

Opinion

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The Pathophysiological Relevance of the Posttrabecular Drainage Pathway for Minimally Invasive Trabecular Glaucoma Surgery Using Stents in Primary Open-Angle Glaucoma

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Abstract

Minimally invasive trabecular glaucoma surgery using stents is a widely used glaucoma surgical procedure worldwide. However, it only partially bypasses the proximal outflow resistance in the juxtacanalicular trabecular meshwork. If the entire trabecular meshwork is removed, 30-60% of the trabecular outflow resistance remains, which is due to the intrascleral venous plexus acting as a distal outflow resistance. Consequently, the resulting reduction in intraocular pressure is very limited, especially since inflammatory trabeculopathy in primary open-angle glaucoma-characterized by high levels of endothelin-1 in the aqueous humor-poses an additional limiting factor for pressure reduction through the contraction of the collector channels.

Keywords: Minimally invasive glaucoma surgery (MIGS); Glaucoma, trabecular meshwork; intrascleral venous plexus

Abbreviations: EVP: Episcleral Venous Pressure; MIGS: Minimally Invasive Glaucoma Surgery; POAG: Primary Open Angle Glaucoma

Opinion

Over the past 20 years, trabecular minimally invasive glaucoma surgery (MIGS) using the iStent inject® (Glaukos Corporation, USA) or the Hydrus® (Alcon, USA) has gained increasing importance in glaucoma surgery. It is considered easy to learn and simple to perform, has relatively few side effects and complications [1], and requires minimal follow-up care. However, these advantages are offset by low pressure-lowering efficacy. Meta-analyses show that, as stand-alone procedures, they do not result in additional pressure

reduction compared to cataract surgery [2], and when performed in conjunction with phacoemulsification, the additional pressure reduction is only 1.49 mmHg, whereas incisional trabecular surgery using, for example, the Kahook Dual Blade® (New World Medical, USA)-which features a larger opening zone-was significantly more effective, with an additional pressure reduction of 3.4 mmHg [3]. In a comparative study between the iStent Inject® and the Kahook Dual Blade®, no improvement in trabecular outflow was achieved with the iStent Inject® in patients with predominantly primary

open-angle glaucoma (POAG) [4]. The cause lies primarily in the post-trabecular outflow system, whose significance for MIGS will be briefly outlined here.

In the eye, intraocular pressure is determined by the balance between aqueous humor production in the ciliary body and aqueous humor outflow. The three known outflow systems are the conventional pathway, consisting of the trabecular meshwork-Schlemm's canal-collector channels – the intrascleral venous plexus and episcleral veins as a functional unit [5]; uveoscleral outflow via the ciliary muscle and the orbital venous and lymphatic systems; and drainage via the retina and the posterior lymphatic system [6,7]. The trabecular drainage complex accounts for the largest share, at 60–70%. This system exhibits two main drainage barriers: The inner or proximal first drainage barrier is the juxtacanalicular trabecular meshwork [8], which is connected via direct contact with the endothelium of Schlemm's canal. Due to the tightly sealed endothelium of Schlemm's canal [9], aqueous humor enters Schlemm's canal primarily via the transcellular route through intracellular pores containing giant vacuoles [10]. Via this venous ring sinus, the aqueous humor flows through the collector channels into the intrascleral venous plexus, which constitutes the outer or distal second drainage barrier [8]. From there, the aqueous humor flows through the episcleral veins into the venous circulatory system.

The structure of the intrascleral venous plexus in connection with the episcleral veins has not yet been extensively studied, particularly in the context of POAG. However, it is known that this complex is regulated by neuronal, humoral, and above all neurocrine mechanisms via numerous neurotransmitters, such as the vasoactive intestinal peptide, substance P, and neuropeptide Y [11]. The pressure resulting from this distal outflow resistance is referred to in the literature as episcleral venous pressure (EVP), which ranges between 8 and 10 mmHg under healthy conditions [12,13,14]. For every 1 mmHg increase in EVP, it is assumed that mean intraocular pressure rises proportionally by approximately 1 mmHg [12]. As defined by the Goldmann equation (and modified versions), EVP is always additive to intraocular pressure [12]. To date, however, there are clinically no consistent and accurate methods for measuring IOP available [15]. What is known so far is that it does not change with age and does not exhibit a day-night rhythm [6]. In addition, two corroborating experimental studies have shown that in normal human eyes, even after a 360° trabeculotomy or complete removal of the trabecular meshwork, approximately 30–60% of the outflow resistance remains [16,17], underscoring the importance of this distal outflow resistance system.

