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Effect of Timolol on Aqueous Humor Outflow Facility in Healthy Human Eyes

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Abstract

Purpose: Hyposecretion of aqueous humor has been postulated to adversely affect trabecular meshwork health and outflow resistance. However, the effect of medications that reduce aqueous humor production on outflow facility in living human eyes is unclear. In this study we evaluated the effect of timolol, an aqueous humor flow suppressant, on outflow facility in healthy eyes.

Design: Prospective, before-and-after study.

Methods: In a multicenter study, 113 healthy participants over age 40 years were included. Intraocular pressure (IOP) was measured in the sitting position by using a pneumatonometer and outflow facility was measured in the supine position by 2-minute pneumatonography. After one week of self-administering timolol 0.05% twice daily in each eye, both measurements were repeated.

Results: Mean IOP decreased from 15.1 ± 3.0 mmHg at baseline to 12.4 ± 2.4 mmHg ($P < 0.001$) after one week of timolol use. Mean outflow facility decreased from 0.23 ± 0.08 $\mu\text{L}/\text{min}/\text{mmHg}$ at baseline to 0.18 ± 0.08 $\mu\text{L}/\text{min}/\text{mmHg}$ ($P < 0.001$) after timolol. The change in outflow facility was negatively correlated with baseline outflow facility ($r = -0.51$, $P < 0.001$).

Conclusion: Timolol reduces outflow facility in healthy human eyes, and this effect is greater in eyes with higher baseline outflow facility. This phenomenon may be related to reduced aqueous humor flow, but the precise mechanism remains to be determined.

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Introduction

Glaucoma is a progressive optic neuropathy and is the second most common cause of blindness in the world, with over 2.5 million people affected in the United States alone.¹ Elevated intraocular pressure (IOP) is the primary risk factor in glaucoma, and lowering IOP is currently the only effective treatment. IOP can be lowered in several ways including reduction of aqueous humor production, or improvement of aqueous humor outflow facility.

Timolol is a nonselective beta-adrenergic antagonist² that has been widely used for glaucoma treatment since the late 1970s. It lowers IOP in healthy volunteers^{3–5} and in patients with open-angle glaucoma^{6–15} or ocular hypertension^{12, 14, 15} by suppressing aqueous humor production 33%–50% as measured by fluorophotometry.^{4, 5, 16–21}

The effect of aqueous humor flow suppression on other parameters of aqueous humor dynamics, including aqueous humor outflow facility is not well understood. Previous investigators have suggested that suppression of aqueous production could cause underperfusion of the trabecular meshwork, leading to a reduction in outflow facility.^{22, 23} However, several studies in patients with ocular hypertension or glaucoma have reported that timolol had no significant effect on outflow facility measured by tonography^{11–13, 19, 24–30} or fluorophotometry,³⁰ while some have even reported an increase in outflow facility^{20, 31, 32}. In these previous studies, all outflow facilities were measured in patients with dysfunctional trabecular meshwork, as indicated by low outflow facility at baseline. The effect of aqueous humor suppression on outflow facility in healthy human eyes (with healthy trabecular meshwork) has not been reported. In this study, we evaluated the effect of timolol on outflow facility in healthy human subjects.

Methods

This prospective before-and-after study was approved by the Institutional Review Boards at Mayo Clinic, University of Michigan, and University of Nebraska Medical Center. The study followed the tenets of the Declaration of Helsinki and was in accordance with HIPAA regulations. All subjects provided written informed consent to participate after discussion of the nature and possible risks of the study.

Study Subjects

One hundred-thirteen healthy participants, ages 40 years and above were enrolled from local area residents, employees, and patients of the ophthalmology departments at Mayo Clinic Rochester, University of Michigan, and University of Nebraska as part of a multi-center study (NCT01677507). Each participant underwent a general health interview and comprehensive ophthalmologic examination including visual acuity, IOP by pneumatonometry, gonioscopy, slit-lamp biomicroscopy, A-scan biometry, ultrasound pachymetry and funduscopy. Subjects were excluded if they had a history or evidence of intraocular surgery, laser treatment, ocular pathology (including narrow angles or any form of glaucoma), ocular trauma within the past 6 months, current use of any IOP-lowering medication, serious hypersensitivity to any components of the study medications, recent changes to systemic medications that may affect IOP, use of any glucocorticoid by any route,

women who were known to be pregnant, and any contraindication for treatment with the study glaucoma medications including severe reactive airways disease and bradycardia.

