Studies of the Ocular Pulse in Primates

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Abstract. Ocular pulse amplitude (OPA) and intraocular pressure (IOP) were measured in groups of human subjects with primary open-angle glaucoma (POAG), ocular hypertension (OHT), low-tension glaucoma (LTG), retinal degenerations (RD), in OHT volunteers treated with single doses of 2% epinephrine, 4% pilocarpine, 0.5% timolol or 1% p-aminoclonidine, and in normal subjects before and after exercise. Compared to normal controls, OHT subjects showed significantly higher IOP and OPA, while OPA was significantly lower in ocular normotensive LTG and RD subject groups. All drug treatments lowered IOP in OHT subjects, but did not change OPA significantly. Exercise in normal volunteers increased calculated ocular perfusion pressure by 22.5%, lowered IOP by 32%, but showed no significant change in OPA. When IOP was elevated ≥ 5 mmHg in lasered monkey eyes peak pulse volume (PPV) was increased significantly in the unlasered eyes. Epinephrine 2% or 1% p-aminoclonidine lowered IOP moderately with no change in PPV, while treatment with 4% pilocarpine or 0.5% timolol reduced IOP and increased PPV significantly. The findings suggest that LTG may be associated with an ocular vascular abnormality. OPA in OHT or normal human subjects did not change when IOP was decreased by antiglaucoma drug treatments or exercise, respectively. These results indicate that OPA may be physiologically autoregulated in human subjects with IOPs in the 11–21 mmHg range. However, laser-induced glaucomatous monkey eyes with higher IOP (30–35 mmHg) did not autoregulate, but showed a low peak pulse volume, which increased when IOP was reduced 5 mmHg or more by means of antiglaucoma drug treatment. **(Surv Ophthalmol 38 [Suppl, May]:**S183–S190, 1994)

Key words. antiglaucoma drugs • intraocular pressure • low-tension glaucoma • ocular hypertension • ocular pulse amplitude • primary open-angle glaucoma

The sensitivity of the Langham ocular pneumatic probe allows for noninvasive determination of the ocular pulse, a parameter which may have potential to evaluate some characteristics of ocular blood flow in a clinical setting. We have had a longstanding interest in the significance of choroidal blood flow in relation to glaucoma, and also in the possible pharmacologic manipulation of the choroidal circulation. In this report, we summarize our experience using the Langham OBF instrument (software version 2.32 for IBM PC) in human subjects, and the effects of major antiglaucoma therapeutic agents. We also describe some limited studies that we have done on similarly drug-treated monkey eyes with the laser-induced model of glaucoma.

Experimental Approach

In all our studies "ocular blood flows" were not determined because, in our opinion, the underlying assumptions and software are not adequately documented to calculate blood flow from the pulse data and because extraocular variables (for example; pulse rate, posture, etc.) are involved in the calculation. Thus, only ocular pulse amplitude (OPA), measured in the supine position, is reported in our human studies while the OPA data obtained in ketamine-sedated monkeys in the seated position was converted into peak pulse volume (PPV) using the pressure-volume relationship experimentally determined in the living monkey eye. PPV represents the volume (capacity) increment of the intraocular vascular bed at the peak of the pulse relative to its

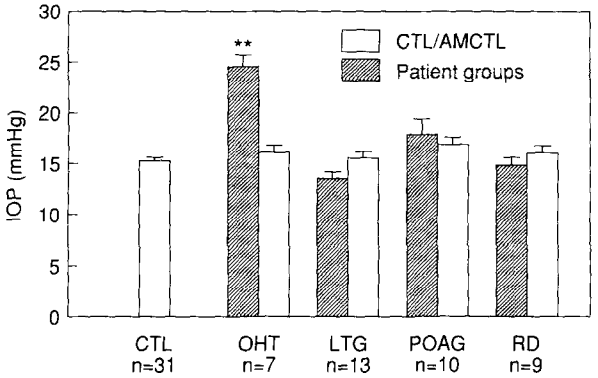

Fig. 1. Intraocular pressures (IOP, mm Hg) measured by Goldmann applanation in groups composed of n subjects (hatched columns) compared to age-matched control (AMCTL) sub-groups (open columns). CTL = normal control group, OHT = ocular hypertensive, LTG = low-tension glaucoma, POAG = primary open angle glaucoma, RD = retinal degenerative disease. **Significantly different at $p < 0.05$.

