Minimally Invasive Glaucoma Surgery

Chelvin C. A. Sng
Keith Barton
Editors

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This book is an open access publication.
ISBN 978-981-15-5631-9 ISBN 978-981-15-5632-6 (eBook)
https://doi.org/10.1007/978-981-15-5632-6

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword

The last decade has witnessed an explosion of novel therapies that have heralded the era of interventional glaucoma. Minimally invasive glaucoma surgery (MIGS) has been the center piece of this movement, providing ophthalmologists and patients with an alternative to topical medications or traditional conjunctival surgery. These procedures share a common approach to minimize normal anatomical and physiological disruption in an effort to reduce risks and hasten recovery and improve quality of life. While it remains to be seen what the impact of MIGS on reducing the global burden of glaucoma will be, this field has generated substantial interest in improving the outcomes of MIGS procedures.

With the vast array of MIGS options now available worldwide, there is a great need for a concise, easily accessible, and complete review of these procedures. Understanding the design, surgical technique variations, complications and management, and patient selection is essential for the successful incorporation of MIGS into clinical practice.

Edited by two well-respected internationally renowned glaucoma specialists, Chelvin Sng and Keith Barton, *Minimally Invasive Glaucoma Surgery* provides a comprehensive review of the field. A unique feature of this book is the global view of MIGS, with a wide international cast of experts contributing to this cutting-edge book. An overview and essential anatomy of the outflow pathways provides the reader with a firm basic foundation for MIGS as a starting point. One can then immerse oneself on a specific procedure with the latest techniques, evidence and results. MIGS procedures can be differentiated based on their outflow target (Schlemm's canal/conventional outflow, suprachoroidal/uveoscleral, and subconjunctival). *Minimally Invasive Glaucoma Surgery* covers each approach with the necessary breadth and depth to assist the beginner, intermediate and advanced surgeon. The book finishes with both controversies and a global view of MIGS discussed in a thought-provoking manner.

Sng and Barton have put together an excellent and comprehensive collection of topics on MIGS, authored by top global experts in the field. This book serves a great reference for those looking to better understand MIGS and the role it plays in glaucoma management.

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Overview of MIGS

1

Jing Wang and Keith Barton

The term, minimally- or micro-invasive glaucoma surgery (MIGS), first coined around 2008 (II Ahmed, personal communication) has entered common ophthalmic parlance and is playing an increasing role in the management of glaucoma patients. In common, the devices and procedures referred to, are safer, less tissue invasive and associated with faster recovery than traditional filtering surgery, such as trabeculectomy or aqueous shunt implantation [1]. While the term initially referred only to *ab interno* Schlemm's canal bypass stents such as the iStent, it has expanded, though with somewhat inconsistent adoption, both by clinicians and by the manufacturers, not all of whom are enthusiastic about applying the MIGS label to their device, to encompass both *ab externo* and *ab interno* canal procedures, suprachoroidal implants, external filtration devices and to some degree, even new types of cyclodestruction. On the horizon are also drug-eluting implants. The US Food and Drug Administration (USFDA) defines MIGS as devices or procedures that lower intra-ocular pressure (IOP) with either an *ab interno* or *ab externo* approach, associated with little or no scleral dissection and minimal or no conjunctival manipulation, though USFDA workshops and guidance have tended to consider only implantable devices [2, 3]. This book covers the techniques that are most commonly regarded as eligible to sit under the MIGS umbrella, whether or not industry or clinicians prefer to call them MIGS. Others, such as the Ex-PRESS shunt (Alcon Laboratories, Inc., Fort Worth, Texas, USA), SOLX Gold Glaucoma Shunt (GGS, SOLX Ltd.,

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C. C. A. Sng, K. Barton (eds.), *Minimally Invasive Glaucoma Surgery*,
https://doi.org/10.1007/978-981-15-5632-6_1

Waltham, MA, USA) and canaloplasty have some similarities to MIGS techniques and devices, but will not be covered in detail.

A number of MIGS devices and techniques have relatively modest efficacy but, potential utility in a very large group of glaucoma patients with disease that is insufficiently severe to justify the invasiveness of conventional filtration surgery and the consequent intensity of postoperative care, yet burdened with medication and the attendant side effects and compliance issues thereof. A simple additional technique at the time of cataract surgery could have significant quality of life benefits for a large number of these patients. On the other hand, some MIGS devices can potentially achieve efficacy approaching that of traditional filtering surgery and are appropriate in selected individuals when larger IOP reductions are required, the exception being cases where glaucoma is very advanced.

Irrespective of the modest efficacy of many MIGS devices and techniques, the favourable safety profile lowers the threshold for early glaucoma surgery, especially when combined with cataract surgery, potentially delaying the requirement for more invasive surgery and associated risks. The additional reduction in the medication burden has the potential to reduce intolerance, improve quality of life and lower the long-term cost of medication while improving adherence.