Measurements

Intraocular Pressure (IOP)—Baseline IOP was measured in both eyes of each subject in the sitting position by using a pneumatonometer (Model 30 Classic, Reichert Inc., Buffalo, NY). The subject was then placed in a supine position and IOP was re-measured after 5 minutes. All IOP measurements were between 9 and 11 AM. Calibration of the tonometer was verified according to the manufacturer's instruction and the tip was cleaned before each set of measurements. Topical proparacaine 0.5% was instilled before each IOP measurement and tonography. The right eye was always measured first.

Outflow Facility by Pneumatography—Outflow facility was measured with the subject in the supine position by using a pneumatonometer with a 2-minute tonography option. Outflow facility was calculated from the pressure decay curves digitized from paper tracing and using Langham's pressure volume relationship tables and a polynomial fitted to the decay curve, as described previously.^{33, 34} The right eye was always measured before the left eye.

Axial Length and Central Corneal Thickness—Axial length (AL) was measured by A-scan biometry and central corneal thickness (CCT) was measured by ultrasound pachymetry.

Study Medications

Intraocular pressure and outflow facility were measured at baseline prior to any medication use. Subjects were then instructed to instill timolol 0.5% solution, one drop every 12 hours in both eyes. The drug was self-administered for one week. After one week of treatment, IOP and outflow facility were remeasured by using the same techniques as used for the baseline measurements.

Statistical analysis

Significance of changes in IOP and outflow facility from baseline in response to timolol were determined by using generalized estimating equation models to account for possible correlation between fellow eyes of the same subject (R Core Team 2018, RStudio version 1.1.456, GEE version 4.13–19, Vienna, Austria). Correlation between baseline outflow facility and changes in outflow facility after timolol treatment was determined by linear regression analysis. Differences were considered significant if *P* was less than 0.05.

Results

One hundred-thirteen healthy participants (27 males and 86 females; 98 Caucasians, 11 African Americans, and 4 other races), ages 40 to 81 years (55.3 ± 8.9 years, mean $\pm$ SD) were included in the study (Table 1). Among these subjects, 200 eyes from 104 subjects had satisfactory 2-minute IOP recordings that were suitable for calculation of tonographic

outflow facility. The other 26 eyes did not have outflow facility tracings of adequate quality for outflow facility calculation.

The mean IOP at baseline was 15.1 ± 3.0 mmHg ($\pm$ SD, $n = 200$ eyes) and decreased to 12.4 ± 2.4 mmHg ($P < 0.001$) after 1 week of timolol therapy (Table 2, Figure 1). The mean outflow facility at baseline was 0.23 ± 0.08 μ L/min/mmHg, and decreased after one week of timolol treatment to 0.18 ± 0.08 μ L/min/mmHg ($P < 0.001$) (Figure 2), a mean change of 24.5%. In a subgroup analysis, the mean outflow facility decreased after one week of timolol treatment compared to baseline at each study site: from 0.22 ± 0.08 to 0.16 ± 0.07 μ L/min/mmHg at the University of Michigan ($P < 0.001$); from 0.23 ± 0.07 to 0.20 ± 0.07 μ L/min/mmHg at the Mayo Clinic ($P = 0.01$); and from 0.24 ± 0.08 to 0.17 ± 0.09 μ L/min/mmHg at the University of Nebraska ($P < 0.001$).

There was a moderate strength negative correlation between baseline outflow facility and the change in outflow facility after timolol treatment ($r = -0.51$, $P < 0.001$), with higher baseline outflow facility being associated with a greater decrease in outflow facility (Figure 3). Outflow facility decreased in 145 eyes (73%), from a mean baseline outflow facility of 0.26 ± 0.07 μ L/min/mmHg to 0.16 ± 0.07 μ L/min/mmHg after timolol treatment. In 53 eyes (26%), outflow facility increased from a mean at baseline of 0.17 ± 0.06 μ L/min/mmHg to 0.22 ± 0.09 μ L/min/mmHg after timolol treatment. Two eyes (1%) did not show any change in outflow facility.

