Correlates of Acute Exercise-Induced Ocular Hypotension

Alon Harris,* Vic Malinovsky,† and Bruce Martin‡

Purpose. To understand those factors that determine the decrease in intraocular pressure (IOP) that occurs during acute dynamic exercise.

Methods. Three aspects of the exercise–IOP relationship were studied. These included graded exercise, with and without CO₂ addition for isocapnia; comparison of the IOP response of trained and sedentary subjects to a fixed external work load; and exercise after ocular β-adrenoceptor blockade. Graded exercise consisted of 7 minutes each at 30 and 90 watts on a cycle ergometer, then progressive work to exhaustion. Trained and sedentary subjects were defined on the basis of the blood lactate response to fixed external work (10 minutes at 90 watts). Selective β₁-adrenoceptor blockade (betaxiolol) and nonselective β-adrenoceptor blockade (levobunolol) were superimposed on graded exercise. Intraocular pressure was measured using applanation tonometry.

Results. Graded exercise: Intraocular pressure decreased in proportion to exercise intensity. Hypocapnia developed in the last minutes of exhausting work, but preventing hypocapnia with CO₂ addition failed to lessen the decrease in IOP. Response to fixed external work load: Intraocular pressure decreased significantly more in sedentary than in trained subjects; this decline was correlated with elevations in blood lactate but not with changes in metabolic rate or plasma osmolarity. Selective and nonselective β-adrenoceptor blockade: Both drugs lowered IOP at baseline and throughout graded exercise; the drugs and exercise had apparently additive ocular hypotensive effects.

Conclusions. Acute dynamic exercise lowers IOP in a graded fashion proportional to relative, not absolute, work load. The IOP decline is correlated with blood lactate but not with PCO₂ or plasma osmolarity changes, and exercise potentiates the ocular hypotensive effects of β-adrenoceptor blockade. Invest Ophthalmol Vis Sci. 1994;35:3852–3857.

Numerous studies show that dynamic exercise acutely reduces intraocular pressure (IOP).¹⁻¹¹ and there is a scattering of evidence suggesting that repeated daily exercise may consistently lower the IOP.¹² Because exercise consequently may yield some benefit for patients with glaucoma and high ocular tension, and because exercise is, in any event, an unavoidable part of daily life, the factors influencing exercise-induced ocular hypotension deserve investigation. Surprisingly, little is known concerning several critical aspects of the exercise–IOP relationship. In this study, we investigated three major areas in which information is either controversial, negligible, or nonexistent. First, recent evidence from our laboratory shows that isometric exercise-induced ocular tension reductions are mediated through an associated hypocapnia;² does this same mechanism operate in dynamic exercise? Second, although some data suggest that IOP decreases most when exercise intensity is greatest,⁹ this information is insufficient to determine whether the absolute amount of exercise performed, or the relative impingement on an individual’s work capacity, is more closely associated with the pressure decline. Third, no experiments have examined the relationship between exercise-induced and drug-induced ocular tension reductions. These investigations into the factors linking exercise and IOP will yield information about the potential mechanisms by which exercise exerts its ocular hypotensive effect and will help determine how exercise could best be used to augment pressure reduction in patients already receiving pharmacologic therapy.
MATERIALS AND METHODS

Experimental Subjects

All subjects in all phases of the study were volunteers, and all signed informed consent to experimental procedures that were reviewed and approved by an institutional human subject protection committee. The research followed the tenets of the Declaration of Helsinki. None of the subjects was receiving medication, and all enjoyed good ocular and systemic health.

Experimental Design

Graded Exercise. Twelve subjects each came to the laboratory on three separate occasions: once for graded exercise, once for identical graded exercise with CO2 addition for isocapnia in the final phases of severe exercise, and once for control (resting) measurements. The three experiments were counterbalanced in order. Exercise consisted of 7 minutes of cycle ergometer work at 90 watts, followed by 2 minutes of rest, then 7 additional minutes of exercise at 90 watts. After 2 additional minutes of rest, progressive exercise to volitional exhaustion was begun, with exercise intensity increased 15 watts per minute from a 90-watt baseline. Baseline intensity and the increment of the increase per minute were adjusted to each subject’s fitness level so that exhaustion occurred after 5 to 8 minutes. Before and after exercise, and during each 2-minute rest period, IOP measurements were made. During exercise, heart rate, blood pressure, minute ventilation, and oxygen uptake were measured, and an antecubital venous blood sample was drawn within 5 minutes of exercise and analyzed for blood lactate concentration and for plasma osmolarity. These same measurements were made in the same time sequence in the control experiment while subjects remained at rest.