MIGS can be categorized according to the tissue they target (or bypass): trabecular meshwork (TM) MIGS, subconjunctival MIGS, suprachoroidal MIGS and newer cycloablation procedures. MIGS devices include iStent Trabecular Micro-Bypass Stent and iStent *inject* (Glaukos Corporation, San Clemente, CA, USA), Hydrus Microstent (Ivantis Inc., Irvine, CA, USA), the XEN Gel Implant (Allergan plc, Dublin, Ireland) and PRESERFLO (formerly InnFocus) MicroShunt (Santen Pharmaceutical Co. Ltd., Osaka, Japan) (Table 1.1). At present, as a result of the

Table 1.1 Procedures and implants that fall broadly within the minimally invasive category of glaucoma surgery though a number of those listed would not be typically described as MIGS

Schlemm's canal	Subconjunctival	Suprachoroidal	Ciliary body coagulation
Stenting iStent Trabecular Micro-Bypass Stent iStent *inject* Hydrus Microstent	Xen Gel Implant PRESERFLO MicroShunt	iStent Supra MINIject (CyPass Micro-Stent)	High-Intensity Focused Ultrasound cyclocoagulation Micropulse diode laser cyclophotocoagulation Endocyclophotocoagulation
Cutting Trabectome (*Ab interno* trabeculotomy) Gonioscopy-assisted transluminal trabeculotomy (GATT) Excimer laser trabeculostomy Kahook Dual Blade (KDB)			
Dilating *Ab interno* canaloplasty (ABiC)			

withdrawal of the CyPass Micro-Stent (Alcon Laboratories, Inc., Fort Worth, Texas, USA), there are no commercially available devices that drain to the supra-choroidal space, though others are in development.

While there are a number of pathways targeted by MIGS devices, most MIGS procedures in which a device is not implanted, are designed to eliminate trabecular meshwork resistance from the outflow pathway: *ab interno* trabeculotomy (Trabectome; NeoMedix Corporation, San Juan Capistrano, CA, USA) and gonioscopic-assisted transluminal trabeculotomy (GATT). Newer surgical instruments such as the Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA, USA) and TRAB360 (Sight Sciences Inc., Menlo Park, CA, USA) are designed for *ab interno* removal of TM tissue to enhance physiological TM outflow system.

Ab interno canaloplasty (ABiC, Ellex Medical Pty Ltd., Adelaide, Australia) differs slightly in that it primarily dilates Schlemm's canal, although a small cut is made through trabecular meshwork to access the canal.

Concurrent with the appearance of the MIGS genre, a number of new cycloablation procedures have also appeared including micropulse diode laser trans-scleral cyclophotocoagulation (MicroPulse P3, IRIDEX IQ810 Laser System, Mountain View, CA, USA), applied externally via a new type of probe and High-Intensity Focused Ultrasound cyclocoagulation (EyeOP1 HIFU, EyeTechCare, Rillieux-la-Pape, France), applied externally but delivering a metered dose of ultrasound energy to the ciliary body. Endocylophotocoagulation (ECP), which was developed in the late 1990s, is analogous to conventional diode laser CPC, but applied via an *ab interno* approach and could also be considered in this category.

1.1 Trabecular Meshwork MIGS Devices and Techniques

Trabecular meshwork (TM) MIGS procedures and devices are numerous. They aim to eliminate trabecular meshwork resistance in the normal physiological outflow pathway in patients with mild-to-moderate glaucoma and ocular hypertension (OHT). They are indicated in combination with cataract surgery. In patients with chronic primary angle closure, the TM outflow system has likely long-standing and irreversible damage; TM MIGS procedures or implants should be approached with caution as the drainage pathway created whether stent or trabeculotomy, may occlude with iris because of the narrow angle. In angle closure, these procedures should generally be considered only after cataract surgery and confirmation that the angle has widened sufficiently that the risk of occlusion is low. In patients with advanced glaucoma, where the maximum possible pressure lowering is often desirable in order to minimize the risk of disease progression, TM MIGS procedures are not ideal as there is an opportunity cost in not achieving IOP control with the first surgical procedure.

All TM MIGS procedures involve direct gonioscopic visualization during surgery. TM MIGS devices include iStent Trabecular Micro-Bypass Stent, iStent *inject* (Fig. 1.1) and Hydrus Microstent (Fig. 1.2) [4–6]. These three devices aim to enhance TM outflow by stenting the Schlemm's canal. iStent Trabecular Micro-Bypass Stent and iStent *inject* are manufactured from heparin-coated titanium.

