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Review

Minimally Invasive Glaucoma Surgery: What Do We Know? Where Should We Go?

Chen Xin[1], Huangzhou Wang[2], and Ningli Wang[1]

[1] Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China
[2] Ophthalmology Department, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Correspondence: Ningli Wang, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, No. 17. Hougou Alley Dongcheng District, Beijing 100005, China. e-mail: wningli@vip.163.com

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With the arrival of a plethora of new and revolving minimally invasive glaucoma surgery techniques, glaucoma specialists currently are fortunate to have various surgical options that aim to recovery of the function of the aqueous outflow system in different ways. Meanwhile, the aqueous outflow system has become the hot point of researching. In ARVO 2019, a special interest group session was held on new perspectives on minimally invasive glaucoma surgery. Ten surgeons, clinical professors, and experimental scientists were invited to report their latest studies and discussed on five hot topics in this special interest group. This review summarizes the special interest group session and posts the issues of greatest concern, providing insight to the aqueous outflow system and areas that require further study.

Introduction

The Special Interest Group (SIG): New Perspectives on minimally invasive glaucoma surgery (MIGS) was held during ARVO on May 2, 2019, in Vancouver, Canada. Five invited speakers and eight discussants, whose clinical and basic research focus on MIGS or aquoeus outflow pathway, met and discussed current highly relevant questions in this area.

In the new era of MIGS procedures, glaucoma specialists currently are fortunate to have various surgical options that aim to restore the function of the aqueous outflow system by different mechanisms. MIGS procedures were developed to lower the intraocular pressure (IOP) with fewer complications compared with the conventional trabeculectomy and glaucoma drainage implant surgeries.[1–3] With the development of MIGS, the aqueous outflow system has become the hot point of research. It is hypothesized that the outcome of canal-based MIGS depends on accurately identifying the specific site of resistance within the drainage system.[4–6] Meanwhile, new discoveries improve our understanding of the aqueous outflow system and promote research to develop new potential treatments.

Five topics were presented. Each topic began with a 7-minute presentation by an invited speaker followed

by a 10-minute discussion led by the discussants, focusing on the main topic and specific issues that need further exploration.

Clinical Outcomes of MIGS Targeting Schlemm's Canal (SC)

Since the beginning of the 21st century, MIGS has developed rapidly with the goal of providing a safer and a less invasive surgical intervention for patients, with mild to moderate glaucoma stages or for those that are intolerant to standard medical therapy. Generally, the MIGS indicates procedures with an ab interno approach, with little or no scleral dissection and without conjunctival manipulation. In this review, from a mechanical point of view, we focused on the MIGS targeting SC and ab externo procedures, working on the trabecular meshwork (TM) pathway, such as canaloplasty, ab externo trabeculotomy, trabectome, ab interno canaloplasty, ab interno trabeculotomy (GATT),[7,8] Kahook Dual Blade Goniotomy (New World Medical, Rancho Cucamonga, CA) iStent and Hydrus microstent (Iventis, Irvine, CA) implantation. In general, the mean 1-year IOP after MIGS procedures ranges between 12 and 16 mm Hg, which is higher than the episcleral venous pressure.[9–15] This raised the question why MIGS procedures that target SC are unable to lower IOP to episcleral venous pressure levels.

For the trabectome, it was reported that the treated area remains opened with no tissue scar remodeling of human corneoscleral rims segments.[16] A series of cases with symptomatic delayed-onset hyphema after trabectome were followed in the absence of further surgeries or trauma.[17] In our patients with GATT, no reported spontaneous hyphema occurred. In a series of patients with good 1-year IOP after GATT, blood reflux remained in the treated area when the patients were examined by the gonioscope with pressure on the sclera. This phenomenon indicates that the tissue leaflets may flap back, or the scar tissues may modify the treated region, which can induce resistance for aqueous humor drainage. Changes in the distal pathway could be another reason for such resistance after canal-based MIGS procedures, which will be discussed elsewhere in this article.

