Effect of Topical Corteolol on the Normal Human Retinal Circulation

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The effect of topical carteolol 1%, a beta-adrenergic blocker with intrinsic sympathomimetic activity, on the retinal circulation was investigated in 15 normal subjects using laser Doppler velocimetry and monochromatic fundus photography. In a double-masked randomized design, one eye received one drop of carteolol 1% and the fellow eye one drop of placebo. Vessel diameter, maximum erythrocyte velocity, and volumetric blood flow rate were determined in a major temporal vein of each eye just before instillation of the drops and then 120 min later. No significant changes in heart rate or mean brachial artery blood pressure were detected after treatment. Intraocular pressure decreased by 28% in the carteolol-treated eye (P < 0.0001) and by 15% in the placebo-treated eye (P < 0.001). No significant changes in vessel diameter, maximum erythrocyte velocity, and volumetric blood flow rate were observed in the carteolol-treated eyes (0.3%, 4.3%, and 3.6%, respectively) or the placebo-treated eyes (0.5%, 5.8%, and 6.7%, respectively). Invest Ophthalmol Vis Sci 33:1853-1856, 1992

The influence of timolol maleate, a beta-adrenergic blocking agent, on retinal blood flow has been investigated using bidirectional laser Doppler velocimetry (BLDV) and monochromatic fundus photography (MFP). After a single instillation of timolol maleate 0.5%, a significant average increase was reported in retinal volumetric blood flow of approximately 13% in normal subjects1 and 8% in eyes with ocular hypertension.2 A somewhat similar effect also was observed after 2 weeks of timolol treatment.3

Carteolol is a relatively new beta-adrenergic blocking agent with partial beta-agonist activity commonly referred to as intrinsic sympathomimetic activity (ISA). Particularly because of its ISA, we were interested in testing whether carteolol could influence retinal volumetric blood flow. Carteolol is the only approved ophthalmic beta blocker in the United States with ISA and enhancement of ocular blood flow could be therapeutically beneficial.

The contribution of ISA to beta-blocker therapeutic potential has been studied extensively for cardiovascular hypertension.4 These studies generally have been inconclusive and do not support expanded indications or pharmacologic profiles. Although a beta blocker with ISA might be expected theoretically to decrease peripheral vascular resistance and perhaps increase peripheral blood flow, no definitive data support this hypothesis. We decided to study whether carteolol has an effect on retinal volumetric blood flow.

Materials and Methods

Fifteen healthy volunteers aged 20-25 years (average, 33 ± 8 yr, ± one standard deviation) with no history of systemic or intraocular disease were included in this study. These eyes had best-refracted visual acuities of 6/6, intraocular pressures (IOP) of 19 mm Hg or less, and normal anterior segments and fundi. All subjects had no evidence of visual field defects by Octopus perimetry (Program 32; Interzeag AG Schlieren, Switzerland) and had optic nerve heads with a cup-to-disc ratio of 0.4 or less. None of the patients was receiving topical or systemic medication at the time of the study. All subjects refrained from ingesting caffeine on the morning of the experimental procedure. Informed consent was obtained from each subject.

After pupillary dilatation with tropicamide 1%, a Polaroid color fundus photograph (Cambridge, MA) of the disc was taken. We used BLDV to measure maximum erythrocyte velocity (V_{max}) in a main superior or inferior temporal retinal vein in both eyes of each subject. The BLDV determinations were made on veins because the minimal flow pulsatility in these vessels simplifies the determination of the average velocity. The location of the measurement site was...
marked on the Polaroid photograph. Detailed descriptions of the BLDV technique and the measurement procedures and protocol we used have been published previously. Therefore, we provide only a summary here.

Fundus photographs were taken in monochromatic light at 570 nm immediately after the BLDV recordings using a Zeiss fundus camera (Carl Zeiss, Oberkochen, Germany) and Kodak Plus X pan film (Eastman Kodak, Rochester, NY). The diameter of the veins (D) at the site of the BLDV recordings was measured from photographic negatives. We obtained D from an average of the diameters measured from six photographs. Fundus photography and BLDV determinations were done in a darkened room with the subject in a sitting position.