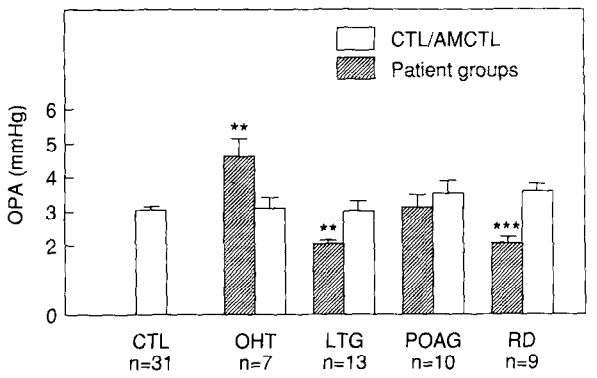

Fig. 2. Ocular pulse amplitudes (OPA mmHg) determined in the same groups of subjects defined in Fig. 1. Significantly different at $p < 0.05$ (**) or $p < 0.01$ (***).

capacity at diastole and is corrected for differences in the intraocular pressure (IOP) of the monkey eyes, while the OPA values obtained in humans may be affected somewhat by the IOP value at which it is measured.

IOP was independently determined by Goldmann applanation in humans and by pneumatonography (Digilab Model 30R) in monkeys.

Results

HUMAN STUDIES

Figs. 1 and 2 summarize the IOP and OPA data for both eyes in groups comprising "n" individual human subjects in the following categories: OHT = ocular hypertensives, LTG = low tension glaucoma, POAG = primary open-angle glaucoma, RD = subjects with retinal degenerative disease. OHT volunteers (age 47.9 ± 7.8 years) were on no topical or systemic or ocular hypotensive medications for at least three weeks prior to the measurements, had no visual field defects or optic nerve head abnormalities and had a history of IOPs ≥22 mmHg. LTG patients (age 64.7 ± 3.4 years) were on various ocular hypotensive agents in both eyes and had typical glaucomatous visual field defects, disk cupping, and a history of IOPs <21 mmHg. POAG patients (age 63.8 ± 5.2 years) were on various ocular hypotensive agents in both eyes, and had typical glaucomatous visual field defects and disk cupping and a history of IOPs ≥22 mmHg before treatment. Diagnoses of patients with retinal degenerative diseases (RD) (age 39.0 ± 2.1 years) were confirmed by indirect ophthalmoscopy and electroretinography.

Each clinical group was compared to an age-matched control subgroup (AMCTL) selected from a pool of 31 normal control subjects (CTL). Consent was obtained from each subject after the nature of the procedure had been fully explained. Fig. 1 shows that, except for the OHT subjects, all the clinical groups showed IOP not significantly different from normal controls, while OPA was significantly lower than normal in both the LTG and RD groups (Fig. 2).

The finding that OHT subjects had both a higher IOP and OPA suggested that there was a higher ocular perfusion pressure in OHT. Therefore, to increase ocular perfusion pressure in normals for comparison to the OHT group, 12 normal subjects were exercised on a stationary bicycle to 80% of their age-adjusted maximum pulse rate. Hemodynamic, IOP and OPA data, after exercise, are shown in Fig. 3 relative to the values before exercise = 100%. Exercise increased the pulse amplitude by greater than 80%. It also increased by 22.5% the calculated ocular perfusion pressure – the difference between IOP and mean ophthalmic arterial pressure (estimated at 0.7 × brachial systolic or diastolic pressure) – and lowered IOP by an average of 5.3 mmHg. However, there was no significant change in OPA in the exercised subjects (Fig. 3).