Dr Wang had reported the postoperative complications and many potential factors for the failure of canal-based MIGS procedures according to his clinical practice. The reported postoperative complications included IOP elevation, sustained hyphema and ciliary body detachment. On the other hand, iris synechia, SC adhesion, collector channel (CC) blockage, and damage in the region distal to CC, are potential reasons for surgical failure.

The Distal Pathway of the Aqueous Outflow System

Another theme of MIGS-related study focuses on the distal pathway, which are structures beyond TM in the conventional aqueous pathway. Such structures include those from the CC to the intrascleral vessels, but also the aqueous veins and episcleral venous plexus. In healthy cadaver human eyes, complete trabeculotomy was able to eliminate 49% of all the outflow resistance at a physiologic perfusion pressure,[18] whereas 71% of the outflow resistance was eliminated at a higher perfusion pressure.[19]

These whole globe perfusion studies provided strong evidence on pressure-dependent resistance changes in resistance in the TM region, and they revealed the existence of an additional resistance distal to SC. Interestingly, the pressure in the SC of monkey eyes was approximately 10% lower than that in the anterior chamber, even when the IOP was greater than 50 mm Hg.[20] However, what are the mechanisms regulating such resistance? How does the resistance changes in primary open-angle glaucoma (POAG) and after MIGS procedures? The answers to these questions are discussed in this review.

What Role Do the CCs Have in the Regulation of Aqueous Outflow?

The study by Fautsch et al.[21] showed that CCs are not evenly dispersed around the eye. Indeed, most CCs join other vessels in the intrascleral vasculature, and others directly proceed to the aqueous vein without any interruption. The authors proposed that the conventional outflow pathway could be studied as separate functional regions, which are composed of a CC, with adjacent SC and TM.[2] Using the same technique, the authors further demonstrated that the CC configuration and its different response to changes in pressure could be a contributing factor to changes in the outflow facility of POAG eyes.[22] Multiscale analysis of segmental outflow patterns showed that CC ostia were associated with regions of high macroscale tracer intensity, and that tracer patterns were relatively insensitive to changes in perfusion pressure.[23] It was also reported that the diameter of CC varies along its

length, being wider at the proximal part. The largest CCs were found in the superonasal and inferonasal quadrants, which also correlated with the regions of greatest outflow.[24,25] These studies showed that CCs play a vital role in regulating the aqueous outflow. Nevertheless, other studies showed that active flow could not be observed in some TM regions near CC ostia, especially in the superior and temporal regions of the eye.[26,27] In addition, the active flow areas decreased with increasing IOP, and this change was reversible by decreasing the pressure from high to normal levels.[28,29] Therefore, many enigmas relevant to CC require further investigations, such as the phenotypes of CCs, their variable resistance, and the distal factors regulating them.

MIGS Procedure-Induced Changes in the Distal Part of the SC

Using high-resolution optical coherence tomography (OCT), Xin et al.[30,31] revealed the structural linkage between the components of the TM–SC–CC complex and highlighted the importance of the synchronized pressure dependent motion of the TM–SC–CC complex in aqueous outflow regulation. In some MIGS-targeting SC procedures, such as canaloplasty and ab interno canaloplasty, the passage of a microcatheter in the SC may disrupt the intraluminal structures, which could interfere with the physiologic regulation of the aqueous humor outflow, even when the IOP is well-controlled. In addition, a circumferential or partial trabeculotomy may directly expose the CC ostia to the anterior chamber pressure independent of the modulating influence of the intervening TM. Considering the vasoactive-related factors in the outer wall of SC, CC, and the more distal portion of the pathway,[32] the long-term exposure to high pressure may potentially induce contraction and degeneration of the vessels, mimicking the effects of arteriosclerosis. In addition, another potential hindrance for the long-term control of IOP in some MIGS procedures could be related to deficit in oscillatory pressure, which is essential for IOP homeostasis. Indeed, Xin et al. reported a loss of pulsatile flow in the aqueous veins of eyes with well-controlled 1-year IOP after circumferential trabeculotomy and canaloplasty. Even with a compensation maximum test, pulsatile fluid remained undetectable in the aqueous vein. This study represented the long-term influence of MIGS targeting SC procedures on the distal pathway (Xin C, et al. 2019;2019 Abstract 5244).[33]

