Jpn J Ophthalmol (2013) 57:133–149
DOI 10.1007/s10384-012-0220-x

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

REVIEW

Effects of antiglaucoma drugs on blood flow of optic nerve heads and related structures

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Received: 12 September 2012 / Accepted: 1 October 2012 / Published online: 16 January 2013

Abstract An association between glaucoma development or progression and compromised ocular blood flow has been postulated as a result of population-based studies and prospective cohort studies. Blood flow in the optic nerve head (ONH) is of primary importance in the pathogenesis of glaucoma. The potential to modify the blood flow in the ONH and its related structures has been reported in various agents, including topical antiglaucoma drugs and systemic drugs such as calcium channel antagonists, which are reviewed in this manuscript. Clinical implications of the improvement in ocular blood flow on the treatment of glaucomatous optic neuropathy require further investigation.

Keywords Blood flow · In vivo measurements · Optic nerve head · Topical antiglaucoma drug · Systemic drugs

Introduction

Data from population-based surveys indicate that 80 million people worldwide are affected by glaucoma, with 11.2 million bilaterally blind, and it is estimated that glaucoma will become the second most common cause of blindness in the world by 2020 [1]. Only a few population-based cohort studies report incidences of the development of open-angle glaucoma (OAG). An incidence of 2.2 % over 4 years was found in individuals of African descent in Barbados [2], and an incidence of 0.6 % over 5 years was found in Caucasian subjects in Rotterdam [3]. Prospective randomized studies [4–9] demonstrated significant efficacy in the reduction of intraocular pressure (IOP) by preventing the progression of visual field damage in OAG, including primary open angle glaucoma (POAG) with high IOP and normal IOP (normal tension glaucoma, NTG). Simultaneously, results of these studies show that in a cohort of glaucoma patients the disease still progresses, even after satisfactory IOP reduction has been achieved. The association of other factors beside IOP has long been considered a possibility in the pathogenesis of glaucoma.

Impaired local circulation in the optic nerve head (ONH) is suspected to be a risk factor associated with the development or progression of glaucoma [10, 11]. Significant correlations were found between glaucoma and not only systemic vascular or circulatory disorders, including diabetes mellitus [12], nocturnal hypotension [13, 14] or migraine [15], but also with altered ocular local circulation in the ONH [16–19] or retrobulbar vessels [20–25] in the eyes of glaucoma patients. This alteration was especially prominent in the eyes with bad or deteriorating visual field damage [18, 19], which suggests an association between impaired blood flow in the ONH and the pathophysiology of glaucoma.

The correlation between blood pressure and ocular perfusion pressure (OPP, blood pressure–IOP) has been studied in prospective cohort studies, where a lower OPP was associated with an increased risk of developing OAG in a 4-year [26] and a 9-year cohort [11]. Lower systolic OPP was associated with a risk of progression of glaucoma in the follow-up period up to 11 years in a study cohort [10]. In population-based studies, a low OPP [27–29] and narrow retinal vessels [30, 31] were significantly correlated with the risk of having POAG. In a case–control study, a

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low OPP was highly correlated with the risk of having OAG and hypertension [32].

At the present time, it is still controversial whether the deficiency in local circulation is a primary or secondary change leading to an increase in IOP or morphological changes in the ONH; however, it was demonstrated in animal experiments that glaucoma-like damage follows a reduction in ocular perfusion without high IOP [33, 34]. Thus, it is speculated that disturbance of local circulation in the ONH has unfavorable effects on the integrity of the ONH. At the same time, the effect of topical and systemic drugs on ONH blood flow has been intensively studied, although verification of their clinical effectiveness in the treatment of glaucoma awaits further investigation.

The purpose of this article is to review studies investigating the effects of topical and systemic drugs on the circulation of the ONH and related structures using various methods.

Factors relating to optic nerve head blood flow

Blood supply to the optic nerve head

The surface nerve fiber layer in the ONH is predominantly supplied with blood flow by branches of the central retinal artery (CRA), which enters the optic nerve approximately 5–12 mm posterior to the globe and reaches the retina. The short posterior ciliary arteries supply the posterior choroid and most of the anterior optic nerve. The medial and lateral short posterior ciliary arteries become confluent and form the arterial circle of Zinn-Haller around the optic nerve, though the circle is occasionally incomplete or not present at all. Branches of the circle and those of the short posterior ciliary arteries primarily supply the prelaminar and laminar regions of the ONH and the peripapillary choroid. The retrolaminar region is also supplied by branches of the circle of Zinn-Haller or the short posterior ciliary arteries, and branches of pial vessels also make a partial contribution [35–40].

Patterns of the vasculature and the actual boundary of its local perfusion vary considerably among subjects and even between the eyes of a single subject. In consideration of the constant contribution of the short posterior ciliary arteries to the arterial supply to most parts of the ONH, drugs that exert effects on the ONH need to be distributed around those arteries in the retrobulbar space.

Distribution of drugs to tissues around the optic nerve head

To exert its desired effect a drug must be distributed at a pharmacologically active concentration to the target tissues. When drugs are introduced topically to the eye, only a marginally small portion penetrates the cornea and distributes to the anterior segment of the eye, such as the aqueous humor, iris and ciliary body. Most of the drug remains in the conjunctival sac and is absorbed into adjacent peribulbar tissues or into the systemic circulation via the local bloodstream.

Retinal distribution of a drug absorbed into the systemic circulation is restricted by the blood–retinal barrier [41]. Permeability of the barrier depends on lipid solubility, and lipophilic drugs are more likely to cross the barrier than hydrophilic drugs. With drugs that affect the ONH circulation, however, incompleteness of the barrier in the peripapillary choroid [42, 43] and the prelaminar region of the ONH [44] may potentially increase exposure of the ONH tissue and its perfusion vessels to drugs diffusing from the surrounding tissues, regardless of their permeability.