Sedentary and Trained Subjects: Response to a Fixed External Work Load. Twenty-eight subjects each came to the laboratory on one occasion for measurements before and after exercise. The work load was identical for all subjects: 10 minutes of exercise at 90 watts on a cycle ergometer. Using a fixed external work load allowed us to “clamp” energy expenditure (O2 consumption) in this group. At the same time, although all the subjects were healthy young adults, they were selected to represent the widest possible range of fitness, and they included primarily sedentary individuals and highly trained competitive cyclists. Choosing a sample that included sedentary and trained persons allowed us to compare groups exhibiting widely varying blood lactate (and hence, varying relative work intensity) at a fixed absolute energy expenditure. Antecubital venous blood samples were taken before and after exercise and analyzed for lactate and osmolarity. Sedentary and trained groups were determined a posteriori on the basis of blood lactate levels with exercise. A priori selection was based on a general interview concerning exercise habits; although no attempt was made to compare systematically a posteriori lactate levels with a priori judgments of fitness, it was clear that a priori screening was reasonably accurate. The uneven sample size in the sedentary and trained groups resulted from the relative ease in recruiting the more fit subjects. Intraocular pressure was also measured before and after exercise, whereas heart rate, blood pressure, minute ventilation, and oxygen uptake were determined before and during exercise.

Exercise After Ocular β-Adrenergic Blockade. Studies of exercise with superimposed ocular β-adrenoceptor blockade (β1-selective (betaxolol), n = 6) and nonselective β-blockade (levobunolol), n = 7) followed protocols identical to those described earlier under “graded” exercise. Subjects were studied in exercise under either drug or no drug conditions, with a third, control, experiment included. The three experiments were counterbalanced in order. The drugs (Betoptic S (Alcon, Forth Worth, TX; betaxolol HCl 0.25%), and Betagan (Allergan, Irvine, CA; levobunolol HCl, 0.5%)) were administered in the left eye only, one drop the night before study and one drop 90 minutes before the experiment.

Intraocular Pressure Measurement

A slit-lamp mounted Goldmann applanation tonometer (Alcon) was used to measure IOP. Before each measurement, one drop of a combination of benoxinate hydrochloride (0.4%) and fluorescin sodium (0.25%) was instilled in the eye. A single measurement in the left eye was made in each phase of the experiment. In each phase of the study, IOP was measured throughout by a single technician.

Ventilatory and Metabolic Measurements

During all phases of the experiments, heart rate was determined by palpation of the radial pulse and arterial blood pressure by sphygmomanometry. Ventilation was determined by directing the subjects’ expired gas through a low-resistance breathing valve into a Stead–Wells spirometer (Collins, Braintree, MA). A Beckman LB-2 CO2 analyzer (San Jose, CA) and an AEI S3A O2 analyzer (Applied Electrochemistry, Sunnyvale, CA) sampled this gas mixture for determination of oxygen uptake; end-tidal PCO2 was measured by directing the CO2 analyzer sampling tube to the mouthpiece. CO2 addition for isocapnia in the first experimental series was made manually from a 100% CO2 tank. Blood lactate was determined using a standard enzymatic method (Sigma, St. Louis, MO); plasma osmolarity was determined using both freezing point depression (Halb micro osmometer, Frankfurt,
Repeated measurements of intraocular pressure under either resting (control) conditions, or after 7 minutes of cycle ergometer exercise at 30 watts, 7 additional minutes at 90 watts, then 6 to 8 minutes of progressive exercise to volitional exhaustion (mean peak work load, 168 watts). Asterisks (*) refer to statistically significant decreases in IOP versus the control series ($P < 0.05$). CO$_2$ addition to maintain isocapnia in the final minute of exhausting work failed to blunt the IOP decline in a third series ("exercise + CO$_2$") involving identical exercise.