A group of six medication-free OHT subjects were given single doses of 2% epinephrine, 4% pilocarpine, 0.5% timolol, or 1% para-aminoclonidine (Apraclonidine®) to lower their IOP (Fig. 4). These drug treatments did lower IOP in the OHT subjects by 4–7 mmHg, but none of the drugs caused a significant change in OPA. Measurements of OPA are shown only for 1% para-

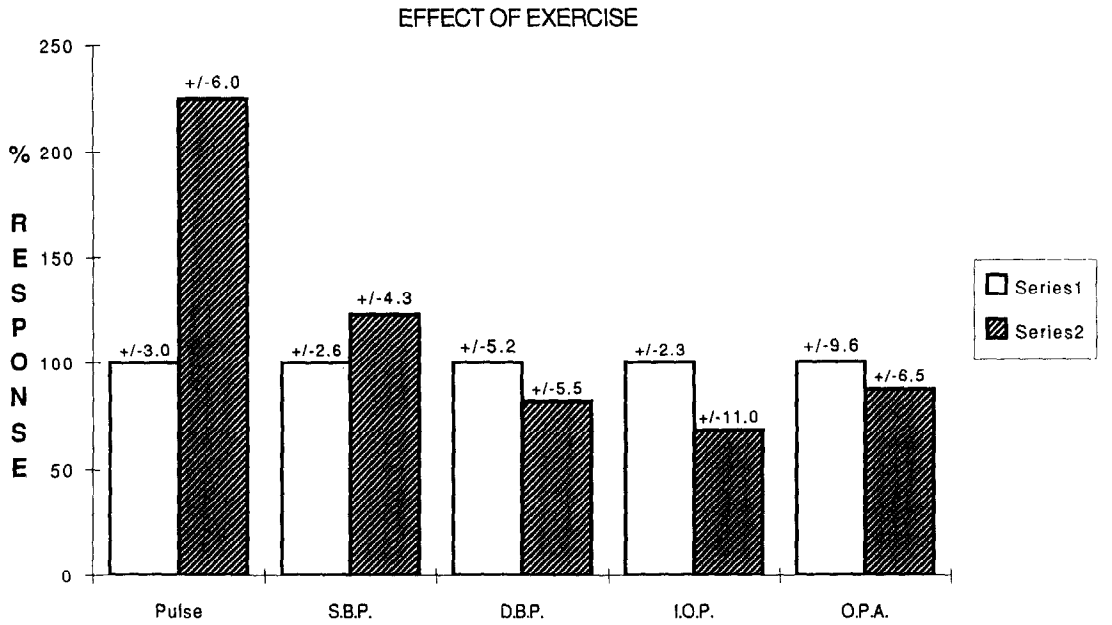

Fig. 3. Effect of exercise (hatched columns, Series 2) on pulse rate, systolic (S.B.P.) and diastolic (D.B.P.) blood pressure intraocular pressure (I.O.P.) and ocular pulse amplitude (O.P.A.). Parameters are plotted relative to values measured before exercise (open colums, Series 1) set = 100%, with +/− SEM above each column.

aminoclonidine treatment (Table 1), which was the most effective agent for lowering IOP from 2–8 hr after drug application (Fig. 4). OPA was significantly decreased at only a single time point (4 hr, Table 1) relative to OPA in the contralateral vehicle-treated eye at the same time point.

STUDIES IN CYNOMOLGUS MONKEYS

Most of these studies were done on a group of four cynomolgus monkeys given two or three laser treatments over an 8–10 week period to one eye so as to develop the unilateral lasered-eye glaucoma model.[5] IOP and pulse amplitude were determined at 7–10 day intervals during the development phase of the glaucoma model. After full development of the unilateral glaucoma, the same group of animals were used for drug treatment experiments.

