

# Effects of Topical Clonidine versus Brimonidine on Choroidal Blood Flow and Intraocular Pressure during Squatting

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**PURPOSE.** Clonidine and brimonidine, two  $\alpha$ -2 agonists, have been shown to reduce intraocular pressure (IOP) in patients with glaucoma. Little is known, however, about the exact role of  $\alpha$  receptors in the control of ocular blood flow in the posterior pole of the eye. Hence, the study was conducted to investigate the effects of topical clonidine versus topical brimonidine on choroidal blood flow and intraocular pressure during squatting.

**METHODS.** This was a randomized, double-masked, controlled, two-way crossover study. Twelve healthy male nonsmoking volunteers, aged between 19 and 35 years were included in the study. Two drops of clonidine or brimonidine were administered in the subjects' study eyes. Continuous measurement using the compact laser Doppler flowmeter was performed during a 6-minute squatting period, to assess choroidal blood flow regulation during an increase in ocular perfusion pressure.

**RESULTS.** Both substances induced a pronounced but comparable ( $P = 0.8$ ) decrease in IOP. Squatting increased mean arterial pressure (MAP) and ocular perfusion pressure ( $P < 0.01$ ). This increase was comparable between the clonidine and the brimonidine study day ( $P = 0.88$ ). Squatting induced an increase in choroidal blood flow that was less pronounced than the increase in ocular perfusion pressure. Compared with baseline the  $\alpha$ -2 agonists decreased choroidal blood flow during squatting ( $P = 0.0026$ ) to a comparable degree ( $P = 0.86$ ). Vascular resistance increased at baseline and during squatting after administration of the  $\alpha$ -2 agonists ( $P < 0.01$ ) in both groups to a comparable degree ( $P = 0.56$ ).

**CONCLUSIONS.** Topical  $\alpha$ -2 agonists may induce changes in choroidal blood flow, even after a single administration. Long-term studies are needed to study potential effects of brimonidine and clonidine in the clinical setting. (*Invest Ophthalmol Vis Sci.* 2007;48:4220–4225) DOI:10.1167/iovs.07-0178

It has been shown in many clinical trials that  $\alpha$ -agonists effectively lower IOP.<sup>1–3</sup> Today, these substances are routinely used as topical antiglaucoma drugs and may be attractive

because of additional neuroprotective properties.<sup>4</sup> However, the beneficial effects of  $\alpha$ -agonists must be weighed against several potential disadvantages in glaucoma treatment: tachyphylaxis, posterior segment vasoconstriction, physiologic depression and fatigue, syncope and systemic hypotension, and topical allergy-like syndrome.<sup>5</sup> The  $\alpha$ -2 agonists exert their ocular hypotensive effect mostly by causing a decrease in aqueous production.<sup>6–8</sup> After chronic treatment, the  $\alpha$ -2 agonist brimonidine increases uveoscleral outflow.<sup>9</sup> Currently, several  $\alpha$ -2 agonists that lower IOP in patients with glaucoma are on the market. Although these drugs share many pharmacological properties, there are also differences. Most important, brimonidine does not appear to have an effect on the central nervous system and therefore does not cause sedation or systemic hypotension.<sup>10</sup>

In addition to the known effect of lowering IOP,  $\alpha$ -2 adrenoceptor agonists are neuroprotective and are associated with the possibility of improved retinal ganglion cell survival.<sup>4,11</sup> It has, also been shown, however, that brimonidine is a very potent vasoconstrictor in the ciliary body of rabbits, thus reducing aqueous humor production.<sup>12</sup> This finding is in keeping with earlier results showing that the early phase of IOP reduction with brimonidine is due to suppression of aqueous flow whereas the later phase is characterized by an increase in uveoscleral outflow.<sup>9,13</sup>

Little is known about the potential vasoconstrictor effects of brimonidine in the posterior pole of the eye. These effects are of clinical importance, because optic nerve head ischemia appears to contribute to glaucoma pathophysiology.<sup>14</sup> In porcine ciliary arteries, brimonidine is a potent vasoconstrictor.<sup>15</sup> Moreover, brimonidine induces vasoconstriction particularly in small retinal vessels, which is of importance, because they contribute most to vascular resistance.<sup>16</sup> When investigating the effects of topical antiglaucoma drugs on ocular blood flow in the posterior pole of the eye in vivo, one has to consider that a decrease in IOP leads to a concomitant increase in ocular perfusion pressure (OPP) making any blood flow data difficult to interpret. In the present study two approaches were chosen to facilitate interpretation. On the one hand, effects of brimonidine are compared with those of clonidine, which is assumed to exert comparable effects on IOP. The rationale for this design was to compare the effects of two  $\alpha$ -2 agonists to ensure that the potential effects of brimonidine or clonidine in the present study are not due to hitherto unidentified actions on other receptors. On the other hand, we investigated choroidal blood flow (CBF) during squatting-induced changes in mean arterial pressure (MAP), thus changing OPP and gaining insight into the pressure–flow relationship.