Germany) and vapor pressure (Wescor 5100B, Provo, UT) techniques.

Statistical Analysis

Paired comparisons (e.g., sedentary versus trained) were made using paired Student’s t-tests; multiple comparisons (e.g., exercise both with and without CO$_2$ addition compared with control) were made by Scheffe’s test after analysis of variance. In all comparisons, $P < 0.05$ was regarded as significant.

RESULTS

Graded Exercise

Graded exercise resulted in graded declines in IOP in 12 subjects (Fig. 1). This decline was not significant after 7 minutes of exercise at 30 watts but reached statistical significance after a subsequent 7 minutes of exercise at 90 watts (Fig. 1). Short-term exercise to volitional exhaustion further reduced ocular tension (Fig. 1). End-tidal PCO$_2$ was constant at 40.7 ± 1.3 mm Hg at 30 watts, 41.2 ± 1.4 mm Hg at 90 watts, and 40.2 ± 1.3 mm Hg in the first 3 minutes of progressive work ($P > 0.05$, not significant). Hypocapnia, as measured in end-tidal gas, only developed in the final minute of exercise before exhaustion (PETCO$_2$ fell to 37.2 ± 1.5 mm Hg from 40.6 ± 1.2 mm Hg 2 minutes earlier; $P < 0.05$); blunting this PCO$_2$ decline in the final minute of exercise with addition of CO$_2$ to inspired gas (PETCO$_2$ at exhaustion was elevated from 37.2 to 39.5 ± 1.2 mm Hg in this series, $P < 0.05$) failed to alter IOP (Fig. 1).

Blood lactate rose after exercise (Table 1), but only to levels suggesting that “volitional exhaustion” in our subjects was something less than that effort required to elicit the maximal oxygen uptake$^{13}$; the limited degree of hypocapnia also reflected the less-than-maximal effort made.$^{13}$ Exercise also produced a slight but significant hemoconcentration, but it had no consistent effect on plasma osmolarity (Table 1). Heart rate, minute ventilation, oxygen uptake, and mean arterial blood pressure increased in a predictable fashion from rest through graded exercise (Table 1). The simultaneous rise in mean arterial pressure and decline in intraocular pressure increased calculated ocular perfusion pressure (derived as $\frac{2}{3}$ MAP–IOP$^{16}$; Table 1).

Intraocular Pressure Responses of Sedentary and Trained Subjects to a Fixed Work Intensity

The 28 subjects showed predictable whole-group changes in heart rate, oxygen uptake, and arterial blood pressure in response to exercise at 90 watts (Table 2). The mean effect on blood lactate was a significant increase, whereas plasma osmolarity was unchanged (Table 2). Intraocular pressure decreased significantly in amounts similar to those seen at this work level in graded exercise (Table 2). The division of subjects a posteriori into sedentary and trained groups on the basis of blood lactate was easily made, because subjects tended to display either virtually no lactate increase (<10 mg/dl) or a substantial lactate increase (>20 mg/dl) at the selected absolute work load. Seventeen subjects (12 men, 5 women) had blood lactate increases <10 mg/dl in exercise and were defined as trained; eleven others (5 men, 6 women) had lactate rises ≥20 mg/dl and were termed sedentary (Table 2). The trained and sedentary groups differed predictably in rest and exercise heart rates$^{13}$; their resting and exercise blood pressures and oxygen uptakes were identical (Table 2). The two groups did not differ in initial IOP, but the exercise-induced IOP decline was twice as great in the sedentary group (Table 2; $P < 0.05$). Taken individually, rather than as groups, the results were similar: Changes in blood lactate, but not in plasma osmolarity, blood pressure, or oxygen uptake, correlated significantly with changes in IOP ($n = 28; \tau = -0.54; P < 0.05$).