The monkeys were seated in specially designed chairs and lightly sedated with ketamine hydrochloride, 1–5 mg/Kg administered intramuscularly. Topical 0.5% proparacaine hydrochloride anesthesia was applied prior to each measurement. Intraocular pressure (IOP) was independently measured with a calibrated pneumatonometer (Model 30R Digilab Inc., Cambridge, MA) immediately prior to pulse amplitude measurements (Langham/Grieshaber OBF System, software version 2.32, Langhorne PA) because the software provided with the OBF system did not accurately measure IOP in monkeys. IOP and pulse amplitude were measured for five sec on each eye prior to drug administration (−0.5 hr), and at 0.5, 2, 4, 6, and 8 hours after drug administration.

The agents evaluated included saline and commercial preparations of timolol 0.5%, epinephrine 2%, para-aminoclonidine 1%, and pilocarpine 4%. The monkeys received the drugs unilaterally with saline administered to the contralateral eye. A wash-out period of at least one week was observed between agents. Drug-treated eyes were compared to the contralateral sa-

TABLE 1

Effects of a Single Dose of 50μl 1% Apraclonidine® on OPA in OHT

Time (hrs)	OPA (mmHg)*		
	Rx	Baseline	Contralateral Control
0	3.9±0.3	3.5±0.2	3.9±0.4
0.5	3.5±0.4	3.8±0.3	3.7±0.4
2	3.3±0.4	3.6±0.3	4.2±0.7
4	2.5±0.5†	3.2±0.3	3.9±0.7
6	2.8±0.2	3.6±0.5	3.3±0.4
8	3.4±0.8	4.2±0.7	4.1±0.9

*Values represent means±SEM.
†$p < 0.05$ compared to contralateral control values.

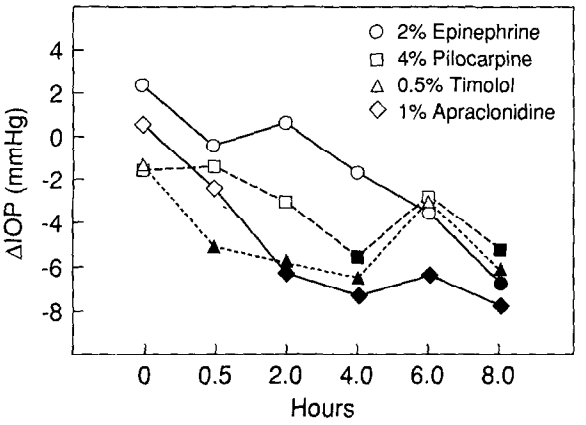

Fig. 4. Mean intraocular pressure response (Δ IOP, mmHg) of ocular hypertensive volunteers (n = 6) to topical treatment with single 50 μl doses of the indicated ocular hypotensive drug (2% epinephrine = circles, 4% pilocarpine = squares, 0.5% timolol = triangles, 1% Apraclonidine® = diamonds). Solid symbols indicate values significantly different ($p < 0.05$) compared to baseline values at 0 time.

line-treated eyes, and each eye was also compared to its baseline (−0.5 hr measurement).

During the development stage of the model, the IOP of lasered eyes fluctuates considerably, at times being the same and at other times showing increased IOP relative to the contralateral unlasered control eyes. IOP and PPV measurements made at 7–10 day intervals during the development phase of the glaucoma model were analyzed in two categories, according to whether the lasered eye IOP showed less than or more than a 5 mmHg increase over the IOP of the contralateral control eye measured at the same time. Table 2 summarizes these data and unexpectedly shows that at times when IOP is elevated by ≥5 mmHg in the lasered eyes the PPV increases significantly in the *contralateral* unlasered control eye.

After full development of the unilateral laser glaucoma monkey model, the same group of animals was used for drug treatment experiments. Table 3 summarizes the IOP and PPV values in six lasered and contralateral unlasered monkey eyes given 50 μl of 2% epinephrine in the lasered eye and vehicle in the unlasered eye measured over an eight-hour period. A moderate lowering of IOP was found in the drug-treated eyes but no change in PPV. Similar treatment with 1% paraaminoclonidine (Table 4) gave a more significant reduction of IOP but also no significant change in PPV, except at the two-hour time point (relative to PPV at 0 time, immediately prior to drug application). Pilocarpine treatment (4%) also significantly lowered IOP in the lasered eye but did