Baseline outflow facility was weakly correlated with age in our study population ($r = -0.25$, $P < 0.001$). Older subjects were associated with lower outflow facilities (Figure 4). Baseline outflow facility was not correlated with either central corneal thickness ($r = 0.02$, $P = 0.78$) or axial length ($r = 0.07$, $P = 0.28$). Also, there were no significant differences in baseline IOP and outflow facility between men and women ($P = 0.29$ for IOP and $P = 0.07$ for outflow facility).

Discussion

Our study found a reduction in outflow facility after 1 week of treatment with timolol eye drops in healthy subjects. We are unaware of previous reports of this finding and could find no reference to it in a search in PubMed. Suppression of aqueous humor production is the main mechanism of action for IOP reduction by beta-adrenergic blockers, such as timolol, but a decrease in outflow facility potentially limits this effect. However, the effect of timolol on aqueous humor outflow facility reported in the literature is variable. While one animal study in cynomolgus monkeys suggested that timolol may lead to a reduction in outflow facility,²² studies in living humans have reported no change or even an increase in outflow facility in patients with ocular hypertension or open angle glaucoma.^{11–13, 19, 20, 24–32} An important distinction, though, is that none of these studies were performed in healthy human eyes.

One possible mechanism for alteration of outflow facility by timolol in our study population may be the blockade of beta-receptors in the trabecular outflow pathway. Thomas and Epstein³¹ reported a significant increase in outflow facility after two weeks of treatment with

epinephrine, a beta-adrenergic agonist, in 16 glaucoma patients. However, after two weeks of combined therapy with timolol and epinephrine, a significant decrease in outflow facility was observed. They postulated that beta-adrenergic receptors mediating outflow may be located in the trabecular meshwork and stimulating them produces an increase in outflow facility, and this effect is blocked by timolol. However, they also observed that blocking the beta-receptors with timolol alone did not decrease outflow facility in glaucoma patients. Similarly, Robinson and Kaufman³⁵ reported that pretreatment with timolol prevented the facility-increasing effect of topical epinephrine and norepinephrine in normotensive cynomolgus monkey eyes. They concluded that the facility-increasing effect of both epinephrine and norepinephrine is mediated by beta-2-adrenergic receptors in the trabecular meshwork endothelium. However, a single treatment with timolol alone had no effect on outflow facility in cynomolgus monkeys. This suggests that the decrease in facility after 1 week of treatment in our study population may not be from an immediate effect of timolol on beta-adrenergic receptors, but a slower onset mechanism of action related to aqueous humor flow suppression.

Hyposecretion of aqueous humor has been suggested as potentially damaging to the trabecular meshwork, leading to a reduction of outflow facility.²³ Becker, in an unpublished observation of the effect of oral acetazolamide, found that healthy human subjects had an initial rapid decrease in IOP, but demonstrated a return toward baseline IOP after several weeks of treatment, and this was associated with a reduction in tonographic outflow facility.²³ Kiland et al.²² in a study of healthy cynomolgus monkeys reported a trend towards a decrease in outflow facility after four weeks of treatment with timolol and dorzolamide, but this did not reach statistical significance. However, after four weeks of treatment with timolol + dorzolamide + prostaglandin, outflow facility was significantly reduced compared to baseline. They suggested that long-term use of medications that suppress aqueous humor formation, such as timolol may cause underperfusion of the trabecular meshwork, reducing the concentration of oxygen and nutrients reaching the trabecular meshwork, possibly leading to changes that decrease outflow facility, and this effect may be exacerbated by medications that redirect aqueous humor outflow away from the trabecular meshwork, such as prostaglandin analogues. Supporting these findings, Lutjen-Drecoll and Kaufman³⁶ demonstrated by electron microscopy marked histological changes in the trabecular meshwork of healthy cynomolgus monkeys after 3–7 months of topical timolol given twice daily. Further, using a human anterior segment organ culture system, Johnson³⁷ demonstrated that perfusion rates of less than 1 $\mu\text{L}/\text{min}$ over 7–21 days resulted in marked trabecular cell loss. This finding suggests that pathological changes in the trabecular meshwork as a result of severe underperfusion may result in reduction of outflow facility. However, timolol eye drops alone may not reduce aqueous humor flow rate enough to induce pathologic changes. Of note, the 1 $\mu\text{L}/\text{min}$ flow rate threshold identified by Johnson is lower than the nocturnal flow rate in humans, when aqueous humor production decreases by approximately 50%³⁸ and lower than the flow rate typically achieved with timolol eye drops.^{4, 5, 16–21}