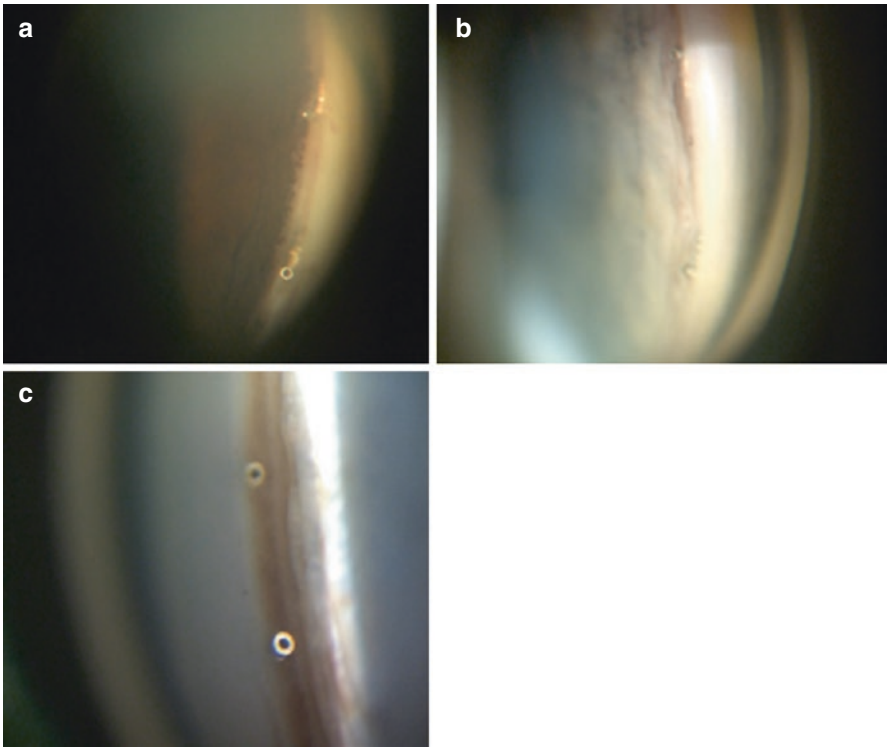

Fig. 1.1 Two iStent Trabecular Micro-Bypass Stents in the Schlemm's canal of two different patients (**a** and **b**) and two iStent *inject* implants in the trabecular meshwork (**c**). (Copyright Moorfields Eye Hospital and Keith Barton; reproduced with permission)

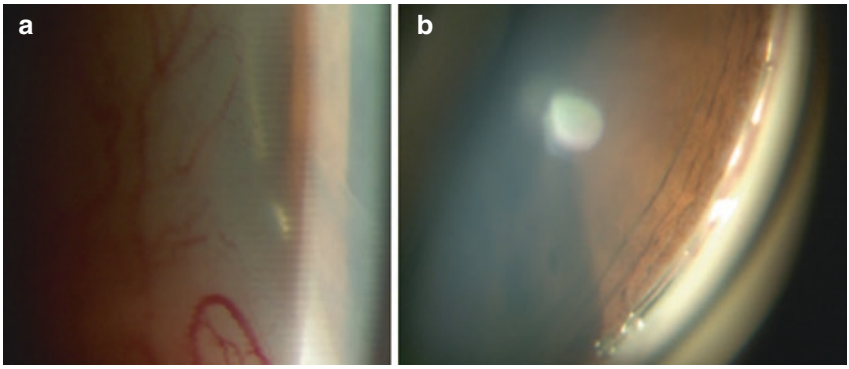

Fig. 1.2 The inlet of a Hydrus Microstent visible externally (**a**) and the Hydrus Microstent in the trabecular meshwork on gonioscopy (**b**). (Copyright Moorfields Eye Hospital and Keith Barton; reproduced with permission)

iStent Trabecular Micro-Bypass Stent is a 1 mm long, L-shaped device with a 120 μm lumen diameter. iStent *inject* is conically shaped, 360 μm in length and 230 μm at its largest diameter. The Hydrus Microstent is made of nitinol and is a crescent-shaped trabecular scaffold of 8 mm in length with a variable lumen diameter between 185 and 292 μm. Company-sponsored prospective randomized controlled trials have compared the effect of cataract surgery on IOP when combined with the iStent Trabecular Micro-Bypass Stent or the Hydrus Microstent to the effect of cataract surgery alone [4, 6]. Both demonstrated a modest but more sustained IOP-lowering effect in the group receiving cataract surgery combined with the TM MIGS device 2 years after surgery. All three are USFDA approved, at the time of writing, for implantation at the time of cataract extraction, but not for standalone surgery. In Europe, they are licensed for both.

Other TM procedures such as *ab interno* trabeculotomy (AIT) or Trabectome, GATT, Kahook Dual Blade and TRAB360 cut rather than stent the TM to varying degrees. Trabectome is the earliest FDA-approved TM removal procedure. It has a disposable 19.5-gauge handpiece with irrigation, aspiration and electrocautery combined. The tip of the Trabectome removes TM tissue and coagulates at the same time. Trabectome surgery is either performed at the beginning of cataract surgery or as a stand-alone procedure [7]. The Kahook Dual Blade is a disposable knife designed to remove a strip of TM tissue via a temporal incision. With a single incision, the Kahook Dual Blade and Trabectome can remove up to 120° of TM tissue, whereas GATT and TRAB360 (Sight Sciences, Menlo Park, CA, USA) can remove the entire TM tissue. GATT can be performed using either an illuminated microcatheter (iTrack, Ellex Medical Pty Ltd., Adelaide, Australia)—designed originally for *ab externo* canaloplasty procedure—or a 5-0 polypropylene or Nylon suture [8]. Under direct gonioscopic view, a micro vitreoretinal (MVR) blade is used to incise the TM wall, after which the catheter or suture is advanced to cannulate Schlemm's canal through the incision. Complete 360° catheterization of Schlemm's canal may not be possible in all eyes. A prospective non-comparative case series has reported sustained IOP lowering for up to 2 years after GATT [9]. As 360° trabeculotomy becomes a popular first-line intervention in primary congenital glaucoma, there has been some interest in treating juvenile open-angle glaucoma with GATT as a primary surgical option.