The concentration of a drug in the posterior parts of the eye is not low enough to be pharmacologically negligible after topical administration. For example, the concentrations of timolol after its topical administration in rabbit's ocular tissues are reported to be 9 μg/g (2.84×10^{-5} M) in the iris and ciliary body, 0.02 μg/g (6.32×10^{-8} M) in the vitreous humor and 0.08 μg/g (2.53×10^{-7} M) in the optic nerve 2 h after application [45]. The concentrations of levobunolol, another topical β-blocker, were 0.5 μg/g (1.72×10^{-6} M) in the iris and ciliary body, 0.004 μg/g (1.37×10^{-8} M) in the vitreous humor and 0.016 μg/g (5.49×10^{-8} M) in the optic nerve [46].

Autoradiography studies show that, in monkey and rabbit eyes, a topically administered drug reached the ipsilateral retrobulbar space adjacent to the optic nerve insertion in 60 min at a concentration of higher than 10^{-8} M, a pharmacologically active level of the drug [47–49]. Additionally, it is speculated that the peribulbar route may play a dominant role in topically administered drug distribution in the retrobulbar space adjacent to the optic nerve insertion at a pharmacologically active concentration [50, 51]. It is also demonstrated by observation of retinal vessels in rabbits, that topically administered drugs distribute to the retina at pharmacologically active levels. In addition, it is shown that topical calcium antagonists [48], β- [52] and α-1-antagonists [53] exert dilatory effects on retinal arteries pre-contracted with an intravitreal injection of endothelin-1 (ET-1).

Topical antiglaucoma drugs

Cholinergic stimulators

Pilocarpine

Pilocarpine is an alkaloid of natural plant origin that is, at present, the most widely used topical parasympathomimetic

medication. The effectiveness of pilocarpine in reducing IOP in the treatment of chronic glaucoma patients is relatively limited; however, it has also been used to achieve miosis during surgical procedures such as peripheral iridectomy since its introduction in the 1870s [54, 55].

The alleged effect of pilocarpine on ocular blood flow was originally controversial. In studies using radioactive microspheres in rabbits, topical administration of pilocarpine showed no significant effect on ocular blood flow in the retina or choroid [56], but tended to decrease blood flow in the iris and ciliary processes, although this decrease was not statistically significant [57]. Pilocarpine showed dose-dependent muscle relaxation in isolated rabbit ciliary arteries [58], which may explain increased ocular blood flow after pilocarpine administration reported in other studies [59], although the effect was at least partly due to its IOP-reducing effects and subsequent increase of OPP.

In a placebo-controlled study in healthy humans, no significant effects of a single drop of 2 % pilocarpine were found on fundus pulsatile ocular blood flow amplitude [60]. Pulsatile ocular blood flow was significantly increased after 3 administrations of 2 % pilocarpine in patients with ocular hypertension (OH) [61]; however, it remained unchanged after a single administration of 4 % pilocarpine in another preceding study [62].

Alpha agonists

Phenylephrine

Phenylephrine, an α-1 agonist with vasoconstricting potential, is commonly used topically for mydriasis prior to intraocular surgery or fundus examination. Single and chronic topical administration of phenylephrine produced significant vasoconstriction in retrobulbar arterioles around the ONH in rabbits [63, 64] and ONH circulation measured using laser speckle flowgraphy was significantly decreased after phenylephrine administration in rabbits, monkeys and humans in vivo [65–67]. Except in preoperative situations it is not usual to use phenylephrine repeatedly; however, the potential threat to the ONH circulation by the drug may not be negligible, especially in those patients with glaucoma, arterial sclerosis, or diabetes mellitus.

Apraclonidine

Apraclonidine hydrochloride is a relatively selective α-2 agonist with an IOP-reducing effect, which is mainly due to suppression of the production of aqueous humor [68, 69]. It was initially found that temporary use of apraclonidine could prevent acute rises in IOP after laser surgery [70–72], and products for chronic administration were developed soon afterwards.

Topical administration of apraclonidine induced blanching of the conjunctiva [73] and decreased conjunctival oxygen tension [74] in humans. Decreased blood flow velocities and increased resistive indices in the ophthalmic artery (OA) were detected by color Doppler imaging (CDI) in normal subjects after a single administration of 1 % apraclonidine [75, 76]. However, other studies failed to find significant effects of apraclonidine on the ONH, peripapillary retinal blood flow [77] or OA blood flow [78].

Brimonidine

Brimonidine is an analog of clonidine highly selective to α-2 adrenoceptors that has a stronger IOP-lowering effect than apraclonidine [79, 80]. In a double-masked trial in 17 POAG patients, administration of 0.2 % brimonidine twice-daily for 4 weeks was associated with no significant changes in blood flow velocity or resistive indices in the retrobulbar vessels, measured using CDI or ocular pulse amplitude, despite a significant decrease in IOP [81]. A significant increase in pulsatile ocular blood flow was reported in POAG patients [82], but other studies in OH patients [83] or NTG patients [84] did not find any significant effect of brimonidine on ocular blood flow. One study reports that retinal autoregulation after postural change was impaired in NTG patients, which was restored by brimonidine treatment [85].