The Effect of Perilimbal Tissue on Resistance in the Distal Part

The distal pathway from the aqueous vein to the episcleral vein passes through the sclera, which constantly bears the load of the IOP. The biomechanical properties of the sclera region influence the course and the response of the vessels that penetrate it. For example, high resistance to aqueous flow can result from the thick sclera in the microphthalmos.[34] The effects of biomechanical properties on the aqueous humor pathways in the perilimbal scleral tissue region and their associated role in IOP control are not well-understood. It has been recently shown in perfused porcine eyes that the IOP is strongly influenced by the tangential modulus of the most anterior region of the sclera. The tangential modulus reflects the tissue stiffness based on the definition as the slope of the static stress–strain curve. According to the study, modifying the biomechanical properties of anterior sclera might be a new target for POAG therapy.[35]

"Biomarker" of MIGS Targeting SC

It is generally accepted that both the proximal and distal portions of the TM outflow pathway play an important role in outflow resistance and IOP. The potential resistance sites in the conventional TM pathway are diverse in POAG. Currently, MIGS targeting SC procedures are mainly designed to reduce or bypass resistance in the TM region. Some procedures are also deemed to dilate SC and/or prevent TM herniation into CC. Therefore, identifying anatomic and physiologic biomarkers related to the disease is an important factor for glaucoma specialists. Recent advances in imaging technologies greatly improved our understanding of aqueous outflow structures in living human eyes. However, these advances are still at the research level and have limited application in the clinical setting.

Episcleral Venous Fluid Wave (EVFW)

SC-based MIGS procedures present an opportunity to gain an insight into aqueous pathways as observed during EVFW, an intraoperative visible blanching or whitening of the episcleral vessels as liquid enters them.[36] The fluid wave indicates patency of distal aqueous veins and may be a prognostic indicator for a successful outcome after SC-based MIGS.[4–6]

Several studies showed that the EVFW is positively correlated with trabecutome[5] and GATT[6] outcomes, and negatively correlated with preoperative IOP. Indeed, poorly defined EVFW had a higher likelihood of surgery failure.

A recent study revealed diverse patterns of the downstream aqueous veins after trabectome and iStent implantation,[4] and a similar degree (approximately 50°) of enhanced circumferential flow through the SC after both surgical procedures. These surgical observations correlated with prior cadaveric laboratory findings, showing that the circumferential flow in SC was limited to 1 or 2 hours on either side of a trabeculotomy.

Moreover, the clinical study demonstrated that, once established, the aqueous veins outflow patterns distal to MIGS sites, retained a fairly radial configuration and did not encroach significantly onto adjacent quadrants.[4] This finding was in line with the ex vivo findings of Gong's SIG presentation, which indicates that the segmentation of aqueous flow is preserved distally in the episcleral veins. Although EVFW is a feasible technique to assess the activity of the distal aqueous pathway, it has some limitations. EVFW does not represent a physiologic event, and the degree of blanching is somewhat arbitrary. In addition, the observation of EVFW is hindered under conjunctival conditions, such as chemosis, subconjunctival blood, and conjunctival scarring. In addition, poor control of perfusion pressure around the surgical interventional site is another confounding factor that limits the ability to quantitatively evaluate distal aqueous drainage. Finally, EVFW is an invasive intraoperative manipulation that would not useful for preoperative decision making.

Angiography of Conventional Aqueous Outflow

Angiography of the conventional aqueous outflow, such as canalograms[37–40] and aqueous angiography,[41–44] is another intraoperative imaging method. In a canalogram, a tracer is injected into SC from a microcatheter after SC exposure. A canalogram yields excellent images showing the outflow around the limbus, but also reveals the reflux of fluorescein crossing the TM to enter the anterior chamber. The first such study[37] proposed that the fluorescein dye under the standard lighting of a surgical microscope could be used as a tracer to visualize the aqueous veins.