TABLE 2

Relationship Between IOP and PPV (mmHg) of Lasered Monkey Eyes with Δ IOP Less Than (<) 5 or Greater Than (>) 5 mmHg Compared to Contralateral Normal Eye

	Δ IOP<5 mm (n=12)		Δ IOP≥5 mm (n=12)	
	Normal Eyes	Lasered Eyes	Normal Eyes	Lasered Eyes
IOP	15.3±0.2	17.4±0.4	14.7±0.3	25.9±1.7
PPV	2.6±0.15	2.3±0.18	3.4±0.21*	2.3±0.12

*=significantly greater $p<0.05$.

TABLE 3

Unilateral Glaucomatous Monkeys Treated with 2% Epinephrine (n=6)

Time (hrs)	0**	0.5	2	4	6	8
Drug-treated (glaucoma) eyes						
IOP	33.8	31.5*	26.7*	27.3*	28.0*	28.8
		p<0.05	p<0.001	p<0.005	p<0.05	ns
PPV	2.3	2.0	2.3	2.3	2.3	2.3
		ns	ns	ns	ns	ns
Control vehicle-treated (normal) eyes						
IOP	16.0	16.3	15.7	15.8	16.2	16.3
		ns	ns	ns	ns	ns
PPV	3.4	3.2	3.4	3.4	3.5	3.4
		ns	ns	ns	ns	ns

*=significantly different from 0 time.
**=prior to drug treatment.
ns=not significantly different from 0 time.

TABLE 4

Unilateral Glaucomatous Monkeys Treated with 1% para-Aminoclonidine (n = 5)

Time (hrs)	0**	0.5	2	4	6	8
Drug-treated (glaucoma) eyes						
IOP	32.6	28.2*	23.4*	21.2*	21.8*	23.2*
		p<0.05	p<0.005	p<0.005	p<0.005	p<0.01
PPV	2.5	3.7	4.5*	3.7	3.4	3.1
		ns	p<0.05	ns	ns	ns
Control vehicle-treated (normal) eyes						
IOP	16.0	16.2	15.6	15.4	15.0	15.4
		ns	ns	ns	ns	ns
PPV	4.2	3.6	4.2	3.4	3.8	3.9
		ns	ns	ns	ns	ns

* = significantly different from 0 time.
** = prior to drug treatment.
ns = not significantly different from 0 time.

TABLE 5

Unilateral Glaucomatous Monkeys Treated with 4% Pilocarpine (n = 6)

Time (hrs)	0**	0.5	2	4	6	8
Drug-treated (glaucoma) eyes						
IOP	31.5	28.3*	25.0*	24.0*	23.5*	23.8*
		p<0.005	p<0.001	p<0.001	p<0.01	p<0.005
PPV	2.3	2.6*	3.2*	3.5	2.9	2.8
		p<0.05	p<0.01	ns	ns	ns
Control vehicle-treated (normal) eyes						
IOP	15.8	15.5	15.7	15.3	15.0	15.3
		ns	ns	ns	ns	ns
PPV	3.6	3.6	3.6	3.9	3.5	3.8
		ns	ns	ns	ns	ns

* = significantly different from 0 time.
** = prior to drug treatment.
ns = not significantly different from 0 time.

increase PPV significantly in the first two hours (Table 5).

In a second study with pilocarpine (Table 6) the drug was administered to one eye of four monkeys with longstanding bilateral laser-induced glaucoma and measurements of IOP and PPV taken in both eyes at 0.5, 2, 4, 6, and 8 hours. (The IOP in eyes of these bilateral laser-treated monkeys ranged from 25 to 36 mmHg before drug treatment). In 15 of the 20 pairs of measurements taken, the IOP of pilocarpine-treated eyes decreased by >5 mmHg. Comparisons of the PPV value in these 15 responsive eyes relative to that in contralateral vehicle-treated eyes showed that a significant increase in PPV correlates with the IOP lowering effect of pilocarpine in longstanding laser-induced glaucomatous monkey eyes.

