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# Eye Microcirculation in Glaucoma. Part 3. Hypotensive Therapy Effect

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## ABSTRACT

Glaucoma is the main cause of irreversible vision loss in developed countries. Currently, glaucoma is defined as a group of multifactorial diseases with similar clinical, morphological, and functional manifestations. The main cause of blindness is progressive death of retinal ganglion cells, leading to optic neuropathy. Currently, mechanical and vascular mechanisms are suggested to play a key role in the development of primary glaucoma. The mechanical process includes compression of the axons caused by increased intraocular pressure. The vascular component suggests reduced blood flow and ocular perfusion pressure. Examination methods of the eye vasculature in glaucoma are constantly being improved and range from invasive, including angiography with fluorescein and indocyanine intravenous administration, to high-tech non-contact types such as color flow Doppler and pulsed wave Doppler, optical coherence tomography angiography, and laser speckle flowgraphy. This review provides the assessment of retrobulbar and ocular blood flow in patients with glaucoma and ocular hypertension receiving different therapies. Rapidly advancing technologies allow developing and studying highly informative methods for assessing ocular blood flow, thus contributing to better understanding of eye microcirculation and the development of new effective glaucoma therapies.

**Keywords:** glaucoma; eye microcirculation; retrobulbar blood flow; perfusion pressure; hypotensive therapy; glaucoma surgery; trabeculectomy; angiography; optical coherence tomography; laser speckle flowgraphy.

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# Микроциркуляция глаза при глаукоме. Часть 3. Влияние гипотензивного лечения

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**АННОТАЦИЯ**

Глаукома — основная причина необратимой потери зрения в развитых странах. В настоящее время под глаукомой понимают группу полиэтиологических заболеваний, объединённых общими клиническими и морфофункциональными проявлениями. Основная причина слепоты — прогрессивная гибель ганглиозных клеток сетчатки, приводящая к оптической нейропатии. Согласно современным представлениям, в развитии первичной глаукомы ключевую роль играют механический и сосудистый компоненты. Механический компонент патогенеза глаукомы подразумевает компрессию аксонов из-за повышенного внутриглазного давления. Сосудистый компонент включает дефицит глазного кровотока и снижение перфузионного давления. Методы исследования состояния сосудистой системы глаза при глаукоме постоянно совершенствуются — от инвазивных, включающих ангиографию с внутривенным введением флуоресцеина и индоцианина, до высокотехнологичных бесконтактных — ультразвуковое исследование в режимах цветового допплеровского картирования и импульсной допплерографии, оптическая когерентная томография с функцией ангиографии и лазерная спекл-флоуграфия. В настоящем обзоре представлены результаты оценки ретробульбарного кровотока и интраокулярной гемоциркуляции при глаукоме и офтальмогипертензии на фоне различных методов лечения. Благодаря стремительному развитию технологий создаются и изучаются высоко информативные методы оценки глазного кровотока, способствующие расширению знаний о глазной микроциркуляции и разработке новых подходов к эффективному лечению глаукомы.

**Ключевые слова:** глаукома; микроциркуляция глаза; ретробульбарный кровоток; перфузионное давление; гипотензивная терапия; глаукомная хирургия; трабекулэктомия; ангиография; оптическая когерентная томография; лазерная спекл-флоуграфия.

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## INTRODUCTION

Currently, glaucoma is one of the leading causes of blindness in the world and affects about 65 million people, so it can be considered a socially significant disease [1, 2]. The number of patients is estimated to reach 111.8 million by 2040 [3]. In the Russian Federation, 1,250,558 glaucoma cases were reported in 2022.

At present, glaucoma is defined as a group of multifactorial diseases with similar clinical, morphological, and functional manifestations. The main cause of irreversible vision loss in glaucoma is progressive death of retinal ganglion cells, causing optic neuropathy. Age, increased intraocular pressure (IOP), and heredity are the leading risk factors. Etiology of primary glaucoma usually includes mechanical and vascular mechanisms. The mechanical process includes compression of the axons caused by increased intraocular pressure, whereas the vascular component suggests reduced blood flow and ocular perfusion pressure [4]. Vascular damage in glaucoma has been studied since the beginning of the last century with continuous improvement of diagnostic methods from invasive to high-tech contact-free ones. In Russia, V.V. Volkov, A.M. Vodovozov, Yu.S. Astakhov, and N.I. Kurysheva are the leading researchers of eye microcirculation in glaucoma. This review analyzes changes in eye hemodynamics while under treatment, both medical and surgical.