The author proposed that good trabecular passage and good egress into the aqueous veins would indicate patent distal outflow pathways. In contrast, poor trabecular passage and poor aqueous veins fluorescein egress would indicate an obstructed TM and a closed CC. The combination of good trabecular passage and poor aqueous veins fluorescein egress would indicate that the site of outflow impairment is mainly in the distal outflow system. Although the canalogram provides a clue for identifying impaired locations, it has a limitation in that these observations do not reflect the naïve status. Indeed, the threading of the catheter through SC and the stepwise retraction of the microcatheter are not physiologic conditions, and the perfusion pressure in SC cannot be controlled.

In aqueous angiography, which was first described by Wessly in 1922, the tracer is injected into the anterior chamber to visualize the aqueous outflow pathways. A recent study used an intraoperative approach to visualize the aqueous outflow pathway.[42] In addition, combining the approach with the anterior segment OCT showed a correlation between the structure and the function of the route. Segmental aqueous outflow has been observed in all species. In living human and nonhuman primates, the signal is mainly nasal. Because aqueous angiography is done without intervening with the TM route, it could be used to identify the natural routes of the aqueous humor outflow.

The optimal placement of MIGS has not been determined yet. An apparatus mimicking the stepwise perfusion of multifluorescence microspheres into the anterior chamber was set up in the laboratory. Aqueous angiography with two-dye perfusion was employed ex vivo to test whether low flow regions could be improved and rescued in cow and cadaver human eyes.[45,46] However, such studies are not yet feasible to be performed in vivo in living human eyes.

OCT-Based Study

OCT is widely used to visualize SC, the CC, and the more distal structures. Recently, Moroi et al.[46] developed an innovative application of OCT angiography to visualize the aqueous veins. In the latest SIG, Dr Moroi presented a case with a fluorescein tracer observed at the time of trabeculotomy and an OCT angiography map obtained 5 years later. In this case, dual imaging systems indicated that this case primarily had an abnormality in the TM that related in elevated IOP. Based on the signal transformation in OCT angiography and on the fluorescein tracer, which revealed a large area of functional aqueous veins, she proposed that the successful 6-year outcome of trabeculotomy

was related to the intact deep and superficial aqueous veins within the healthy sclera.

The role of tissue biomechanics has been investigated in the TM. Indeed, TM stiffness plays an important role in the regulation of aqueous humor outflow. TM pulsatile movement, an indicator for TM stiffness, can be assessed using phase-sensitive OCT.[47] This technique was used to assess the reduction in TM motion in POAG cases in vivo, compared with healthy controls (Gao K, et al. 2019;ARVO Abstract 4842).[48]

New Insights on SC

In 1827, Friedrich Schlemm discovered a circular blood-filled vessel in the limbal region of a hanged person. The canal was later shown to be not directly connected to the anterior chamber, and was coined the name "Schlemm's canal." SC is a flattened tube that is lined with endothelial cells that are connected by tight junctions. Its inner wall is the final barrier that the aqueous humor should cross before entering the lumen of SC.[49] SC represents a unique basal-to-apical direction flow[50,51] and a continuous endothelial monolayer lying over a discontinuous basal lamina.[52,53] SC undergoes morphologic changes associated with IOP variations,[54,55] which elicited questions about the properties of SC: Is it a lymphatic or a blood vessel?