In POAG, significant changes occur in the three outflow systems as the disease progresses. Since POAG is associated with a primary mitochondriopathy [18,19], the resulting increase in free radicals and the loss of antioxidant defense systems lead to oxidative stress [20], which can be detected both systemically in serum and, most notably, in the aqueous humor [21]. Consequently, POAG leads to widespread inflammation that affects not only the retinal ganglion cells, microglia, and the lamina cribrosa, but also the anterior segment of the eye [15,18]. As a result of this inflammation, there

is a significant increase in endothelin-1 [23]—the most potent endogenous vasoconstrictor—in the aqueous humor, as well as elevated levels of the transforming growth factor TGF- β [24], tumor necrosis factor TNF- α [25], and interleukin IL-6 [26]. The associated inflammation of the trabecular meshwork [27] leads to significant biochemical changes and structural remodeling [28,29,30]. In addition, the elevated endothelin-1 levels in the aqueous humor in POAG cause a contraction of the smooth vascular muscle of the downstream collector channels [31,32]. This means that the proportion of functioning collector channels involved in aqueous humor drainage decreases, and its outflow into the episcleral venous system is impeded [33]. Since the system comprising the trabecular meshwork, Schlemm's canal, collector channels, intrascleral venous plexus, and episcleral veins is regarded as a continuum [5], the inflammatory remodeling processes described above in POAG mean that the entire conventional outflow system is affected. This is particularly important because it means that the juxtacanalicular trabecular meshwork—as the internal resistance—is affected just as much as the intrascleral venous plexus—as the external resistance.

Ultimately, distal resistance in the conventional outflow system is still poorly understood and has rarely been studied under conditions of POAG. For example, most animal studies were conducted on healthy animals, so the results cannot be directly applied to the intraocular inflammatory conditions seen in POAG. Furthermore, the processes described here make it clear that trabecular MIGS using various stents can have only a very limited pressure-lowering effect. Much more research will be needed in the future to achieve scientifically evidence-based, positive results.

Acknowledgement

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Conflict of interest

None.

References

1. Gillmann K, Baudouin C, Masood I, Miguel A, Grise Dulac A, et al. (2026) A Systematic and Narrative Review of Safety and Complications in Minimally Invasive Glaucoma Surgery (MIGS) Between 2014–2024. *Clin Ophthalmol* 20: 564425.
2. Bicket AK, Le JT, Azuara Blanco A, Gazzard G, Wormald R, et al. (2021) Minimally Invasive Glaucoma Surgical Techniques for Open-Angle Glaucoma: An Overview of Cochrane Systematic Reviews and Network Meta-analysis. *JAMA Ophthalmol* 139(9): 983-989.
3. Yuan PHS, Dorling M, Shah M, Panarelli JF, Durr GM (2025) Combined Microinvasive Glaucoma Surgery with Phacoemulsification in Open-Angle Glaucoma: A Systematic Review and Meta-analysis. *Am J Ophthalmol* 270: 154-163.
4. Sherman T, Nagar A, Daas A, Danieliute L, Alaghand P, et al. (2026) Comparative Study of Outflow Capacity and Intraocular Pressure in the Kahook Dual Blade and iStent Inject-A Consecutive Case Series. *Clin Ophthalmol* 20: 528124.
5. Carreon T, van der Merwe E, Fellman RL, Johnstone M, Bhattacharya SK (2017) Aqueous outflow-A continuum from the trabecular meshwork to the episcleral veins. *Prog Retin Eye Res* 57: 108-133.
6. Toris C B, Gagrani M, Ghatge D (2021) Current methods and new approaches to assess aqueous humor dynamics. *Expert Review of Ophthalmology* 16(3): 139-160.