Alpha-1-antagonist

Bunazosin

Bunazosin is a selective and potent α-1-adrenoceptor antagonist that is used clinically as a systemic antihypertensive and a topical antiglaucoma drug with an IOP-decreasing effect. It exerts a vasodilating effect on isolated canine ophthalmic and ciliary arteries by antagonizing the effect of α-adrenoceptor agonists [86], and a significant increase of choroidal capillary blood flow, measured by thermal diffusion flowmetry, is reported after a single administration of bunazosin in rabbits [87]. Bunazosin also reportedly inhibited the ET-1 induced disturbance of circulation in the ONH as measured by hydrogen gas clearance flowmetry and, in retinal arteries in rabbits, as measured by fundus photography [88]. Using laser speckle flowgraphy in rabbits, similar ameliorative effects of bunazosin on impaired ONH circulation were found after repeated intravitreal injections of 20 pmol ET-1 twice-weekly followed by the administration of Bunazosin for 4 weeks [89], and again with intravenous injections of 50 mg/kg L-nitro-L-arginine methyl ester (L-NAME), a non-selective nitric oxide synthase inhibitor [90].

A double-masked study in 15 healthy volunteers reports that a single drop of topical 0.3 % bunazosin did not significantly affect pulsatile ocular blood flow of the treated eyes, despite a significant decrease in IOP [91].

Beta-antagonists

Timolol

Timolol is one of the most widely used antiglaucoma β-antagonists and has a potent IOP-decreasing effect. It is a non-selective beta-blocker, and blockage of β_2 receptors may lead to vasoconstriction in vessels. β receptors are found in ocular tissues, including the retina [92]. However, the effect of timolol on ocular blood flow is controversial.

Using the intraluminal microvascular corrosion casting technique, constriction in the arterioles supplying the ciliary processes after 0.5 % timolol administration was observed in rabbits [63], and decreased choroidal blood flow was found in bovine arteries in vitro using radiolabelled microspheres [93]. Another investigation found timolol induced relaxation of rabbit ciliary arteries in vitro at relatively high concentrations [94], and a biphasic effect of L-timolol is reported in rabbits using colored microspheres, where the topical administration of the drug induced an initial decrease followed by a marked increase in blood flow in ocular tissues including the retina [95]. Significantly reduced perfusion in the choroid and retina was found after a single administration of 0.5 % timolol in ocular hypertensive rabbits using microspheres [59], while other preceding studies failed to find a significant change in blood flow [57, 96]. According to in vivo studies in rabbits using laser speckle flowgraphy, blood flow in the iris did not change significantly [97], but it increased significantly in the ONH in timolol treated eyes [98]. In another study, ONH circulation was not significantly changed in monkeys, despite a decreased IOP [99].

The effect of timolol on ocular blood flow is also controversial in humans. Studies in normal volunteers using the Heidelberg retinal flowmeter (HRF) reported that blood flow in the ONH significantly decreased [100] or was unchanged [101] after a single administration of timolol. Another double-masked study in 140 POAG and OH patients found no significant effect on ONH blood flow after 6 months of treatment with timolol twice-daily using HRF [102]. In another study using laser speckle flowgraphy, blood flow in the ONH of normal subjects did not significantly change after administration of 0.5 % timolol twice-daily for 3 weeks [103].

In a double-masked study in OH patients using laser-Doppler velocimetry (LDV), blood flow rates in a major retinal vein increased after a single administration of timolol corresponding to decreased IOP [104]. Conversely, a decrease of blood flow through a major retinal vein after administration of timolol twice-daily for 2 weeks was also reported using LDV [105]. In a double-masked study using CDI in patients with either POAG or OH, the authors concluded timolol did not cause substantial hemodynamic changes in retrobulbar vessels [106]. Among other studies using CDI in POAG patients, one found a significant increase in resistive index in the temporal posterior ciliary arteries [107], while another found a significant decrease in resistive index and an increase in mean end diastolic velocity of the CRA [108].

Most other investigations report insignificant effects of timolol on blood flow in the ONH or retrobulbar vessels using HRF [109], CDI [110–112], or choroidal circulation as pulsatile ocular blood flow [113–115].

Carteolol

Carteolol is another non-selective β-antagonist characterized by its intrinsic sympathomimetic activity (ISA) [116, 117]. ISA is a partial β-adrenergic agonist response elicited by a β-adrenergic antagonist because of its structural specificity, which allows competitive binding to the receptors and partial interaction at the activation site of the receptor. Thus, carteolol may potentially have a vasodilating effect, or at least more of an effect than a β-blocker without ISA such as timolol. However, the actual influence of ISA in vivo is not clearly understood.

Blood velocity in the iris measured by laser speckle flowgraphy and iris blood flow rates measured by microspheres were both significantly increased after a unilateral single administration of 2 % carteolol, not only in the carteolol treated rabbit eyes, but also in the contralateral vehicle treated eyes [118]. Blood velocity in the ONH measured by laser speckle flowgraphy did not change significantly after a single drop of 2 % carteolol; however, it significantly increased after twice-daily 20-day administration in both carteolol and contralateral vehicle treated eyes in rabbits [119].

Another study in rabbits found the plasma levels of carteolol to be 5.55 ng/ml after a topical administration of 2 % carteolol twice-daily for 3 weeks, and after a continuous intravenous injection (5 μg/kg/h) to achieve approximately the same plasma levels of carteolol, it significantly increased the blood flow in the ONH measured using the hydrogen clearance method [120]. Conversely, a study on the bovine arterial system of perfused eyes found that the maximal IOP-reducing dose of carteolol significantly reduced blood flow in the iris, ciliary body and choroid as measured by radiolabelled microspheres [93]. Thus, the theoretical advantage of carteolol over timolol with regard to its peripheral circulation cannot always be seen in practice.