## TOPICAL HYPOTENSIVE THERAPY

### Beta-Blockers

Carteolol, a non-selective beta-adrenergic receptor blocker, is not widely used as a local hypotensive agent to treat glaucoma and ocular hypertension. The hypotensive effectiveness of 1% and 2% carteolol twice daily is similar to that of 0.25% and 0.5% timolol. Topical administration of carteolol in healthy volunteers had no effect on respiratory function, although bronchospasm was observed in patients with asthma [5]. A potential side effect of beta-adrenergic receptor blockers is a decrease in ocular perfusion caused by local vasoconstriction; however, beta-adrenergic receptor blockers with sympathomimetic activity, such as carteolol, maintain or even improve ocular perfusion by vasodilation or minimizing vasoconstriction [5]. Among all topical beta-blockers for glaucoma, carteolol and its comparative vasoactive effect were studied most extensively.

After 3 weeks of beta-blocker use in healthy volunteers, laser speckle flowgraphy revealed an improvement in optic disc perfusion, which was more significant in patients receiving carteolol compared with timolol [6]. In healthy individuals receiving topical carteolol, blood flow velocity in the optic disc also increased significantly in fellow eyes receiving placebo. The authors explained this by the sympathomimetic effect rather than its beta-adrenergic antagonism [6, 7].

Based on color flow Doppler of retrobulbar blood flow in patients with primary open-angle glaucoma (POAG), Montanari et al. suggested that sympathomimetic activity of carteolol can reduce peripheral vascular resistance in the short posterior ciliary arteries, thus improving perfusion of the optic disc [8]. Mizuki and Yamazaki noted a significant increase in blood flow velocity in the ophthalmic artery and volumetric blood flow in the peripapillary area after carteolol administration for 7 days in healthy individuals [9]. Altan-Yaycioglu et al. [10] reported that one month of carteolol therapy in patients with POAG decreased peripheral resistance index in the central retinal artery (CRA), whereas betaxolol decreased it in both the CRA and short posterior ciliary arteries. In contrast, timolol had a slight vasoconstrictive effect. According to Chen et al. [11], carteolol treatment for 12 weeks decreased vascular resistance in patients with normal-tension glaucoma.

Grunwald and Delehanty [12] showed that 2 hours after instillation of 1% carteolol had no effect on the size of retinal vessels, erythrocyte velocity, and volumetric blood flow velocity in the temporal branch of the central retinal vein. Kawai et al. [13] also found no effect of carteolol on the diameter, blood flow velocity, and ocular perfusion pressure in the CRA on days 30, 60, and 90 of POAG therapy. After 6 months of carteolol therapy in patients with normal-tension glaucoma, Lin et al. [14] revealed a decrease in vessel density (VD) in the inferior temporal quadrant of the peripapillary retina.

### Carbonic Anhydrase Inhibitors

Acetazolamide was developed in the 1950s and represents the first generation of systemic carbonic anhydrase inhibitors [15]. It is a strong inhibitor of most carbonic anhydrase isoforms (out of 15 currently described in human) [16] and slows down aqueous production, thus decreasing IOP by up to 30% [17]. Inhibition of various carbonic anhydrase isoforms present in other tissues causes several systemic side effects, limiting the use of acetazolamide [17]. Acetazolamide penetrates the cornea poorly, which prevents its topical administration. Therefore, second-generation carbonic anhydrase inhibitors, dorzolamide and brinzolamide, were developed. Merck released 2% dorzolamide eye drops in 1995, and Alcon Laboratories received approval for 1% brinzolamide therapy in 1996 [18, 19]. Both drugs effectively reduce IOP and have fewer side effects compared with systemic drugs.

In 2004, Iester et al. [20] studied the effect of 1-month brinzolamide therapy on retinal blood flow in patients with glaucoma. A significant increase in blood flow was observed in the temporal and nasal quadrants. In 2021, Lin et al. [14] analyzed the OCT and OCTA outcomes

of 6-month dorzolamide therapy in 24 patients with normal-tension glaucoma. They reported an increase in vessel density of the peripapillary retina mainly in the superior nasal quadrant, whereas the retinal nerve fiber layer thickness did not change.

