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CLINICAL INVESTIGATION

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Retinal blood flow during dynamic exercise

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Abstract ● Background: Exercise acutely lowers intraocular pressure (IOP) and raises arterial pressure. We wondered whether the resultant increase in ocular perfusion pressure would alter retinal blood flow. ● Methods: To investigate this question, 11 healthy volunteers each performed progressive cycle ergometer exercise until exhaustion was reached in 5–10 min. Immediately after exercise, retinal blood flow and arteriovenous passage time were determined by video fluorescein angiography. Ten other volunteers performed repeated episodes of cycle ergometer exercise at approximately 60% of the maximal aerobic capacity, immediately prior to estimates of macular leukocyte velocity and density via blue-field stimulation. ● Results: Progressive exercise lowered IOP and elevated calculated ocular perfusion pressure. Within the retinal circulation, this exercise tended to raise mean dye velocity, as it significantly narrowed the superior temporal artery and vein; as a result, calculated retinal blood flow was unchanged. Simultaneously, retinal arteriovenous passage time was substantially shortened. Blue-field simulation showed that exercise increased macular leukocyte velocity while leaving leukocyte density unchanged. ● Conclusions: These results show that the normal retinal hemodynamic response to increases in perfusion pressure on dynamic exercise includes vasoconstriction that normalizes flow and faster capillary and overall retinal blood transit.

Introduction

Intraocular pressure falls during and for some minutes after dynamic exercise [12, 13]. Because this brief but substantial ocular hypotension occurs in tandem with sizable increases in arterial pressure on exercise, calculated ocular perfusion pressure increases greatly [9]. This pressure rise poses a challenge for retinal blood flow autoregulation. We hypothesized that retinal or preretinal vasoconstriction would provide constant flow while perfusion pressure is increased during exercise. This response would be analogous to the mechanism by which some other portions of the brain autoregulate flow during exercise [11]. In this study we investigated retinal blood flow regulation in persons with healthy eyes. By defining the normal response, we could eventually compare this with various disease states: both diabetes and glaucoma may be characterized early in their course by abnormal retinal flow responses to altered physical or chemical conditions [7, 8].

Methods

Subjects

Young adults with no history of eye, heart, or lung disease volunteered to participate in the experiments. All signed informed consent to procedures that had been reviewed and approved by a human subjects protection committee. The research conformed to the tenets of the Declaration of Helsinki. Eleven persons (mean age

25±5 years) participated in experiments involving fluorescein angiography, 10 other persons (mean age 22±2 years) in studies using blue-field entoptic simulation. Sample sizes were reduced whenever angiographic recordings were of insufficient quality, or when the necessity for immediate angiography took precedence over other readings.

Exercise

All measurements of ocular hemodynamics by necessity were performed with subjects seated at rest. Comparison of resting conditions with exercise were made by obtaining data at rest, and subsequently by making measurements immediately after exercise. For this reason, exact quantitation of exercise intensity during the ocular measurements was impossible, since measurements by necessity were made in the transition from exercise to rest. The kinetics of heart rate, blood pressure, and oxygen uptake typically show response half-times of approximately 2 min to a step change in work load [20]; blue-field and fluorescein angiography measurements were typically complete within the first 90 s after exercise cessation. For experiments involving fluorescein angiography, exercise was performed on a bicycle ergometer, with exercise beginning at zero load and increased by 20–40 W/min until volitional exhaustion occurred in 5–10 min.

Due to the nature of exercise, the experiments could not be performed in double- or single-masked fashion. A control series was not included, since repeated measurements of retinal flow parameters using fluorescein angiography yield consistent results with relatively low coefficients of variation [21]. Work load was controlled, and oxygen uptake, carbon dioxide production, and minute ventilation were monitored by an automated open-circuit spirometry system (Medical Graphics, St. Paul, Minn.). Angiography began immediately afterward. In studies involving blue-field entoptic simulation, three repeated measurements were required under both resting and exercise conditions. Because of cumulative fatigue, the exercise intensity in this phase of this experiment was lowered to approximately 60% of the maximal oxygen uptake, as estimated from resting heart rate and predicted age- and sex-dependent maximal heart rate [1]. Five minutes of exercise, sufficient to reach a metabolic, circulatory, and respiratory steady state [20], immediately preceded each of the three repeated measurements involving blue-field simulation.

Intraocular pressure (IOP) was measured using applanation tonometry (Goldmann) before and within 10 min after exercise. Before and immediately after exercise, blood pressure was determined manually by sphygmomanometry.