In human studies, the effect of a single drop of 1 % carteolol, measured by LDV, was insignificant on the vessel diameter of a retinal vein and on the blood flow through it [121]. Conversely, other studies found significantly increased blood flow after administration of 2 % carteolol twice-daily for 7 days in the ONH using laser speckle flowgraphy [103, 122], in the peripapillary retina using HRF [123] and in the OA using CDI [123].

Betaxolol

Betaxolol is a β-1 selective adrenoceptor antagonist with a weak calcium channel blocking action that contributes to its vasodilating effect. β-2 Receptor occupancy by betaxolol in the systemic circulation was reportedly negligible and its β-1 receptor occupancy was <20 %, much less than that of timolol (65 %) [124]. According to an in vitro study using isolated rabbit ciliary arteries and an isometric tension recording method, betaxolol showed a vasodilating effect at a relatively high concentration of 100 μM [94]. Another study in isolated bovine retinal micro arteries in vivo showed that betaxolol had a relaxing effect on K^+-induced contractions in a dose-dependent manner similar to a Ca^{2+} channel blocker [125]. Another study using the intraluminal microvascular corrosion casting technique, however, failed to find a significant effect of 30-day treatment of betaxolol or timolol on arterioles supplying the anterior optic nerve [126].

Using the hydrogen clearance method, a significant increase in blood flow was found in the ciliary body and retina of rabbits after a two-drops administration of 0.5 % betaxolol, but it decreased after timolol or carteolol administration [127]. Another study investigated the effect of 0.5 % betaxolol treatment twice-daily for 20 days on the iris and ONH of rabbits using laser speckle flowgraphy, and the blood velocity in both tissues was significantly increased by approximately 10 % in the betaxolol treated eyes [128]. In a study using HRF, double administration of betaxolol significantly inhibited a decrease in choroidal blood flow, induced by intravitreal injection of ET-1, for 24 h in rabbits [129].

In a double-masked study in healthy human volunteers using laser speckle flowgraphy, 0.5 % betaxolol administration twice-daily significantly increased blood velocity in the ONH after a 21-day chronic administration [130], while a single drop of betaxolol did not show any significant effects [122].

A single-masked study in 10 OH patients using LDV found a significant increase in blood flow in a retinal vein of 15.0 % 2 h after administration of 0.5 % betaxolol [131]. Another study using LDV to measure retinal venous blood flow found a significant increase in blood flow after administration of 0.5 % betaxolol twice-daily for 14 days [105], although the influence of increased perfusion pressure after IOP reduction was a factor.

There are several studies using CDI that found significant effects of betaxolol on blood flow in the retrobulbar vessels. In a double-masked study in 13 NTG patients, 0.25 % betaxolol administration twice-daily for 1 month tended to increase end-diastolic velocity by 30 % and to decrease resistive index significantly in ophthalmic, nasal, and temporal posterior ciliary arteries and CRA without IOP decreases, while timolol did not show these effects [112]. In a double-masked study in 11 POAG patients with ocular vasospasm (i.e., significant increase of blood flow velocity in the OA or significant decrease of resistive index in the OA during hypercapnia), 0.25 % betaxolol treatment twice-daily for 4 weeks resulted in a significant decrease in the resistive index measured by CDI in the OA and an increase in the resistive index in the CRA and temporal posterior ciliary arteries, while no significant hemodynamic changes were seen after timolol treatment [110]. Similar decreases in the resistive index are also reported in other studies in the CRA and temporal posterior ciliary arteries in 10 POAG patients [107], and in 31 POAG patients [132].

Thus, a relatively larger number of reports found beneficial effects of betaxolol on ocular blood flow compared with other topical β-blockers in both experimental animal and human studies.

Levobunolol

Levobunolol is a non-selective β-antagonist, which after administration in vivo is converted into an equipotent and polarized metabolite, dihydrobunolol (DHB) [133]. The polarity of DHB decreases its diffusion in the retina and choroid, and it has a decreased risk of vasoconstriction. According to studies using liquid chromatography, the concentrations of the sum of levobunolol and DHB were lower compared with timolol in the choroid-retina and optic nerve, despite a higher concentration of levobunolol and DHB in the aqueous humor compared with timolol [46]. Levobunolol caused vasodilation in isolated rabbit ciliary arteries pre-contracted with high-K solution, histamine, phenylephrine and ET-1. The cause was postulated to be the blockade of Ca^{2+} entry and a change in Ca^{2+} sensitivity in vascular smooth muscle [134].

Studies in healthy volunteers using the blue-field simulation technique and LDV failed to find a significant change in blood flow parameters after a single administration of levobunolol, while only the volumetric blood flow rate in the retinal vein increased compared with the contralateral control eyes [135]. The volumetric blood flow rate in the retinal vein showed a slight increase, with borderline significance after treatment with 0.5 % levobunolol twice-daily for 1 week associated with decreased IOP

[136]. In a study in 10 POAG patients using CDI, blood flow in retrobulbar arteries was unchanged after administration of 0.5 % levobunolol twice-daily for 1 month [107]. In another double-masked study evaluating pulsatile ocular blood flow and blood flow velocities in the CRA and the OA using CDI after a single dose of levobunolol or timolol, the parameters remained unchanged after levobunolol treatment, but pulsatile ocular blood flow significantly decreased after timolol treatment [60]. Conversely, several studies have found increased pulsatile ocular blood flow after a single drop of topical 0.5 % levobunolol [137] or treatment with levobunolol twice-daily for 1 week [115].

Nipradilol

Nipradilol is a non-selective β-blocker with relatively weak α-1-blocking activity that was registered as a topical glaucoma therapy in Japan [138]. It also has nitroglycerin-like NO-releasing activity; it is one of the most potent vasodilators [139]. Systemically applied nipradilol exerted a vasodilating effect comparable to that of nifedipine or nitroglycerin, whereas other β-blockers constricted or did not change the diameter of rat mesentery arterioles in vivo [140].

