical staff to study the aetiology of diseases such as glaucoma, that is, to provide with a new tool which will enable to know if there is a cause-effect relationship between daily activities of patients and IOP variations in real time.

Fortunately, we are at a point where technology has evolved in such a way that biomedical implants wirelessly powered are now a reality.

## 2. State of the art

There have been many efforts in different parts of the world over time to build an IOP monitoring system. In this section, we only present a few researches to give the reader a broad idea of what has been done in terms of IOP monitoring systems but references [4–8] are included in case the reader wants to know more about researches not mentioned in this chapter.

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Between the first researches carried out, there is the one done by Tufte et al. when in 1962 in Honeywell, they developed piezoresistive sensors with silicon membranes [9].

In 2000, Mokwa, Schnakenberg and collaborators proposed the design and fabrication of an implantable intraocular system for continuous IOP measurement through OPHTAL project [10]. The system consisted of a pressure sensor connected to the integrated circuits altogether in an artificial contact lens. Three prototypes were fabricated. The last one is shown in **Figure 1**.

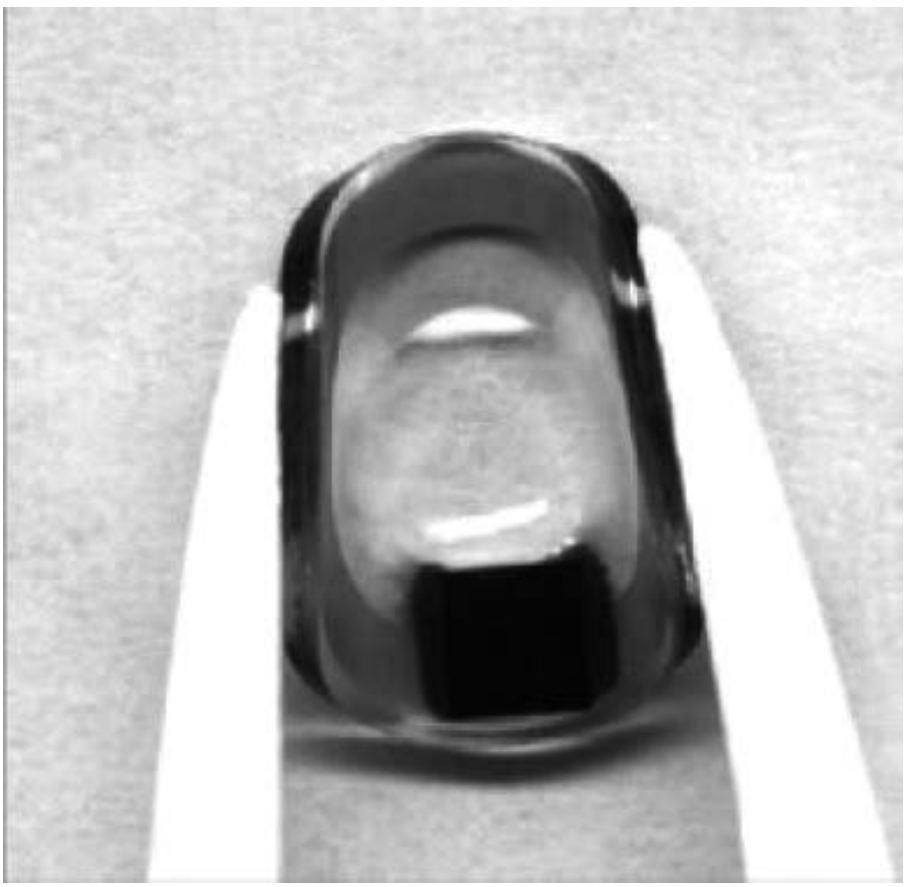

**Figure 1.** Third pressure sensor prototype.

Humayun and collaborators proposed in 2008 a prototype sensor to measure IOP [11]. Two sensor designs were fabricated, one with a variable capacitor and the other one with a variable capacitor and a variable inductor (**Figure 2**).

The pressure sensor response showed a high sensitivity (>7000 ppm/mmHg) in both designs, confirming a resolution of less than 1 mmHg for biomedical applications. The authors also conducted a 6-month study in animals to verify the implant bio-stability *in vivo* and no surgical or post-operation complications were found.

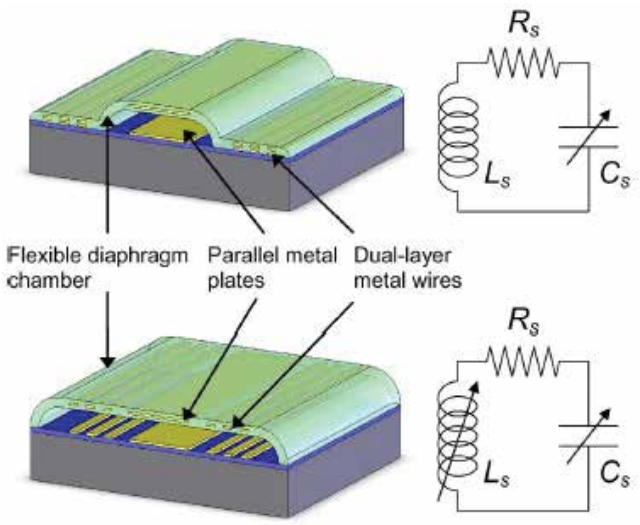


**Figure 2.** Sensor design variations (cross-sectional view).

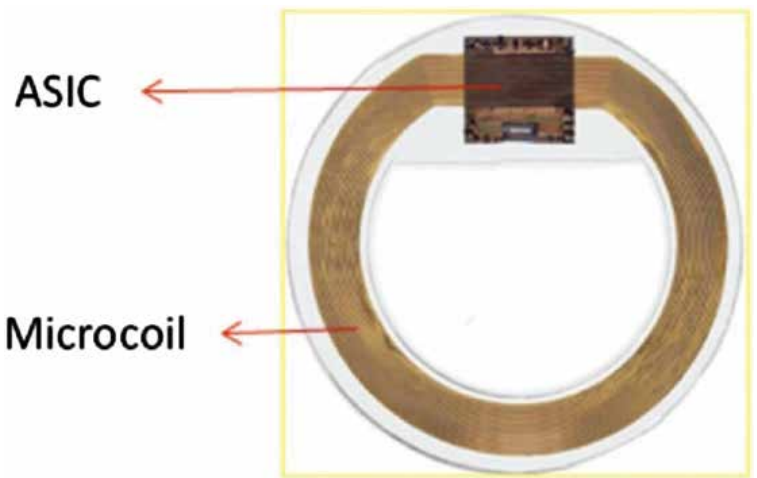


**Figure 3.** Sensor device.

In 2011, Melki and collaborators published a study with the purpose of determining the biocompatibility of an IOP sensor in rabbits and comparing IOP measurements from the sensor with other IOP sensor devices [12]. **Figure 3** shows the photograph of the sensor encapsulated in a silicon rubber.

The intraocular sensor was implanted in six New Zealand white rabbits. The upper part of the sensor contains the Application-Specific Integrated Circuit (ASIC). The external diameter of the coil was of 11.3 mm, the inner diameter was of 7 mm and the thickness was of 0.9 mm.

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The animals were observed and examined in intervals of up to 25 months after surgery. From the obtained results, it was found that the sensor had acceptable tolerance by the eye of the rabbit since no evidence of significant inflammation or scar formation was observed in *in vivo* tests. The measurements made with pneumotonometry, tonometry and with the sensor resulted in standard deviations of 2.70, 3.35 and 0.81 mmHg, respectively.

## 3. Merging medicine and engineering

As seen in the previous section, all efforts to build a continuous IOP monitoring system proposed a wireless power transmission method. This obeys to the fact that having a battery inside the eye to power the biomedical implant can be both bulky and most importantly health threatening to the patient due to the hazardous chemicals it contains.

If we are to develop a continuous IOP monitoring system, we need to approach the problem with a multidisciplinary focus.

### 3.1. Medical considerations

The human eyeball measures approximately 2.5 cm in diameter so there is a restriction in terms of the maximum area that the implant can have to be successfully implanted in the patient. Among medical factors that come into play for implanting a continuous IOP monitoring system are the following:

- The location of the implant must not interfere with the vision and movement of the eye.
- Surgery should be as less invasive as possible.
- Implant design must be such that it allows the physician to implant the monitoring system in the shortest time possible.

#### *3.1.1. Electromagnetic radiation*

At frequencies between 10 MHz and 30 GHz, organic tissue warming is the major effect in electromagnetic energy absorption and temperature increases of more than 1 or 2°C can have adverse health effects [13].

A great number of physiological effects have been observed in cellular studies and with animals when electromagnetic energy is absorbed in levels that cause an increment in body temperature of more than 1 or 2°C [14]. These effects include alterations in neural and neuromuscular functions, increased permeability of the blood-brain barrier, ocular damage, changes in the immune system associated with stress, haematological changes, reproductive changes and changes in cell morphology.

Experimental data available indicate that human exposition in a resting position to electromagnetic fields for 30 min, which produce a specific absorption rate (SAR) in the whole body of 1–4 W $kg^{-1}$, will result in an increase of temperature of less than 1°C. Exposition to electro-

magnetic fields more intense producing SAR values of more than 4 W $kg^{-1}$ may overwhelm the thermoregulatory capacity of the body and produce warming tissue harmful levels. **Table 1** shows basic restrictions for exposure to time-varying electric and magnetic fields for frequencies up to 10 GHz.

| Nature of the exposition | Frequency range | Current density for head and trunk ($mA \cdot m^{-2}$) (rms) | SAR average for the whole body ($W \cdot kg^{-1}$) | Localized SAR (head and trunk) ($W \cdot kg^{-1}$) | Localized SAR (limbs) ($W \cdot kg^{-1}$) |
|---|---|---|---|---|---|
| Occupational exposure | Up to 1 Hz | 40 | --- | --- | --- |
| | 1–4 Hz | 40/*f* | --- | --- | --- |
| | 4 Hz to 1 kHz | 10 | --- | --- | --- |
| | 1–100 kHz | *f*/100 | --- | --- | --- |
| | 100 kH to 10 MHz | *f*/100 | 0.4 | 10 | 20 |
| | 10 MHz to 10 GHz | --- | 0.4 | 10 | 20 |
| General public exposure | Up to 1 Hz | 8 | --- | --- | --- |
| | 1–4 Hz | 8/*f* | --- | --- | --- |
| | 4 Hz to 1 kHz | 2 | --- | --- | --- |
| | 1–100 kHz | *f*/500 | --- | --- | --- |
| | 100 kH to 10 MHz | *f*/500 | 0.08 | 2 | 4 |
| | 10 MHz to 10 GHz | --- | 0.08 | 2 | 4 |

**Table 1.** Basic restrictions for time-varying electric and magnetic fields exposition for frequencies up to 10 GHz.

### 3.2. Engineering considerations

Regarding technological restrictions for the localization of the implant, we can find the following:

- The implant must have the maximum area possible.
- The implant should be placed as near as possible from the exterior of the body.

Both of the previous considerations are based on the fact that the implant needs to maximize power transfer and magnetic coupling.

IOP measurement requires the size of the implant not to be so large neither so bulky so it can be implanted into the eye of the patient without causing any discomfort. This is the reason why several IOP monitoring systems are based on radiofrequency identification (RFID) technology [15].

Given that power consumption is a key factor in IOP monitoring system design, we may classify electronic implants based on their power consumption briefly as described below.

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*3.2.1. Active electronic implant*

An active electronic implant will have active electronic components such as diodes and transistors. By using active electronic components, there is the drawback of higher power consumption. On the other hand, by using transistors and diodes the electronic implant would have the advantage of having more precise and reliable pressure measurements.

*3.2.2. Passive electronic implant*

The passive option consists of having pure passive electronic components (resistors, capacitors and inductors). The main advantage of this proposal is that power demand would be much lower than its active counterpart so a possible health risk in the patient due to tissue warming is greatly reduced.

Both types of implants will be discussed in more detail in Section 5.

## 4. Health issues due to tissue warming

A vital requirement when designing electronic implants is to limit temperature increment of the implant in order to prevent damaging organic tissue. In general, temperature variation in a body can be described by a partial differential equation of heat conduction which expresses the variation in the temperature of a body with respect of time, but in order for this equation to be used in human tissue, Pennes incorporated a few extra terms into the partial differential heat conduction equation to describe the warming effect of basal metabolism and the influence of blood in temperature regulation of tissue [16]. Pennes bio-heat equation can be written as follows:

$$C\rho\frac{\partial T}{\partial t} = \nabla\cdot\left(K\nabla T\right) + A - B\left(T - T_b\right) \tag{1}$$

where $A$ is the heat production rate due to metabolic processes per volume unit, $B$ is the perfusion constant and $T_b$ is the blood temperature (it is assumed as a constant at $T_b$ = 37°C).

The bio-heat equation may be applied to human tissue without any external sources of heat. For our case of study, however, the temperature increase in human tissue is also caused by power dissipation of the electronic implant and by electromagnetic radiation coming from the external device that will be supplying wireless power to the implant.

### 4.1. Joule heating

When considering an electronic implant inside the human body, power dissipation by electronic circuitry has to be considered. Assuming that heat dissipation per volume unit of an implant is $P_i$, this can be incorporated in the bio-heat equation as a source of heat and is expressed as

$$P_i = V_i * I_i \tag{2}$$

where $V_i$ is the biasing voltage of the electronic circuitry and $I_i$ is the total electric current circulating through the implant.

### 4.2. Electromagnetic energy contribution

If a biological tissue is exposed to electromagnetic radiation, the electric field $E$ and the magnetic field $H$ penetrate the tissue causing it to warm up due to electromagnetic deposit. On the other hand, SAR is the specific absorption rate and it is defined as the differential with respect of time, of the increment of dissipated energy by a material. The SAR is related with the magnitude of the electric field $|E|$ so, once we know the electric field distribution in the tissue, we can obtain the SAR from which we can obtain the generated heat per volume unit per time unit to include the term to the bio-heat equation.

In order to have a complete bio-heat equation, we need to include Joule heating and electromagnetic energy contribution. The complete bio-heat equation can be expressed as

$$C\rho\frac{\partial T}{\partial t} = \nabla\cdot\left(K\nabla T\right) + A - B\left(T - T_b\right) + \rho SAR + P_i \tag{3}$$

Eq. (3) needs to be solved for each particular case of study to know how many degrees of temperature will the tissue increase caused by the implant. For the graphic shown in **Figure 4**, Eq. (3) was solved using Matlab software. **Figure 4** shows a graphic of how an electronic implant heats the tissue of the sclera when exposed to an electromagnetic energy radiation and joule heating. Details of the implant design and characteristics are shown in **Table 2**.

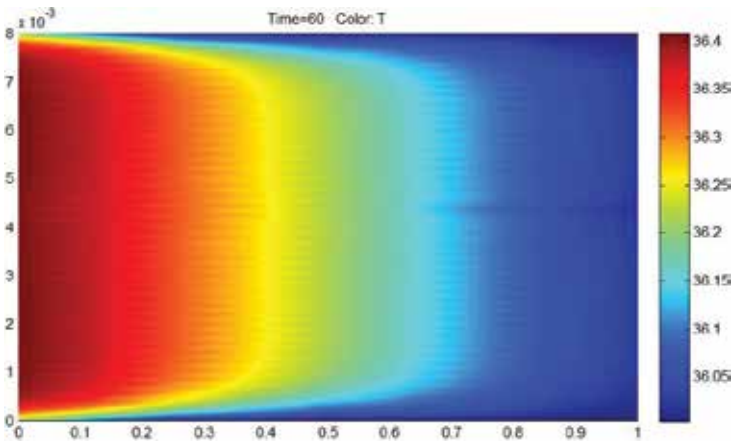


**Figure 4.** Warming graphic of the sclera. Exposition time: 60 s.

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| Parameter | Value |
|---|---|
| Number of turns | 18 |
| Metal thickness | 0.035 mm |
| Inner radius | 1 mm |
| Outer radius | 10 mm |
| Width of metal tracks | 0.25 mm |
| Distance between tracks | 0.25 mm |
| Resistance | 150 Ω |
| Inductance | 7.84 μH |
| Quality factor (*Q*) | 3.28 |

**Table 2.** Proposed electrical parameters for the simulated reader coil.

## 5. Implant fabrication with passive and active electronic circuits

As stated in Section 3, we can classify electronic implants based on the nature of their components. Next, we describe both options.