## METHODS

### Subjects

Twelve healthy, male, nonsmoking volunteers were included in the study. All subjects signed a written informed consent to participate.

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The study protocol was approved by the Ethics Committee of the Medical University of Vienna and adhered to the guidelines of Good Clinical Practice and the Declaration of Helsinki. Each subject passed a screening examination, including medical history, physical examination, and a 12-lead electrocardiogram. Furthermore, an ophthalmic examination, including slit lamp biomicroscopy and indirect funduscopy, was performed as part of the prestudy screening. Inclusion criteria were normal ophthalmic findings, ametropia of less than 3 D, anisometropia of less than 1 D, and an IOP between 10 and 18 mm Hg measured using applanation tonometry. Subjects were excluded if any abnormality was found unless the investigators considered it to be clinically irrelevant. An abnormality was defined as an alteration from the normal values of the Department of Medical and Chemical Diagnostics at the Medical University of Vienna.

## Study Design

A randomized, double-masked, controlled, balanced, two-way crossover study was performed in 12 healthy male nonsmoking volunteers, aged between 19 and 35 years. Two study days were scheduled for each subject with washout periods of at least 7 days between the study days. Two drops of either clonidine (Isoglucon 0.125%; Boehringer Ingelheim, Ingelheim am Rhein, Germany) or brimonidine (Alphagan 0.2%, Allergan Pharmaceuticals Ltd., Westport, Ireland) were administered in the subjects' right eyes on the two study days, according to the randomization list.

A study schedule is shown in Figure 1. On the trial days, baseline measurements of ocular and systemic hemodynamics and IOP were performed after the subject had a 20-minute resting period in a sitting position. CBF was measured continuously over 2 minutes at baseline with a compact laser Doppler flowmeter. Thereafter subjects were asked to squat for 6 minutes and CBF measurement was continued. Squatting was performed in a position in which the upper and the lower leg were as close as possible to a right angle. This position was achieved by slowly removing the chair in which the subjects were seated for baseline measurements. Accordingly, neither the position of the head relative to the instrument nor the position of the head versus the heart was changed during squatting compared with baseline measurements. In addition, care was taken that the upper arm, from which measurements of blood pressure were taken, was kept at heart level. For the subjects' security, a nurse stood behind them during the squatting periods. The IOP was measured at baseline and at the end of the squatting period. After a resting period of 30 minutes the drugs were installed into the study eye with a time gap of 5 minutes between the two drops. The hemodynamic measurements during 2 minutes without and 6 minutes with squatting were repeated 60 and 120 minutes after the administration of the medication. Blood pressure was

measured in 10-minute intervals throughout the study period and in 1-minute intervals during the measurement of CBF. Pulse rate (PR) and ECG were monitored continuously.

## Procedures

**Noninvasive Measurement of Systemic Hemodynamics.** Systolic, diastolic, and mean arterial blood pressures (SBP, DBP, MAP) were measured on the upper arm with an automated oscillometric device. PR was automatically recorded from a finger-pulse oximetric device. An ECG was recorded with a standard device (CMS monitor; Hewlett-Packard, Palo Alto, CA).

**Measurement of IOP.** The IOP was measured with a Goldmann applanation tonometer (Applanation Tonometer AT900; Haag-Streit, Köniz, Switzerland). One drop of oxybuprocaine with fluorescein was used to anesthetize the cornea.

**Ocular Perfusion Pressure.** Ocular perfusion pressure was calculated as  $\frac{2}{3}$  MAP - IOP.<sup>17</sup> This formula is based on evidence that the pressure in choroidal veins almost equals the IOP.<sup>18,19</sup> During squatting, we observed only small changes of IOP over baseline after 6 minutes of squatting. Hence, we used a linear regression model to extrapolate the IOP values at the other time points of squatting.