Another possible explanation for the reduction in outflow facility by timolol is that changes in outflow facility in response to decreased aqueous humor flow are not pathologic, but are instead pressure regulatory mechanisms. Acott et al.³⁹ hypothesized and reviewed the

evidence that resistance within the conventional outflow pathway is continually adjusted in response to cell stretch from sustained IOP changes. The proposed mechanism involves extracellular matrix turnover, requiring hours to days, which would be consistent with the findings in our study. This mechanism also may explain why a reduction in outflow facility was detected in our study of healthy subjects, but not previous studies of glaucoma patients with presumably dysfunctional trabecular meshwork that may not be able to respond to pressure changes. Further potential evidence for a compensatory change in outflow facility in response to aqueous humor flow reduction comes from studies of circadian aqueous humor dynamics.^{40–42} In healthy subjects, the reduction of aqueous humor production at night is partially compensated by a reduction in outflow facility, resulting in a relatively stable circadian IOP when measured in a constant body position. However, it is not known if the change in outflow facility is a response to the reduction in flow rate, or a concurrent change that occurs due to another mechanism.

A reduction in outflow facility with timolol treatment also may help explain the frequently observed phenomenon of tachyphylaxis. Previous studies have reported that some patients using timolol exhibited a reduction in efficacy over a few days of therapy. This clinically observed phenomenon has been termed “short-term escape”.^{6, 7, 43, 44} One possible explanation for this phenomenon is the finding in a study in albino New Zealand rabbits that the number of beta-adrenergic receptors in ocular tissues increases within days of beginning timolol administration.⁴⁵ Neufeld demonstrated that the number of beta receptors in ocular tissues increases with continued timolol therapy. The time course of this alteration of receptor numbers is a matter of days and would seem to correlate with the short-term escape.⁴⁵ As well, Johnson et al.³⁰ found that the degree of aqueous humor suppression decreased after six weeks of timolol treatment compared to one week of treatment. However, increase in the number of beta receptors does not explain the decrease in outflow facility with timolol. Instead, these may be concurrent effects that both reduce efficacy in some patients.

Our study found that eyes with higher baseline outflow facility had a larger decrease in outflow facility after timolol treatment. This is consistent with the notion that healthy trabecular meshwork cells are required to produce a decreased outflow facility as a compensatory response to decreased aqueous flow rate or intraocular pressure, and this phenomenon is not a pathologic effect of hypoperfusion. Although none of our subjects had glaucoma, it is certainly possible that the spectrum of baseline outflow facilities represents a spectrum of trabecular meshwork health. Interestingly, 26% of eyes demonstrated an increase in outflow facility after treatment. These were generally eyes with lower baseline outflow facility, potentially indicating subclinical trabecular meshwork dysfunction. This is consistent with studies that demonstrated an increase in outflow facility in patients with glaucoma and ocular hypertension treated with timolol.^{20, 31, 32} However, it is unknown what changes at the cellular level or extracellular matrix may occur that decrease flow resistance in eyes with low baseline outflow facility. It is also possible that this relationship is the result of regression to the mean, in which a group of eyes may have had outflow facility measurements lower than their normal, and the increase in outflow facility after treatment in this group was a return to baseline. Further research is required to clarify the association between baseline outflow facility and outflow facility change, and the inclusion of a placebo control arm would be helpful.