Combined Influence of $\beta$-Adrenoreceptor Blockade and Exercise

After $\beta_1$-selective adrenoreceptor blockade (betaxolol; $n = 6$) and nonselective $\beta$-blockade (levobunolol;
TABLE 1. Metabolic Responses During Graded Exercise and at the Time of IOP Measurement After Maximal Exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>30 Watts</th>
<th>90 Watts</th>
<th>3–5 Minutes After Maximal Work Rate (Mean 168 Watts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td>80 ± 3</td>
<td>101 ± 6*</td>
<td>137 ± 8*</td>
<td>125 ± 7*</td>
</tr>
<tr>
<td>Minute ventilation (l/min BTPS)</td>
<td>7.3 ± 0.8</td>
<td>18.5 ± 1.1*</td>
<td>34.5 ± 4.1*</td>
<td>-</td>
</tr>
<tr>
<td>Oxygen uptake (l/min STPD)</td>
<td>0.28 ± 0.06</td>
<td>0.83 ± 0.9*</td>
<td>1.39 ± 0.11*</td>
<td>-</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>118 ± 4</td>
<td>120 ± 4</td>
<td>136 ± 5*</td>
<td>134 ± 5*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78 ± 3</td>
<td>74 ± 4</td>
<td>75 ± 3</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>Calculated ocular perfusion pressure (mm Hg) (2/3 MAP-IOP)</td>
<td>46 ± 2</td>
<td>47 ± 3</td>
<td>55 ± 3*</td>
<td>51 ± 2*</td>
</tr>
<tr>
<td>Blood lactate (mg %)</td>
<td>37.6 ± 3.5</td>
<td>-</td>
<td>-</td>
<td>40.7 ± 3.8*</td>
</tr>
<tr>
<td>Plasma osmolarity (n = 7) (mosmol/l)</td>
<td>287 ± 4</td>
<td>-</td>
<td>-</td>
<td>282 ± 3</td>
</tr>
</tbody>
</table>

mosmol = Milliosmole; STPD = standard temperature and pressure dry; BTPS = body temperature and pressure saturated.
* Statistically significant change (P < 0.05).

n = 7), resting IOP was reduced (Fig. 2). Subsequently, graded exercise lowered IOP in a fashion parallel to that seen under non-drug conditions: exercise and each drug had apparently additive effects as ocular hypotensive agents (Fig. 2).

DISCUSSION

In this study, we found that dynamic exercise lowered intraocular pressure in a graded fashion dependent on exercise intensity. Exercise-induced ocular hypotension was independent of PCO2 and most closely related to relative, rather than absolute, work load. The ability of exercise to reduce IOP was unaltered by ocular β-adrenergic blockade: Resting IOP was lowered by the drug, but subsequent exercise-induced reductions paralleled those seen under non-drug conditions.

Past work shows that both isometric and dynamic exercise lower IOP. In isometric exercise, the IOP decline is blunted, if not blocked, by maintaining isocapnia during and after the episode of physical ef-

TABLE 2. Metabolic and Intraocular Pressure Responses to a Fixed External Work Load (10 minutes at 90 Watts) in Trained and Sedentary Subjects

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n = 28)</th>
<th>Trained (n = 17)</th>
<th>Sedentary (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td>76 ± 4</td>
<td>130 ± 6</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Oxygen uptake (l/min STPD)</td>
<td>0.29 ± 0.04</td>
<td>1.55 ± 0.11</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>118 ± 5</td>
<td>155 ± 8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76 ± 4</td>
<td>70 ± 5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasma osmolarity (mosmol/l)</td>
<td>286 ± 5</td>
<td>286 ± 3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Blood lactate (mg/dl)</td>
<td>12 ± 1</td>
<td>29 ± 5</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>16.3 ± 0.4</td>
<td>13.0 ± 0.5</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Rest

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (b/min)</th>
<th>Blood lactate (mg/dl)</th>
<th>IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects (n = 28)</td>
<td>70 ± 5</td>
<td>11 ± 2</td>
<td>16.3 ± 0.5</td>
</tr>
<tr>
<td>Trained (n = 17)</td>
<td>80 ± 6</td>
<td>13 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Sedentary (n = 11)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