1.2 Subconjunctival MIGS Devices

The XEN Gel Implant (Allergan; formerly known as XEN Gel Stent, AqueSys Inc.) (Fig. 1.3) and PRESERFLO (formerly InnFocus) MicroShunt (Santen Pharmaceutical Co. Ltd.) (Fig. 1.4) are the two currently available subconjunctival MIGS devices [10, 11]. The XEN Gel Implant is a soft porcine-derived collagen implant that is inserted, *ab interno*, from the anterior chamber to subconjunctival space. Six millimetres long and with an internal diameter of 45 μm, the XEN is preloaded in an injector. Its major potential advantage over traditional filtering

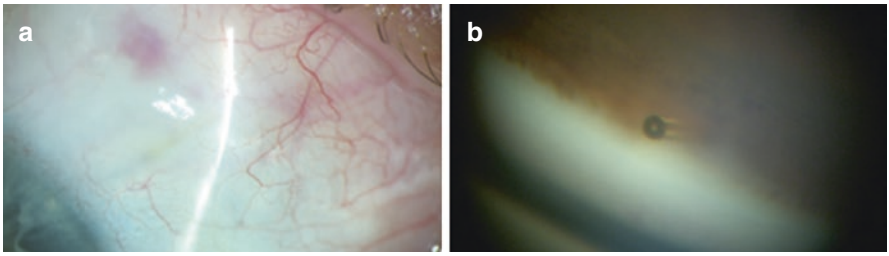

Fig. 1.3 XEN Gel Implant visible under the conjunctiva with a diffuse overlying drainage bleb (**a**) and the XEN Gel Implant visible in the anterior chamber (**b**). (Copyright Moorfields Eye Hospital and Keith Barton; reproduced with permission)

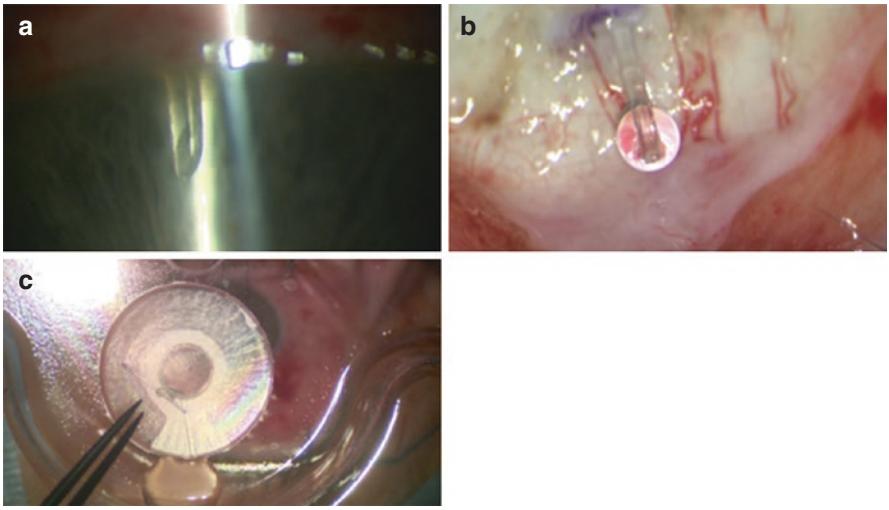

Fig. 1.4 The PRESERFLO MicroShunt in the anterior chamber (**a**), an external view showing aqueous drainage during implantation and before conjunctival closure (**b**) and the device prior to implantation (**c**). (Copyright Moorfields Eye Hospital and Keith Barton; reproduced with permission)

surgery is the avoidance of a conjunctival incision. However, the lack of conjunctival dissection requires precise placement of the XEN under the conjunctival tissue as the lumen of the XEN is easily blocked by Tenon's capsule. This explains a significantly higher rate of needling with the XEN [12]. Similar to the XEN Gel Implant, the PRESERFLO MicroShunt is also a tube that diverts aqueous humour from the anterior chamber to the subconjunctival space. The MicroShunt differs from the XEN in that it is implanted via an *ab externo* approach, necessitating conjunctival dissection. Unlike the XEN, the MicroShunt is of purely synthetic construction—poly(styrene-*block*-isobutylene-*block*-styrene) or SIBS. A randomized controlled trial comparing the MicroShunt with mitomycin C (MMC) to trabeculectomy with MMC for primary open angle glaucoma (POAG) is currently ongoing

(ClinicalTrial: NCT01881425). This is currently the only MIGS device that has been compared to trabeculectomy in a randomized clinical trial.

The IOP-lowering efficacy of subconjunctival MIGS, in selected cases, appears to approach that of traditional filtering surgery, thereby offering the possibility that they might have utility in more advanced or normal pressure glaucoma. On the other hand, subconjunctival MIGS are bleb-forming procedures and serious bleb-related complications such as infection, leakage and implant exposure have been reported [13].