Our study also found that increasing age was associated with lower baseline outflow facility in our subjects. This is consistent with the findings of most previous studies that have reported age-related decreases in tonographic outflow facility in human eyes.^{46–50} However, this has not been a universal finding, as several studies reporting tonographic outflow facility in humans did not find a significant relationship between age and outflow facility.^{51–53} Two other studies reported trends suggesting lower outflow facility in older subjects, but did not reach statistical significance.^{54, 55} These apparently contradictory results may be a reflection of the inherent variability in tonography. In contrast, total outflow facility measured by 2-level constant pressure perfusion of the anterior chamber in rhesus monkeys consistently demonstrates a decrease in outflow facility with age.^{56–60} It is worth noting that, while our study found a statistically significant relationship between age and baseline outflow facility, the strength of the relationship was weak in our subjects.

Compared with previous studies investigating the effect of timolol on outflow facility, our study has several important advantages. Our study was a multi-center design with a standardized protocol. This design provided a much larger sample size than all previous studies, and thus was appropriately powered to detect this effect. One potential limitation of the study was that the measurements were performed by different people in different centers and this may have resulted in inter-observer variabilities. However, a subgroup analysis indicated that timolol treatment reduced outflow facility in the study populations at each site, suggesting that the measurements were consistent at each site and the results are generalizable to different healthy populations.

In summary, our study found that timolol reduced aqueous humor outflow facility in eyes with healthy trabecular meshwork (as indicated by normal baseline outflow facility) after one week of treatment. Eyes with higher baseline outflow facility showed a greater decrease in outflow facility. Compensatory physiologic changes in the trabecular meshwork in response to reduced aqueous flow rate and intraocular pressure may provide an explanation for the decreased outflow facility in healthy eyes. However, the precise mechanism remains to be determined. The reduction in outflow facility may partially negate the overall IOP lowering effect of timolol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Timolol decreased outflow facility in healthy human eyes.
- This effect was greater in eyes with higher baseline outflow facility.
- Older age was associated with lower outflow facility.

Figure 1.

Comparison of Post-timolol Intraocular Pressure (IOP) with Baseline IOP. IOP decreased from 15.1 ± 3.0 mmHg at baseline to 12.4 ± 2.4 mmHg after 1 week of timolol treatment ($P < 0.001$). Points below the identity line had a reduction of IOP after timolol treatment.

Figure 2.

Comparison of Post-timolol Outflow Facility with Baseline Outflow Facility. Outflow facility decreased from 0.23 ± 0.08 $\mu\text{L}/\text{min}/\text{mmHg}$ at baseline to 0.18 ± 0.08 $\mu\text{L}/\text{min}/\text{mmHg}$ after 1 week of timolol treatment ($P < 0.001$). Points below the identity line had a reduction of outflow facility after timolol treatment.

Figure 3. Correlation of Outflow Facility Change with Baseline Outflow Facility. Higher baseline outflow facility was associated with greater decrease in outflow facility after timolol treatment ($P < 0.001$).

Figure 4. Correlation of Baseline Outflow Facility with Age. Older subjects were associated with lower outflow facilities ($P < 0.001$).

Table 1.

Subject Characteristics

Characteristic	
Men	27
Women	86
Age (yrs)	
Mean $\pm$ SD	55.3 $\pm$ 8.9
Range	40 – 81
Race	
White	98
Black	11
Other	4
CCT (μ m)	551 $\pm$ 39
Axial Length (mm)	23.93 $\pm$ 1.23

SD = Standard deviation

CCT = Central corneal thickness

Table 2.

Effect of Timolol on Intraocular Pressure and Outflow Facility

	Baseline mean $\pm$ SD	Timolol mean $\pm$ SD	<i>P</i>
IOP (mmHg)	15.1 $\pm$ 3.0	12.4 $\pm$ 2.4	< 0.001
Outflow Facility (μ L/min/mmHg)	0.23 $\pm$ 0.08	0.18 $\pm$ 0.08	<0.001

Both IOP and outflow facility decreased significantly after 1 week of treatment with timolol in healthy human eyes.

IOP = Intraocular pressure