Fluorescein angiography

High-resolution video fluorescein angiograms were obtained using a scanning laser ophthalmoscope (Rodenstock). A computer determined arteriovenous passage time from digitized angiograms by calculating the time between dye appearance (defined as attainment of 10% maximum dye intensity) in the temporal superior artery and the corresponding temporal vein [22]. Mean dye velocity was measured in the artery approximately 900 μm from the rim of the optic disk [22]. At this same location, cross-sectional assessments of venous and arterial diameter were performed. Micrometer diameter data were calculated after marking the vessel margins, perpendicular to the vessel segment. Absolute values could be assessed from the number of pixels measured between the two points [22]. A 20° field was used, so that a digitization of 512×480 provided a pixel resolution of about 6 μm. The average number of pixels representing an artery was 20, and the average vein had 24 pixels; consequently, the resolution of the technique was 4–5%. Diameter measurements of one vascular segment consisted of three trials; all measurements were done in masked fashion by a single, trained observer.

Blue-field entoptic simulation

Retinal leukocyte velocity and density in the perimacular capillary bed (a 14° zone surrounding fixation) was estimated subjectively using an Oculix 1000 system of blue-field entoptic illumination (Berwyn, Pa.) with concurrent computer simulation [17]. Aided by a single trained operator, the subjects matched the pulse-synchronized computer simulation of retinal leukocytes with those of their own cells. The order of adjustment was the same in all subjects during each trial: density, velocity, and pulsatility. After each reading, this simulation density and velocity were randomized. Subjects were encouraged not to change the pulsatility setting unless it interfered with their ability to make velocity and density comparisons.

Statistical analysis

Paired comparisons were made between the resting and exercise conditions using paired, two-tailed *t*-testing; $P<0.05$ was regarded as statistically significant.

Results

Exercise to volitional exhaustion immediately prior to fluorescein angiography predictably increased mean arterial pressure (Fig. 1, $n=7$) and decreased IOP (Fig. 1; $n=9$; both $P<0.05$). Ocular perfusion pressure, calculated as 2/3 (mean arterial pressure)−IOP [15, 16], was increased substantially by exercise (Fig. 1; $P<0.05$). The

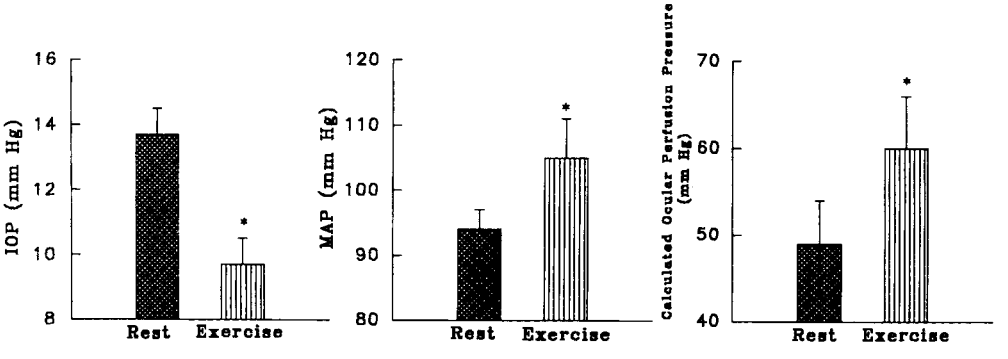

Fig. 1 Intraocular pressure (*IOP*), mean arterial pressure (*MAP*), and calculated ocular perfusion pressure (2/3 MAP-IOP) before and immediately after short-term progressive cycle ergometer exercise to volitional exhaustion. Exercise significantly lowered IOP ($P<0.05$; $n=9$) and elevated MAP ($P<0.05$; $n=7$). These changes resulted in a significant increase in calculated ocular perfusion pressure ($P<0.05$; $n=7$)