### 5.1. Passive RLC implant

For this kind of approach, an Resistive Inductive Capacitive (RLC) passive circuit is proposed as an IOP sensor like the one shown in **Figure 5**. The capacitor would be a variable capacitor, sensitive to variations in pressure.

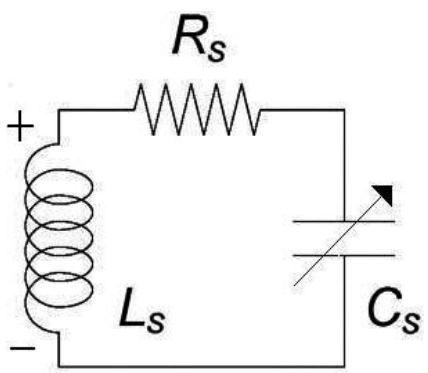


**Figure 5.** Electric diagram of the circuit proposed as an IOP sensor.

The resonance frequency of the RLC circuit shown in **Figure 5** is given by Eq. (4) where we can note that if the value of capacitance varies, the resonance frequency of the circuit will change too.

$$f = \frac{1}{2\pi\sqrt{L_s C_s}} \tag{4}$$

From electromagnetic theory, we know that if we place two inductors close enough and we make a time-varying electric current circulate through one of the coils, it will induce a voltage in the other coil. This is the principle by which wireless energy transfer is done. **Figure 6** shows a Maxwell-Wien circuit which could act as the external device in charge of both delivering power to the implant and reading data from it.

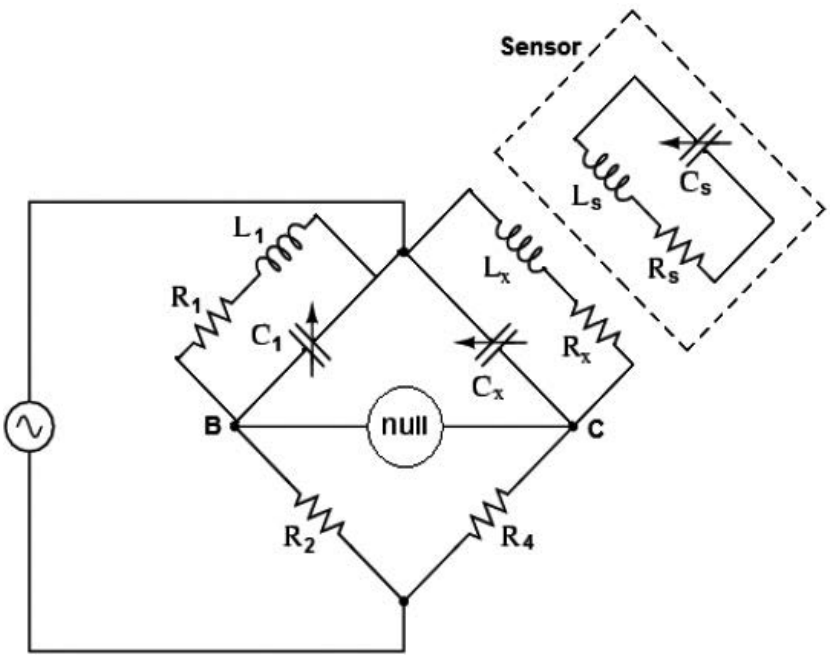


**Figure 6.** Maxwell-Wien bridge circuit coupled with the coil from the implant.

The implant is shown inside the dotted lines. If the RLC circuit in the implant formed by $R_s$, $L_s$ and $C_s$ is placed near the inductor $L_x$, a magnetic coupling will be created. By being $L_x$ and $L_s$ coupled, a change in the capacitance of $C_s$ will change the value of the resonance frequency of the RLC circuit of the sensor which will in turn modify the impedance of $L_x$ coil.

Eq. (5) shows how the impedance of the external device coil will vary by being coupled with the coil of the implant [17]

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$$Z_x = j2\pi f L_x \left[ 1 + k^2 \frac{\left(\frac{f}{f_0}\right)^2}{1 - \left(\frac{f}{f_0}\right)^2 + \frac{1}{Q} j \frac{f}{f_0}} \right] \tag{5}$$

where $f$ is the resonance frequency of the external device, $k$ is the coupling factor between both coils, $Q$ is given by

$$Q = 2\pi f_0 L_s / R_s \tag{6}$$

And $f_0$ is the resonance frequency of the implant described previously in Eq. (4).

The main disadvantage for this approach is the lack of precision and accuracy in the measurements. If we were to obtain precise and accurate measurements with a very small error, then both coils would have to be at the exact same place each time a measurement is to be taken. We could assume that the implant is always fixed so in order to make this kind of approach to work properly, the system design must be done to ensure that the coils will remain in the same position for each measurement and no misalignment will occur.

Another important issue to be noted is the transmission medium between coils. So far, we have considered air as the transmission medium between coils. Much more realistic calculations and simulations may be performed if organic tissue is considered as the transmission medium [18].

### 5.2. Electronic implant using transistors

Designing an electronic implant using transistors needs special care since they require a much larger amount of power compared to passive RLC implants. Electronic circuit design must be done in such a way that warming of the tissue does not exceed 1°C to avoid organic tissue damage. Tissue warming is the main disadvantage of designing electronic implants using transistors. On the other hand, they are very precise and accurate since measurements depend only on having enough power available in the implant rather than if the coils are misaligned or not.

The active electronic circuit for the implant can be divided into three sub-modules, which are reviewed below.

#### *5.2.1. Rectifier and regulator circuit*

As mentioned in Section 5.1, a time-varying electric current circulating through one coil will induce a time-varying voltage in the other coil. Biasing in electronic circuits, however, requires

a direct current (DC) voltage so that is when the rectifier and the regulator circuits come into play.

*5.2.1.1. Rectifier circuit*

A rectifier circuit changes an alternating current into a direct current. It has a small error though, since at the output the voltage has a little ripple. **Figure 7** shows a full-wave rectifier with P-type metal-oxide semiconductor (PMOS) transistors.

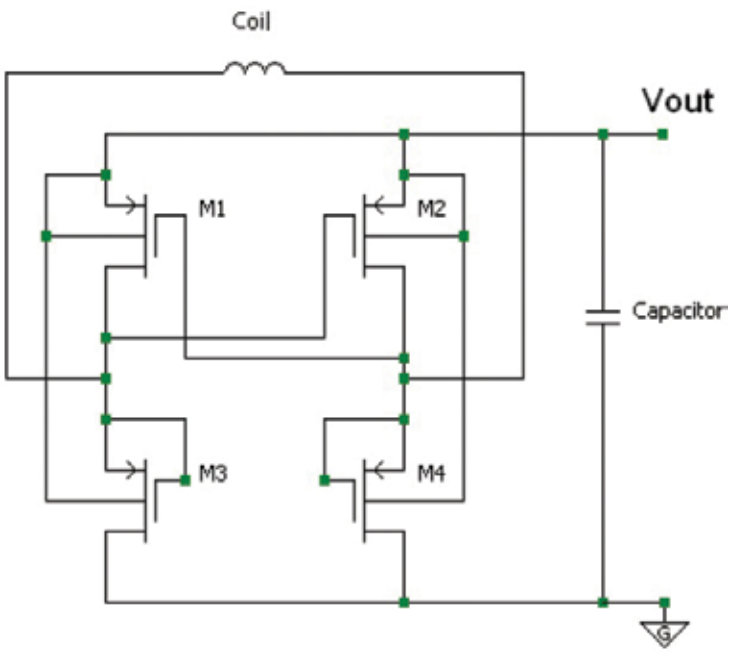


**Figure 7.** PMOS rectifier circuit.

*5.2.1.2. Regulator circuit*

To get rid of the small ripple at the output of the rectifier, a regulator circuit is often added.

The aim of the regulator is to deliver a stable power supply voltage for proper operation of the rest of the circuits in the implant. It has a minimum voltage needed at the input below which it will not deliver a constant voltage. If the input voltage is, on the other hand, greater than the minimum, then the regulator will output a constant voltage. This is the circuit responsible for making active electronic implants independent of coils distance. If the distance between coils is enough for the regulator to provide an output, it will provide a steady voltage regardless of how close the coils are. If on the contrary, the distance between coils is not close enough, then the voltage regulator simply will not provide any voltage at all. **Figure 8** depicts a Complementary Metal-Oxide Semiconductor (CMOS) topology for a voltage regulator circuit.

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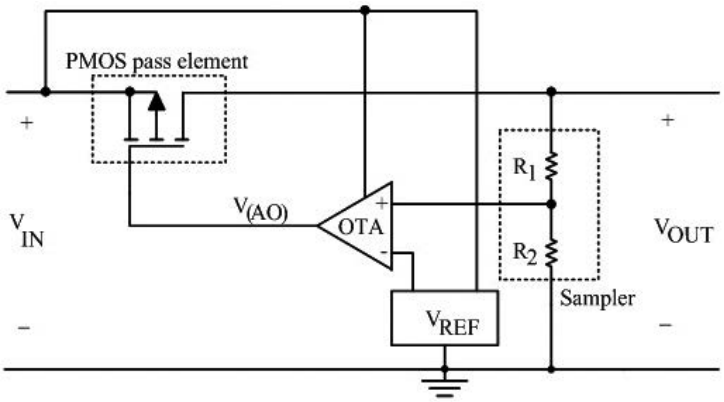


**Figure 8.** Topology of a voltage regulator. Taken with permission from [19].

### *5.2.2. Signal-conditioning circuit*

Once we have a stable DC voltage, we can move on to the next sub-module of the implant. If the sensor is in charge of transforming an analogue physical signal into an electric variable, the signal-conditioning circuit has the task of taking the analogue electric signal and manipulate it in such a way that it meets the requirements for the next stage in the system. For our case, the next stage would be the transmission circuit.

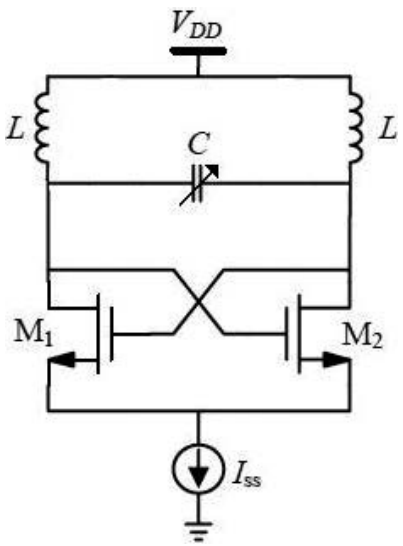


**Figure 9.** Cross-coupled LC VCO topology.

There are many electric circuit designs that can be used as a signal-conditioning circuit. Here, we take a brief look at a voltage-controlled oscillator (VCO) [20]. As seen in Section 2, most

pressure sensors are variable capacitors which change their value of capacitance according to a change in pressure. On the other hand, a VCO is an oscillator with an oscillating frequency that depends on the value of its capacitor. If we connect the pressure sensor with the VCO, then we would have a signal-conditioning circuit for IOP monitoring. In **Figure 9**, a cross-coupled LC VCO topology is shown.

*5.2.3. Transmission circuit*

The transmission circuit sub-module takes the conditioned signal and transmits it back to the external device. A power amplifier (PA) circuit can achieve the latter. Since we are discussing circuits for an electronic implant, it would be desirable to have a low-power amplifier to deal with the transmission. There are many PAs from where we can choose; there are linear amplifiers (Classes A, B and AB) or switched-mode amplifiers (Classes E and F). In **Figure 10**, a class E PA is shown. Switched-mode amplifiers have a higher efficiency than linear ones (50–70% in the case of linear vs. a theoretical 100% in switched-mode amplifiers). Chapter 5 in [21] has a deeper explanation in power amplifiers for biomedical implants.

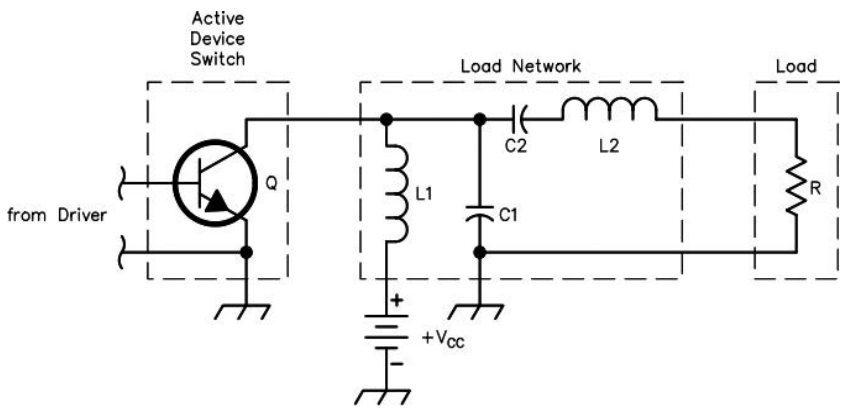


**Figure 10.** Class E power amplifier. Taken with permission from [22].

## 6. Sensor and circuit integration

At this point, the reader may ask: Why do we even need this section since at present, sensors and electronic circuits can be fabricated on the same substrate? And the answer is: Because it depends on what type of application we want to develop.

It is true that nowadays it is possible to fabricate sensors and circuits in the same substrate. The inconvenience with actual fabrication processes is that they use a rigid silicon wafer as a substrate. For many applications, this is enough, but for biomedical applications this approach is not useful. That is why in Section 2 all proposals that have active circuits in their designs (such as the one shown in **Figure 3**) tend to divide the fabrication process of the implant. On

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one hand, they fabricate the coil in a flexible substrate such as parylene, silicone rubber or polyimide so the implant can adapt to the curved surface of the eye. On the other hand, all electronic circuitry and in general all IOP sensors too are fabricated in a rigid silicon wafer. The final step involves connecting the coil with the sensor and the electronic circuits.

The main drawback from this approach is the potential damage that the silicon wafer can cause to the tissue of the eye. Fortunately, there has been a significant advance in terms of electronic circuit fabrication on a flexible substrate. In **Figure 11**, an electronic circuit fabrication process with Carbon Nanotubes (CNT) on a flexible substrate and photographs of the final chip are shown.

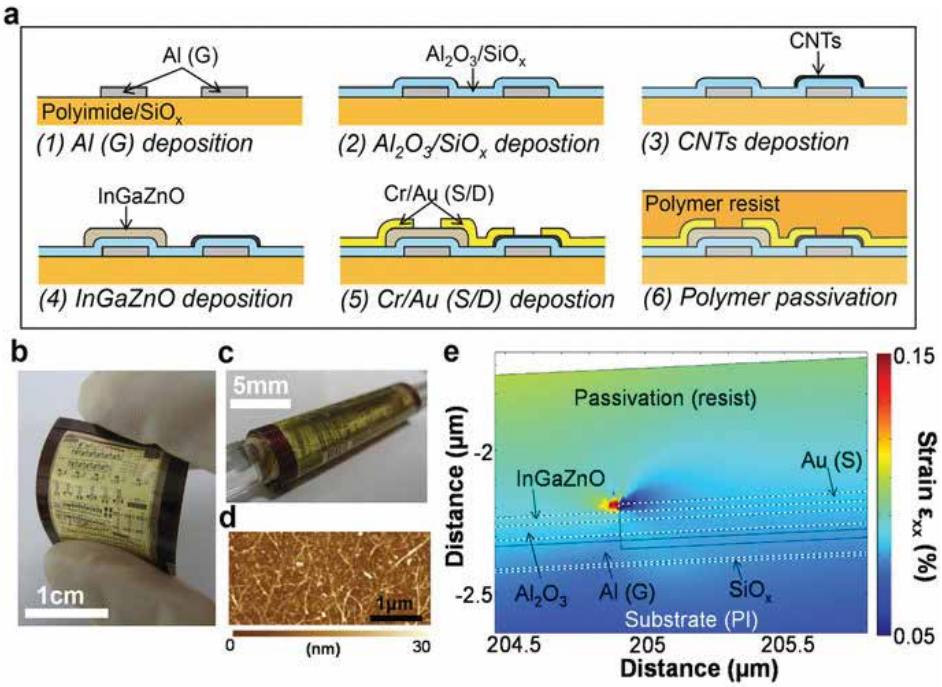


**Figure 11.** Circuit fabrication process on a flexible substrate. (a) Fabrication process of flexible InGaZnO-CNT CMOS logic circuits. Photographs of flexible CMOS circuits under (b) bending by hand and (c) rolling over a glass bar (~2.6-mm radius). (d) Atomic Force Microscopy (AFM) image of CNT network film for p-type type thin-film Transistors (TFT). (e) FEM simulation plot modelling the strain distribution in the InGaZnO channel region under bending ($r$ = 2.6 mm). Taken with permission from [23].