1.3 Suprachoroidal MIGS Devices

Until recently, CyPass Micro-Stent was the only available suprachoroidal MIGS. It is a fenestrated micro-stent of 6.35 mm long with an external diameter of 510 μm and an internal diameter of 300 μm. It is made of a biocompatible polyamide material. The COMPASS trial is a randomized controlled trial comparing the effect of combined cataract surgery and CyPass insertion to cataract surgery alone in 505 POAG patients [14]. Two years after surgery, the IOP was lower on less medication in the group that underwent combined CyPass Micro-Stent implantation and cataract surgery than those that had cataract surgery alone. A prospective series of CyPass Micro-Stent implantation as a solo procedure in POAG patients with uncontrolled IOP demonstrated effective IOP lowering and avoided conventional filtering procedures in 83% of patients at 1 year follow-up [15]. After the COMPASS study was extended to 5 years after surgery (COMPASS XT), there was a significantly higher rate of endothelial cell loss in the combined CyPass Micro-Stent and cataract group compared to the cataract group alone. For this reason, the manufacturer (Alcon Laboratories, Inc., Fort Worth, Texas, USA) voluntarily withdrew the CyPass Micro-Stent from the market in August 2018, although it is estimated that there are currently around 33,000 implanted CyPass Micro-Stents in the world and managing the risk of endothelial loss may be an ongoing concern for several years after the withdrawal [16].

The iStent Supra (Glaukos) is a suprachoroidal stent made of polyethersulfone and heparin-coated titanium with a lumen diameter of 165 μm. The iStent Supra is not commercially available and there have been no prospective published efficacy studies at the time of writing.

1.4 Cyclophotocoagulation (CPC) Procedures

Cyclophotocoagulation procedures are also minimally invasive though they differ in that they reduce aqueous production by coagulating ciliary body tissue and are often not included within the MIGS genre.

Endocyclophotocoagulation (ECP) is an *ab interno* cycloablative procedure. An endoscopic camera equipped with an 810 nm diode laser probe in a single 18–20 gauge fibreoptic probe. The ciliary body epithelium is directly visualized during

treatment; usually 240–300° of ciliary body are treated with one incision. Two incisions are required for a full 360° treatment [17]. There is no prospective randomized controlled trial on the efficacy of ECP. A case series comparing ECP combined with cataract extraction and cataract extraction alone found slightly lower IOP in the combined group. A retrospective case series comparing ECP with a second glaucoma drainage device (aqueous shunt) in patients with failed previous aqueous shunt surgery found similar IOP outcome at 1 year [18]. Post-operative complications of ECP include inflammation, hypotony, uncontrolled IOP, cystoid macular oedema (10%) and phthisis. Intracameral triamcinolone is suggested to prevent fibrinous inflammation after ECP. Despite its *ab interno* approach, ECP theoretically can cause significant tissue damage and serious complications such as phthisis. Caution should therefore be taken in high-risk eyes.

Micropulse diode laser is a newer method of delivering diode laser to ocular tissue. Conventional laser application is continuous with a single pulse that lasts from 0.1 to 0.5 s. In conventional diode cyclophotocoagulation, the duration of a single laser pulse is usually as long as few seconds. Micropulse mode laser delivers the energy in pulses with pre-set *on* and *off* periods. The *off* period is longer than the *on* period allowing the tissue to cool down and minimize damage. Micropulse laser has been used in the treatment of retinal diseases and glaucoma. In one prospective randomized series, micropulse cyclophotocoagulation is shown to be as efficient, resulting in similar IOP with less complications compared with conventional CPC.

1.5 Overview Summary

Subconjunctival drainage of aqueous humour has been the cornerstone of glaucoma surgery. MIGS devices targeting subconjunctival drainage achieve lower IOP than those targeting Schlemm's canal and suprachoroidal drainage, at the cost of possible bleb-related and higher hypotony-related complications. MIGS targeting the trabecular outflow system such as iStent Trabecular Micro-Bypass Stent or iStent *inject*, Hydrus Microstent and AIT are best suited for patients with moderate OHT or mild to moderate POAG requiring cataract surgery. The IOP-lowering effect of these trabecular devices is limited by episcleral venous pressure (EVP) which limits the maximal IOP reduction to the mid-teens. Subconjunctival draining devices (XEN Gel Implant or PRESERFLO MicroShunt) can be used as solo glaucoma procedure and have better potential to achieve single digit IOP levels. The long-term efficacy of sub-conjunctival MIGS is still unknown as there are few published data on these devices. They both require anti-metabolite (MMC) use as subconjunctival scarring is inevitable with the diversion of aqueous humour to the subconjunctival space. Suprachoroidal drainage devices aim at a potential space where IOP lowering is not limited by EVP and bleb formation is avoided. Scarring in the suprachoroidal space remains an issue. Suprachoroidal devices can potentially be used as an adjunct to traditional glaucoma surgery if further IOP-lowering is required.