The effect of nipradilol on isolated rabbit ciliary arteries was studied in vitro using an isometric tension recording method, during which it provoked a dose-dependent (10 μM to 1 mM) relaxation in the arteries pre-contracted with high-K^+ solution or phenylephrine, likely due to NO produced by denitrification of nipradilol itself and α-1-blocking activity [141].

Two studies using laser speckle flowgraphy in rabbits found significantly increased tissue blood velocity in the ONH of 13–15.9 % after treatment with 0.25 % nipradilol twice-daily for 14–15 days [122, 142]. Ocular and periocular distribution of topically administered nipradilol was studied in monkeys using a radioactive agent, and its effect on ONH blood velocity was studied in healthy humans using laser speckle flowgraphy [47]. In monkeys, nipradilol concentrations were studied using [^{14}C] nipradilol after a hemilateral single administration. The concentration in the periocular tissue around the optic nerve insertion and posterior retina–choroid was significantly higher on the ipsilateral side compared with the contralateral side, suggesting a distribution of nipradilol to the retrobulbar tissues through periocular tissues.

In healthy human subjects, ONH blood velocity significantly increased in only the nipradilol treated eyes after hemilateral administration of 0.25 % nipradilol twice-daily for 7 days [47]. In a double-masked study using LDV in normal humans, retinal arterial blood flow and diameter significantly increased at 4 h after a single administration of nipradilol, without significant changes in OPP, and IOP was significantly decreased in both eyes [143]. Another human study using CDI found that a single drop of nipradilol significantly decreased the pulsatile index in the CRA suggesting dilation of the artery [144].

Prostaglandin analogues

Latanoprost

Latanoprost is a prostaglandin $F_2\alpha$ analogue and is one of the most widely used antiglaucoma drugs with a strong IOP-reducing effect [145–147]. It is likely that synthetic prostaglandins used as glaucoma drugs may exert microvascular effects in the eye, as many naturally occurring prostaglandins have significant effects on the cardiovascular system. The mechanism of vascular effects of prostaglandin analogues is not yet clear. The effect of latanoprost on isolated rabbit ciliary arteries was studied using an isometric tension recording method, and latanoprost evoked a dose-dependent relaxation that was not inhibited by L-NAME, calcitonin gene-related peptide (CGRP), indomethacin or the removal of endothelium, suggesting that the effect was independent of intrinsic prostaglandins, CGRP, or NO [148]. Conversely, an increase in ONH blood flow after topical latanoprost, unoprostone, or travoprost administration was reversed after pretreatment with indomethacin in vivo, suggesting involvement of intrinsic prostaglandins [149–151].

The effect of topical latanoprost on ONH blood flow was investigated using laser speckle flowgraphy in rabbits, cynomolgus monkeys and healthy humans. The blood velocity in the ONH was significantly increased in latanoprost treated eyes in both animals and humans after once-daily 7-day administration, which was independent of IOP reduction and abolished by systemic pretreatment with indomethacin, suggesting involvement of the production of endogenous prostaglandins contributing to its in vivo effects [149].

A double-masked study using HRF in healthy humans did not find significant effects of a single drop of 0.005 % latanoprost on blood velocity or blood flow in the ONH and peripapillary retina [152]. However, another open-label study in POAG patients using HRF found that blood velocity in the ONH, blood volume and flow at the peripapillary retina was significantly increased after 6 months of treatment with 0.005 % latanoprost [153].

In a double-masked study using laser speckle flowgraphy and CDI in healthy humans, tissue circulation in the ONH was significantly increased 45–270 min after a single administration of latanoprost, while blood velocity in the vessels changed very little [154].

A double-masked study in POAG and OH patients using CDI failed to find a significant effect on blood flow in the

retrobulbar arteries 12 h after latanoprost administration for 1 week [106]. Several studies using CDI also found no significant effect of 4 weeks of treatment with latanoprost on ocular blood flow [155, 156]. Conversely, a statistically significant increase in peak systolic velocity of the OA [157] and a decrease in the resistive index in both the CRA and posterior ciliary arteries [132] are reported in patients with POAG or OH. Several studies evaluated the effect of latanoprost on pulsatile ocular blood flow in healthy subjects, and in most of them, 0.005 % latanoprost significantly increased pulsatile ocular blood flow by 16.7–40 % [158–160]. Other studies in patients with POAG or NTG also report a significant increase in pulsatile ocular blood flow [161–164].

Unoprostone

Unoprostone is a prostaglandin-related compound that was first used clinically in Japan [165]. It resembles naturally occurring oxygenated metabolites of docosahexaenoic and docosatetraenoic acids, and 0.12 % isopropyl unoprostone has an IOP-reducing effect equivalent to 0.5 % timolol in humans [165, 166].

Using an isometric tension recording method in rabbit ciliary arteries, isopropyl unoprostone evoked a dose-dependent relaxation after pre-contraction with excess-K^+ solution [167], similar to latanoprost. Neither unoprostone isopropyl nor unoprostone free acid showed a significant vasoactive effect on isolated perfused porcine retinal arterioles without pre-contraction; however, both of them produced a pronounced dilatation in pre-contracted arterioles with ET-1 [168]. The effect of unoprostone on the ONH circulation was studied in rabbits using a hydrogen gas clearance flowmeter. A single administration of the drug had no significant effect in normal rabbit eyes; however, intravitreal injection of 10 μl of 0.06 % unoprostone significantly increased ONH blood flow at 1–3.5 h after injection and partly inhibited the decrease in ONH blood flow induced by ET-1 [169].