**Laser Doppler Flowmetry.** Continuous measurement of subfoveal CBF was performed by laser Doppler flowmetry.<sup>20</sup> With this technique, the vascularized tissue was illuminated by coherent laser light. Light scattered by moving red blood cells undergoes a frequency shift. In contrast, static tissue light-scattering cells do not change the light frequency, but lead to a randomization of light directions, impinging on red blood cells. Hence, red blood cells receive light from numerous random directions. Because the frequency shift is dependent not only on the velocity of the red blood cells, but also on the angle between the wave vectors of the incident and the scattered light, scattering of the light in tissue broadens the Doppler shift power spectrum. From this spectrum, the average velocity of red blood cells (VEL), the volume of red blood cells (VOL), and the CBF (VEL × VOL) can be determined based on a theory of light-scattering in tissue in relative units.<sup>21</sup>

In the present study, a compact laser Doppler flowmeter (Institut de Recherche en Ophthalmologie [IRO], Sion, Switzerland), which has been described previously, was used for the measurements of CBF.<sup>22</sup> Briefly, a polarized laser source ( $\alpha = 785$  nm, 100  $\mu$ m) is relayed with a 1:1 optical system and focused on the subject's retina. The scattered light is collected by an optical system organized with six fibers arranged around the central fixation point along a circle 180  $\mu$ m in diameter. All measurements were performed in the fovea by asking the subjects to fixate at the beam, which appeared as a small spot. The

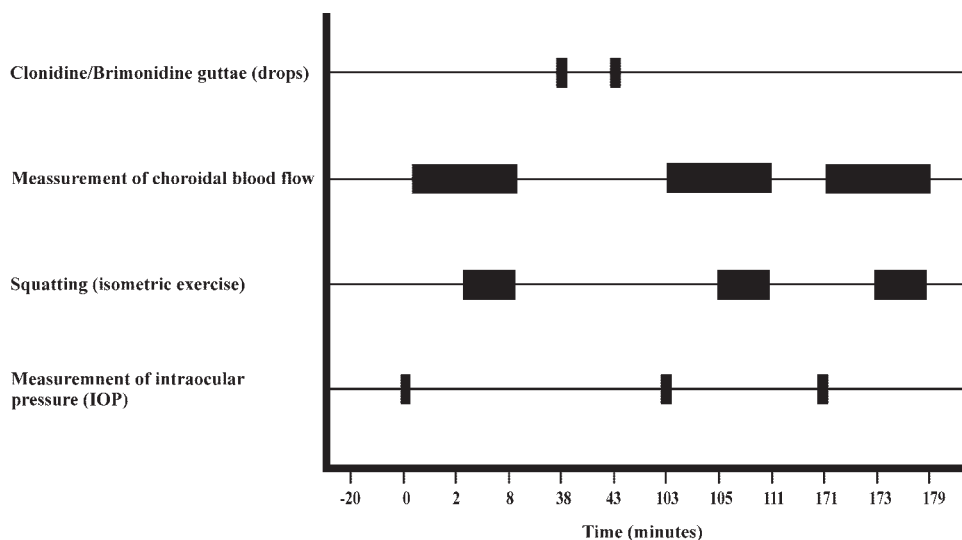


FIGURE 1. Study schedule.

fovea was chosen, because the retina is avascular there. For statistical analysis, only the portions of the signal that were within 15% of the baseline direct current (DC) were taken for analysis. Compared with previous fundus camera-based systems for the assessment of CBF, the new system offers two major advantages. Adjustment of the detector relative to the measurement on the retina is omitted, because the system uses confocal optics. In addition, the system is portable, which facilitates measurements during squatting.

### Statistical Analysis

All statistical analyses were performed on computer (Statistica ver. 5; StatSoft Inc., Tulsa, OK). All outcome variables were calculated for each subject individually and then averaged. The effect of squatting on the outcome parameters was assessed with repeated-measures ANOVA. The interaction between time and treatment was used to assess differences between drugs. Post hoc analysis using planned comparisons was performed, to assess potential effects of the drugs versus baseline by using the time effect. For data description, the relative change in hemodynamic parameters induced by squatting on the two study days was calculated. Data are presented as the mean  $\pm$  SEM.  $P < 0.05$  was considered the level of significance.

### RESULTS

No adverse events were observed during the study. Both study drugs were well tolerated by the participants.