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Anatomy of the Aqueous Outflow Drainage Pathways

2

Kay Lam and Mitchell Lawlor

2.1 Introduction

Minimally invasive glaucoma surgery (MIGS) encompasses a group of procedures aiming to lower intraocular pressure (IOP) with reduced surgical times, more rapid postoperative recovery and a better safety profile compared with traditional filtration surgery. Increasing aqueous humour (AH) outflow may be achieved either through facilitating the existing pathways of Schlemm's canal and the suprachoroidal space or to bypass the normal angle anatomy to create a full thickness fistula into the subconjunctival space. Because of the importance of the anterior chamber angle in the pathogenesis of glaucomatous damage, an understanding of angle anatomy and aqueous outflow structures is critical to surgical planning and device selection for particular glaucoma subtypes. This chapter reviews the clinically relevant anatomy and functionality of the outflow apparatus in the human eye.

2.2 Aqueous Humour Outflow

Intraocular pressure, the main risk factor for glaucoma, is determined by the production, circulation and drainage of AH. The major drainage pathways are the trabecular outflow pathway (conventional outflow) and uveoscleral outflow pathway (unconventional outflow). Aqueous draining through the trabecular outflow system will traverse the trabecular meshwork, through the juxtacanalicular connective tissue, into Schlemm's canal and the collecting channels, and finally into the aqueous veins which then drain into the episcleral venous system. AH draining through the

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C. C. A. Sng, K. Barton (eds.), *Minimally Invasive Glaucoma Surgery*,
https://doi.org/10.1007/978-981-15-5632-6_2

uveoscleral route passes through the ciliary muscle bundles into the suprachoroidal space and then through the sclera into the orbital vessels [1].

The relative contribution of each of these outflow pathways is difficult to determine as it changes depending on the species studied and the method of measurement used. Nonetheless, it is clear that in humans, trabecular meshwork is the major pathway for aqueous outflow accounting for approximately 70–95% of drainage [2, 3]. Uveoscleral outflow in healthy subjects had traditionally been thought to represent a much smaller proportion of AH drainage in healthy humans than primates, though formal aqueous flow studies have reported a value of about 35% in young adults and 3% for individuals over 60 years of age [1, 4]. Aside from the relative contribution of outflow of the two pathways, there are a number of other important differences. Firstly, outflow from the anterior chamber across the trabecular meshwork into Schlemm's canal is pressure dependent, whereas uveoscleral outflow is pressure independent in the physiological range [5, 6]. Secondly, with advancing age, both the trabecular meshwork and uveoscleral outflow facility gradually decline, although there is a relatively greater decline in the uveoscleral contribution to AH drainage overall [2]. To compensate for this, production of AH also decreases with age and therefore IOP is relatively unchanged in the healthy aging human eye [2]. In contrast, eyes with primary open-angle glaucoma have higher outflow resistance in the trabecular outflow pathway than in age-matched normal control eyes, while secretion of AH is not changed [7, 8].

2.3 Trabecular Meshwork

The main ocular structures related to the trabecular outflow pathways are located around the scleral sulcus, a circular groove of the inner sclera, adjacent to the corneoscleral limbus [9]. The sulcus begins at the peripheral termination of Descemet's membrane and extends to the scleral spur, a ridge of inner scleral fibres that run parallel to the limbus, and project inward. This important landmark divides the conventional from the unconventional or uveoscleral outflow. It is best viewed by gonioscopy as no imaging device yet consistently identifies the scleral spur. The scleral spur may also play a role in preventing the ciliary muscle from causing Schlemm's canal to collapse [10]. Schlemm's canal, a circular tube, lies in the outer aspect of the scleral sulcus, while the trabecular meshwork lies at its inner aspect. The trabecular meshwork comprises connective tissue beams or lamellae that are interconnected in several layers to form a porous structure (Fig. 2.1). Each trabecular beam is covered by flat epithelial-like trabecular meshwork cells thought to provide self-cleaning phagocytic activity to maintain the porous structure. Anteriorly, the trabecular beams are attached to the peripheral cornea near the end of Descemet's membrane (Schwalbe's line) and extend posteriorly to ciliary body stroma and scleral spur. The spaces of the trabecular meshwork range in size from 20 to 75 μm and progressively decrease in size posteriorly. The trabecular band covers the internal aspect of Schlemm's canal and is relatively featureless in the unpigmented eye. However, when the meshwork is pigmented, the pigment is concentrated over the canal of Schlemm. Thus, the anterior nonpigmented portion of the trabecular meshwork does not filter, while the posterior pigmented portion of the trabecular meshwork does.