## 7. Summary

In this chapter, we presented an overview of how an electronic implant can be designed. We showed what has been done in this area over the years and we pointed to a major medical concern that is tissue warming when it comes to implanting the IOP sensor into a patient.

From an engineering perspective and despite the tremendous advance that has been made in this area, there are still key issues that must be tackled in the years to come such as power efficiency in wireless power transfer. Another aspect, not less important, is the possibility to have electronic circuits fabricated in the same flexible substrate along with the pressure sensor. This is an area of recent creation that has though an immense growth potential. Microelectronic devices fabricated in a flexible substrate can have applications not only in intraocular pressure monitoring but in many other biomedical applications. And these circuits can not only have biomedical applications demand but also in other numerous engineering fields such as energy harvesting, domotics and wearable technology (clothing and accessories).

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Section 3

# Managing Intraocular Pressure Dynamics

Chapter 6

# Managing Intraocular Pressure: Innovation in Glaucoma Management

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Ana Isabel Jiménez and Covadonga Pañeda

Additional information is available at the end of the chapter

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**Abstract**

Primary open-angle glaucoma is a progressive ocular neuropathy that if left untreated may lead to blindness. The main risk factor for developing glaucoma is increased intraocular pressure. Intraocular pressure is regulated by the balance of aqueous humour synthesis and secretion into the eye and outflow from the eye; therefore, most therapies for glaucoma seek lowering intraocular pressure to avoid disease progression. There are several types of drugs in the market for the treatment of glaucoma, but there are still unmet needs to be overcome; therefore, significant effort has been put in the last few years to develop new medicines with innovative mechanisms of action as well as devices to improve quality of life in glaucoma patients. The present review offers a thorough revision of the latest advances in the glaucoma therapy field, focusing on innovative approaches, new targets and new mechanisms of action.

**Keywords:** glaucoma, innovation, therapy, oligonucleotides, devices, stem cells, gene therapy

## 1. Introduction

Primary open-angle glaucoma (POAG) is a multi-factorial optic neuropathy characterized by retinal ganglion cell degeneration and progressive visual field loss [1]. The underlying molecular changes leading to ocular tissue damage in glaucoma are largely unknown, but it has been shown that reduction in intraocular pressure (IOP) correlates with a decrease in disease progression. As such, treatment in glaucoma is mainly oriented towards reducing IOP to reach a target reduction of approximately 25–30% from the patient's baseline [2]. Pressure in the eye is maintained by balancing the amount of fluid contained within the anterior and

posterior chambers; thus, reduction in IOP is achieved either by reducing the amount of aqueous humour (AH) secreted into the eye or by increasing its outflow [1]. AH is produced by the epithelial cells of the ciliary processes through a complex mechanism that involves ultrafiltration, active transport and diffusion; AH is thereafter secreted into the posterior chamber. AH circulates from the posterior chamber around the lens and through the pupil into the anterior chamber and exits the eye trough one of two pathways: the conventional pathway or the uveoscleral route. AH exiting the anterior chamber through the conventional route crosses the trabecular meshwork (TM) to reach the Schlemm's canal (SC) located at the limbus. Contraction of the ciliary muscle causes the TM to expand and SC to open resulting in increased outflow through this route. The main source of outflow resistance through this route is the extracellular matrix of the TM and the inner wall endothelium of the SC. Through the unconventional or uveoscleral route, AH flows from the iris angle through the anterior face of ciliary muscle into the connective tissue located between the muscle bundles to finally reach the suprachoroidal space. The fluid is thereafter drained through the sclera or the perivascular spaces into the episcleral tissue where it enters the venous circulation. In contrast to the conventional route, the main source of AH outflow resistance is the ciliary body [3].

The eye is a contained organ that is partially isolated from the rest of the body; this isolation provides a certain immune privilege and limits the amount of compound needed to perform proof-of concept studies. In addition, the eye has a sophisticated structure with many different cell types and specialized barriers making it an ideal organ for studying delivery of larger compounds. As such, the eye has often been used to study new mechanisms of action and to obtain initial data for new compounds in development. Therefore, it is not surprising that most innovative new classes of drugs have, at some point, been tested in the eye, among these new classes of drugs are aptamers, antisense oligonucleotides (ASO), short interfering RNAs (siRNA), antibodies, stem cells, gene therapy and different types of delivery approaches and devices.

Here, we will review innovative programs developing drugs for the treatment of glaucoma focusing on the latest advances oriented towards lowering IOP, paying particular attention to the mechanisms used by these drugs and devices.

## 2. Pharmacological innovation

Progressive and irreversible loss of vision is the most feared complication for glaucoma. While current treatments focus on lowering IOP, up to date no therapies have been approved to address the critical issue of visual field deterioration. For this reason, high unmet needs remain for the development of innovative approaches to treat such aspect of the disease. Fortunately, beyond classic eye drop medicines, various exciting therapies are emerging in the field. Overall, these techniques aim to provide either a novel alternative to reduce IOP or a protection and regeneration of retinal ganglion cells (RGCs) to ultimately reverse vision loss. In this section, we will describe novel techniques for the treatment of glaucoma. Interestingly, these complex strategies have been combined in order to achieve broader efficacy.

Traditionally, drug discovery has been based on screening large libraries of compounds to select products with specific activities. However, in the last decades, advances in the molecular

biology field have allowed the search for active candidates to become more rational. As a result, new pharmaceuticals with innovative mechanisms of action, target specific design and improved pharmaceutical properties have emerged. Some of the advantages of these new compounds include increased specificity, reduced toxicity and the ability to address targets that cannot be engaged by traditional small molecules. Among these new pharmaceuticals are biologicals, stem cells, gene therapy and therapies based on oligonucleotides.

Developing innovative compounds for the treatment of glaucoma entails thus targeting the function of cells and tissues related to IOP control; these tissues include the ciliary muscle, the TM, the SC, collector channels and aqueous veins. The latest discoveries in molecular biology allow the identification of key molecules that control AH dynamics in these tissues, and these molecules can be used as starting point for new therapeutic strategies and discovery of new targets. In order to fully take advantage of these approaches, the characteristics of these specific tissues have to be taken into account when designing the therapeutic strategy. The following characteristics are particularly interesting when developing innovative glaucoma therapies:

1. The TM is composed of phagocytotically active cells; this facilitates the entrance of compounds that exert their action inside the cell. Phagocytosis may be enhanced by some surgical procedures.
2. Many of the cells of the TM are non-proliferative, terminally differentiated cells; this prolongs the action of certain therapies that can exert their action inside cells such as genetic therapies, antibodies and oligonucleotide-based therapies.
3. The TM and the SC are structures with the ability to present antigens and induce tolerance; this may work in favour of some therapies that usually induce an immune response.
4. Tissues responsible for IOP control are located in the anterior chamber and are more accessible than tissues of the back of the eye; therefore, invasive procedures are not usually required.

### 2.1. New drug targets

As mentioned above, current approaches to develop new drugs for the treatment of glaucoma are aimed towards decreasing IOP to avoid further damage to the glaucomatous eye. Five drug-types are currently approved to treat glaucoma: alpha agonists, beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogues and cholinergic drugs. Given the information available from the field of genetics, it is surprising that no new targets have reached the clinic since prostaglandin analogues, but this may change in the near future. Here, we review the information and mechanistic data existing for three new targets against which several compounds are currently under clinical development.

#### *2.1.1. Rho-associated protein kinase (ROCK) inhibitors*

##### *2.1.1.1. Description and biological function*

The Rho family consists of three guanosine triphosphate (GTP)-binding proteins named RhoA, RhoB and RhoC, which belong to the Ras-superfamily of GTPases [4]. Rho proteins

bound to guanosine diphosphate (GDP) remain inactive in the cytoplasm of the cell; upon binding of GTP, these proteins become active and translocate to the cellular membrane where they exert their function [5]. The Rho activation and inactivation cycle is regulated by GTP-ase activating proteins (GAP) and guanine nucleotide-exchange factors (GEFs) that catalyse GTP and GDP exchange [6]. Rho proteins are ubiquitously expressed and participate in the regulation of cytoskeletal dynamics, thus playing a central role in cell morphology, adhesion and migration, as well as in numerous signalling pathways [7]. Increased levels of RhoA expression have been detected in optic nerve head of glaucomatous eyes [8].

One of the most comprehensively studied effectors of Rho proteins is the Rho-associated coiled-coil containing protein kinases (ROCK), which are serine-threonine kinases composed of a catalytic domain, a coiled-coin Rho-binding site and an auto-inhibitory domain [9]. In humans, ROCKs exist as two isoforms, ROCK1 and ROCK2, expressed in a wide variety of tissues including the TM and the ciliary muscle cells [10]. Multiple studies indicate that ROCK regulate the contractile properties of the TM, synthesis of extra-cellular matrix (ECM) and outflow of AH through the TM; factors known to be involved in AH dynamics [11]. In addition, ROCK1 and ROCK2 knock-out mice exhibit lower values of IOP when compared to those of their wild-type littermates [12].

*2.1.1.2. Mechanism of action*

Upon activation, ROCK phosphorylates a large number of substrates inducing their activation or inhibition; many of these substrates, such as the myosin light chain (MLC), the myosin phosphatase (MLP) and actin-binding LIM kinase (LIMK), actively participate in cytoskeletal dynamics and cell motility of the TM, SC and ciliary muscle [13, 14]. The contraction/relaxation status of these structures influences the resistance to AH outflow and as a result modulate IOP homeostasis. In consequence, the results of multiple studies have proposed a role of ROCK inhibitors in enhancing AH drainage through the TM by altering the cytoskeleton [15]. NF-κβ is another downstream effector of the ROCK pathway; its activation controls the translation of pro-inflammatory mediators such as interleukins or TNF-$\alpha$.

The anti-fibrotic activity of ROCK inhibitors seems also to be relevant to the therapeutic role of these agents in glaucoma. Post-operative scaring is one of the main causes of filtration surgery failure; scaring tissue formed at the TM leads to poor IOP control and allows silent disease progression. The differentiation of fibroblasts to myofibroblasts during wound healing and scar formation is mediated by TGF-β that facilitates the contractile response of fibroblasts. ROCK inhibitors such as Y-27632 and AMA0526 have demonstrated to improve surgical outcome in animal models of glaucoma filtration surgery [16, 17]. Additionally, ROCK inhibitors such as Y-39983 and fasudil have been found to improve blood flow to the optic nerve head, seemingly due to their action on MLC that regulates the contraction of smooth muscle cells in the blood vessels irrigating this area [18, 19]. Finally, it has been shown that ROCK may also have an effect on central nervous system (CNS) targets involved in neuronal survival and axonal regeneration thus giving ROCK inhibitors an added-on value to their role on AH dynamics [20].

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*2.1.1.3. Drugs in development*

**Y-27632** was the first identified ROCK specific inhibitor, and **SNJ-1656** (also known as Y-39983/RKI983; Senju and Novartis Pharmaceuticals) was the first ROCK inhibitor to demonstrate an IOP-lowering effect in human subjects [21]. Despite its effect in humans, the clinical development of this compound was halted in Phase II due to insufficient efficacy and a poor tolerability profile [22]. ROCK inhibitors currently undergoing clinical trials in glaucoma include ripasudil (KowaCompany, Ltd; Japan), netarsudil (Aerie Pharmaceuticals, Inc; USA), PG324 (Aerie Pharmaceuticals, Inc; USA) and AMA0076 (Amakem; Belgium).

**Ripasudil hydrochloride hydrate**, formerly known as K-115 (Glanatec® ophthalmic solution 0.4%), was approved in Japan in September 2014 for the treatment of glaucoma and ocular hypertension when other therapeutic drugs are not effective or cannot be administered, at the dosage of one drop per eye, twice daily (b.i.d) [23, 24]. Compiled data from Phase II and III clinical trials indicated that this drug achieved a 15% IOP reduction (3.5 mmHg), being conjunctival hyperaemia the most frequently reported adverse event with incidence rates ranging from 55 to 74% [25, 26]. Non-clinical studies proved that ripasudil inhibited both ROCK1 and ROCK2 (IC50 0.051 and 0.019 μmol/L, respectively) and mechanistic studies performed in rabbits demonstrated that its ocular hypotensive effect is due to increased drainage of AH through the TM and SC [27]. Ripasudil induces cytoskeletal changes secondary to ROCK inhibition that lead to the retraction and rounding of the TM cells decreasing the compaction of the TM allowing aqueous outflow. Additionally, *in vitro* studies demonstrated that ripasudil reduced outflow resistance and increased SC endothelial cell permeability [28].

**Netarsudil** (Rhopressa™ ophthalmic solution, 0.02%), formerly known as AR-13324, is a ROCK and a norepinephrine transporter (NET) inhibitor currently in Phase III clinical trials [29]. In a Phase II study, this product achieved a 22% reduction in mean diurnal IOP after 28 treatment days when administered in eye drops once daily (*q.d)*. However, non-inferiority versus latanoprost was not met [30]. IOP reduction is thought to be achieved by three different mechanisms of action: increasing AH outflow through the TM, reducing the pressure in the episcleral vein and reducing AH synthesis. Real-time effect of netarsudil on AH dynamics was evaluated *in vivo* both in albino and pigmented mice using a custom-made optical coherence tomography system [31]. This technique confirmed that the IOP-lowering effect of netarsudil is related to its action both in proximal and distal steps of the outflow pathway. It was noted that the observed cytoskeletal changes induced by netarsudil caused the expansion of the conventional outflow tissues such as the TM and the SC avoiding its collapse at elevated IOP. As a NET inhibitor, netarsudil is thought to decrease AH secretion since elevated norepinephrine levels activate $\alpha 2$ adrenergic receptors responsible for AH production at the ciliary processes [32]. Finally, netarsudil is also thought to have vasodilator properties as it reduces episcleral venous pressure in rabbits facilitating AH drainage to the bloodstream [32]. Similarly to ripasudil, ocular hyperaemia was the most frequently reported AE during clinical development with incidence rates of 57% which improved during the course of the study decreasing to 24% after 28 treatment days.

**Roclatan**™, formerly known as PG323, is a fixed dose combination (FDC) of netarsudil 0.02% and latanoprost 0.005%, which combines the previously described mechanisms of action with

the capacity of the prostaglandins of increasing AH outflow through the uveoscleral pathway [33, 34]. This fixed combination currently in Phase III clinical trials achieved clinically and statistically superiority in terms of ocular hypotensive efficacy when compared to its individual active components at the same concentrations. However, incidence rates of ocular hyperaemia were superior in the FDC than those observed in the latanoprost group (40 vs. 60%).

**AMA0076** is a locally acting ROCK inhibitor currently in Phase II clinical trials specifically designed to reduce IOP while minimizing side effects such as hyperemia. *In vivo* studies conducted in an acute hypertensive rabbit model showed that AMA0076 prevented IOP elevation more efficiently than latanoprost and bimatoprost. *In vitro* studies conducted in rabbit ocular tissues demonstrated that AMA0076 was able to induce reversible changes in cell shape and decreased the number of actin filaments and focal adhesions that may facilitate AH outflow [35].