There were no significant differences between the baseline measurements on the two study days (Table 1). As expected, squatting induced a significant increase in MAP and PR during all pretreatment squatting periods ( $P < 0.001$  vs. baseline each, Table 2, Fig. 2). There were no differences, however, in MAP increase ( $P = 0.54$  between groups) and PR increase ( $P = 0.88$  between groups) on the two study days. Squatting caused only small changes in IOP with a small nonsignificant increase during squatting. IOP decreased significantly after administration of the  $\alpha$ -2 agonists ( $P < 0.001$  vs. each baseline; Fig. 3). This effect was comparable on both study days ( $P = 0.8$ ). One hour after drug administration, clonidine reduced IOP by  $29.1\% \pm 3.2\%$ ; after 2 hours, the effect was slightly more pronounced ( $33.8\% \pm 3.6\%$ ). With brimonidine the IOP-lowering effect was  $27.6\% \pm 2.7\%$  and  $31.9\% \pm 3.3\%$  at the two time points, respectively.

Calculated baseline OPP increased after administration of the medication due to the decrease in IOP ( $P < 0.01$  versus baseline,  $P = 0.88$  between groups). The squatting-induced increase in calculated OPP was comparable between study days ( $P = 0.59$  between groups). As expected, CBF increased during squatting on both study days ( $P < 0.001$  versus baseline). After administration of clonidine and brimonidine baseline CBF decreased ( $P < 0.01$  versus pretreatment). Again, this effect was comparable on both study days ( $P = 0.86$  between groups). During squatting, CBF values after drug administration

also were lower than before clonidine and brimonidine instillation ( $P < 0.01$  versus baseline), but again there were no differences between the two study days ( $P = 0.31$  between groups).

During squatting, vascular resistance increased ( $P < 0.001$  versus baseline) indicating some regulatory capacity of the choroid in face of the increase in OPP. At baseline, both drugs increased vascular resistance ( $P < 0.01$  versus pretreatment), but to a comparable degree ( $P = 0.42$  between groups). In addition, the two drugs induced a more pronounced increase in vascular resistance during squatting compared with the pretreatment squatting period. This effect tended to be more pronounced with clonidine than with brimonidine ( $P = 0.08$  between groups), but it did not reach the level of significance.

### DISCUSSION

Previous studies have shown that, due to an unknown mechanism, the choroid can maintain its blood flow despite squatting-induced changes in perfusion.<sup>23-27</sup> Whether this can be interpreted as autoregulation in its strictest sense is unclear, because squatting induces a pronounced change in the neural input to the choroid. Some degree of choroidal autoregulation is evident from animal trials in which perfusion pressure was manipulated mechanically.<sup>28</sup> Obviously, autoregulation is difficult to investigate in humans, because it is impossible to alter OPP without affecting neural, hormonal, and metabolic systems. In recent years, several techniques were proposed to alter OPP in vivo, such as artificial increase of IOP by the application of a suction cup, exercise-induced changes in systemic blood pressure, and pharmacologic interventions.<sup>24-27,29-31</sup> In the present study we used squatting, because we have shown that the reproducibility of pressure-flow curves during this type of intervention is sufficient for the study of drug effects in an adequate study design.<sup>24-26</sup>

In previous trials we have shown that blockade of the  $ET_A$  receptor as well as inhibition of NO significantly alters the pressure flow relationship during squatting.<sup>24,25</sup> In the present study, we focused on two  $\alpha$ -adrenergic agonists that are used as topical antiglaucoma drugs. The effect of these drugs is of interest, because altered autoregulation appears to be a contributing factor in the pathophysiology of glaucoma.<sup>14,32</sup> In the present study topical administration of both clonidine and brimonidine showed a decrease in CBF, most probably due to a direct vasoconstrictor effect. Because both drugs decreased IOP under baseline conditions, it is unlikely that the reduction in blood flow is caused by an indirect effect on perfusion pressure. Our results are compatible with previous findings in animal models showing pronounced vasoconstrictor effects of brimonidine in the rabbit ciliary body<sup>12</sup> and with in vitro data showing vasoconstrictor effects in isolated porcine ciliary arteries.<sup>15</sup>

Previous animal experiments indicate that, in the choroid, sympathetic vasoconstriction is mediated by  $\alpha$ -1 adrenoceptors.<sup>33,34</sup> In the rat choroid, electrical stimulation of the preganglionic cervical sympathetic nerve induced pronounced vasoconstriction, which was blocked by both nonselective and selective  $\alpha$ -1 antagonists.<sup>33</sup> By contrast,  $\alpha$ -2 blockade only potentiated the vasoconstriction during sympathetic stimulation. Based on these results, one could hypothesize that part of the vasoconstrictor response of the choroid during squatting is due to activation of the sympathetic system associated with  $\alpha$ -1 activation. Because there is no study available on the effect of specific  $\alpha$ -antagonists on the choroidal pressure flow relationship during squatting, this hypothesis remains unproven. It would be compatible, however, with the results of the present study, in which vasoconstrictor effects of the topical antiglau-