Results of timolol (0.5%) treatment are shown in Table 7. Both IOP and PPV change very significantly toward the parameter values determined in the contralateral vehicle-treated control eyes. However, timolol has a systemic/contralateral effect because IOP was lowered and PPV increased in the control eyes as well.

Discussion

Our results on OPA and IOP in human LTG subjects (Figs. 1 and 2) confirm studies reported in the literature[2] and by other participants at this

TABLE 6

PPV in Pilocarpine-Treated Glaucomatous Monkey Eyes

Four bilateral glaucomatous monkeys treated in one eye with 4% pilocarpine. IOP and PPV measured in both eyes at 0.5, 2, 4, 6 and 8 hrs. Of these 20 pairs of measurements 15 showed a decrease in IOP ≥5 mm Hg in the pilocarpine-treated eye relative to the contralateral untreated eye.

PPV in untreated contralateral glaucomatous eyes = 2.19 ± 0.32 (n = 20)

PPV in pilocarpine-treated glaucomatous eyes showing ≥5 mm ↓ IOP = 3.67* ± 0.55 (n = 15)

* = significantly greater, p < 0.001.

TABLE 7

Unilateral Glaucomatous Monkeys Treated with 0.5% Timolol (n = 6)

Time (hrs)	0**	0.5	2	4	6	8
Drug-treated (glaucoma) eyes						
IOP	33.8	30.8*	27.5*	23.5*	23.2*	22.5*
		$p<0.01$	$p<0.001$	$p<0.005$	$p<0.005$	$p<0.001$
PPV	2.4	4.8*	4.3*	4.0*	3.5*	3.1*
		$p<0.01$	$p<0.01$	$p<0.001$	$p<0.001$	$p<0.05$
Control vehicle-treated (normal) eyes						
IOP	16.3	16.2	15.2*	15.2*	14.5*	15.0
		ns	$p<0.05$	$p<0.05$	$p<0.05$	ns
PPV	3.5	6.1*	5.3*	5.1*	4.3	4.1
		$p<0.05$	$p<0.05$	$p<0.05$	ns	ns

* = significantly different from 0 time.
** = prior to drug treatment.
ns = not significantly different from 0 time.

conference that LTG is associated with an ocular vascular, probably choroidal, abnormality. We interpret the low OPA in these patients as an apparent decrease in choroidal capacity. This conclusion is based on similar results in patients having retinitis pigmentosa[4] and also findings reported for patients with diabetic retinopathy,[3] both conditions where vascular capacity is lost due to vascular degeneration and/or nonpatent vessels.

Our results with OHT subjects also replicate previous findings.[9] Since OPA has been reported to be positively correlated with IOP,[8] the higher OPA value may just be a reflection of the higher IOP in OHT subjects. Therefore, one might anticipate that if the IOP was reduced to the normal range, then OPA would also decrease toward the normal range. However, the elevated OPA that we find in OHT subjects did not show a consistent change in response to treatment with any of the four ocular hypotensive agents that we tested and remained significantly elevated even at the six to eight-hour time period when the IOP was reduced by 5–8 mmHg to the level found in normal subjects (Fig. 4 and Table 1). This finding suggests that there may be a vascular pathology associated with OHT which causes an increase in the ocular pulse pressure. In an attempt to verify this by comparison to normal subjects, we analyzed OPA and IOP in response to acute increased pulse pressure caused by exercise.[1,6] Exercise of subjects 23–40 years of age in average physical condition resulted in a 5.5 mmHg reduction of IOP, an 82% increase in systemic pulse amplitude and a 22.5% increase in the calculated mean ocular perfusion pressure (Fig. 3). We expected that the increase in ocular perfusion pressure would cause an increase in OPA, but there was only a small and nonsignificant decrease of 13% in OPA of the exercised normal subjects. This finding indicates that the normal choroidal vascular system probably has significant autoregulatory properties to maintain OPA, and it appears to compensate for changes that would have increased ocular blood flow, namely a 30–40% reduction of IOP and an even greater percentage increase in pulse pressure.