### *2.1.2. Adenosine receptor ligands*

#### *2.1.2.1. Description and biological function*

Adenosine is an endogenous nucleoside modulator of both intracellular and extracellular origin. Adenosine half-life is very limited (~1.5 seconds) as it is rapidly metabolized to inosine and hipoxantine; this is why extracellular levels of adenosine, which usually range from 20 to 200 nM, are considered a good indicator of cellular homeostasis. Adenosine levels increase, even up to the micromolar range, in response to cellular stress conditions such as tissue hypoxia or ischemia. In fact, adenosine levels in AH are significantly elevated in ocular hypertensive individuals when compared to normotensive individuals [36, 37].

Adenosine receptors (ARs) belong to the family of G protein-coupled receptors (GPCR) [37]. Four subtypes of AR have been identified (A1, A2A, A2B and A3), and all of them are involved in regulation of cAMP production through different pathways: A1 and A3 down-regulate cAMP levels inhibiting adenylyl cyclase, whereas A2A and A2B receptors activate adenylyl cyclase, increasing cAMP production. ARs are expressed in numerous ocular tissues such as ciliary body, TM, SC and retina. Activation/inactivation of ARs impacts AH formation, outflow and consequently IOP homeostasis. Additionally, ARs are also involved in retinal function, impacting blood flow and neuronal survival [36].

#### *2.1.2.2. Mechanism of action*

Activation of A3 receptors results in activation of $Cl^-$channels in the non-pigmented ciliary epithelial (NPE) cells of the ciliary epithelium where AH is produced [38]. Studies conducted in A3AR knockout mice and in mice treated with A3AR antagonists showed that absence or inhibition of this receptor significantly decreases IOP when compared to native or untreated animals [39]. On the contrary, mice treated with A3AR agonists show enhanced chloride release resulting in increased AH production and rise in IOP. AR can also affect AH outflow; there are two pathways by which AR agonists increase conventional outflow through the TM and SC: cell volume modification mediated by ion transport and ECM remodelling [36]. A1, A2A and A3 AR agonists have shown to increase $Ca^{2+}$ in the cells of the SC and to diminish

TM cell volume [40]. Outflow resistance in the TM is dependent on the composition of the ECM; activation of A1 ARs triggers signalling cascades that lead to the expression of high levels of metalloproteases such a MMP-2 and MMP-9, enzymes participating in ECM remodelling enhancing AH outflow and decreasing IOP. On the contrary, A2A and A2B AR activation increase ECM deposition and therefore difficult AH outflow increasing IOP [41].

In view of the previously exposed mechanisms, it can be concluded that AR ligands play a key role in IOP control. In general terms, adenosine binding to A1AR in the TM reduces outflow resistance. However, A2A AR stimulation may result in IOP increase or decrease depending on the alterations to the resistance in the SC. Finally, activation of A3 AR mediates activation of $Cl^-$channels in the NPE cells inducing AH production, while A3 AR antagonists prevent adenosine-induced activation of $Cl^-$ channels decreasing IOP.

#### *2.1.2.3. Drugs in development*

Numerous AR ligands (both agonists and antagonists) are being developed with the purpose of exploiting their potential for modulation of IOP. The adenosine analogues that are currently in glaucoma clinical trials include trabodenoson (Inotek Pharmaceuticals, US), OPA-6566 (Acucela, US and Otsuka Pharmaceutical, Japan), ATL-313 (Santen Pharmaceutical) and CF-101 (Can-Fite Bio Pharma, US).

**Trabodenoson**, formerly known as INO-8875/PJ-875, is a highly selective A1 AR agonist administered in eye drops currently in Phase III clinical trials. The IOP-lowering effect of four different doses of trabodenoson ranging from 50 to 500 μg was evaluated when administered b.i.d during 28 consecutive days in a Phase II clinical trial [42]. Administration of trabodenoson resulted in a dose-related IOP reduction; the highest dose tested achieved a statistically significant IOP reduction in 25% (6.5 mmHg) when compared to placebo. All the doses tested showed a good tolerability profile. The proposed mechanism of action for trabodenoson involves activation of the A1 adenosine receptor that promotes phosphorylation of the extracellular signal-regulated kinases ERK1 and ERK2, resulting in increased secretion of MMP-2 and changes in the ECM that decrease TM resistance to the AH outflow.

**OPA-6566** and **ATL-313** are two A2A agonists currently in Phase I clinical trials; at this point of development, little information on their clinical development is available. Both drugs are anticipated to increase AH outflow via the conventional pathway of the TM and SC rather than the uveoscleral pathway.

**CF-101** is an A3 AR agonist orally administered presently in Phase II clinical trials. Recently, CF-1001 failed to meet its primary endpoint as no statistically significant differences in IOP were found between the CF101 group and the placebo group after 16 treatment weeks.

### *2.1.3. Nitric oxide donors*

#### *2.1.3.1. Description and biological function*

Nitric oxide (NO) is a gaseous endogenous signalling molecule synthesized by nitric oxide synthases (NOS) that catalyse the oxidation of the amino acid L-arginine to form NO and

L-citrulline. There are three NOS isoforms: the neuronal NOS (nNOS or NOS-1), the endothelial NOS (eNOS or NOS-3) and the inducible NOS (iNOS or NOS-2). NOS-1 and NOS-3 are activated by the calcium/calmodulin complex in response to an increase in calcium and produce NO in the pico- or nanomolar scale. On the contrary, NOS-2 activation is calcium independent and produces NO in a micro- to millimolar scale [43].

NOS-3 is expressed in TM, SC, ciliary body and uveal vascular endothelium. NOS-1 is located in nerve fibres in the cornea and lens epithelium and iNOS is detected after directed stimulation in the TM and in the ciliary body and vessels. This expression pattern of NOS enzymes in the anterior segment of the eye suggests that NO plays a key role in the regulation of AH dynamics. In fact, levels of NO and NOS expression are diminished in glaucomatous human eyes. In addition, NOS-3 knock-out mice exhibit elevated IOP levels due to a reduction in the conventional outflow, whereas the opposite effect is observed in NOS-3 over expressing transgenic mice [43, 44].

*2.1.3.2. Mechanism of action*

NO stimulates soluble guanylatecyclase (sGC) leading to the elevation of intracellular cyclic guanosine monophosphate (cGMP levels), a secondary messenger that interacts with protein kinases and phosphodiesterases. Multiple studies indicate that the NO-cGMP pathway regulates IOP levels increasing AH outflow through the conventional route and by reducing AH secretion [43].

Cytoskeletal changes at the TM seem to be the underlying mechanism mediating the increase in AH outflow induced by NO. NO induces vascular smooth muscle cells (VSMC) relaxation by stimulation of cGMP synthesis that subsequently activates protein kinase G (PKG). This results in inhibition of the Rho-kinase cascade and leads to inhibition of the MLC-2 phosphorylation. Analogously to VSMCs, TM cells also exhibit contractile properties and modulation of these properties by NO is thought to mediate changes that result in a reduction in outflow resistance. Additionally, it has been demonstrated that inhibition of multi-drug resistance-associated protein-4 also induces TM cellular relaxation mediated by cGMP-PKG pathway [45]. NO could also mediate its IOP-lowering effects by targeting cells of the SC. In fact, Rho-kinase inhibition mediated by NO-cGMP regulates actin dynamics and cell contractility in cultured SC cells [46].

*2.1.3.3. Drugs in development*

**Latanoprostene bunod** (LBN; BOL-303259-X; Bausch & Lomb) is a novel nitric oxide-donating prostaglandin F2a analogue currently in Phase III clinical trials [47]. In the eye, LBN is metabolized to two moieties. The first, latanoprost acid, is an F2alpha prostaglandin analogue, while the second, butanediol mononitrate, releases nitric oxide, which activates the soluble cGMP signalling pathway. LBN achieves IOP control simultaneously enhancing AH outflow through the conventional and the uveoscleral routes. Doses ranging from 0.006 to 0.040% of LBN solution were administered once a day to patients with OAG or OHT for 28 consecutive days. LBN at 0.024 and 0.040% achieved statistically significant reductions in mean IOP when compared to latanoprost. During the Phase III clinical trial LBN 0.024% (QD) was not only

non-inferior to timolol maleate 0.5% dosed twice daily (b.i.d) after 3 months of treatment but also provided significantly greater IOP reduction. LBN exhibited a similar safety profile than prostaglandins being conjunctival hyperaemia the most frequently reported AE.

### 2.2. New mechanisms of action

New drug targets are certainly playing an important part in modernising the way glaucoma will be treated in the future. But innovation in glaucoma is not only focused in the discovery of new drug targets, but it is also taking advantage of new and exciting mechanisms of action that seek to solve unmet needs that current treatments cannot solve. In the following section, we will give an overview of drugs using innovative mechanisms of action, focusing on those that have in the past few years entered in clinical development for glaucoma. It should be noted that although antibodies fall into this category of drugs using new mechanisms of action, they have not been included in this section since, up to the authors' knowledge, there are no clinical programmes currently developing antibodies for the treatment of glaucoma. A section on neuroprotective drugs has been included at the end of this section to highlight the importance these drugs are acquiring in the glaucoma pipeline.

#### *2.2.1. Oligonucleotide-based compounds*

Oligonucleotides have in the past decades turned out to be an interesting therapeutic approach, particularly due to their ability to address intracellular targets. Oligonucleotides can be designed to target specific genes or RNAs with the aim of altering gene expression or even exert a direct interaction by binding to molecules. The main classes of oligonucleotides that are currently being developed as therapeutic tools are aptamers, ASOs, siRNAs and microRNAs (miRNAs) [48].

##### *2.2.1.1. Aptamers*

Aptamers are RNA or DNA oligonucleotides that form a 3D structure designed to interact with large or small molecules. Aptamers typically bind to proteins but can be designed to act upon other types of molecules [49]. Aptamers, contrary to antibodies, are chemically synthetized products that do not require biological steps in their production processes; this results in products that are very well controlled without significant variability among batches. Aptamers have not been widely tested in the context of glaucoma. Pegaptanib, a first-in-class FDA-approved aptamer for the treatment of age-associated macular degeneration (AMD), has been briefly studied for the treatment of neovascular glaucoma [50]. This compound binds to a subtype vascular endothelial growth factor (VEGF), $VEGF_{165}$, hampering its ability to bind to its cell surface receptor thus impairing neovascularization [51]. In addition, ARC81, an anti-transforming growth factor-β (TGF-β) aptamer, has been studied for the reduction in corneal scaring, a common complication of glaucoma filtration surgery [52].

##### *2.2.1.2. Antisense oligonucleotides (ASOs)*

ASOs are single-strand RNA or DNA oligonucleotides, of approximately 15–25 bp, that mediate mRNA degradation by an RNaseH-mediated mechanism [53]. These compounds have

been widely used to study cell function and lately applied to therapeutics. There are two FDA approved ASOs; vitravene, an intravireally administered ASO for the treatment of cytomegalovirus retinitis in AIDS patients and mipomersen, an intravenously administered ASO for the treatment of familiar hypercholesterolemia [54, 55]. The main advantage of this class of compounds is that they modulate gene expression without altering the genetic code, and that their action upon their target gene can be rapidly modified. In addition, as other oligonucleotides, ASOs are chemically synthetized, with all the advantages this entails. On the other hand, ASOs are labile products that require chemical modifications to increase their stability; these modifications can potentially increase their toxicity [48, 56].

There are two ASOs under development for treatment of different types of glaucoma; Aganirsen (GS-101) and ISTH0036. Aganirsen is a 25-bp ASO targeting insulin receptor substrate-1 (IRS-1) administered in eye drops; this compound is being developed for the treatment of corneal neovascularization and has also been tested in neovascular glaucoma [57]. ISTH0036 is a fully modified phosphorothioate 14-bp oligodeoxynucleotide with a 3 + 3 LNA-gapmer pattern targeting TGF-β2. TGF-β2 is an anti-proliferative and anti-inflammatory factor that is upregulated in the AH of POAG patients. Increases in TGF-β2 correlate with deposition of fibrillar extracellular matrix in the TM, one of the hallmarks of POAG [58]. These extracellular depositions in the TM hamper AH outflow and consequently result in IOP increase. ISTH0036 is currently being tested in a Phase I dose-finding clinical study in patients with advanced glaucoma undergoing filtration surgery due to uncontrollable elevated IOP. The compound is administered intravitreally (IVT) at the end of trabeculectomy; the outcomes of the study are safety, tolerability and effect on IOP.

*2.2.1.3. Short interfering RNAs (siRNAs)*

siRNAs are double-stranded RNA molecules of approximately 19–25 bp that mediate gene silencing by blocking translation of specific mRNAs into their corresponding protein [59]. These molecules, although usually larger than ASOs, are in general more potent and stable than ASOs. Depending on the target tissue and the level of expression of the target gene, these compounds can be administered in eye drops avoiding invasive administration methods, if deeper regions need to be accessed IVT administration may be required [60]. In addition, once the siRNA has entered the RISC complex its action lasts for quite some time, this means that a single molecule would be able to mediate the degradation of several mRNAs thus amplifying the effect of the compound. This prolonged action is particularly interesting in the case of glaucoma as it could avoid sudden increases in IOP due to skipped doses.

Bamosiran (SYL040012) is a 21-bp unmodified siRNA targeting adrenergic receptor β2 (ADRB2) for the treatment of glaucoma. This compound is administered in eye drops and penetrates the eye to reduce synthesis of AH by blocking the ADRB2 at the ciliary body and possibly also at the TM [61, 62]. In contrast to traditional beta-blockers, bamosiran acts only locally in the eye; this is because the molecule is rapidly degraded when it reaches systemic circulation, thus reducing the likelihood of systemic side effects. This characteristic makes bamosiran a safe compound for the treatment of individuals with risk of heart disease or other alterations in which beta-blockers are contraindicated.

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QPI-1007 is a 19-bp siRNA targeting Caspase-2. This product, administered by IVT injection, is under development for the treatment of several optic neuropathies, including glaucoma [63]. Caspase-2 is specifically activated during ganglion cell death leading to irreversible loss of vision, thus reducing its expression could potentially protect retinal ganglion cells from apoptosis.

*2.2.2. Gene therapy*

Gene therapy is a technique that uses genetic material to modify the disease state, usually using a vector to transfer the genetic material. For ophthalmic affectations, distinct viral vectors can be used for the delivery of such genetic material. Most-studied vectors include adenovirus (AdV), adeno-associated virus (AAV), herpes simplex virus (HSV) and lentivirus; all of them offering distinct pros and cons [64]. While large advancement has been achieved in different eye diseases, gene therapy for glaucoma has faced substantial limitation due to the lack of obvious genetic alterations. Indeed, causative and risk factor genes such as myocilin (MYOC), optineurin (OPTN), Cytochrome P450 1B1 (CYP1B1), caveolin (CAV1/CAV2) and TANK-binding kinase 1 (TBK1), among others, represent less than 10% of glaucoma cases worldwide [65]. Up to date, only one gene therapy trial for glaucoma has been listed (Trial ID: US-0589). This Phase I study proposes to evaluate the safety of SCH-412499 (rAd-p21) after a single injection into the sub-conjunctival space of the eye in glaucoma subjects prior to trabeculectomy. The treatment uses an AdV vector for the expression of p21 WAF-1/Cip1, a potent cyclin-dependent kinase inhibitor to reduce wound healing process and fibroproliferation after filtering surgery [66]. No results have been disclosed yet; however, pre-clinical studies demonstrated a safe profile with strong anti-proliferative effect after filtration surgery in animal models [67, 68].

In collaboration with Mayo Clinic (Rochester, USA), Oxford BioMedica plc (Oxford, UK) is developing a novel gene therapy approach for the treatment of chronic glaucoma. Pre-clinical studies have been undertaken to determine the feasibility of the LentiVector® platform for the delivery and expression of cyclooxygenase (COX-2) and prostaglandin F2$\alpha$ (PGF-2$\alpha$) genes to reduce IOP in glaucomatous patients. According to the company's announcement, pre-clinical studies demonstrated a good tolerance for the LentiVector® when used at high doses, with the ability to transduce proper target cells following transcorneal injection into the anterior chamber. Moreover, data showed a long-term gene expression for up to 5 months. Although pre-clinical efficacy studies on IOP have been planned, no additional results have been published.