In 2014, Chen's team provided the first evidence on the high expression of prosper-related homeobox 1 (Prox1), a master regulator of lymphatic development, by SC endothelium (SCEs).[56] This discovery was corroborated by two other independent studies.[57,58] The expression of the factor promotes the commitment of developing tissues to lymphatic fate by budding from the veins to form the primitive lymph sac.[57,60] In addition, signaling through the vascular endothelial growth factor receptor-3, another lymphatic marker, is also involved in SC development.[59] Although SCEs do not express the lymphatic vessel endothelial hyaluronan receptor-1 or podoplanin,[56–59] they show high levels of CCL21,[61] which promotes lymphatic drainage. Moreover, transient or low levels of the lymphatic fate transcription factors FOXC2 and SOX18 were also present.[57,62] Several studies have provided evidence that SC originates from blood vasculature and acquires lymphatic-like properties along the developmental process.[57,63–68]

The complexity of the signaling pathway involved in SC development and in the initiation and maintenance of aqueous humor drainage have been demonstrated in multiple transgenic mice models.[56–60,68–70] It has been shown that SCEs are postnatally determined to acquire a lymphatic phenotype through the upregulation of Prox1. Tie2 is expressed before Prox1 in SCEs and is maintained at a high level to critically regulate SC integrity during the adulthood. Besides, the impairment of angiopoietin-TEK signaling may induce primary congenital glaucoma; and signaling through vascular endothelial growth factor C/vascular endothelial growth factor receptor-3 is considered another determinant for the development of SC. In contrast with SC, the TM originates from the mesoderm. SC interacts with the TM during its development, especially the most inner region of the TM. Thus, congenital glaucoma can be genetically divided into subclasses, which is a major prerequisite for the choice of the treatment of importance, the lymphatic fate had been reprogrammed to the original blood endothelial cell fate in a rodent model, even in the adulthood.[57,65] Aqueous humor outflow positively regulated SC formation and influences Prox1 expression.[56,57,67] SC in aged mice exhibited reduced aqueous humor drainage and a senescent endothelium. The latter had a lower expression of lymphatic vessel markers and increased expression of blood vessels and mesenchymal features.[60,69] Interestingly, the age-related changes in SC could be rescued by a TIE2-agonistic antibody that can potentially treat POAG.[60,62,68–70]

These experimental results might somehow explain the clinical outcome. Indeed, when we perform canaloplasty on patients with POAG with failed trabeculectomy, the microcatheter could be easily inserted around the entire circumference and the postoperative IOP gradually becomes controlled, compared with subjects receiving circumferential trabeculotomy alone.[71,72] This finding indicates that a more collapsed SC, as a result of damage from trabeculectomy, could have a lumen that remains open. The surgical procedure permits drainage of the aqueous humor into SC. Consequently, the increased shear stress from the enhanced aqueous flow across SCE might trigger an alteration in SCE phenotype and recovery of normal drainage.[55,73]

Considering that it shares both structural and functional similarities with the lymphatic vessels, SC might be targeted with lymph specific therapies. In this SIG, using a preclinical model Dr Chen presented an example showing that the molecular targeting of SC via a newly identified lymphatic factor can effectively lower IOP and treat glaucoma. As a surgically reachable space, SC could also provide a site to improve drug delivery and introduce a regenerative treatment to this region.[74–76]

Another topic of interest is the role of immune cells in the aqueous humor pathways of the eye.[77] Because the behavior of immune cells could be modulated by interactions with endothelial cells, SCEs are likely to have important roles in immune responses.

Nevertheless, many mechanistic questions related to immune cells and SC functions remain unclear at this stage.

New Treatment Targeting the Aqueous Outflow Pathway

Topical medication and laser therapy are common choices in the clinic before considering incisional surgery. Current pressure-lowering topical medications largely suppress aqueous humor production or enhance its clearance through unconventional pathways. However, recently cytoskeletal and nitric oxide agent have been introduced to improve the conventional outflow.[78–80] Laser treatment could be used in two ways: it can increase the aqueous outflow through procedures such as laser trabeculoplasty,[81,82] or it can decrease aqueous production by laser cyclophotocoagulation through transscleral or endoscopic approaches.[83,84] In this SIG, Dr Johnstone presented a novel pressure-lowering mechanism using transscleral micropulse laser, which we focus on in this review.