In a double-masked study in human subjects including NTG patients using HRF, most parameters of blood flow were significantly increased 1–2 h after a single drop of unoprostone without a significant decrease in IOP [170]. In a placebo-controlled study in vasospastic NTG patients, treatment with 0.15 % unoprostone isopropyl twice-daily for 1 week was associated with no significant alteration in ocular hemodynamics [171].

According to a double-masked study in healthy subjects using laser speckle flowgraphy and CDI, a significant increase in blood velocity in the ONH, increased peak systolic blood velocity, decreased end-diastolic velocity and resistive index in the CRA were found after treatment with 0.12 % unoprostone twice-daily for 7 days [172]. Increased blood velocity in the ONH was also reported in a double-masked study using laser speckle flowgraphy after treatment with unoprostone twice-daily for 21 days [173]. Another randomized study evaluated pulsatile ocular blood flow in patients with POAG or OH, and found it was significantly increased after treatment with 0.15 % unoprostone twice-daily for 1 month; however, the extent of the pulsatile ocular blood flow increase was approximately half of that obtained with 0.005 % latanoprost once-daily [164].

The antagonistic action of unoprostone to ET-1 was studied in a double-masked study using pulsatile ocular blood flow in subjects receiving a continuous intravenous administration of ET-1. Significant decreases in pulsatile ocular blood flow due to ET-1 were significantly blunted when 0.12 % topical unoprostone was co-administered [174]. Repeated intravitreal injections of ET-1 decreased ONH blood flow as measured by laser speckle flowgraphy accompanied by glaucomatous changes in the optic disc, which were suppressed by subconjunctival unoprostone [175].

Bimatoprost, travoprost, and tafluprost

Bimatoprost [176, 177], travoprost [178, 179] and tafluprost [180–182] are commercially available topical prostaglandin $F_2\alpha$ analogues, which are reportedly equivalent or even more potent, in terms of IOP reduction, than latanoprost.

Vasoactive effects of these drugs were studied in isolated porcine ciliary arteries using a myograph system, and bimatoprost reportedly showed a vasoconstricting effect at high concentrations (higher than 0.1 μM), while travoprost did not show any significant effect in a similar situation [183, 184]. In Dutch rabbits, administration of 0.004 % travoprost once-daily for 7 days significantly increased the ONH tissue blood velocity as measured by laser speckle flowgraphy, which persisted for 24 h after administration and was abolished by indomethacin pretreatment, suggesting an association with endogenous prostaglandins [151].

The effects of 0.03 % bimatoprost and 0.004 % travoprost on ocular blood flow were studied in comparison with 0.2 % brimonidine and 0.25 % betaxolol in a double-masked study in 19 healthy humans using CDI. Bimatoprost caused a significant increase in end diastolic velocity of the OA, and travoprost reduced resistive index and increased blood velocity in the OA and its branches 1 h after a single administration of the drugs [185]. The effect of treatment with 0.03 % bimatoprost once-daily for 1 month was studied using the same method, and no significant changes in blood flow velocities or resistive index in ophthalmic, posterior ciliary, or CRA were found, despite a significantly reduced IOP in 26 patients with

OAG or OH [186] or in 22 patients with NTG [187]. Another study in 42 patients with NTG did not find significant changes in blood velocities in the short posterior ciliary arteries after 1 month of treatment with latanoprost or bimatoprost [156].

Topical 0.0015 % tafluprost administration significantly increased retinal blood flow measured using LDV in cats [188], and topical latanoprost significantly increased ONH blood flow measured using laser speckle flowgraphy in monkeys [67]. Another study in rabbits using laser speckle flowgraphy found tafluprost, latanoprost and travoprost increased ONH blood flow after repeated topical administration [189]. Tafluprost, latanoprost and travoprost significantly prevented ET-1 induced reductions in ONH blood flow in vivo and contraction of ciliary arteries in vitro in rabbits, and the effects of tafluprost were stronger than that of the other prostaglandin analogues [190].

Carbonic anhydrase inhibitors

Dorzolamide

Carbonic anhydrase catalyzes the rapid interconversion of carbon dioxide and water into protons and bicarbonate ions. Among the many subtypes of carbonic anhydrase, CA-II is predominantly distributed in the ciliary process in humans and inhibition of CA-II decreases the rate of aqueous humor production and reduces IOP [191–194].

Dorzolamide hydrochloride is the first water-soluble topical carbonic anhydrase inhibitor (CAI) developed that distributes at a sufficient level in the ciliary process for inhibition of CA-II, and it causes significant IOP reduction at extremely low plasma concentrations, which minimizes the potential severe systemic adverse effects of CAIs [195–198].

The ONH blood flow in rabbits measured by HRF increased significantly by 8.4 ± 4.3 % after treatment with 2 % dorzolamide twice-daily for 1 week with a significant IOP decrease [199]. However when the effect of topical dorzolamide on the ONH circulation was studied in rabbits using laser speckle flowgraphy, the tissue blood velocity in the ONH was not significantly altered after treatment with 1 % dorzolamide twice-daily for 20 days, despite a significant decrease in IOP [200].

A double-masked study in normal subjects using LDV and monochromatic fundus photography, however, failed to find significant changes in venous diameter, maximum erythrocyte velocity, or volumetric blood flow rate after a single drop of 2 % dorzolamide hydrochloride [201]. Several follow-up studies using HRF [202, 203] or CDI [204] failed to find significant changes in ocular blood flow. Studies in NTG patients using CDI found unchanged retinal arterial and venous diameters and flow velocities in the ophthalmic, CRA, and posterior ciliary arteries [155, 205, 206].