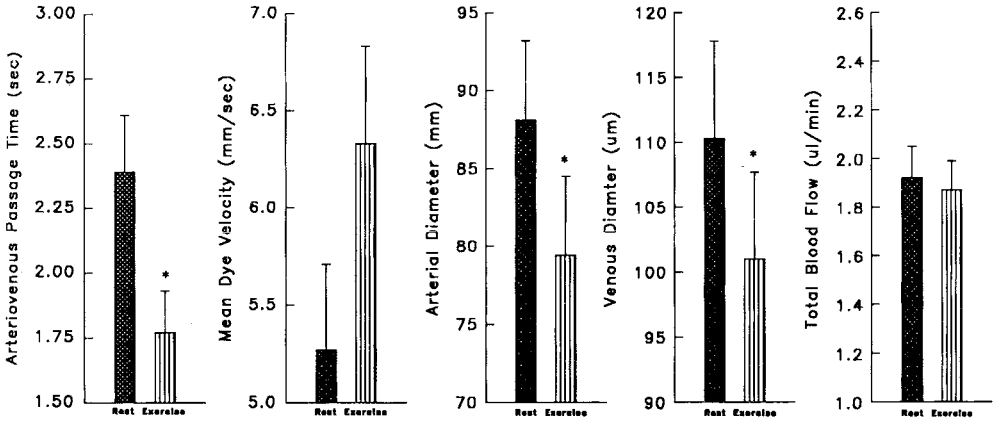

Fig. 2 Retinal hemodynamics at rest and immediately after dynamic exercise: from left, retinal arteriovenous passage time, arterial mean dye velocity, superior temporal arterial and venous diameters, and total blood flow. Exercise reduced retinal dye passage time and tended to raise mean dye velocity; however, an exercise-induced narrowing of the artery and vein resulted in unchanged total retinal flow, calculated as mean dye velocity$\times\Pi\times\left[\frac{(\text{arterial diameter})^2}{4}\right]$. *Asterisks* $P<0.05$ versus resting conditions

Table 1 Metabolic response to progressive dynamic exercise

Number of subjects	10
Gender (M/F)	8/2
Body weight (kg)	75±5
Exercise duration (min:s)	9:59±1:08
Peak work load (W)	235±20
Peak minute ventilation (l/min)	91±6
Peak oxygen uptake	
(l/min)	3.06±0.27
(ml/kg/min)	40.6±2.4
Peak CO_2 production (l/min)	3.60±0.27
Peak respiratory exchange ratio (VCO_2/VO_2)	1.19±0.03

fall in IOP was similar to that found in previous studies utilizing short-term intense dynamic exercise [9, 12]. Peak work load, minute ventilation, oxygen uptake, and CO_2 production are shown in Table 1. The respiratory exchange ratio (VCO_2/VO_2), also shown in Table 1, easily exceeded 1.10 at volitional exhaustion, suggesting that subjects were, on average, quite close to their maximal work load [20].

Fluorescein angiography revealed that retinal arteriovenous passage time was reduced by the immediately preceding exercise (Fig. 2; $P<0.05$). In the superior temporal artery, mean dye velocity was slightly but not significantly elevated (Fig. 2). Exercise significantly narrowed both the superior temporal artery and the corresponding vein (both Fig. 2; both $P<0.05$). Total blood flow in the superior temporal artery, calculated as mean dye velocity$\times\Pi\times\left[\frac{(\text{arterial diameter})^2}{4}\right]$, was unchanged by exercise (Fig. 2).

Cycle ergometer exercise at 60% VO_2max increased estimated macular capillary leukocyte velocity sizably and significantly (Fig. 3; $P<0.05$). In contrast, estimated capillary density was unaltered by this exercise (Fig. 3).

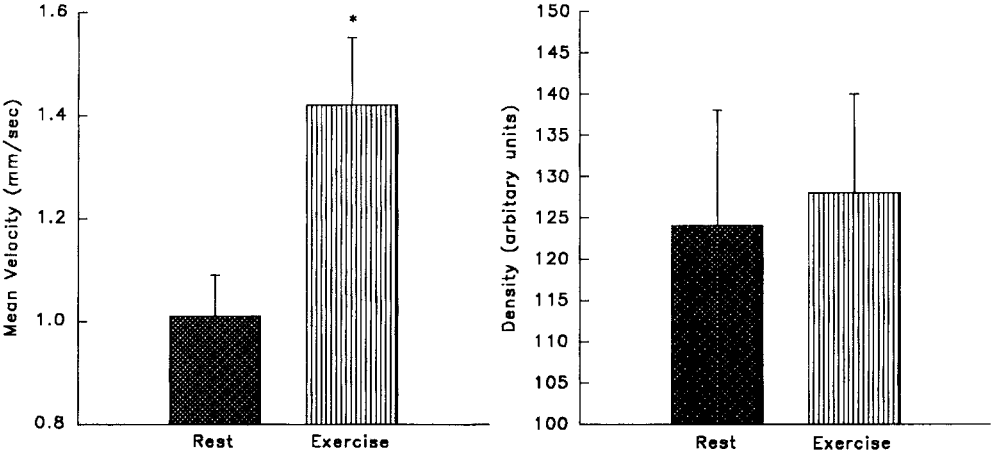

Fig. 3 Macular retinal capillary velocity and density as estimated by blue-field entoptic simulation immediately after steady-state cycle ergometer exercise at 60% VO2max. Prior exercise significantly increased estimated velocity (*left*) while leaving density unchanged (*right*). *Asterisk* $P<0.05$ versus resting conditions

Discussion

In this study we found that the ocular perfusion pressure response to exercise did not increase retinal blood flow: both retinal arteries and veins were narrower under exercise conditions, so that the tendency for arterial dye velocity to rise resulted in no increase in calculated retinal flow. There was, at the same time, evidence that retinal capillary transit is accelerated by exercise: both estimated macular capillary flow velocity and whole-retinal arteriovenous passage time were accelerated after physical exertion.