Laser Treatment

The recently developed micropulse laser, a subthreshold laser technique,[85,86] has been considered as a potential alternative to traditional glaucoma laser procedures to further decrease the risk of associated side effects without compromising the efficacy of laser treatment. The technique includes micropulse diode laser trabeculoplasty and micropulse transscleral cyclophotocoagulation. The latter is the main focus in this SIG session. The traditional TSCP delivers continuous high-intensity laser energy at 810 nm to the ciliary body in the infrared region, where the energy is strongly absorbed by melanin in the pigmented ciliary epithelium.

The continuous laser approach allows the build up of thermal energy and subsequent photocoagulative thermal reaction in the pigment epithelium of the ciliary body's secretory epithelium. In contrast, micropulse diode laser trabeculoplasty and micropulse transscleral cyclophotocoagulation uses a customized probe to deliver a series of repetitive short bursts of laser energy in an on-and-off fashion to target the ciliary body. During the on cycle the pulses of light emit energy, and the structures are allowed to cool during the off cycle, thus, protecting them from the time-dependent spread of thermal damage. The approach is designed to reduce the destruction of the surrounding tissues, which potentially results in fewer ocular complications without compromising the IOP-lowering efficacy of the treatment.[86]

A topic of discussion was the experimental results of studies designed to assess the effects of micropulse diode laser trabeculoplasty and micropulse transscleral cyclophotocoagulation and its potential to target the aqueous outflow system tissues (Johnstone M, et al. 2017;ARVO:58; Abstract 3468).[87] The presentation began with a video of the effects after the instillation of pilocarpine, thus, providing a comparison of the effects of a drug known to improve the conventional outflow.[88] Three different experimental approaches were used: (1) real-time observation and video before, during, and after the laser procedure, (2) comparison of high-resolution OCT images before and after the procedure. and (3) histologic analysis after the procedure. The study identified changes in the configuration of TM and SC that may enhance the conventional aqueous outflow. It also identified ciliary bodies and scleral shrinkage in the path of the laser. The resulting enlargement of the suprachoroidal space may provide a basis for enhancing the uveoscleral outflow.

Damage to the ciliary epithelium of the pars plicata was absent, which suggests that the procedure was not decreasing the IOP through ciliary epithelium ablation. Indeed, multiple mechanisms of action are likely to be involved; however, the mechanisms of chronic inflammation and alterations in the vascular supply could not be addressed because the study was designed to only identify acute effects. In addition, several laser parameters that could be modified warrant further study to assess their effects on the physiologic mechanisms of the outflow.

Rapid developments in the arena of new medications, alternative drug delivery systems (Johnstone M, et al. 2019;ARVO:60, 2825)[89,90] and laser treatments offer long-term IOP lowering. In addition, gene therapy, stem cell strategies,[91–94] and other novel approaches are in different stages of development. With this variety of choices, it is important to identify technologies that can predict glaucoma outcomes so that a personalized treatment approach can be recommended for each patient.

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ARVO SIG "New perspectives on MIGS" Participants.

Ningli Wang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China; Haiyan Gong, Department of Ophthalmology, Boston University School of Medicine, Boston, Massachusetts; Murray Johnstone, Department of Ophthalmology, University of Washington, Seattle, Washington; Sayoko E. Moroi, Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan; Lu Chen, Center for Eye Disease and Development, Vision Science Graduate Program, and School of Optometry, University of California, Berkeley, California; Ying Han, Department of Ophthalmology, University of California, San Francisco School of Medicine, San Francisco, California; Carol B. Toris, University of Nebraska Medical Center, Omaha; James C.H. Tan, Doheny Eye Institute and Department of Ophthalmology, University of California Los Angeles, Los Angeles, California; Ting Xie, Stowers Institute for Medical Research, Department of Anatomy and Cell Biology, University of Kansas School of Medicine, Kansas City, Kansas; Yiqin Du, Department of Ophthalmology, University of Pittsburgh, Pittsburgh; Xinyuan Zhang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China; Huaizhou Wang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China; Chen Xin, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

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