## Alpha-Adrenergic Agonists

In the 1960s, Boehringer Ingelheim developed clonidine, a precursor to selective alpha-2 adrenergic agonists [21]. 0.125% and 0.25% eye drops were effective in reducing IOP, but had severe systemic side effects, including systolic and diastolic hypotension, bradycardia, and sedation. Notably, clonidine instillation decreased ocular perfusion [22]. Addition of a para-amino group to clonidine led to the development of second-generation alpha-agonist apraclonidine* with lower severity of side effects [23]. Third-generation alpha-agonist brimonidine tartrate, approved for clinical use in 1996, includes a quinoxaline bicyclic ring with bromine substitution, which increases the selectivity of alpha-2 receptors [24]. The mechanism of the brimonidine hypotensive effect is through activating presynaptic alpha-2 receptors resulting in the decreased release of catecholamines, adenylate cyclase, and cyclic adenosine monophosphate, which decreases aqueous production in the ciliary body epithelium [25]. Alpha receptors can cause smooth muscles to constrict, thus leading to vasoconstriction and reduction of blood flow to the ciliary muscle and aqueous production [26].

Lin et al. [14] studied the effect of alpha-2 adrenergic agonist brimonidine on retinal blood supply in patients with glaucoma. They found no changes in vessel density of the peripapillary retina after 6 months of therapy.

## Prostaglandin Derivatives

The first prostaglandin introduced in clinical practice in 1996 was 0.005% latanoprost, developed in Sweden [27]. It is an isopropyl ester prodrug, prostaglandin PGF2a analog with high selectivity for the FP prostanoid receptors. Latanoprost has low tropism for prostanoid receptor responsible for inflammatory reactions and high tropism for IOP-reducing receptors [28]. The hypotensive effect of prostaglandin derivatives is based on activation of uveo-scleral outflow achieved by relaxing the ciliary muscle, degrading its extracellular matrix, and changing the collagen structure therein [28]. Later, other prostaglandin derivatives with comparable hypotensive effect were released, including 0.004% travoprost, 0.03% bimatoprost, and 0.0015% tafluprost; however, latanoprost remains the most common prostaglandin, accounting for about 65% of prescriptions for prostaglandin derivatives [29].

A study of the latanoprost monotherapy effect on retinal blood flow was performed in 2021. Liu et al. [30] performed OCTA before treatment and 3 weeks later. They noted a significant correlation between an IOP decrease and increase in vessel density in the optic disc area and peripapillary retina [30].

Kurysheva used tafluprost as initial therapy for patients with newly diagnosed glaucoma and found a significant increase in ocular perfusion pressure, whereas vessel density was reduced in the optic disc area and unchanged in the peripapillary and macular areas [31].

Tsuda et al. [32] determined optic disc blood flow in patients with normal-tension glaucoma using laser speckle flowgraphy. They revealed that topical tafluprost increased volumetric blood flow velocity (MBR) in the optic disc area, which indicated a significant improvement in eye hemodynamics.

## Combination Therapy

As glaucoma has no severe clinical symptoms at early stages, patients often seek medical advice at stages when the effectiveness of first-choice monotherapy is insufficient. Therefore, the majority of patients with diagnosed glaucoma require additional medications to lower IOP and prevent further disease progression [33]. Fixed combinations are recommended in these cases; most of them contain a beta-blocker with prostaglandin derivative or carbonic anhydrase inhibitor. Fixed combinations improve patient compliance, reduce preservatives to be instilled, and provide better tolerance and lower cost [34]. Combinations may contain drugs with different mechanisms of action, which provides a potentially additive hypotensive effect, but challenges assessment of their effect on ocular blood flow.