Besides these two emerging gene therapy treatments for glaucoma, most investigational developments are still in pre-clinical phases, showing relative effect on IOP. For example, the COX-2 and PGF-2$\alpha$ gene therapy models previously described demonstrated a prolonged decrease in IOP in large animal models [69]. Similarly, using lentiviral-based dual expression vector to deliver prostaglandin F synthase, significant reduction in IOP has been achieved [70]. However, the overall reduction in IOP produced by these vectors was not as extensive as that observed for topical PG eye drops. Likewise, different gene therapy strategies to modulate the RhoA or Rho-kinase pathways showed an efficient but moderate IOP-lowering effect [71, 72]. In an elegant way, gene therapy has also been adapted to steroid-induced glaucoma.

In these patients, topical instillation of glucocorticoids is known to produce ocular hypertension by producing a downregulation of the matrix metalloproteinase 1 (MMP1) gene in the TM. Because the patients are under an on and off treatment schedule with glucocorticoids, a new self-complementary AAV has been generated for the expression of MMP1 under the control of a glucocorticoid response element. This allows for the induction of MMP1 expression only after the administration of glucocorticoids, a strategy that presents great advantages. Using this novel system, a reduction in IOP was detected in large animal model and would be highly beneficial in clinic [73].

In addition to cell transduction and adequate gene expression modulation, the route of administration is a critical factor for effective gene therapy. Interestingly, optimum delivery and transduction of AdV have been found through the TM and the SC, structures from where the AH flows [74]. However, the complexity of the whole outflow tract, which includes various cell-types harbouring different transduction properties, may impair the overall efficacy of gene therapy. Moreover, the possible systemic exposure with unwanted side effects is an important downside of direct release of viral vectors that can drain into the retinal venous circulation. Although we are still a long way from the instauration of gene therapy in glaucoma treatment, the advancement achieved in the field is encouraging and sustains the feasibility of such technique in human.

### *2.2.3. Stem cell therapy*

Once glaucoma has reached advanced stages with irreversible vision loss, the nearly unique alternative is to replace the retinal ganglion cells of the optic nerve to restore functional vision. Hence, future objectives aim at regenerating the optic nerve in blind eyes using stem cell therapy. While the majority of clinical trials using stem cells have been conducted in neuroretinal degenerative diseases, trials in glaucoma are only starting to emerge. This is because the replacement of RGCs is a most tricky task and will depend on (1) cell engraftment, differentiation and migration to the ganglion cell layer, (2) the growth of axons into the optic disc and (3) the establishment of effective synapse connection [75]. To do so, cells can be implanted into different compartments of the eye, although most commonly tested sites are intravitreal or sub-retinal. The stem cells used can be of various sources and are often engineered *in vitro* through gene therapy [76]. Autologous transplantation of genetically modified cells that originate from the same patient has been favoured due to larger safety window, reducing host-defense mechanism and immune reaction such as those produced by AdV viral vectors. Because of the novelty of these methodologies, the primary goals of current registered clinical trials are towered first on safety outcomes (monitoring of adverse and serious adverse reaction), and secondary outcomes on efficacy (visual acuity, eye fundus and visual field improvement). In general, patients with advanced stages of glaucoma are recruited because of the lack of previous safety studies involving humans.

A novel Phase II trial aims to test the efficacy and safety of adipose-derived regenerative cells for the treatment of glaucomatous neurodegeration (NCT02144103). After liposuction, cells are harvested and isolated from fat tissues and injected into the same patient by subtenon administration. The rationale behind the use of adipose-derived mesenchymal stem cells is based on

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their capacity to differentiate into retinal pigment epithelium cells. Another promising treatment uses autologous bone marrow-derived stem cells (BMSC): after prior isolation and culture, these cells are injected intravitreally into the worst eye of the patient (NCT02330978). Safety parameters are the first objective of this Phase I trial, although an improvement in visual acuity and visual field are expected in secondary outcomes. Mechanisms for such potential effects remain uncertain. Surprisingly, in animal models, BMSCs have been shown to survive after intravitreal injection, although without showing any apparent differentiation ability. There are actual evidences that BMSC cannot pass the vitreoretinal interface, suggesting that BMSCs may act in a paracrine manner, most likely by providing neuroprotection, rather than by differentiating into RGCs [77]. A larger clinical trial is currently running to evaluate the efficacy of such BMSC therapy, comparing distinct injection sites for various ophthalmic diseases, including glaucoma (NCT01920867). Routes of injection include retrobulbar, subtenon, intravenous, intravitreal and intraocular, which may provide valuable information on the ability of BMSCs to improve visual acuity depending on the delivery site. Overall, big hopes are expected from these trials and their success would definitively represent important breakthrough.

Aside from clinical trials, numerous pre-clinical studies are underway to explore the capacity of different stem cell populations to provide neuroprotection or regeneration of optic nerves. For example, a novel stem cell therapy has been explored to prevent the loss of TM function and cell number observed in glaucoma. The TM and SC operate to drain out the AH and play pivotal role in sensing IOP fluctuation. In conjunction with the modulation of the extra-cellular matrix and enzymes activity, these two structures adapt to adjust the resistance to fluid flow. The aim of this new stem cell therapy, although still at pre-clinical stages, is to obtain new functional TM-like cells to restore functional outflow tract. Recently, in a mouse model of glaucoma, transplantation of induced pluripotent stem cells (iPSC) differentiated into TM cells was shown to reduce neuronal loss and IOP [78]. Surprisingly, the cell transplant led to increased proliferation of pre-existing TM cells. Obviously, further investigation will be needed to confirm the feasibility of these innovative therapies and to efficiently apply them to regular clinical practice.

#### *2.2.4. Neuroprotective drugs*

Transport of neurotrophic factors (NTFs) along RGCs axons is critical for cell survival, and unfortunately, this process is found altered in glaucoma. Indeed, the mechanical compression of the optic nerve hinders retrograde travelling of NFTs, leading to induction of the apoptotic cascade. Neuroprotective therapy thus aims to prevent RGCs cell death and damage of the optic nerve. Neuroprotective drugs have been initially developed for the treatment of various neuropathic diseases and their success raised the possible application for the prevention of vision loss in glaucoma. Pre-clinical studies have clearly demonstrated the efficacy of neuroprotective therapy for glaucoma; however, it has not yet been translated into clinic. When looking retrospectively, the development of such therapies has been hampered by the failure of Memantine to meet its primary outcome in Phase II trials, and consequently the drop from clinical development. This drug belongs to a new class of Alzheimer's disease medications that inhibits NMDA receptors to counteract the toxic effect of L-glutamate accumulation into the nervous system. It has been shown to strongly reduce RGCs loss in various animal species [79]. Unfortunately, Memantine

failed to demonstrate any protective properties in glaucoma patients [80]. Consequently, companies became skeptical over undertaking such risky clinical trials. Up to date, the main difficulty relies on the fact that long-term efficacy for neuroprotection is extremely hard to prove. Nonetheless, the rationale behind this therapy remains valid and is still currently explored, mostly that a myriad of signalling pathways can be modulated to protect RGCs. The fact that many of these targets act through an IOP independent manner provides an appealing approach to treat patients with normal tension glaucoma. This chapter will explore some of these avenues, focusing on survival factors, apoptotic mechanisms and oxidative stress.

One of the best strategies to achieve neuroprotection focuses on the delivery of NTFs to RGCs using cell therapy. A Phase I clinical trial has been completed to evaluate the safety and efficacy of the NT-501 CNTF Implant after intravitreal injection into one selected eye (Neurotech Pharmaceuticals, Inc; NCT01408472). The implant contains human cells (designated NTC-201) that originate from a retinal pigment epithelial cell line genetically engineered to produce human ciliary neurotrophic factor (CNTF). A role for CNTF in neuroprotection of the retina has been established in a wide number of pre-clinical studies, which was shown to promote cell survival of RGCs in most animal models [81]. In human, such implant has been previously proved to release CNTF consistently over a 2-year period without producing systemic exposure, hence avoiding the need for multiple injections [82]. Outcomes have not been reported yet but studies suggest favourable pharmacokinetic of the implant with possible treatment of chronic retinal degenerative diseases. Overall, MSCs and BMDS transplant represent a valuable tool for long-term delivery of various NTFs as well as anti-inflammatory cytokines that may prevent apoptosis of RGCs.

Activation of apoptosis is a key mechanism in RGCs cell death and increasing amount of anti-apoptotic agents are currently being investigated for the treatment of glaucoma. Since apoptosis often occurs in early stages of the disease, its detection is of prime importance to prevent irreversible damage lost. A new Phase I study is evaluating the ability of ANX776 to identify RGC apoptosis as part of a new detection of apoptosing retinal cells (DARC) technique (NCT02394613). The primary purpose of the study is to develop a new diagnosis tool for glaucoma in healthy patients. As previously described, QPI-1007 is a promising candidate to achieve neuroprotection by reducing the expression of Caspase-2 (NCT01965106 and NCT01064505). Interestingly, brimonidine, a selective alpha2-adrenergic agonist, has been shown to protect against optic nerve damage independently of its IOP-lowering effect, most likely by inducing the production of the anti-apoptotic proteins Bcl-2 and Bcl-XL [83]. Effectively, in a clinical trial, normal tension glaucoma patients treated with brimonidine displayed preserved field function as compared to those that were given timolol [84]. Curiously, other classic IOP reducing agents have been proved to yield neuroprotective effect because of a dual mechanism of action. A different example is the beta adrenergic blocker Betaxolol. This drug interacts with other channels such as the sodium and L-type calcium channels, an affinity that was proposed to contribute to the protection of the visual field observed in treated patients [85]. Interestingly, a Phase III trial named 'Stop Retinal Ganglion Cell Dysfunction Study' is currently running to compare the protective effect of numerous hypotensive medications routinely used in clinic (NCT02390284). The trial recruits patients with normal vision and eyes are evaluated for changes in the pattern electroretinogram (PERG) and retinal nerve fibre layer (RNFL) thickness.

| Therapy | Description | Phase/stage | Outcome | Trial ID |
|---|---|---|---|---|
| ASO | Intra-vitreal injection of ISTH0036 as an addition to filtration surgery | Phase I/recruiting | Safety and tolerability | NCT02406833 |
| siRNA | Bamosiran eye drops for POAG | Phase II/completed | Safety, dose finding, IOP-lowering effect | NCT02250612 |
| siRNA | QPI-1007 injection in primary angle closure glaucoma | Phase II completed | Safety and tolerability and pharmacokinetics | NCT01965106 |
| Gene therapy | Intraocular delivery of p21 WAF-1/Cip1 gene before glaucoma surgery | PhaseI/unknown | Safety and tolerability, fibroproliferation and wound healing | US-0589 |
| Gene therapy | LentiVector® platform for the delivery of COX-2 and PGF-2$\alpha$ to reduce IOP | Pre-clinical | Safety, IOP-lowering effect | |
| Stem cell therapy | Subtenon injection of adipose-derived regenerative cells | Phase II/recruiting | Safety, change in visual acuity, eye fundus, visual field | NCT02144103 |
| Stem cell therapy | Intra-vitrial injection of BMSCs | Phase I/recruiting | Safety, change in visual acuity and visual field, optical coherence tomography, RGC function | NCT02330978 |
| Stem cell therapy | Retro-bulbar, subtenon, intra-venous, intra-vitreal and intraocular injection of BMSCs | Phase II/recruiting | Change in visual acuity and visual field | NCT01920867 |
| Stem cell therapy, neuroprotection | Delivery of NT-501 CNTF Implant | Phase I/completed | Safety, vision, visual field, nerve fibre layer, optic nerve topography | NCT01408472 |
| Neuroprotection | RGCs protection by hypotensive eye drops | Phase III/recruiting | Change in PERG, RNFL | NCT02390284 |
| Neuroprotection | Single intra-venous injection of ANX776 as new detection of apoptosing retinal cells (DARC) technique | Phase I/active | Safety and DARC count | NCT02394613 |

**Table 1.** Current clinical trials for new mechanisms of action for glaucoma.

Anti-oxidants also represent an attractive alternative to prevent long-term RGC damage. Due to high metabolic activity during visual transduction, retinal cells are particularly sensitive to oxidative stress, mainly in elderly. Increased levels of reactive oxygen species (ROS) and associated DNA damage have been reported in glaucoma patients [86]. Numerous pre-clinical studies in glaucoma animal models have shown a neuroprotective benefit for a large variety of anti-oxidant such as Vitamin E, Coenzyme Q10, Ginkgo biloba extract and other Chinese medicines [79]. One clinical trial previously addressed the impact of oral versatile anti-oxidants on glaucoma progression, comparing Ginkgo biloba and $\alpha$-tocopherol for 3

months (NCT01544192), however no clear benefits have been reported, and other similar studies failed to find differences among treatments (**Table 1**) [87].

## 3. Innovation in medical devices and surgical procedures

There are two types of surgical procedures aimed at lowering IOP, trabeculoplasty and trabeculectomy. The former is aimed towards treating the TM with LASER to diminish AH resistance and increase drainage into collecting channels or into the outside of the eye. In the latter, a part of the TM is removed to reduce resistance to outflow. These approaches usually reduce IOP for a period of up to 5 years, but additional medical or surgical interventions are commonly required after this period due to scaring or secondary complications. Improvements in surgery thus seek using artificial channels that enlarge drainage routes or shunts that bypass the TM draining the AH directly to the SC or to the suprachoroidal space [88]. In the last decade, minimally invasive glaucoma surgery (MIGS) has gained popularity due to its minimal tissue destruction, short surgery time and fast post-operative recovery. Here, we present an overview of glaucoma draining devices that are in development for these procedures.

### 3.1. Drainage devices to the SC or to the sub-conjunctival space

The SC is an endothelium-lined channel derived from the TM located at the joining point of the sclera and cornea. The TM is composed of three layers: the innermost uveal meshwork, the middle layer section composed of connective tissue called the corneoscleral meshwork and the third layer, also known as juxtacanalicular tissue. The juxtacanicular tissue is a non-fenenstrated endothelial layer immersed in fibres and a rich extra-cellular matrix that lines the inner wall of the SC. In humans, 75% of the resistance to AH outflow is exerted by the TM, mainly by the juxtacanalicular portion and the deposition of glycosaminoglycans in the TM ECM [89]. As such, bypassing the TM draining the liquid to the SC has been widely used as an approach to alleviate elevated IOP. Several devices are currently under development with the aim of improving the outflow through the TM.

#### *3.1.1. Devices in development*

**The Glaukos iStent** (Glaukos Corporation, Laguna Hills, CA, USA) is a heparin-coated micro stent that bypasses the TM by creating a pathway from the anterior chamber to the SC [90]. Implantation of this device in patients undergoing cataract surgery resulted in a sustained decrease in IOP (IOP ≤ 21 mmHg) in 72% of patients 12 months after implantation compared to 50% in the control group. Twenty-four months after surgery 61% still had IOP levels below 21 mmHg whereas in the control group 50% of patients maintained the targeted IOP. Other outcomes included in the study, such as decrease in IOP ≥ 20% and medications reduction, were also positive for the device-implanted patient group. Further studies have shown that sustained elevated IOP may affect the shape of the SC and therefore implanting one iStent may not be sufficient to achieve a sustained decrease in IOP. To solve this issue studies implanting several iStents have been performed showing promising data [91].

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**The Hydrus microstent** (Ivantis Inc., Irvine, CA, USA) is an intra-canalicular scaffold made of nitinol that is surgically implanted into the SC during cataract surgery. This device is manufactured to follow the curve of the SC and widens the opening of the canal avoiding its collapse. The efficacy of this device has been studied in patients undergoing cataract surgery and the results of these studies show that reduction in washed out diurnal IOP ≥ 20% was higher in the implanted group compared to the cataract surgery alone group 24 months after surgery (80 vs. 46%). Implantation of the device was also able to reduce the use of hypotensive medications [92].