TABLE 1. Baseline Parameters of Ocular and Systemic Hemodynamic Measurements on the Two Study Days

	Clonidine Day Baseline	Brimonidine Day Baseline
MAP (mm Hg)	77 $\pm$ 2	78 $\pm$ 2
PR (beats/min)	69 $\pm$ 5	68 $\pm$ 4
IOP (mm Hg)	13 $\pm$ 2	13 $\pm$ 2
CBF (AU)	23.6 $\pm$ 3.5	21.8 $\pm$ 2.2
OPP (mm Hg)	38.1 $\pm$ 1.7	39.3 $\pm$ 1.4
Resistance of the choroidal vessels (AU)	2.2 $\pm$ 0.4	2.0 $\pm$ 0.2

Data are presented as means  $\pm$  SEM.

TABLE 2. MAP at Baseline and during Squatting

	Clonidine Day			Brimonidine Day		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
Baseline	77 ± 2	74 ± 2	74 ± 2	78 ± 2	74 ± 3	77 ± 2
Squatting minute 1	96 ± 4	90 ± 3	93 ± 3	92 ± 3	87 ± 3	91 ± 3
Squatting minute 2	104 ± 4	95 ± 3	100 ± 3	99 ± 3	93 ± 3	95 ± 3
Squatting minute 3	104 ± 4	97 ± 3	98 ± 3	103 ± 13	96 ± 2	97 ± 2
Squatting minute 4	101 ± 3	99 ± 3	98 ± 3	104 ± 2	98 ± 3	100 ± 2
Squatting minute 5	103 ± 3	100 ± 3	102 ± 2	100 ± 3	97 ± 2	98 ± 2
Squatting minute 6	101 ± 3	101 ± 3	101 ± 3	102 ± 2	96 ± 2	100 ± 1

The drugs were topically administered after period 1. Period 2 represents the squatting period as scheduled 60 minutes after administration of the second drop of the medication. Period 3 represents the squatting period as scheduled 60 minutes after the second squatting period. Data are presented as means ± SEM.