Retinal volumetric blood flow rate, Q, was calculated from the relation: \( Q = V_{\text{mean}} \cdot \pi D^2/4 \), where \( V_{\text{mean}} \) represents the mean velocity of whole blood. We assumed that \( V_{\text{mean}} = C \cdot V_{\text{max}} \) with C being a constant which is the same for all vessels measured. In this study, a value of \( C = 1/1.6 \) was adopted, based on the work of others who studied the relationship between \( V_{\text{max}} \) and \( V_{\text{mean}} \) in glass tubes.

After baseline BLDV and MFP, the heart rate was determined, and systolic and diastolic brachial blood pressures were measured by sphygmomanometry. Two drops of topical proparacaine HCl 0.5% were instilled in each eye, and the IOP was measured by Goldmann applanation tonometry. In a double-masked randomized design, one eye of each subject received one drop of carteolol 1% ophthalmic solution, and the fellow eye received placebo, consisting of the vehicle of the carteolol ophthalmic solution.

Two hours later, the experimental procedure was repeated. The subjects were asked to refrain from eating or drinking during this 2-hr period.

Mean brachial artery blood pressure, \( BP_m \), was calculated according to the formula \( BP_m = BP_s + \frac{1}{2}(BP_t - BP_d) \), where \( BP_s \) and \( BP_d \) are the brachial artery systolic and diastolic pressures. Perfusion pressure, PP, was calculated as \( PP = \%BP_m - IOP \).

All measurements of vessel diameter were done by one trained examiner and all \( V_{\text{max}} \) determinations, by another. Each examiner was masked with regard to: (1) the results of the other, (2) whether measurements were obtained at baseline or after treatment, and (3) the eye that had received carteolol.

The data were analyzed statistically using paired student t-tests (two-tailed), linear regression, and correlation analysis. The presence of a normal distribution was assessed by the Wilk-Shapiro normality test. Findings with an error probability value smaller than 0.05 were considered to be statistically significant.

### Results

No significant change in heart rate or \( BP_m \) was observed after treatment. The average IOP decreased significantly by 28% in the carteolol-treated eyes (\( P < 0.0001 \), by paired student t-test) and by 15% in the placebo-treated eyes (\( P < 0.001 \)). The average percentage decrease in IOP was significantly larger in the carteolol-treated eyes than in the placebo-treated eyes (\( P < 0.001 \)). The PP showed a significant average increase of 8% in the carteolol-treated eyes (\( P < 0.005 \)) and a nonsignificant average 3% increase in the placebo-treated eyes (\( P > 0.05 \), Table 1). No significant difference was observed between the average percentage change in perfusion pressure in carteolol- and placebo-treated eyes.

Average values of D, \( V_{\text{max}} \), and Q before and after placebo and carteolol treatment and their percentage changes are summarized in Table 2. After treatment, the average percentage changes from baseline in D, \( V_{\text{max}} \), and Q were not statistically significant in the placebo-treated eyes (0.5%, 5.8%, and 6.7%, respectively) and in the carteolol-treated eyes (0.3%, 4.3%, and 3.6%, respectively, Table 2). By comparison with the placebo-treated eyes, no significant differences in the percentage changes in D, \( V_{\text{max}} \), and Q were observed in the carteolol-treated eyes.

The smallest average percentage change in Q that

### Table 1. Average heart rate, mean brachial artery blood pressure (\( BP_m \)), intraocular pressure, and perfusion pressure before and after the instillation of placebo and carteolol