Conversely, treatment with dorzolamide thrice daily for 6 months significantly increased ONH blood flow and POB in a double-masked study using HRF in 140 patients with POAG or OH [102]. In a study using CDI to investigate retrobulbar blood flow in patients with POAG, treatment with 2 % dorzolamide thrice daily for 15–30 days significantly decreased the resistive index in the posterior ciliary arteries compared with the pretreatment measurement [78]. Another study in 42 patients with NTG using CDI also reports a significant increase in peak systolic blood flow velocity in the short posterior ciliary arteries after treatment with 2 % dorzolamide thrice daily for 1 month [156]. Vascular reactivity, increased diameter, velocity, and flow in response to normoxic hypercapnia, are reportedly decreased in patients with POAG, and improved after treatment with dorzolamide for 2 weeks [207].

Brinzolamide

Brinzolamide is another topical CAI, which became commercially available following dorzolamide. In a study in rabbits, ONH blood flow measured with HRF increased significantly by 11.2 ± 1.8 % after treatment with 2 % brinzolamide twice-daily for 1 week [199]. A double-masked study in normal subjects using CDI found no significant change in blood flow in the retrobulbar arteries after treatment with brinzolamide twice-daily for 2 weeks [208]. In another study in patients with glaucoma using HRF, treatment with 1 % brinzolamide twice-daily for 4 weeks significantly increased retinal blood flow in temporal and nasal areas [209].

Systemic drugs

Carbonic anhydrase inhibitors

Acetazolamide

Acetazolamide is an orally administered systemic CAI, prescribed for patients with intracranial hypertension, and has been used for treatment of glaucoma because of its potent ocular hypotensive effect [210]. A study which investigated the effects of systemic CAIs, acetazolamide and dorzolamide on retinal cells in enucleated rat eyes found that a decrease in pH in the extracellular space and an increase in pH within the retinal cells were followed by an increase in the diameter of the retinal capillaries of up to 105 % concomitant with changes in pH [211]. In a study in porcine eyes in vivo, increased oxygen tension in the retina

and optic nerve and significant dilation of the retinal arterioles were found after intravenous administration of 500 mg dorzolamide [212]. In addition, blood flow in the retina and choroid significantly increased after intravenous administration of 10 mg/kg acetazolamide in ocular hypertensive rabbits [59].

A double-masked study investigated POB, blood velocity and resistive index in the OA using CDI in normal subjects. An intravenous administration of 500–1000 mg acetazolamide significantly increased POB and blood velocity in the OA, and decreased resistive index in a dose-dependent manner with a significant decrease in IOP [213]. In another double-masked study in normal subjects, an increase in POB and blood flow velocity in the OA was also found after intravenous administration of 1000 mg acetazolamide, and no involvement of NO in this hemodynamic effect was found [214]. Conversely, one report found a decrease of blood flow velocity and pulsatile ocular blood volume in the OA in 15 normal subjects despite a decrease in IOP after intravenous administration of 1000 mg acetazolamide [215].

Calcium channel antagonists

Calcium channel antagonists have been widely used in the treatment of systemic disorders, including systemic hypertension, angina pectoris, cardiac arrhythmias and migraine [216]. The primary effect of calcium channel antagonists is to inhibit intracellular calcium ion influx and reduce blood vessel tone, which leads to relaxation of vascular smooth muscle cells, vasodilation and increasing blood flow in several organs [217–219]. Six functional subclasses of calcium channels have been identified: L, T, N, P, Q, and R [220]. The L-type calcium channel is the predominant type in skeletal, cardiac and vascular smooth muscle.

Calcium channel antagonists may alter IOP when administered systemically or topically. A decrease in IOP has been shown in several reports in rabbits [221, 222] and also in humans after systemic [223] or topical [224, 225] administration of calcium channel antagonists. This effect was explained by relaxation of ciliary muscles and trabecular meshwork and an increased outflow facility [226, 227]; however, the effect of oral calcium channel antagonists on IOP was insignificant in recent placebo-controlled studies in patients with NTG [228, 229].

The effect of calcium channel antagonists on isolated arteries is reported in several studies in vitro. Nitrendipine suppressed contraction of bovine isolated retinal arteries induced by ET-1 [230]. In other studies using myograph systems, lacidipine, nifedipine and amlodipine were found to inhibit ET-1 induced vasoconstriction in porcine ciliary arteries [231, 232].

The effect of intravenous nicardipine on ONH circulation was studied in cats, and a significant increase in ONH blood flow and pO_2 immediately in front of the ONH was found after administration of 20 and 100 μg/kg nicardipine, using HRF and an oxygen-sensitive microelectrode, respectively [233]. In another study in rabbits using laser speckle flowgraphy, increased blood flow was found after an intravenous injection of 5 μg/kg pranidipine in the ONH, choroid and retina [234]. A significant increase in ONH blood flow is also reported in rabbits after intravenous nilvadipine [228, 235] or lomerizine [235, 236] administration, using laser speckle flowgraphy and the hydrogen gas-clearance method [228, 236]. The effect of topical iganidipine, which is a dihydropyridine derivative calcium channel antagonist and extremely water soluble, on ocular blood flow has been investigated in animals. A significant increase in ONH blood flow was found after topical administration of iganidipine using the hydrogen gas-clearance method in rabbits [237], or laser speckle flowgraphy in rabbits and monkeys [49].