**InnFocus Microsunt**, previously known as the MIDI Arrow (InnFocus Inc., Miami, FL, USA), is made of poly(styrene-block-isobutylene-block-styrene) SIBS, a synthetic thermoplastic elastomeric biomaterial that does not cause inflammation. The implant is used in conjunction with Mitomycin C to modulate would healing post-surgery. This device is placed in the anterior chamber and drains into the scleral surface [93]. The device was implanted in 23 eyes that had failed maximum tolerated glaucoma medication. The patients were followed for a period of 3 years; 14 patients received the implant alone whereas the rest were implanted concomitantly to cataract surgery. Years 1, 2 and 3 after the procedure 100, 91 and 95% of the patients fulfilled the success criteria of the study (IOP ≤ 14 mm Hg and IOP reduction ≥20%), and the mean number of glaucoma medications was reduced from 2.4 ± 0.9 to 0.3 ± 0.8, 0.4 ± 1.0 and 0.7 ± 1.1, respectively. Adverse events of the procedure included transient hypotony (13%) and transient choroidal effusion (8.7%); both adverse events resolved spontaneously [94].

**The XEN45 Gel Stent** (Allergan, Dublin, Ireland) is a soft flexible implant initially developed by AqueSys but later acquired by Allergan. The device is manufactured in collagen-derived gelatine cross-linked with glutaraldehyde and is injected through the anterior chamber into the sub-conjunctival space. The device swells upon hydration creating the channel. The XEN45 is approved in Europe, Turkey, Canada and Switzerland for reduction in IOP in patients with POAG where previous medical treatments have failed and is in late stage development in the USA. In Europe, the device can be used in conjunction with cataract surgery or as a standalone procedure. The data obtained from clinical trials show a mean drop of 47% from preoperative IOP in the standalone procedure and a 40% decrease when combined with cataract surgery. The main adverse events of this procedure include intra-operative sub-conjunctival or anterior chamber bleeding (1.2%), cataract-related complications (0.8%), post-operative hyphema (2.6%), self-limiting choroidal effusion (1%) shallow anterior chamber (0.8%), viscoelastic injection into the anterior chamber (0.6%) and anterior chamber tap to release retained viscoelastic (0.4%).

### 3.2. Drainage devices to the suprachoroidal space

There are several devices designed to drain AH from the anterior chamber to the suprachoroidal space, where the fluid is reabsorbed by the scleral channels of the choriocapillaries. These devices are based on the existence of a difference in hydrostatic pressure between the supra-choroidal space and the anterior chamber; this difference favours unidirectional flow from the anterior chamber to the suprachoroidal space reducing IOP. The materials used to manufacture these devices vary from gold to non-biodegradable polymers; materials that are inert, non-biodegradable and biocompatible to ensure proper function of the device.

### *3.2.1. Devices in development*

**The CyPass** (Transcend Medical, Menlo Park, CA, USA) is a fenestrated polyamide supraciliary device that connects the anterior chamber with the suprachoroidal space. The device is implanted during cataract surgery and its efficacy has been tested in a multi-centre, prospective study enrolling 136 subjects with two cohorts. Cohort 1 was composed of subjects with OAG requiring cataract surgery that had uncontrolled IOP (IOP; ≥21 mmHg, $n = 51$), whereas cohort 2 was composed of subjects with OAG requiring cataract surgery with controlled IOP (<21 mmHg, $n = 85$). Glaucoma medications were stopped post-surgery but could be restarted if needed. The results of the study indicate that there was a reduction of 37% in mean IOP 24 months after surgery. There was a statistically significant decrease in the need for glaucoma medications in both cohorts [95]. Further development of this device includes a randomized controlled trial that is currently underway (**Table 2**).

| | Device | Manufacturer | Material | Status | Trial ID |
|---|---|---|---|---|---|
| Devices draining to the SC or to the sub-conjunctival space | iSTENT | Glaukos Corporation | Non-ferromagnetic titanium | FDA approved in patients undergoing cataract surgery. Phase IV | NCT00326066 |
| | Hydrus microstent | Ivantis | Nitinol (alloy of nickel and titanium) | Phase III | NCT01539239 |
| | InnFocus Microshunt | InnFocus | Poly(styrene-block-isobutylene-block-styrene) SIBS | Phase IV | NCT02177123 |
| | XEN45 | Allergan (AqueSys) | Collagen-derived gelatine | Phase IV | NTC02006693 |
| Devices draining to the suprachoroidal space | CyPass | Transcend Medical | Non-biodegradable polyimide | Safety and Efficacy | NCT01085357 |
| | SOLX gold shunt | SOLX | Gold | Phase III | NCT01282346 |
| | Aquashunt | OPKO health | Polypropylene | Safety and Efficacy | NCT00834223 |
| | STARflo | iSTAR Medicals | Silicone microporus material | Safety and Efficacy | NCT02272569 |

**Table 2.** Devices in development for glaucoma.

**The SOLX gold shunt** (SOLX Inc., Waltham, MA, USA) communicates the anterior chamber with the suprachoroidal space via 19 channels formed between the two 24-karat medical-grade gold plates that form the shunt. The device is approved in Europe but still investigational in the USA. Several clinical trials have been conducted for this device with different outcomes. Success for this device was defined as a target IOP between 5 and 22 mmHg and an IOP decrease ≤20%. Most clinical studies for this device have yielded a success rate around 80%. In contrast, in a study performed by Hueber and co-workers enrolling 31 patients implanted with the device and followed up for a period of 4 years most patients (97%) failed

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the established success criteria. This difference outcome may be due to a fibrotic reaction to the device in this particular trial [96].

**The Aquashunt** (OPKO Health Inc., Miami, FL, USA) is a device made of polypropylene curved to accommodate the eye's shape. The results from a clinical study enrolling 15 patients with uncontrolled IOP indicate that eight of the patients achieved an IOP reduction of 31%, four of which needed concurrent medical therapy to reach satisfactory IOP after a period of 12 months. Further clinical studies have not been initiated [96].

**The STARflo** glaucoma implant (iSTAR Medical SA, Wavre, Belgium) is made of a microporous silicon elastomer and implanted intrascleraly into the suprachoroidal space. Clinical data are available from a limited number of cases, and it shows a reduction in the pre-operative IOP of 37.0 mmHg to a post-operative IOP of 14.3 mmHg 12 months after implantation. The reduction in glaucoma medication intake went from 3.25 medications/day to 1.5 intake/day.

## 4. Conclusions

Current medical therapy for glaucoma is insufficient to avoid the deleterious effects of this progressive ophthalmic neuropathy. In the last decade, significant efforts have been made in order to develop new products that use novel approaches to address the unmet needs of a disease that is still the second cause of blindness. This review gives an overview of these approaches, focusing on new targets that regulate AH balance in the eye or that are involved in fibrosis and scaring; processes that complicate the long-term success of glaucoma filtration surgery.

New mechanism of actions such as therapies based on oligonucleotides, gene therapy and stem cells is also reviewed. Products based on these mechanisms of action are already showing promising results in the clinical setting and may represent new options for patients that have uncontrolled IOP and that do not respond to current therapy.

A brief overview of neuroprotective approaches is also given; products based on this approach represent an excellent complementary option for IOP reduction strategies.

Finally, improvements in medical devices used to increase AH outflow are also reviewed. New devices achieve significant reduction in IOP and many can be used as stand-alone procedures offering an option to patients and settings where glaucoma medications are not a medically viable option.

Innovation in glaucoma may eventually change current disease treatment paradigms in order to offer solutions to a wider number of patients for whom current treatment options cannot stall disease progression. Achieving a sustained IOP reduction that warrants optic nerve protection over time is the main goal to be achieved, and some of these products may contribute towards that goal. As it has been the case for current glaucoma therapy, significant advances in quality of life of glaucoma patients may come from combining different approaches together to treat glaucoma in a comprehensive way.

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Chapter 7

# Laser Trabeculoplasty and Aqueous Dynamics

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Additional information is available at the end of the chapter

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**Abstract**

For the past four decades, laser trabeculoplasty has been a staple in the treatment armamentarium against glaucoma. Although the exact mechanism of laser trabeculoplasty has not been fully elucidated, its clinical utility in lowering intraocular pressure has been well established. Aqueous dynamic studies uniformly reveal an increase in aqueous outflow facility at the trabecular meshwork. Accumulating evidence suggests that the mechanism is the result of complex cellular and biochemical processes. Histopathological studies of the trabecular meshwork tissue after argon laser suggest an additional mechanical role. The traditional treatment algorithm for glaucoma placed laser trabeculoplasty as an intermediary between medical therapy and incisional surgery. However, because of the safety profile of selective laser trabeculoplasty, recent studies have challenged this treatment paradigm. One such study was a multicenter trial headed by our department that compared laser trabeculoplasty and medical therapy as initial treatment for glaucoma. We showed a similar efficacy between the two modalities, reinforcing the possibility of using laser as the initial treatment in the right clinical setting.

**Keywords:** trabeculoplasty, SLT, ALT, outflow facility

## 1. Introduction

Laser trabeculoplasty entered the treatment armamentarium of glaucoma in 1979 when Wise and Witter showed that application of argon laser to the trabecular meshwork significantly reduces intraocular pressure (IOP) [1]. In an era when medically uncontrolled glaucoma patients underwent incisional surgery, argon laser trabeculoplasty (ALT) was welcomed as a much-needed intermediary treatment that bridged medications to surgery. The Glaucoma Laser Trial (GLT) showed that ALT was as effective as medical therapy as initial treatment for glaucoma [2, 3]. However, post-laser complications due to photocoagulative damage like lack of repeatability were major limitations for initial treatment with

ALT to be widely adopted [4, 5]. In 1995, Latina and Park introduced selective laser trabeculoplasty (SLT), a Q-switched, frequency-doubled, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser [6]. In contrast to its predecessor, SLT delivers a fraction of the energy delivered by ALT, avoiding most of the untoward effects that can arise from thermal damage [7]. Due to its superior safety profile and potential repeatability, SLT has challenged the traditional treatment paradigm [8].

The production and maintenance of IOP is dependent on the balance between the rate of aqueous humor production and outflow. Since the 1950s, this balance was conceptualized by the Goldmann equation, which states IOP equals the rate of aqueous production divided by outflow facility plus the episcleral pressure (IOP = F/C + Pv) [9]. This was based on the assumption that aqueous flow in living tissue can be expressed in linear terms. Therefore, at best, this equation is an approximation of the complex physiologic conditions that determine IOP [10]. Laser trabeculoplasty targets the trabecular meshwork, which is the site of the conventional outflow pathway, lowering IOP by increasing outflow facility.

The IOP-lowering effect of laser trabeculoplasty is well established in clinical practice [11]. However, the exact mechanism by which this is achieved is only now being unraveled. In this chapter, we present the current knowledge on the effect of laser trabeculoplasty on aqueous humor dynamics in the anterior chamber. Further, we will discuss the shifting perspectives in the use of laser trabeculoplasty in the clinical setting.

## 2. Mechanisms of action of laser trabeculoplasty

### 2.1. The mechanical theory of laser trabeculoplasty

The settings of the argon laser are 50-μm spot size, 0.1-s pulse duration, and power starting at 600 mW. However, operating parameters are not standardized, and settings are dependent on the operator and an arbitrary tissue end point with blanching and vaporization bubble formation. The laser is applied to the trabecular meshwork and sets in motion a physiologic pathway that may require 1–2 months before its IOP-lowering effect can be appreciated [12]. In the original pilot study for ALT, Wise and Witter hypothesized the mechanism to be through mechanical tightening of the trabecular meshwork surrounding the laser treatment spots supporting the original mechanical theory [1].

The histopathological changes seen after ALT are the sequelae of photocoagulative thermal energy applied on the surface of the trabecular meshwork. All studies performed in the past several decades showed significant thermal damage associated with treatment spots. The thermal damage was characterized by crater formation and surrounding coagulative changes in the uveal and corneoscleral layers of trabecular meshwork. Crater formation was associated with disruption of collagenous beams, fibrinous exudates, and lysis of trabecular endothelial cells [13, 14]. Recent studies demonstrated a dose-dependent change in the size and depth of the coagulative damage with increasing laser energy [15, 16]. One study showed the presence of an endothelial membrane overlying the trabecular meshwork

in patients who experienced failure after ALT, revealing a possible mechanism for IOP rise after trabeculoplasty [17].

SLT is a frequency-doubled 532-nm Nd:YAG laser with a fixed setting of 400 μm spot size and pulse duration of 3 ns. The power is variable and dependent on the operator. Its main advantages compared to ALT are its superior specificity to pigmented trabecular cells and reduced photocoagulative and collateral damage [18]. Selective killing of pigmented trabecular cells has been demonstrated in cultured trabecular cells [19]. This is owed mostly to the short pulse duration, which is shorter than the thermal relaxation time of most tissues. Thermal relaxation time is the time needed for a chromophore to cool down by converting electromagnetic energy into thermal energy. The rapid pulse of energy delivered by SLT prevents excessive thermal diffusion and damage to the adjacent tissue.

Studies uniformly show less structural damage in trabecular meshwork treated with SLT compared to those treated with ALT. The ultrastructural changes arising from SLT are not visible with light microscopy and scanning electron microscopy (SEM), where trabecular beams appear intact and similar in appearance to the adjacent, untreated tissue. However, significantly damaged trabecular beams have been reported in the tissue treated with energy levels higher than those used in the usual clinical setting, one study at 2.0 mJ and another at 1.0–4.6 mJ [16, 17]. Transmission electron microscopy (TEM) of SLT-treated regions show extracellular pigment granules with a characteristic "cracked" appearance [13, 16]. Of note, this characteristic change was seen even at lower energy settings (0.4 mJ). This finding aligns with a study that showed SLT using low energy (0.3–0.5 mJ) had comparable success with treatments using conventional energy (0.6–1.0 mJ) [20].

The mechanical theory of trabeculoplasty states that laser-induced thermal burns to the trabecular meshwork cause tissue contraction and tightening of the trabecular ring. A mechanical stretch is applied to the intervening tissue, effectively opening the untreated portions of trabecular meshwork and widening Schlemm's canal, leading to increased aqueous outflow [21]. However, the mechanical theory alone does not fully explain the mechanism of laser trabeculoplasty. First, cross-sectional increase of Schlemm's canal was only noted to increase in eyes with IOP high enough to mechanically collapse the trabecular meshwork (>40 mmHg), not accounting for eyes with lower IOPs [22]. Second, although photocoagulative damage is apparent shortly following treatment, increased aqueous outflow and IOP reduction do not occur until several weeks later [23]. Third, significant IOP lowering is seen in SLT which does not induce the coagulative changes seen in ALT. In the following section, we will highlight the cellular and biochemical pathways leading to increased aqueous outflow and lower IOP (**Figure 1**).

### 2.2. The cellular theory of laser trabeculoplasty

Attrition of trabecular cells has been observed with normal aging and is correlated with progressive decline in aqueous outflow facility. In glaucoma, the rate of trabecular cell loss is significantly increased compared to non-glaucomatous eyes [24, 25]. Laser-induced trabecular cell division, migration, and repopulation have been observed [26]. These findings suggest that

trabecular cells play a central role in trabecular meshwork function and laser trabeculoplasty lowers IOP by stimulating meshwork cells.

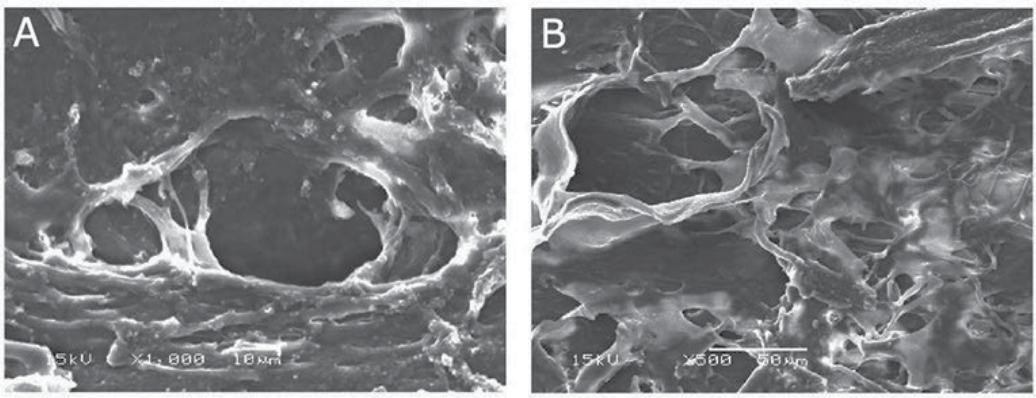


**Figure 1.** (A) Electron microscopy of trabecular meshwork treated with ALT showing characteristic crater formation and coagulative damage. (B) SLT-treated trabecular meshwork at high energy levels (2.0 mJ/pulse) shows tissue scrolling near treatment areas. These changes are not observed in therapeutic levels (<1.0 mJ/pulse) [13]. Modified with permission from [16].