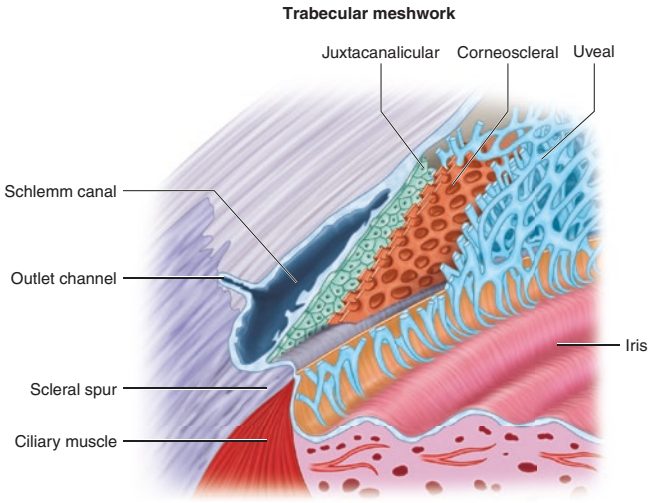

Fig. 2.1 Three layers of trabecular meshwork (shown in cutaway views): uveal, corneoscleral, and juxtacanalicular

This is clinically important as any trans-trabecular devices should target the posterior pigmented trabecular meshwork if the goal is the maximize flow into Schlemm's canal.

2.4 Schlemm's Canal

Schlemm's canal is an endothelial-lined circular tube with one of the highest hydraulic conductivities in the body [6]. Its pores, which range in size from 0.1 to 3 μm in diameter, allow passage not only of AH but also of particulate matter such as cells and ferritin. Additionally, the endothelial lining of Schlemm's canal changes in response to pressure gradient alterations. Elevated IOP leads to an increase in both the number and size of cellular out-pouchings or giant vacuoles while decreased IOP leads to a reduction [11]. AH is transmitted from the trabecular meshwork, through Schlemm's canal, to the distal venous collector system. AH exits Schlemm's canal through collector channels that are spaced at irregular intervals from the outer wall of the canal of Schlemm. They are approximately 25–30 in number and are predominately located in the nasal quadrants [12]. The collector channels ultimately lead to the episcleral venous system; there are two systems of intra-scleral channels: firstly, a direct system of four to six larger veins of Asher that drain directly into the episcleral venous system, and secondly, an indirect system of finer more numerous channels, which form an intrascleral plexus before ultimately draining into the veins of Asher. While the larger conjunctival veins of Asher are readily visible, the intra-scleral plexus is difficult to examine.

Multiple studies suggest that dysfunction of the intrascleral outflow plexus is related to glaucoma; eyes with more advanced disease show downstream collector

obstruction or atrophy [13] and functional outflow through human trabecular meshwork does not occur homogenously—there are regions of preferential flow adjacent to the location of collector channels. Corroborating this are studies showing that the total juxtacanalicular tissue adjacent to collector channels is expanded nearly twofold compared with the juxtacanalicular regions between collector channels [14]. As canal-based MIGS procedures aim to improve the flow of AH into the venous collector channels, estimating functionality preoperatively or intraoperatively would provide valuable information for both patient selection and prognostication. The finding of an "episcleral venous fluid wave", seen as downstream visible blanching of veins, may be a surrogate marker of anatomic patency of the conventional outflow system from the anterior chamber to the episcleral and conjunctival collectors [15].

2.5 Uveoscleral Outflow

The second route for AH outflow within the eye is through the unconventional outflow pathway (or uveoscleral pathway). The characterization of this pathway was first provided by Anders Bill in his pioneering work that estimated the outflow using tracer studies [16]. Unlike the trabecular outflow route, the uveoscleral outflow route is not a distinctive structural pathway with channels and tubes. Rather, AH passes through, around and between tissues of the ciliary muscle, supraciliary space and suprachoroidal space. Compared to the conventional pathway, the uveoscleral pathway is less well understood. Nonetheless, new devices that can provide surgical access to these spaces have led to a renewed interest in this anatomical region.

The anterior portion of the ciliary body extends into the chamber angle and there is no epithelial barrier between the anterior chamber and the ciliary muscle [17]. Similarly, there is no continuous cellular layer on the anterior iris face, so aqueous has direct access from the anterior chamber to the interstitial spaces of the ciliary muscle, and then through to the supraciliary and suprachoroidal spaces [16].

The supraciliary space is a narrow area between the outer surface of the ciliary body and the internal surface of the sclera anteriorly. Posteriorly, the suprachoroidal space is located between the choroid and the internal surface of the sclera. This subspace is approximately 30 nm thick and is composed of layers of pigmented collagenous processes derived from each tissue, forming a delicate collagen meshwork [18]. This space forms a transitional zone between the choroid and sclera and does not contain overt fluid under normal physiologic conditions.

The mechanism of how fluid from the supraciliary and suprachoroidal spaces exits the eye remains contested: Bill traced the route of radioactive-labelled proteins and other large molecules and proposed that the fluid seeps through sclera and episclera by diffusion into the orbit and then is absorbed by the orbital vasculature [16, 19, 20]. In contrast, Barany and others have suggested that the fluid is osmotically absorbed by the choroid and passes into the vortex veins [21–23].

Evidence of the potential IOP-lowering effect of the suprachoroidal space is derived from the clinical observation that a cyclodialysis cleft from trauma often

leads to hypotony. However, harnessing a cyclodialysis cleft to control IOP has remained challenging due to uncontrolled low pressures and then conversely pressure spikes on closure of the cleft. A number of new MIGS devices target this space with the view to obtaining a controlled IOP with appropriate pressure reduction and minimal hypotony.