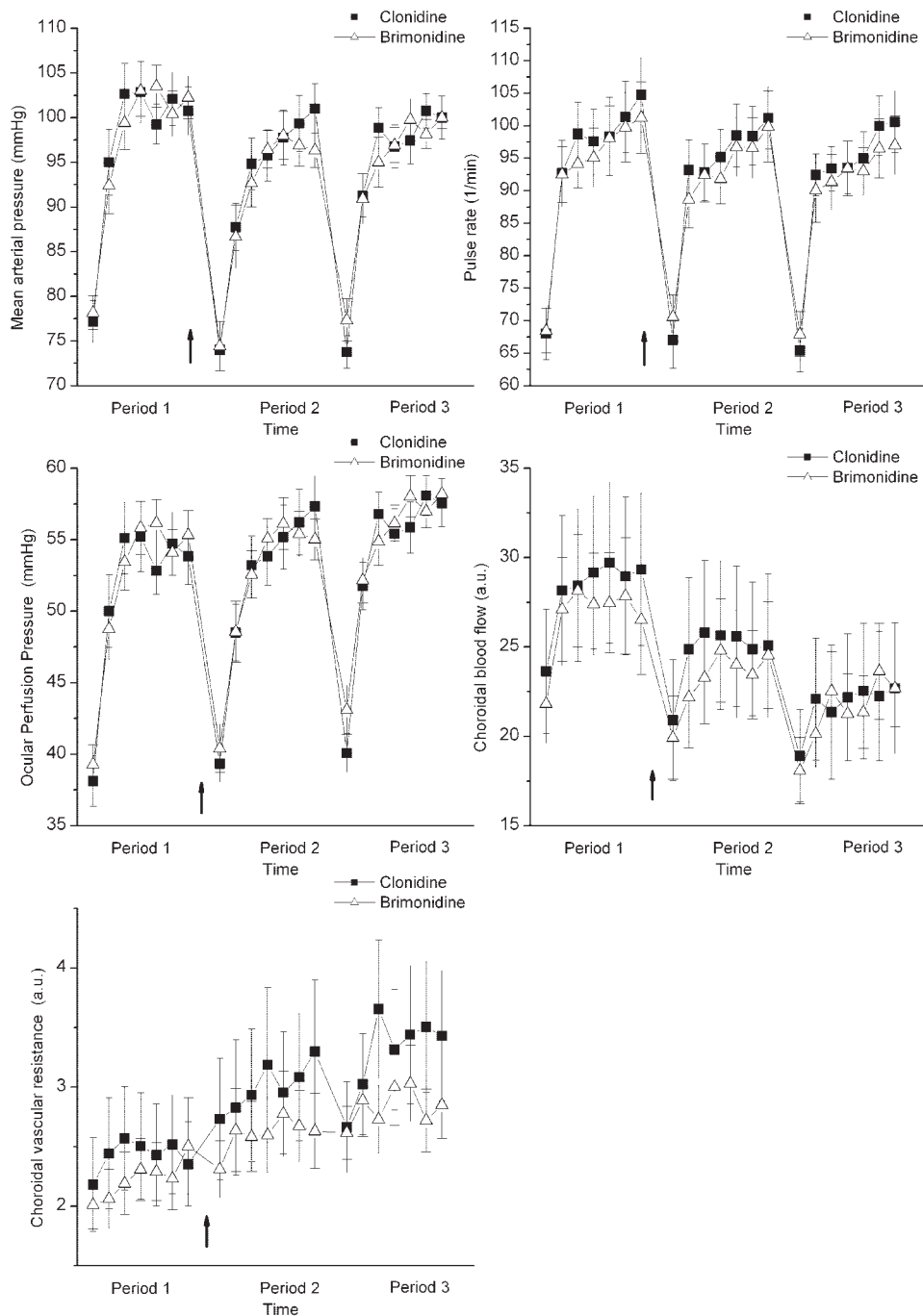
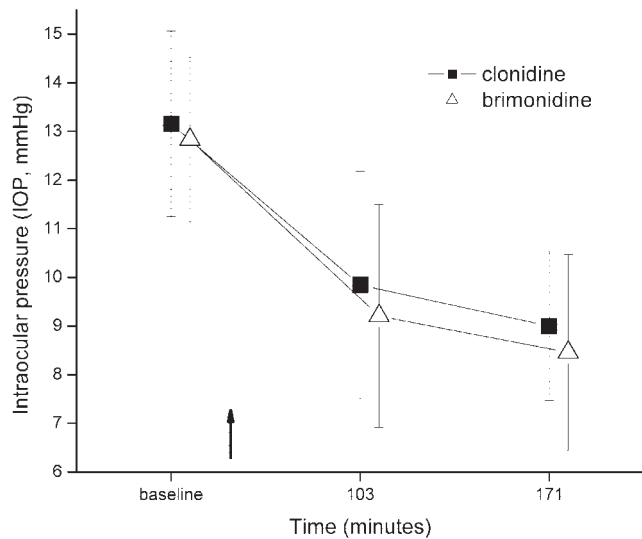


FIGURE 2. Effects of clonidine and brimonidine on MAP, PR, OPP, CBF, and vascular resistance during squatting. Data are presented as the mean ± SEM (n = 12). The drugs were topically administered after period 1. Period 2 represents the squatting period scheduled 60 minutes after administration of the second drop of the medication. Period 3 represents the squatting period scheduled 60 minutes after the second squatting period. Arrows: time of administration of the medication. For details of timing see Figure 1.



**FIGURE 3.** Effects of clonidine and brimonidine on IOP. Arrow: time of administration of the medication. For details of timing see Figure 1. Data are presented as the mean  $\pm$  SEM ( $n = 12$ ).

coma drugs was evident with both  $\alpha$ -agonists. Although brimonidine is more selective for the  $\alpha_2$  receptor than is clonidine, prejunctional ( $\alpha_2$ ) as well as postjunctional ( $\alpha_1$ ) effects of the drugs were described.<sup>35</sup>

With regard to potential detrimental effects of  $\alpha$  agonists on ocular blood flow, the short time effects of clonidine and brimonidine in the present study cannot necessarily be extrapolated to the clinical setting. Long-term studies are necessary for the study of effects that are potentially clinically relevant. Available long-term studies, though not directly comparable to the present trial due to the use of other methods for blood flow evaluation showed no change in ocular blood flow in patients with primary open-angle glaucoma.<sup>36–39</sup>

In conclusion, the present study indicates that the choroidal pressure–flow relationship during squatting is significantly altered by short-term administration of clonidine and brimonidine in humans. Most likely an  $\alpha$ -receptor-mediated vasoconstrictor effect is responsible for this effect. Further studies are needed to clarify whether long-term treatment with topical  $\alpha$ -receptor agonists may reduce blood flow in patients with glaucoma.

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