Sugiyama et al. [35] performed a comparative assessment of optic disc hemodynamics in patients with normal-tension glaucoma after 3 months of therapy with latanoprost/carteolol and latanoprost/timolol. Carteolol improved blood flow perfusion, which could be caused by its vasodilatory effect, but timolol had no effect. Karaśkiewicz et al. [36] described a 14% increase in ocular perfusion pressure in patients with POAG after a month of therapy with a fixed combination of bimatoprost/timolol. Kurysheva reported that a fixed combination of tafluprost/timolol increased ocular perfusion pressure by 43% and decreased vessel density of the optic nerve head by 30%, whereas vessel density of the macula and peripapillary retina remained unchanged [31]. According to Feke et al. [37], 6-week dorzolamide/timolol combination therapy in patients with POAG significantly increased ocular perfusion pressure compared with brimonidine/timolol. Rolle et al. [38] also reported that a fixed combination of dorzolamide/timolol improved ocular blood flow in the neuroretinal rim area after 4 weeks.

* Not registered in Russian Federation.

### Surgical Treatment

As mentioned above, ocular perfusion pressure plays an important role in blood supply to the posterior segment and, consequently, in the development and progression of glaucoma. In turn, ocular perfusion pressure depends on intraocular and blood pressure, which means that any IOP lowering therapy will improve ocular blood flow [39]. Monotherapy and fixed combinations can reduce IOP to 30% and 40% of baseline value, respectively, the hypotensive effectiveness of surgical treatment is not determined by a percentage decrease in IOP and provides lower values.

A significant surgical reduction in IOP may subsequently change ocular blood flow in the macular and peripapillary areas [40]. In 2022, Gillmann et al. [41] showed that selective laser trabeculoplasty increased vessel density in the peripapillary and macular areas, which returned to baseline after 6 months; this result confirmed that the vasculature state depends on IOP.

Among various surgical procedures, the correlation between vascular changes and trabeculectomy has been most studied. Studies have revealed an increase in optic disc blood flow, end-diastolic velocity in the CRA and short posterior ciliary arteries. James assessed postoperative pulsatile ocular blood flow and found a 29% increase. He attributed these changes to a significant IOP decrease in IOP, whereas Yang and Hulbert considered this to be a result of changes in ocular rigidity caused by glaucoma surgery [42, 43]. Berisha et al. [44] demonstrated a 19% increase in perfusion pressure 2–10 weeks after trabeculectomy. Kuerten et al. [45] described a significant increase in blood flow velocity in the CRA in the long-term post-trabeculectomy period, correlating with IOP changes. With the advent of OCTA, several studies have demonstrated an improvement in microcirculation after trabeculectomy represented by increased density of peripapillary vessels [46, 47]. However, despite the hypotensive effect of surgical procedures, some studies have not revealed significant changes in vessel density in the macula or peripapillary retina [48, 49]. Takeshima et al. [5] studied the effect of trabeculectomy on blood flow parameters in the optic disc area using laser speckle flowgraphy in patients with POAG. The study revealed a significant change in several tested waveform parameters and no changes in volumetric blood flow velocity in the postoperative period (1–6 months). Thus, an IOP decrease caused by trabeculectomy may stabilize optic disc microcirculation [50].

## CONCLUSION

Changes in ocular blood flow play an important role in the development and progression of glaucoma. However, further studies of eye hemodynamics are warranted to determine whether circulatory disorders in the optic disc area are the cause or result of glaucomatous optic neuropathy. Currently, rapidly advancing technologies allow developing and studying highly informative methods for assessing ocular blood flow, thus contributing to its better understanding and the development of new effective glaucoma therapies.

## ADDITIONAL INFO

**Author contributions:** S.Yu. Petrov, E.N. Orlova, T.N. Kiseleva, T.D. Okhotsimskaya, A.A Glushchuk: conceptualization, writing—original draft, including translation into English, writing—review & editing before and after publication. All the authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** С.Ю. Петров, Е.Н. Орлова, Т.Н. Киселева, Т.Д. Охоцимская, О.И. Маркелова, А.А. Глущук — формулирование замысла/идеи исследования, целей и задач, создание и подготовка рукописи: написание черновика рукописи, включая его перевод на иностранный язык, критический анализ черновика рукописи, внесение замечаний и исправлений членами исследовательской группы, в том числе на этапах до и после публикации. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

**Источники финансирования.** Отсутствуют.

**Раскрытие интересов.** Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

**Оригинальность.** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

**Доступ к данным.** Все данные, полученные в настоящем исследовании, доступны в статье.

**Генеративный искусственный интеллект.** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

**Рассмотрение и рецензирование.** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

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