ALT on human corneoscleral explants stimulated a nearly twofold increase in DNA replication and fourfold increase in cell division in the early post-laser period [26, 27]. During the first 2 days following ALT, the increased cell division was noted predominantly in the anterior meshwork near Schwalbe's line. After 2 weeks, the laser burn sites displayed migration of and repopulation of new trabecular cells. Interestingly, the replicative effect of the laser was widespread with the untreated 180° of the meshwork showing evidence of cell division as well, raising the possibility of cellular signaling as a potential mechanism. A similar study performed in vivo on cynomolgus monkeys compared the effect of ALT and SLT on trabecular cell division [28]. SLT-treated eyes had a significantly greater rate of cell division compared to ALT.

Trabeculoplasty with both ALT and SLT has been demonstrated to recruit monocytes to the trabecular meshwork. In one study, SLT was demonstrated to induce a fivefold increase of monocytes [29]. This is thought to occur through an upregulation of several cytokines and chemotactic factors, which will be discussed in more detail in the following section. Autologous monocytes introduced in the anterior chamber of rabbit eyes resulted in a significant reduction in outflow facility and IOP [30].

### 2.3. The biochemical theory of laser trabeculoplasty

Trabecular cells synthesize and are surrounded by extracellular matrix (ECM) products such as collagen, glycosaminoglycans (GAGs), proteoglycans (PG), fibronectin, and other structural elements [31, 32]. There is mounting evidence that ECM of trabecular meshwork plays an important role in the regulation of aqueous outflow [24]. It is a major component of the juxtacanalicular meshwork (JCM), which is thought to be the site of greatest aqueous flow

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resistance [33]. Along with trabecular cell loss, increased fibrillar ECM deposition around elastic-like fibers, or sheath-derived plaques, has been identified as a common feature in various forms of open-angle glaucoma [25, 34]. Alterations in ECM components have been observed following laser trabeculoplasty.

GAGs, a major component of ECM, are large carbohydrate polymers composed of repeating disaccharide units. They are thought to fill the intertrabecular spaces of the JCM, regulating aqueous flow by forming viscoelastic gel-like solutions [35]. Trabecular meshwork GAGs are abundant and exist in the form of hyaluronic acid, keratan sulfate, chondroitin sulfate, and heparan sulfate [36]. Chondroitin sulfate forms a sheath surrounding the elastic-like fibers in the JCM, and increased levels seem to correlate with elevated IOPs. Rabbit eyes with dexamethasone-induced ocular hypertension (OHTN) showed an increase in chondroitin sulfate and decrease in hyaluronate levels [37, 38]. Later, the same group discovered elevated chondroitin sulfate levels and decreased hyaluronate and heparan sulfate levels in human eyes with glaucoma [39]. Hyaluronic acid levels were noted to be 77% reduced and chondroitin levels were elevated 24% in glaucomatous trabecular meshwork [40]. Trabeculoplasty has been shown to modulate GAG synthesis patterns by trabecular cells. Argon laser treatment of organ cultures reverted the composition to a normal GAG expression pattern in 7–10 days [22].

Proteoglycans (PG) are another major component of ECM and are composed of a protein core bound to several GAG chains. Diminished ECM turnover at the JCM is associated with aqueous flow resistance. Several lines of evidence point to the role of proteoglycans as important modulators of trabecular meshwork ECM turnover. SLT treatment of cat eyes revealed an elevated presence of biglycan, prolargin, keratocan, and fibromodulin compared to non-lasered controls [31]. The laser-induced change in GAG and PG may offer new insight into the biologic mechanism of laser trabeculoplasty. The exact role of the increased expression of glycoproteins with trabeculoplasty is still not known and further research is warranted.

Matrix metalloproteinases (MMP) are a group of zinc endopeptidases that are involved in ECM degradation and turnover [41]. Trabecular cells maintain ECM homeostasis by expressing several members of the MMP family including, collagenase, gelatinase A (MMP-2), stromelysin-1 (MMP-3), gelatinase B (MMP-9), and MMP-14 [42]. Laser-induced upregulation of MMP-2, MMP-3, and MMP-9 has been demonstrated after ALT and SLT and is thought to play a key role in ECM modulation and IOP reduction [43]. This is mediated through reactive secretion of cytokines interleukin-1β (IL-1β) and tumor necrosis factor $\alpha$ (TNF-$\alpha$) [44]. The same factors are thought to mediate laser-induced recruitment of trabecular meshwork monocytes after SLT [29]. Of note, upregulation of MMP is the basis for mechanism of topical prostaglandin analogs and upcoming adenosine signal-mediated medications.

Although the IOP-lowering effect of laser trabeculoplasty is well established in clinical practice, its precise mechanism is not fully understood. It is likely a complex interaction of mechanical, cellular, and biochemical factors that culminate in increased outflow facility and lowered IOP. In the following section, we will move beyond mechanism of action and discuss the measured effect of laser trabeculoplasty on aqueous humor dynamics.

## 3. Aqueous dynamics of laser trabeculoplasty

Tonography is performed either by applanation (Goldmann) or indentation (Schiøtz) of the cornea, displacing aqueous fluid and temporarily increasing IOP. The elevated IOP can induce a reduction in aqueous production. The reduction of inflow is indistinguishable from increased outflow, causing an overestimation of true outflow facility termed "pseudofacility" [45]. On the other hand, fluorophotometry is a noncontact method that determines aqueous flow by measuring the disappearance of fluorescein from the anterior chamber [46]. It is thought by some to be a more accurate method as it avoids tonographic sources of error such as ocular rigidity and pseudofacility. Despite its drawbacks, tonography yields internally consistent and reproducible results and continues to have value as a clinical and research tool [47–49].

A decrease in outflow facility with age has been reported using tonography, fluorophotometry, and perfusion studies of normal eyes [50–52]. An approximately 30% decline in outflow facility has been observed in eyes <40 years of age (0.33 μl/min/mmHg) compared to >60 (0.23 μl/min/mmHg) [50, 53]. The age-related decline in outflow facility in OHTN and glaucoma occurs parallel to non-glaucomatous eyes. However, the absolute value of outflow facility is significantly lower in these entities compared to age-matched controls [54, 55]. This finding was corroborated by a 10-year longitudinal study of tonographic outflow facility in hypertensive eyes which demonstrated a progressive decline with age [56]. Atropine was found to reduce, but not eliminate age-related decline outflow facility, suggesting that intrinsic changes in the trabecular meshwork were likely at play [57]. This declining outflow facility has been correlated with the progressive trabecular cell loss and changing ECM composition, both of which has been demonstrated to reverse following laser trabeculoplasty [24].

The effect of ALT on the tonographic outflow facility has been extensively studied. In previously untreated POAG patients, a 63.5% increase in tonographic outflow facility was measured with a 33% reduction in IOP [58]. A similar study on patients already on topical therapy showed a comparable 64% increase in outflow facility and 29% reduction in IOP [59]. Furthermore, this efficacy of ALT did not change in patients on maximum therapy with 64% increase in tonographic outflow facility and 29% reduction in IOP. Medications prior to laser treatment do not appear to alter the effect of ALT on tonographic outflow facility. Fluorophotometric aqueous outflow increased by 25.9% after ALT [60]. The same study showed no significant increase in outflow until 1 week after laser application. The latency in treatment response is contrary to the mechanical theory where laser-induced structural changes are visible immediately following treatment. Instead, it is in keeping with the timing of trabecular cell activation and ECM remodeling following treatment. A study comparing the effect of ALT on fluorophotometric and tonographic outflow showed an increase in outflow facility using both methods [61]. The fluorophotometric outflow increased from 0.016 to 0.075 μl/min/mmHg, while tonographic outflow increased from 0.112 to 0.151 μl/min/mmHg. The difference in outflow facility values highlights the measurement errors inherent in tonography [45, 62].

The effect of SLT on tonographic outflow facility is comparable to ALT. In previously untreated OHTN, 360° treatment with SLT caused a 55.5% increase in outflow facility and 21% reduction

in IOP [63]. A study by the same group compared the effect of 180° vs. 360° treatment on tonographic outflow facility [64]. The 180° and 360° groups achieved an increase in outflow facility of 37.5 and 41%, respectively. Although there was a trend favoring the 360° group, there was no statistically significant difference between the two groups. This observation is in concordance with the observation of trabecular cell division even in untreated areas after trabeculoplasty [27]. Fluorophotometric measures showed a 41.2% increase in outflow facility after SLT [65].

## 4. Selective laser trabeculoplasty as initial treatment

Several retrospective and prospective studies comparing the clinical effectiveness of ALT with SLT showed no demonstrable short-term or long-term difference between the two modalities [23, 66–70]. Although IOP reduction is comparable, the true advantage of SLT over ALT lies in its superior safety profile and repeatability. SLT delivers a fraction of the energy output of ALT resulting in less pain and inflammation associated with treatment [23]. The incidence of iritis, post-laser IOP spikes, and peripheral anterior synechiae is significantly reduced with SLT compared to ALT [71–73]. Furthermore, the lack of trabecular meshwork scarring makes SLT more amenable to repeat treatment [4, 74–77].

The current treatment paradigm for glaucoma starts with medical therapy in the form of eye drops, followed by laser trabeculoplasty, and culminates with surgery. This treatment progression was born from the perceived superior safety profile of medications compared to laser therapy and surgery. As discussed above, the selective laser trabeculoplasty (SLT) has significantly improved the safety of laser therapy and challenges the existing treatment paradigm.

Topical eye drops have long been the initial treatment of choice due to its relative safety in the armamentarium of glaucoma treatments. Medical therapy, however, is not without drawbacks. Medication compliance rates among glaucoma patients are notoriously low with reported nonadherence rates ranging from 30 to 80% [78–80]. Nonadherence is an immense problem and is clearly a significant risk factor for vision loss in glaucoma patients [81]. Difficulty in instilling drops, medication side effects, prohibitively high costs, and complex drop regimens further contribute to this problem [82]. A decline in quality of life has also been reported as a direct result of these challenges associated with medications [83]. Finally, cost studies have revealed significant cumulative savings of SLT over medications and filtering surgery [84, 85].

SLT has shown to have a comparable reduction in IOP compared to single medical therapy. However, SLT has the clear advantage in light of medication compliance, cost, and side effects. This begs the question: Should SLT be offered as the initial treatment for glaucoma? This prompted the evaluation of SLT versus medication as the initial therapy for glaucoma in a multicenter, prospective, randomized clinical trial. Better known as the SLT/MED trial, our study randomized patients to receive SLT (100 applications, 360°) or medication (prostaglandin analog). After 1 year of follow-up, there was a similar IOP reduction between the two groups with a 26.4 and 27% reduction in SLT and medication groups, respectively. There was a trend toward more treatment steps necessary for adequate IOP control in the medication arm with

27% requiring additional drops compared to 11% in the SLT group receiving additional laser [8]. Other prospective studies have been done which corroborate with our findings [86–88].

## 5. Conclusions

Histopathological findings suggest SLT has mainly a biologic effect while ALT has an additional mechanical effect [13, 16]. However, accumulating evidence seems to favor the cellular and biochemical theory of trabeculoplasty for both ALT and SLT. Aqueous dynamics studies following ALT reveal no significant changes in outflow until 1 week following laser, suggesting the mechanical theory may play a smaller role than previously thought. Nevertheless, the exact mechanism of laser trabeculoplasty is becoming better understood but further studies are needed.

Although the exact mechanism is somewhat uncertain, the clinical utility of laser trabeculoplasty is clearly established. Comparative studies of ALT and SLT do not seem to yield a statistically significant difference in efficacy [66–69]. The SLT/MED study showed a comparable reduction in IOP between patients receiving SLT and medications as initial treatment [8]. In light of low medication adherence rates, drug side effects, and cost of medical therapy, this study reinforces the possibility of using SLT as an initial treatment in the right clinical setting.

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Chapter 8

# Glaucoma Surgery and Aqueous Dynamics

Parul Ichhpujani

Additional information is available at the end of the chapter

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**Abstract**

Reduction in intraocular pressure is the only proven method to treat glaucoma. When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or incisional surgeries are introduced. In this chapter, we discuss the physiological basis for the established surgical procedures as well as the newer surgical procedures. Most new surgical innovations have been designed according to natural physiology by routing aqueous as nature intended, through the Schlemm's canal. This has been possible because of better understanding of the outflow system and the availability of micro-technology to manipulate it.

**Keywords:** trabeculectomy, glaucoma drainage device, minimally invasive glaucoma surgery, outflow resistance

## 1. Introduction

Glaucoma is defined as a group of disorders that result in death of ganglion cells due to axonal damage at the level of the lamina cribrosa of the optic nerve.

Intraocular pressure (IOP) is considered to be the only alterable risk factor for diagnosis and treatment of glaucoma. IOP reduction is attained either by increasing outflow or by reducing aqueous humor production [1]. Therefore, basic understanding of aqueous humor circulation is important for successful management of glaucoma. Aqueous humor pathways have been discussed in detail in a prior chapter in the book. This chapter focuses on the various surgical modalities available to reduce or bypass the outflow resistance.

## 2. Site of outflow resistance

Evidence suggests that the majority of outflow resistance in the trabecular meshwork is generated in the inner wall endothelium of Schlemm's canal and its underlying matrix in the juxtacanalicular trabecular meshwork [2]. Rosenquist et al. has shown that following trabeculotomy, close to half (49%) of outflow resistance is eliminated at a perfusion pressure of 7 mm Hg [3]. In another study, Grant has shown that nearly two-third (71%) resistance is eliminated at a perfusion pressure of 25 mm Hg [4]. Schuman et al. have shown that 35% of resistance is eliminated at a perfusion pressure at 10 mm Hg, when 1 O'clock hour of the tissue from the outer wall of Schlemm's canal was ablated using the excimer laser [5]. These studies suggest that one-third to half of the outflow resistance lies distal to the inner wall of Schlemm's canal at normal pressure and partly outflow resistance is related to pressure-dependent changes in the outflow pathway. As the intraocular pressure increases, Schlemm's canal collapses and reduces outflow and effective filtration.

## 3. Restoration of the outflow facility

Excision of sites causing increased outflow resistance would result in restoration of outflow. It is not possible for a surgeon to precisely pinpoint the area which needs to be excised for an individual patient, therefore, logically, surgeons would like to address all aspects of the outflow system.

The current gold standard, trabeculectomy, has done well for many medically refractory glaucoma patients. Despite its efficacy in lowering IOP, ease of the surgical procedure, it is fraught with potential sight threatening issues. Glaucomatologists and bioengineers are leaving no stone unturned to find a better alternative to address the flaws of trabeculectomy.

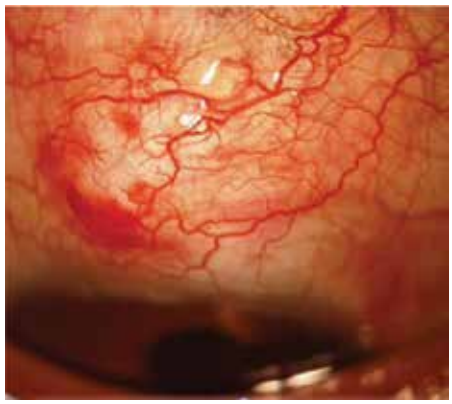

**Figure 1.** Failing trabeculectomy bleb with corkscrewing of conjunctival vessels secondary to scarring.

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### 3.1. Surgeries addressing trabecular meshwork

- *Trabeculectomy:* Opening a pathway through the meshwork, either by removing tissue or punching a hole (trabeculectomy) encourages aqueous outflow into Schlemm's canal.