Numerous studies have shown that acute exercise lowers intraocular pressure, a result duplicated in our experiments [9, 12, 13]. We were specifically interested in the acute coupling of lowered IOP after exercise to elevated mean arterial pressure; the combination sizably increases calculated ocular perfusion pressure. Exercise thus serves at one level as a "real world" example of a pressor stress for ocular hemodynamic regulation. Both the cerebral circulation as a whole and the ocular circulation more locally autoregulate flow (via vasoconstriction) when perfusion pressure increases [2, 16]. Exercise, however, provokes physiological changes more complicated than a simple pressor response: most importantly, exercise increases sympathetic drive [18]. In the cerebral circulation, sympathetic activation gives rise to different segmental vascular responses than does an uncomplicated, acute rise in arterial pressure [2, 5, 6]: exercise superimposes these two conditions. Our results, consequently, are valid only for the specific circumstances of exercise itself, and may not necessarily extend to other conditions characterized solely by acute hypertension or acutely increased sympathetic activity. Additionally, our results only apply to the consequences of short-term physical activity; more prolonged exercise might yield quite different results. Nonetheless, our limited purpose is adequate, since short-term exercise (at least at the milder intensities) is undoubtedly the most commonly encountered pressor and sympathetic stress faced by the ocular circulation. In diabetic retinopathy and some of the glaucomas, the failure to demonstrate autoregulation of blood flow in the face of physical or chemical stressors may be a useful early index of disease [8, 15].

Despite increased ocular perfusion pressure during exercise, the retina maintains constant flow. This must be effected by vasoconstriction at some or several levels in the cerebral vasculature. Our results cannot define which segmental level of vessels most significantly increase vascular resistance. Both arterioles and large arteries (up to perhaps 150–200 μm in diameter [5]) regulate cerebral vascular resistance: the larger arteries, as well as the arterioles, respond to physiological signals such as sympathetic stimulation or blood pressure alterations [5]. If these results apply to the ocular portion of the cerebral circulation (there are important regional differences in flow regulation [5, 6]), then the superior temporal artery (diameter ~90 μm) would stand intermediate within a range of vessels that all vasoconstrict in response to increased driving pressure [2]. In other words, the narrowing of the superior temporal artery after exercise may represent its own active vasoconstriction and would be paralleled for some distance both upstream and downstream in the arterial tree by similar vessel narrowing [2, 5].

The specific mechanisms responsible for retinal (and cerebral) arterial and venous vasoconstriction in exercise is unclear. Pressure-induced autoregulation may result from either direct myogenic or indirect metabolic factors [10]. The mechanism underlying either response remains unidentified: endogenous nitric oxide apparently plays no role [3, 19]. Our finding of both venous and arterial vasoconstriction cannot distinguish between myogenic and sympathetic factors, since both cause venoconstriction in most tissues [4, 14].

At the same time that total retinal blood flow was constant, we found two independent indices of more rapid retinal capillary transit. One of these was the reduction in arteriovenous fluorescein dye passage time, a duration weighted heavily, though not determined entirely, by retinal capillary passage time. We also found bluefield simulation evidence for increased macular capillary leukocyte velocity, with capillary density unchanged, in exercise. It appears paradoxical that total flow could be constant while capillary transit velocity accelerates and overall arteriovenous passage time decreases. The several possible explanations for these results include (1) that arterial and arteriolar vasoconstriction redistribute flow within the retina, creating areas of relatively increased and decreased flow, the regions of increased flow giving rise to more rapid whole-retinal arteriovenous dye passage, and (2) that estimates of capillary density and leukocyte velocity are limited to the macula; other portions of the retinal microcirculation may display different capillary dynamics.

In conclusion, the demands of dynamic exercise (which include a profound sympathetic stimulation and greatly increased ocular perfusion pressure) do not exceed the capacity of the normal retina to maintain constant blood flow. This autoregulatory response of the healthy retina appears to parallel that seen under exercise conditions in the brain as a whole [11].

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