As favorable effects on the systemic administration of calcium channel antagonists, including nifedipine on glaucomatous visual field defects, have been reported [238–240], the involvement of altered ocular blood flow has been investigated. The effect of nifedipine on ocular blood flow was evaluated in several studies; however, most of them failed to find a significant effect. Blood velocity in the OA, CRA and the short posterior ciliary arteries measured by CDI is reportedly not significantly affected by oral nifedipine administration in patients with NTG or POAG [241, 242]. In other studies in patients with NTG, a significant effect of nifedipine administration for 3 as well as 6 months on ocular pulse amplitude [243] or blood velocity in the retrobulbar vessels [244] was found only in those individuals with a vasospastic reaction after cold water provocation in the nail fold capillaries [243], or those individuals with improvements in contrast sensitivity [244].

The results of studies using nimodipine, which can to cross the blood–brain barrier because of its high lipid solubility [245], are also reported. A single oral dose of 30 mg nimodipine significantly increased retinal capillary blood flow in NTG patients with vasospastic hyperactivity, while no such effect was seen in healthy age-matched volunteers [246]. In another double-masked study, pulsatile ocular blood flow and blood flow in the ONH and choroidal tissues, assessed using HRF, significantly increased by 14 ± 14, 18 ± 16, and 12 ± 14 %, respectively, after a single oral administration of 60 mg nimodipine [229]. However, other double-masked studies failed to find a significant effect of 60 mg oral nimodipine on ONH blood flow assessed using HRF [247], macular leukocyte velocity, or density [248] in patients with NTG despite

Table 1 Summary of the effects of drugs on human optic nerve head blood flow and methods used to measure blood flow

Drug	Changes in human ONH blood flow (approximate maximum change)	Methods
Alpha-agonists		
Phenylephrine	Decrease (10–15 %)	LSFG [66]
Apraclonidine	Not significant	HRF [77]
Beta-antagonists		
Timolol	Not significant	LSFG [99], HRF [101, 102, 109]
	Decrease (20–25 %)	HRF [100]
Carteolol	Increase (10–15 %)	LSFG [103]
Betaxolol	Increase (10–15 %)	LSFG [130]
Nipradilol	Increase (30–35 %)	LSFG [47]
Prostaglandin analogues		
Latanoprost	Increase (25–30 %)	LSFG [149, 154], HRF [153]
	Not significant	HRF [152]
Unoprostone	Increase (15–40 %)	LSFG [172, 173], HRF [170]
	Not significant	HRF [171]
Carbonic anhydrase inhibitor		
Dorzolamide	Increase (5–15 %)	HRF [102]
Calcium channel antagonists		
Nimodipine	Increase (15–20 %)	HRF [229]
Nilvadipine	Increase (20–40 %)	LSFG [228, 252], HRF [249]

LSFG laser speckle flowgraphy, *HRF* Heidelberg retinal flowmeter, *ONH* optic nerve head

improvements in contrast sensitivity or visual field testing, respectively.

Additionally, there are several reports in patients with NTG using HRF [249], laser speckle flowgraphy [228], or CDI [249, 250] that found a significant increase in optic disc blood flow or decrease of resistive index in the CRA or posterior ciliary arteries after oral administration of 4 mg oral nilvadipine for 4–12 weeks. Topical verapamil significantly increased capillary blood speed in the ONH measured by HRF [225] and decreased vascular resistance in the CRA measured by CDI [251] in double-masked placebo-controlled studies and in normal volunteers [225, 251].

In a 3-year prospective randomized placebo-controlled study in patients with NTG, 2 mg nilvadipine administered twice-daily significantly increased ONH blood flow velocity measured by laser speckle flowgraphy. The mean slope of the mean deviation of the Humphrey visual field analyzer (30–2 program) was −0.27 dB/year for the control group and −0.01 dB/year for the nilvadipine-treated group, which was significantly different [252].

Conclusion

At clinical doses almost all of the topically administered antiglaucoma drugs have the potential to increase the circulation in ocular fundus tissues, including the ONH, in human eyes. Reported effects of drugs on human ONH blood flow assessed using laser speckle flowgraphy or HRF

Table 2 Summary of the effects of drugs on human retrobulbar arterial blood flow measured using color Doppler imaging

Drug	Changes in blood flow (artery): "increase" means increase in blood velocity or decrease in resistive index
Alpha-agonists	
Apraclonidine	Decrease (OA) [75, 76]
	Not significant [78]
Brimonidine	Not significant [81]
Beta-antagonists	
Timolol	Not significant [106, 110–112]
	Decrease (CA) [107]
Carteolol	Increase (OA) [123]
Betaxolol	Increase (CA or OA) [107, 110, 112, 132]
Levobunolol	Not significant [60, 107]
Prostaglandin analogues	
Latanoprost	Increase (CA) [132], increase (OA) [157]
	Not significant [106, 154–156]
Travoprost	Increase (OA) [185]
	Not significant [156, 186, 187]
Bimatoprost	Increase (OA) [185]
Carbonic anhydrase inhibitor	
Dorzolamide	Not significant [155, 204–206]
Brinzolamide	Not significant [157, 208]
Acetazolamide	Increase (OA) [213]; decrease (OA) [215]
Calcium channel antagonists	
Nifedipine	Not significant [241, 242]
Nilvadipine	Increase (CA) [249, 250]

OA ophthalmic artery, *CA* ciliary arteries

are summarized in Table 1, and those on human retrobulbar arteries assessed using CDI are summarized in Table 2. At present, it remains unverified whether pharmacologically induced increases in ONH blood flow can modify the progression of glaucomatous damage. This is also the case for systemic drugs, which could also affect ONH blood flow. Therapeutic effects of increases in ONH blood flow of topical or systemic antiglaucoma drugs require further investigation by future studies. However, it must be noted that potential effects of antiglaucoma drugs on glaucoma-related tissues may have clinical implications in patients whose ocular circulation is already substantially compromised by other coexisting morbidities.

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