2.6 Physiological Characteristics of Unconventional Outflow

Aqueous entry into the uveoscleral pathway begins through the interstitial spaces of the ciliary muscle, and ciliary muscle tone has an important influence on outflow. Administration of pilocarpine, which causes contraction of the ciliary muscle fibres and compression of extracellular space, causes uveoscleral outflow to decrease by 90% in cynomolgus monkeys [24]. In contrast, administration of atropine has the opposite effect: it causes relaxation of the muscle fibres, expansion of the extracellular space and thereby increases uveoscleral outflow [25]. Various prostaglandins also increase uveoscleral outflow by modifying the extracellular matrix between ciliary muscle bundles, thus reducing outflow resistance and allowing increased flow through these spaces [26].

Measuring outflow of the uveoscleral pathway is challenging because of intrinsic challenges in measuring the flow rate. Measurements can either be direct or indirect. Direct measurements involve injecting a tracer molecule into the anterior chamber and measuring its accumulation in ocular tissues and blood. While accurate, these tests are invasive and thus not generally suitable for human subjects. Only one study has reported direct measurements of uveoscleral outflow in the living human eye: Bill and Phillips [16] measured outflow in two normal eyes that were not receiving topical pilocarpine or atropine and found uveoscleral outflow accounted for 4–14% of total outflow.

Indirect techniques calculate uveoscleral outflow using a modified Goldmann equation, which requires the measurement of four other parameters, each with inherent variability. This method tends to yield large standard deviations with considerable variability.

These limitations notwithstanding, the uveoscleral outflow pathway appears to be relatively insensitive to IOP differences, even over the range of 4 to 35 mmHg [19]. This observation in part has meant that the majority of surgical targets to lower IOP have focused on the pressure-dependent trabecular outflow system. However, once the ciliary muscle is bypassed (through a shunt or a cyclodialysis cleft), most of the resistance it offers is lost [27] and the uveoscleral pathway becomes pressure dependent, with outflow increasing fourfold [28]. When the uveoscleral pathway is turned into a pressure-dependent pathway, as noted above, its capability of lowering IOP is so significant that the postoperative IOP can reach the low teens or single digits [29–31].

2.7 Conjunctival Lymphatic System

The human lymphatic system plays an important role in body fluid homeostasis, lipid absorption and immune function [31–33]. Fundamentally, the lymphatic system removes excess arterial fluid that is unable to be absorbed by the venous system from the interstitial space and acts to enhance immune surveillance. Traditionally seen as passive channels for fluid and immune cells, recent discoveries have drastically changed our view of lymphatic vasculature, which lags far behind our knowledge of the vascular system. Lymphatic vessels are now appearing to have diverse functions with remarkable specialization depending on tissue microenvironment [34].

Despite this limited knowledge, it appears conjunctival lymphatics are particularly important for the success of glaucoma surgical outcomes [35–37]. In the normal eye, conjunctival lymphatics are not involved in AH flow pathways, and lymphatics have no communication with conjunctival veins [38]. However, glaucoma filtering surgery alters the normal pathways. Aqueous humour is diverted into the subconjunctival space, which is equivalent to interstitial tissue fluid, where conjunctival lymphatic vessels exist. Animal studies confirm that the presence of lymphatic drainage pathways is associated with persistence of subconjunctival drainage pathways, which in turn play a key role in determining surgical outcomes of glaucoma filtration surgery [39]. Thus, understanding conjunctival lymphatic drainage is critical to optimize glaucoma therapeutic interventions.

Conjunctival lymphatics remain difficult to study because of their transparent, colourless nature and very thin vessel walls with absent basement membrane or pericytes. The lymphatic system is a series of unidirectional, thin-walled vessels that transport lymph to the lymphatic nodes, which eventually empty into the blood veins via the thoracic duct.

Conjunctival lymphatics in monkeys start with blind-ended terminals located in the superficial conjunctiva between the epithelium and Tenon's capsule [40]. These tubular vessels are of uneven calibre with numerous branch communications that are responsible for the initial drainage of interstitial fluid. The mechanism of fluid uptake appears to be transient fluid pressure gradients between the interstitial fluid and the initial lymphatic [41, 42]. The fluid then drains into valved precollectors, which are mostly located in the deep layer under Tenon's capsule. These connect to larger collectors and eventually empty into the preauricular and submaxillary lymph nodes [43, 44]. The lymphatics appear to be relatively evenly distributed in the bulbar conjunctiva, with no difference between each quadrant or between the limbus or fornix regions.

Our knowledge of conjunctival lymphatics is still rudimentary, but an understanding of this system's role in interstitial fluid drainage is crucial to optimizing and targeting aqueous drainage in glaucoma therapy. Understanding the lymphatic vessels structure and function, distribution in the conjunctiva and eventually their functional assessment prior to filtration surgery will have significant implications for surgical glaucoma treatments that create a conjunctival bleb.

2.8 Conclusions

Lowering IOP has been central to glaucoma care for over a century. New surgical devices are able to exploit different aspects of aqueous outflow to reduce IOP. A complete understanding of outflow pathways is important to develop new treatment strategies, improve current ones, and to better target the right operation for particular glaucoma subtypes.

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