  Despite modulation of the subconjunctival space into a porous matrix, the procedure is **not** a physiological bypass and remains dependent on the size of the ostium, tension in the sclera flap, as well as wound healing and its modulation [6].

  A decrease in the hydraulic conductivity of the bleb capsule results in an increase in fluid pressure within the bleb, altering its mechanical and biochemical environment resulting in progressive scarring (**Figure 1**) and consequent bleb failure [7].

  In addition, these incisional surgeries can result in decreased quality of life due to bleb-related foreign body sensation, induced astigmatism, and secondary cataracts.

- *Trabeculectomy with collagen implants:* The development of tissue engineering has offered a plausible solution to reduce postoperative fibrosis and scarring. The use of collagen-glycosaminoglycan copolymers leads to random and relatively loose reorganization of regenerating myofibroblasts, fibroblasts, and the secreted extracellular collagen matrix, resulting in reduced scar formation [8]. These implants offer a potential alternative to antifibrosis agents as they produce more loosely organized, yet more abundant bleb tissue than a bleb created without antimetabolites.

  Ologen (Aeon Astron Corporation, Taipei, Taiwan) (also named iGen) is the commonly available collagen implant, which consists of >90% lyophilized porcine atelocollagen and <10% lyophilized porcine glycosaminoglycan. This implant also acts as a spacer to mechanically separate the subconjunctival and episcleral tissues to prevent fibrosis. The implant is placed subconjunctivally over the scleral flap posteriorly and only a small portion covers the scleral flap (**Figure 2**), else the implant would act as a mechanical tamponade and prevent outflow from the subscleral space [9].

- *iStent:* Trabecular bypass devices such as iStent reduce IOP by bypassing the thin layer of juxtacanalicular tissue, without the need for creating a hole in the sclera and a filtration bleb. iStent bypasses the meshwork, creating a direct route from the anterior chamber into Schlemm's canal (**Figure 3**).

  There is also a second-generation model called the iStent inject (Glaukos Corporation), which has been CE marked for use in Europe. It contains a head facing the anterior chamber that is 230 μm in width with four inlets for the passage of aqueous into the device and out through Schlemm's canal.

  Zhou and Smedley have shown in their cultured autopsy eye perfusion experiments that adding successive bypass shunts produces a step-wise increase in outflow. The first shunt has the maximum IOP reducing effect, reducing IOP from 21.4 ± 3.8 to 12.4 ± 4.2 mm Hg, successive addition of up to four stents placed into SC produced step-wise reduction in system pressure [10].

Hunter et al. showed in anterior segment perfusion models with the iStent inject that outflow facility increases from 0.16 ± 0.05 μL/min/mm Hg to 0.38 ± 0.23 ($P < 0.03$, $n = 7$), and then an additional iStent inject further increased outflow facility to 0.78 ± 0.66 ($n = 2$) [11].

- *Ex-PRESS:* The Ex-PRESS device relies on nonphysiologic subconjunctival flow as its mechanism of IOP lowering. In eyes with prior failed trabeculectomies, Ex-PRESS can help to reestablish the aqueous flow without having to repeat the original procedure [12]. The Ex-PRESS fits easily in the middle ground between a repeat trabeculectomy and a larger glaucoma drainage device like a Baerveldt, Molteno, or an Ahmed tube shunt.
- *Viscocanalostomy:* In viscocanalostomy, inner wall of the endothelium is disrupted and communication is established between the lumen of the canal and the juxtacanalicular space. Bed of canal is scraped with a forceps or trabecular aspiration. This leads to the removal of a homogenous external trabecular membrane in one coherent plane that allows aqueous humor to egress through the remaining inner trabecular layers [13].

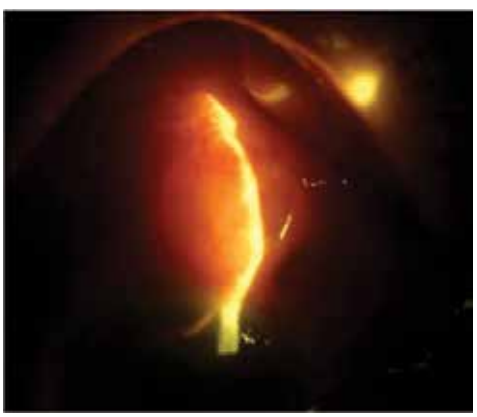

**Figure 2.** Ologen implant in subconjunctival space.

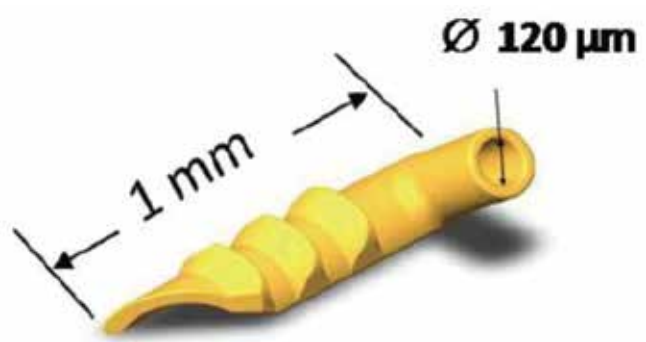


**Figure 3.** First-generation iStent.

### 3.2. Surgeries addressing Schlemm's canal

The detailed mechanism of aqueous humor dynamics across the endothelial lining of Schlemm's canal from the Juxtacanalicular trabecular meshwork (JCT) via giant vacuoles and pores has been discussed in detail in a prior chapter. The number of giant pores and vacuoles is less in glaucomatous eyes as compared to normal eyes, thus accounting for the increase in outflow resistance [14].

- *Viscocanalostomy:* Dilating Schlemm's canal with viscoelastic material may remove the stenosis-related resistance, as discussed earlier.
- *Canaloplasty:* Canaloplasty is an ab externo procedure that entails 360° intubation of Schlemm's canal (**Figure 4**), along with suture-assisted distension of the canal in order to restore physiologic outflow via the conventional pathway without the formation of a fistula or bleb. Potentially, the suture tension may increase TM permeability, similar to the action of pilocarpine [15] as well as help to maintain a patent canal lumen, similar to the intraocular tensioning suture [16].

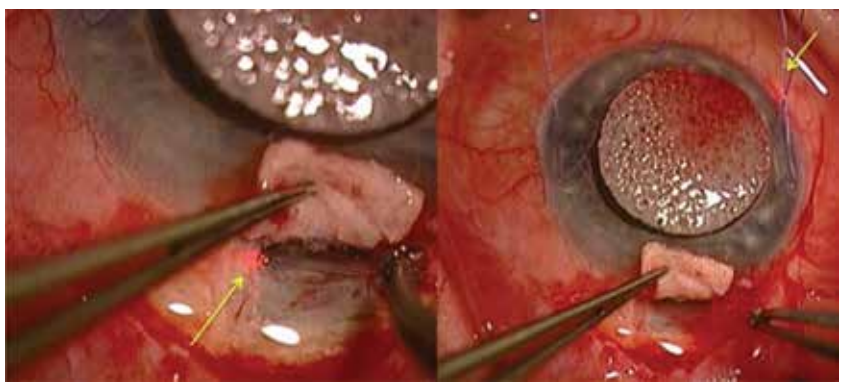

**Figure 4.** Nonpenetrating Schlemm's canaloplasty using the iScience cannula.

### 3.3. Surgeries addressing collector channels

The collector channels connecting the aqueous veins and the distal part of the outflow pathways originate in the outer wall of Schlemm's canal. These collector channels are not evenly distributed around Schlemm's canal circumferentially. The outflow is closer to areas with larger collector channels.

- *Minimally invasive glaucoma surgery (MIGS):* The advent of microinvasive glaucoma surgery has brought new dimension to glaucoma treatment. Minimally invasive glaucoma surgery is likely to provide medication-sparing, conjunctival-sparing, ab interno, more physiological approach to IOP reduction for patients with mild-to-moderate glaucoma that is safer than traditional incisional glaucoma surgery.

MIGS stents, e.g., iStent, Hydrus, give better results when positioned close to a patent collector channel, thus increasing the possibility of surgical success.

- *Canaloplasty:* Schuman et al. have shown that when the IOP is elevated, trabecular meshwork herniates into the ostia of collector channels and reduces the passage for aqueous outflow. Cannulating the whole of Schlemm's canal, as in canaloplasty, and injecting viscoelastic material may "pop" open these herniations and enable 360° access to collector channel ostia for the egressing aqueous [17].

### 3.4. Surgeries addressing episcleral venous system

Theoretically, IOP should directly correlate with the episcleral venous pressure (EVP). However, when the entire TM is removed, 25% of total resistance still remains, underscoring the importance of EVP measurement in an accurate and reproducible way [18]. Episcleral venous pressure is highly variable and may range from 3 to 14 mm Hg. In addition, if the pressure gradient differential is low and resistance is also located distally in the episcleral venous system, restorative outflow surgery has less chance of being effective than if the pressure gradient differential is high.

In cases with elevated episcleral venous pressure, incisional filtration surgery can help lower the IOP, but it is associated with a high incidence of choroidal effusion or hemorrhage.

Preoperative IOP reduction may be attained by intravenous mannitol and other systemic antiglaucoma medications. Additionally, the flow through the scleral flap may be adjusted to allow for a higher IOP in the early postoperative period. Using a releasable suture allows controlled reduction of IOP. Drainage implants may also be a good choice if the flow through the implant is kept to a minimum in the early postoperative period.

Another way of classifying various surgical procedures depends on how the procedure influences the aqueous dynamics.

#### *3.4.1. Surgeries that bypass conventional aqueous outflow pathway*

- Trabeculectomy
- Nonpenetrating deep sclerectomy
- Glaucoma drainage devices:

  Most conventional shunts consist of a tube designed to shunt aqueous from the anterior chamber to a distal plate via a tube to the posterior subconjunctival space, from where aqueous is directly absorbed into the sclera and episcleral vasculature to enter the orbital circulation, bypassing both the conventional and uveoscleral pathways. The primary tube-plate junction includes a rim through which the tube empties onto the explant plate surface to avoid closure of the tube orifice following eventual encapsulation of the device by fibrosis [19].

- Viscocanalostomy, canaloplasty

- Trabeculotomy
- Goniotomy
- Ab interno trabeculotomy or Trabectome surgery:

  Selective removal of the TM and inner wall of SC is performed using the Trabectome; while leaving the rest of the outflow system (outer wall of SC, collector channels, and aqueous veins) relatively intact. A strip of TM and inner wall of SC spanning 80–100° is ablated and removed under direct gonioscopic visualization. The simultaneous aspiration of tissue debris reduces the inflammatory stimuli and opportunity for scarring among shards of incised or ruptured tissues remaining after traditional goniotomy or trabeculotomy [20].

*3.4.2. Surgeries that increase the uveoscleral outflow*

- ExPRESS shunt
- iStent
- Suprachoroidal gold SOLX shunt:

  This shunt is an ab externo suprachoroidal trans-limbal shunt and works as a "controlled" cyclodialysis, draining aqueous into the suprachoroidal space. The anterior end of this 24-karat gold device is placed into the anterior chamber over the sclera spur via a scleral incision and the posterior end positioned in the suprachoroidal space (**Figure 5**). It includes several channels through its body. Aqueous flows both through the channels in the body of the shunt and around its body [21].

- Cypass:

  This mini shunt is placed in the supraciliary and suprachoroidal space to increase uveoscleral outflow by creating a small cyclodialysis (**Figure 6**) [22].

  Along the length of the stent are microholes that allow for circumferential egress of aqueous into the suprachoroidal space and the distal end of the stent allows longitudinal egress of fluid.

- Hydrus:

  Hydrus is implanted using s a preloaded injector via a clear corneal incision and is inserted into and sits within Schlemm's canal, wherein it extends 3 clock hours. It does not block the collector channel ostia in the posterior portion of Schlemm's canal as it has a scaffold design, and it has a 1 mm inlet portion, which resides within the anterior chamber. As a standalone procedure, it can be inserted through a 1–1.5 mm corneal incision. Once inserted into Schlemm's canal, it can dilate it by four to five times the natural width of the canal [23].

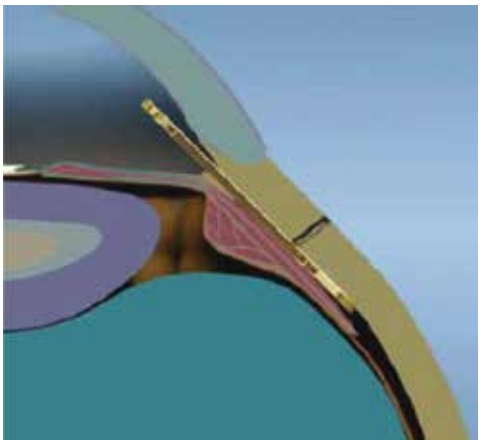

**Figure 5.** Gold SOLX shunt in suprachoroidal space.

**Figure 6.** CyPass shunt *in situ*.

### *3.4.3. Surgeries that decrease aqueous production*

Cycloablative procedures reduce IOP by destroying the ciliary body epithelium that produces aqueous humor. Modalities include:

- Contact (transscleral) cycloablation
  - Cyclocryotherapy [24]

- Diode/Nd:YAG [25]

- Noncontact cycloablation
  - Nd:YAG/Diode
- Transpupillary argon green cyclophotocoagulation
- Endoscopic ablation

  In endoscopic cyclophotocoagulation (ECP), the laser is applied under direct endoscopic view causing localized shrinkage of the ciliary processes due to thermal coagulation (**Figure 7**). This causes an initial reduction in blood supply to the ciliary processes, and a consequent reduction in aqueous production. Partial reperfusion of the ciliary body over 4–6 weeks means that the rates of hypotony and phthisis are lower than those associated with other methods of cyclodestruction.

  Earlier cycloablative procedures were reserved only for refractory cases, but recent studies have shown that endocyclophotocoagulation can be used for the treatment of mild-to-moderate glaucoma. It is conjunctival-sparing, blebless, and can be combined with cataract surgery [26, 27].

Despite all the aforementioned advances, the quest for a perfectly predictable and physiological glaucoma procedure with rapid recovery and a greater margin of safety is ongoing.

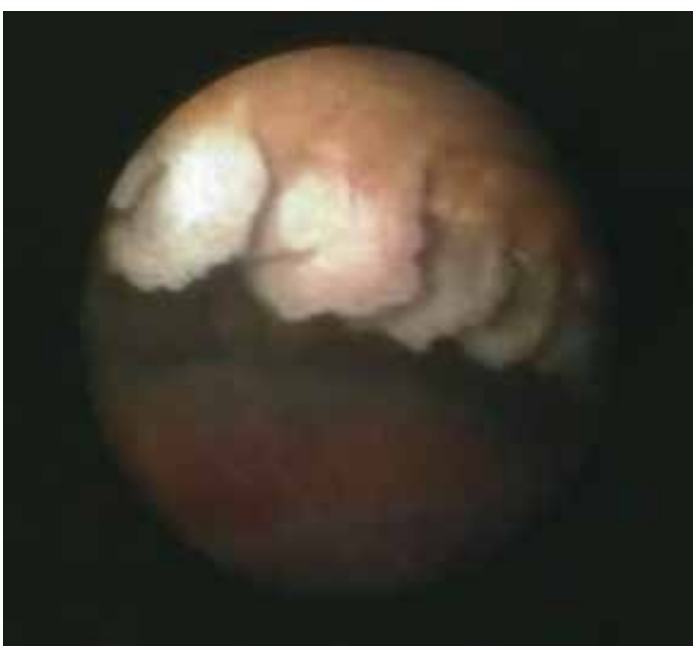

**Figure 7.** Shrinkage of ciliary processes following ECP.

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Written for ophthalmology residents and practitioners, this book provides the most comprehensive resource covering all the major aspects of aqueous humor and intraocular pressure dynamics. In addition to chapters on the conventional and new technologies for intraocular pressure assessment, there is a novel chapter on the engineering perspectives of continuous monitoring of the intraocular pressure. Based on the newer insights in aqueous outflow, this text offers a rational approach to the medical and surgical management of glaucoma.

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