Because the high OPA persists in OHT even when IOP is acutely restored to the level found in normal subjects, we conclude that higher OPA in these patients is more likely to be an adaptive change in the ocular vascular system associated with, and apparently counteracting, the pathology causing ocular hypertension. It is possible that a higher OPA could serve to protect the retina and the optic nerve head against the effects of ocular hypertension. The high OPA that occurs in spite of the elevated IOP in these subjects indicates a greater pulse volume and higher choroidal perfusion, which may help to maintain an adequate nutritional status for the optic nerve head and the retina. However, at an IOP of 22 mmHg or greater this protective mechanism may be at its maximum and no longer sufficient, leading to glaucomatous damage and necessitating ocular antihypertensive therapy. In POAG subjects, even when their IOP is in the normal range, such protective mechanisms may be attenuated by the age-difference and/or the disease process in comparison with OHT, which may help explain the difference in progression of glaucomatous damage between these two groups of patients.

Measurements of the ocular pulse in monkeys have been much more difficult for us than measurements in humans, both for technical reasons

and because of limited access to monkeys for such experimental studies. The recorded trace of pulse amplitude in cynomolgus monkey eyes exhibits much more variability than human tracings due to blinking, environmental stimuli, lack of fixation and smaller amplitude. Furthermore, calibration of the pulse is uncertain because the probe is not necessarily matched to the smaller monkey eye, and because of undocumented changes in the software updates provided by the manufacturer of the OBF system. These difficulties are partly offset by the higher average pulse rate in monkeys which gives 8–12 pulses during a five-second recording period. Because of these difficulties the absolute values for the OPA and PPV are uncertain for the monkey data across time, but they should be comparable for measurements made at the same time in the same animal.

A value for the mean ocular pulse amplitude was obtained from measurements of three separate pairs of pulses in the five-second trace in which the two pulses forming each pair are similar. Using the mean IOP (independently determined by pneumatonograph) and the amplitude of the ocular pulse, the IOP at systole and at diastole were determined. The volume of blood that had entered the eye at the peak of the pulse was then calculated from the pressure/volume relationship experimentally determined in the living monkey eye by Paterson and Paterson.[7] These parameters (IOP and PPV) were determined during the development of the laser-induced glaucoma model[5] in four monkeys and gave the unexpected result that PPV does not decrease when IOP increases in the lasered eye, but the *contralateral* eye shows a *higher* PPV (Table 2). This result may seem paradoxical, but it is understandable if a higher IOP in one eye causes a systemic or bilateral compensatory autoregulation, which is manifested in the eye with normal intraocular pressure but not in the eye with increased IOP. This may be because the compressive effect of higher IOP on the choroidal blood vessels decreases PPV in that eye.

Tables 3–6 summarize our drug-treatment results in the four cynomolgus monkeys after full development of the unilateral glaucoma. The lasered glaucomatous eyes were treated with standard antiglaucoma therapeutic agents analogous to the treatments of the OHT human subjects reported in the first part of this paper. All four agents, 2% epinephrine, 1% para-aminoclonidine, 4% pilocarpine, or 0.5% timolol caused a significant IOP response in glaucomatous eyes. The two adrenergic agonists, epinephrine and para-aminoclonidine, were equally effective as ocular hypertensives (Tables 3 and 4). However, epinephrine did not change PPV in these eyes, while para-aminoclonidine showed a consistent trend over the first four hours, but statistically increased PPV at only one time point. There is no simple interpretation of these results, because there could be at least two effects of the drugs on PPV, one resulting from the change in IOP and the other caused by a direct action of these agents on the ocular blood vessels themselves. Lowering IOP should decrease the compressive force on choroidal vessels and increase the ocular pulse pressure, leading to an increase in PPV. However, since epinephrine may have vasoconstrictive properties in the choroid, this IOP effect could be counteracted by a direct decrease in compliance of choroidal blood vessels resulting in little overall change in PPV. Based on this hypothesis, it would appear that epinephrine is more vasoconstrictive than is para-aminoclonidine on intraocular blood vessels.