7. Sauntharajan B, Gupta N, Zhou X, Gümel E, Stanisz G, et al. (2026) Identification and Mapping of a Posterior Ocular Lymphatic Outflow (POLO) Pathway Through Choroidal Lymphatics. *Transl Vis Sci Technol* 15(7): 23.
8. Sampaolesi R, Sampaolesi JR, Zárate J (2014) Episcleral Venous Pressure. In: *The Glaucomas*. Springer, Berlin, Heidelberg.
9. Campbell M, Cassidy PS, Ocallaghan J, Crosbie DE, Humphries P (2018) Manipulating ocular endothelial tight junctions: Applications in the treatment of retinal disease pathology and ocular hypertension. *Prog Retin Eye Res* 62: 120-133.
10. McMenamin PG, Lee WR, Aitken DA (1986) Age-related changes in the human outflow apparatus. *Ophthalmology* 93(2): 194-209.
11. Wu F, Zhao Y, Zhang H (2022) Ocular Autonomic Nervous System: An Update from Anatomy to Physiological Functions. *Vision (Basel)* 6(1): 6.
12. Sultan M, Blondeau P (2003) Episcleral venous pressure in younger and older subjects in the sitting and supine positions. *J Glaucoma* 12(4): 370-373.
13. Toris CB, Yablonski ME, Wang YL, Camras CB (1999) Aqueous humor dynamics in the aging human eye. *Am J Ophthalmol* 127(4):407-1412.
14. Zeimer RC, Gieser DK, Wilensky JT, Noth JM, Mori MM, et al. (1983) A practical venomanometer. Measurement of episcleral venous pressure and assessment of the normal range. *Arch Ophthalmol* 101(9): 1447-1449.
15. Moster M, Ichhpujani P (2009) Episcleral Venous Pressure and Glaucoma. *Journal of Current Glaucoma Practice* 3(1): 5-8.
16. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM (1989) Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. *Curr Eye Res* 8(12): 1233-1240.
17. McDonnell F, Dismuke WM, Overby DR, Stamer WD (2018) Pharmacological regulation of outflow resistance distal to Schlemm's canal. *Am J Physiol Cell Physiol* 315(1): C44-C51.
18. Jassim AH, Inman DM, Mitchell CH (2021) Crosstalk Between Dysfunctional Mitochondria and Inflammation in Glaucomatous Neurodegeneration. *Front Pharmacol* 12: 699623.
19. Duarte JN (2021) Neuroinflammatory Mechanisms of Mitochondrial Dysfunction and Neurodegeneration in Glaucoma. *J Ophthalmol*: 4581909.
20. Kumar DM, Agarwal N (2007) Oxidative stress in glaucoma: a burden of evidence. *J Glaucoma* (3): 334-343.
21. Benoist dazy C, Pereira B, Chiambaretta F, Dutheil F (2016) Oxidative and Antioxidant Stress Markers in Chronic Glaucoma: A Systematic Review and Meta-Analysis. *PLoS One* 11(12): e0166915.
22. Vernazza S, Tirendi S, Bassi AM, Traverso CE, Saccà SC (2020) Neuroinflammation in Primary Open-Angle Glaucoma. *J Clin Med* 9(10): 3172.
23. Lampsas S, Kandarakis SA, Vakalopoulos DG, Lampsas A, Oikonomou E, et al. (2024) Endothelin-1 Plasma and Aqueous Humor Levels in Different Types of Glaucoma: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)* 60(7): 1117.
24. Agarwal P, Daher AM, Agarwal R (2015) Aqueous humor TGF- β 2 levels in patients with open-angle glaucoma: A meta-analysis. *Mol Vis* 21: 612-620.
25. Balaiya S, Edwards J, Tillis T, Khetpal V, Chalam KV (2011) Tumor necrosis factor-alpha (TNF- α) levels in the aqueous humor of patients with primary open-angle glaucoma. *Clin Ophthalmol* 5: 553-556.
26. Pinazo Durán MD, Zanón Moreno V, García Villanueva C, Martucci A, Peris Martínez C, et al. (2025) Biochemical, molecular, and genetic biomarkers in the tear film, aqueous humor, and blood of patients with primary open-angle glaucoma. *Front Med (Lausanne)* 10:1157773. Erratum in: *Front Med (Lausanne)* 12: 1675008.
27. Saccà SC, Paluan F, Gandolfi S, Manni G, Cutolo CA, et al. (2020) Common aspects between glaucoma and brain neurodegeneration. *Mutat Res Rev Mutat Res* 786: 108323.
28. Buffault J, Labbé A, Hamard P, Brignole Baudouin F, Baudouin C (2020) The trabecular meshwork: Structure, function, and clinical implications. A review of the literature. *Journal Français D'Ophtalmologie*, Elsevier Masson 43 (7): e217-e230.
29. Karimi A, Razaghi R, Padilla S, Rahmati SM, Downs JC, et al. (2022) Viscoelastic Biomechanical Properties of the Conventional Aqueous Outflow Pathway Tissues in Healthy and Glaucomatous Human Eyes. *J Clin Med* 11(20): 6049.
30. Bermudez JY, Montecchi Palmer M, Mao W, Clark AF (2017) Cross-linked actin networks (CLANs) in glaucoma. *Exp Eye Res* 159: 16-22.
31. Ghanem AA, Elewa AM, Arafa LF (2011) Endothelin-1 and nitric oxide levels in patients with glaucoma. *Ophthalmic Res* 46(2): 98-102.
32. Gonzalez JM Jr, Ko MK, Hong YK, Weigert R, Tan JCH (2017) Deep tissue analysis of distal aqueous drainage structures and contractile features. *Sci Rep*. 7(1): 17071.
33. Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP (2014) Anatomical changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures. *Invest Ophthalmol Vis Sci*. 55(9): 5834-5841.