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>% Change</th>
<th>Significance*</th>
</tr>
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<tbody>
<tr>
<td>Heart rate</td>
<td>70 ± 11†</td>
<td>67 ± 11</td>
<td>3 ± 12</td>
<td>( P &gt; 0.05 )</td>
</tr>
<tr>
<td>( BP_m ) (mm Hg)</td>
<td>81 ± 11</td>
<td>79 ± 12</td>
<td>2 ± 6</td>
<td>( P &gt; 0.05 )</td>
</tr>
<tr>
<td>Intraocular pressure (mm Hg)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>14.4 ± 2.3</td>
<td>12.1 ± 1.7</td>
<td>14.7 ± 11.8</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Carteolol</td>
<td>14.1 ± 2.0</td>
<td>10.1 ± 1.8</td>
<td>28.3 ± 8.3</td>
<td>( P &lt; 0.0001 )</td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>39.6 ± 7.1</td>
<td>40.8 ± 8.3</td>
<td>3.1 ± 9.8</td>
<td>( P &lt; 0.005 )</td>
</tr>
<tr>
<td>Carteolol</td>
<td>39.8 ± 7.0</td>
<td>42.8 ± 7.9</td>
<td>7.6 ± 7.9</td>
<td>( P &lt; 0.005 )</td>
</tr>
</tbody>
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* Paired Student’s t-test.
† ±1 SD
Table 2. Average venous diameter (D), maximum velocity of red blood cells (V_max), and volumetric blood flow rate (Q) before and after the instillation of placebo and carteolol

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>% Change</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>149 ± 22†</td>
<td>149 ± 22</td>
<td>-0.5 ± 3.2</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Carteolol</td>
<td>153 ± 23</td>
<td>151 ± 18</td>
<td>-0.3 ± 4.6</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>V_max (cm/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.73 ± 0.32</td>
<td>1.8 ± 0.27</td>
<td>5.8 ± 15.8</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Carteolol</td>
<td>1.75 ± 0.34</td>
<td>1.80 ± 0.32</td>
<td>4.3 ± 17.2</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Q (µl/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>12.0 ± 5.4</td>
<td>12.3 ± 5.0</td>
<td>6.7 ± 18.3</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Carteolol</td>
<td>12.3 ± 4.0</td>
<td>12.5 ± 3.9</td>
<td>3.6 ± 19.0</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>

* Paired student’s t-test. † ±1 SD.

would have been detectable in this study was calculated to be approximately 10% (P < 0.05). This value was approximately 9% for V_max measurements and 2% for D measurements. These sensitivity estimations were based on D, V_max, and Q determinations obtained before and after the instillation of the placebo drops, assuming that the differences found were random variations of the measurements.

No significant correlations were found between changes in IOP, BP_m, or PP and changes in volumetric blood flow rate in the placebo- or the carteolol-treated eyes.

Discussion

Our results show that there were no statistically significant changes in D, V_max, or Q after instillation of carteolol. The sensitivity of the technique was approximately 10% for Q measurements. Therefore, changes in average Q of 10% or larger would have been detected in our study.

In a previous study of the effect of timolol maleate, another beta-adrenergic blocking agent, we found statistically significant average increases of 11% in V_max and 13% in Q. After timolol treatment, the changes in average V_max and Q were similar to the 13% average increase in PP. Therefore, it was suggested that the changes in Q probably were produced by the changes in PP.

In the current study, however, average perfusion pressure increased after carteolol by only 8%; in our previous study, after timolol instillation, PP increased by an average of 13%. This smaller change in PP could explain the lack of a statistically significant effect of carteolol on the retinal circulation, especially in view of the autoregulatory capacity of the retinal vasculature which is known to maintain nearly constant blood flows despite changes in PP.

In the current study, we estimated PP using the formula PP = \(\frac{1}{2}BP_m - IOP\). Blood pressure in the central retinal artery was estimated as two thirds of the BP_m. A more accurate measurement of PP can be obtained, however, by measuring retinal artery blood pressure.

Others studied the effect of topical carteolol on retinal artery systolic blood pressure and found evidence suggesting that this pressure was significantly reduced after treatment. In view of these data, the increase in PP we obtained may be an overestimation of the actual change in this parameter.

We also cannot exclude the possibility that the ISA of carteolol, which is not seen with timolol, may lead to a difference in the retinal circulatory response to these two drugs. In the cardiovascular system, for example, beta-adrenergic blockers with ISA have been shown to decrease vascular resistance after acute and chronic exposure, whereas those without ISA increased vascular resistance. Although specific changes produced by such drugs with and without ISA on ocular tissues are not known, a different action on the retinal vasculature could explain, in part, the difference between the significant increase in retinal blood flow produced by timolol and the lack of such an increase after carteolol.

Key words: human retinal circulation, carteolol, laser Doppler velocimetry, retinal autoregulation, maximum erythrocyte velocity

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References

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