Exercise

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (b/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Blood lactate (mg%)</th>
<th>IOP (mm Hg)</th>
<th>ΔIOP (rest-exercise, mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects (n = 28)</td>
<td>117 ± 5</td>
<td>158 ± 7</td>
<td>67 ± 4</td>
<td>16 ± 2</td>
<td>13.7 ± 0.6</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>Trained (n = 17)</td>
<td>139 ± 8</td>
<td>158 ± 7</td>
<td>73 ± 5</td>
<td>49 ± 8</td>
<td>11.7 ± 0.8</td>
<td>4.7 ± 0.4</td>
</tr>
<tr>
<td>Sedentary (n = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Statistically significant change (P < 0.05).
Previous experiments show that dynamic exercise induces ocular hypotension in rough proportion to exercise intensity. When exercise is mild, IOP may not significantly change; when exercise is intense, IOP falls substantially. We confirmed these findings by showing a graded IOP decline with increasing exercise intensity, although our data lack the time controls required to substantiate this result further. These results leave unanswered the question whether exercise reduces IOP in proportion to absolute or relative work intensity. Our findings using sedentary and trained subjects, each at the same external work load, showed that relative work intensity is the better correlate of IOP reduction. This result implies that a physiologic response tied to relative work intensity (e.g., blood lactic acid levels, sympathetic neural drive, or circulating catecholamines), rather than one tied to absolute work intensity (e.g., heat production, cardiac output, or metabolic rate), causes ocular hypotension. Studies of prolonged exercise find increased plasma osmolarity to be a close correlate of, and a potential mechanism for, ocular hypotension. We found no such associations in this study in acute exercise: There was no mean change in osmolarity as IOP fell. In prolonged work, a progressive systemic dehydration can develop that is paralleled by aqueous humor dehydration and subsequent IOP reduction, an effect not present in the short term. However, the possibility remains that exercise increased plasma colloid osmotic pressure, thereby reducing aqueous formation. Past work shows that acute exercise increases plasma protein concentration in parallel with increasing hematocrit; these changes, significant for water movement between the vascular compartment and the extracellular fluid, cannot be detected by measuring plasma osmolarity. It is also possible that exercise changes the concentration of a specific plasma constituent that, due to varying reflection coefficients at the blood-aqueous barrier, alters aqueous formation. Finally, the possibility that exercise could alter blood-aqueous barrier permeability must be considered. However, studies show that exercise-like pharmacologic interventions (chronic sympathetic stimulation or phenylephrine administration) increase, rather than decrease, protein and fluid leakage into the anterior compartment.

Exercise was as effective in acutely lowering IOP in β-blocked eyes as it was in untreated eyes; the combined effect of intense dynamic exercise and β-adrenergic blockade was a maximal reduction in IOP. This additive effect of exercise and β-blockade is one line of evidence that the two modalities reduce IOP using different mechanisms. The other line is more theoretical: Exercise profoundly stimulates the sympathetic nervous system (α and β), whereas selective and non-selective β-blocking drugs have opposite effects:

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**Figure 2.** Influence of graded exercise on intraocular pressure with and without pretreatment with a selective β1-adrenergic blocking drug (betaxolol; (A)), or a non-selective β-blocker (levobunolol; (B)). Compared with control, graded exercise lowered IOP in progressive fashion; both drugs significantly lowered IOP at rest; the ocular hypotensive effects of both drugs and exercise appear to be additive. Asterisks (*) refer to statistically significant differences compared with control (P < 0.05).
Therefore, the two “treatments” must lower IOP by different mechanisms. One of these mechanisms is well defined: Both selective and nonselective β-adrenergic blocking drugs lower IOP by reducing aqueous inflow.22 23 In contrast, exercise could reduce IOP by colloid osmotic effects or, conceivably, by increasing aqueous drainage through a β-agonist-like action.22 24

In conclusion, our results indicate that the ocular hypotensive effect of acute dynamic exercise is unrelated to PCO₂ changes, dependent on relative, not absolute, work load, and additive to the hypotensive effects of β-adrenergic blocking agents. These results imply that increasing age, declining fitness, or the use of standard β-adrenergic blocking drugs will not blunt the hypotensive actions of acute exercise.1 Whether repeated daily exercise can be used to augment the therapeutic value of hypotensive glaucoma medications remains to be determined.

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Key Words
intraocular pressure, betaxolol, levobunolol, glaucoma, lactic acid

References