Pilocarpine was also effective in reducing the IOP of glaucomatous monkey eyes (Table 5) and also showed a significant increase in PPV within the first two hours. Cholinergic agents, including pilocarpine, have little direct vascular effect. Thus, the results with pilocarpine indicate that the increase in PPV was solely in response to a decrease in the IOP. We had the opportunity to study the effect of 4% pilocarpine in an additional group of four bilateral glaucomatous monkeys with longstanding glaucoma (duration >12 months). Pilocarpine-treated glaucomatous eyes were compared with contralateral vehicle treated glaucomatous eyes. At times when the pilocarpine-treated eyes were five or more mmHg lower than the IOP of contralateral eyes, PPV was found to be significantly elevated (see Table 6).

The most effective agent tested in the glaucomatous monkeys was 0.5% timolol. IOP was decreased and PPV was increased for the entire eight hours of observation. However, this response also occurred in the contralateral eye (Table 7). A significant contralateral/systemic drug effect of timolol treatment could increase PPV in both eyes due to systemic hemodynamic changes and, therefore, it is difficult to determine if timolol has a direct action on intraocular blood vessels.

Overall, our findings suggest that lowering IOP in the glaucomatous monkey model has a direct effect of increasing PPV, probably by reducing the compressive force on the choroidal vasculature caused by elevated ocular pressure (as shown, for example, by the pilocarpine data).

However, when using the adrenergic agents there may be additional direct drug effects on the vascular system, as suggested by the epinephrine and para-aminoclonidine data, and there may be further complicating factors due to systemic hemodynamic effects of the administered drugs, which appears to be the case for timolol.

In terms of improved ocular blood flow in the laser-induced glaucomatous monkey eye by the most commonly used antiglaucoma drugs, the rank order of effectiveness is timolol > pilocarpine > para-aminoclonidine. Epinephrine treatment appears to have little capacity to improve PPV in the monkey eye, despite being an effective ocular hypotensive agent.

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Discussion

DR. SILVER: I have two comments about the exercise work. The first is that blood flow is not only related to the magnitude of pulse amplitudes, but it is also related to the timing characteristics of the pulse. One of the more obvious timing factors is the number of pulses per unit time that are flowing into the eye. For instance, when the pulse rate has increased by almost a factor of two, the amount of blood flow in the pulsatile component will be up, even if the amplitudes are constant.

DR. MITTAG: There is no question about it that blood flow is increased, but mostly because of the pulse rate. Actually, there is another factor. The cardiac force of contraction is also increased in exercise, but we did not really measure that. All of those factors will increase blood flow, but I was astonished to find that pulse amplitude was not changed.

DR. SILVER: The other comment that I was going to make was that in 1991 Dick Farrell, Maurice Langham, George Michelson, Peter Schilder and I presented a paper at ARVO (*Invest Ophthalmol Vis Sci 32[suppl]:*864, 1991). We reported on measurements of pulse rate, brachial pressure, intraocular pressure, tonometry and Doppler sonography, before and after acute exercise. We noticed that before exercise, which is the normal state, the pulsatile versus steady component of flow in the ophthalmic artery had a certain ratio to one another; after exercise, the pulsatile component went up dramatically, but at the expense of the steady component. We had the idea that one was basically converting the steady component of flow into pulsatile. So we made further measurements, attempting to find verification. When we looked at calculated pulsatile flow values, rather than just pulse amplitudes, we found that indeed the amount of flow in the pulsatile component increased in proportion to the amount of exercise we could manage to get our subject to do. The average intraocular pressure decreased in the exercised state, while the intraocular pressure pulse amplitudes remained about the same: this gave rise to a significant rise in the pulsatile component of flow. So I think that, in terms of trying to understand what is happening in the exercised patient, it is important to take into account the timing of the pulses (the pulse rate). Then, on a more refined basis, it is really necessary to recognize that the time course during the pulse gives additional information. If that information is taken into account, one might better understand what is happening.