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EFFECT OF ISOMETRIC EXERCISE ON CHOROIDAL BLOOD FLOW IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION (AMD)

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Abstract

Aim—To investigate the choroidal vascular regulation in age related macular degeneration (AMD) we compared the regulatory responses induced by isometric exercise in control subjects and patients with AMD.

Methods—Seventeen eyes of 17 patients with dry AMD in the study eye and 19 eyes of 19 controls were included in this study. Both groups were well matched in regards to age, race and gender. Brachial artery blood pressure determinations and laser Doppler flowmetry (Oculix) measurements of relative foveolar choroidal blood velocity, volume, and flow were obtained in the study eye of each subject during 30 seconds of baseline, and then, during 3 minutes of isometric exercise consisting of squeezing a hand grip in each hand. Similar measurements were then also obtained during the two minutes following the cessation of exercise. Using non-paired, two-tailed t-test, changes in circulatory parameters during exercise and following the end of exercise were compared between AMD patients and control subjects. The slope for the relationship between circulatory changes and perfusion pressure changes was calculated and compared between AMD patients and controls using linear regression analysis. Analysis of data was performed in a masked fashion. Circulatory measurements are shown in arbitrary units (AU).

Results—There were no statistically significant differences between the changes in ChBVel, ChBVol and ChBFlow observed in control subjects and AMD patients during the isometric exercise phase and after exercise.

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Conclusions—Our results suggest that the response of the choroidal circulation to this type of isometric exercise resulting in a moderate increase in blood pressure does not seem to be affected by AMD.

Keywords

Isometric exercises; choroidal blood flow; Age-Related Macular Degeneration (AMD)

Our previous studies[1-3] have suggested that foveolar choroidal blood flow is decreased in patients with age related macular degeneration (AMD) in comparison to normal subjects, and that eyes with more severe AMD features have decreased foveolar choroidal blood flow in comparison with eyes with less severe AMD . The purpose of this cross-sectional study was to investigate whether AMD is associated with disturbances of the choroidal blood flow regulatory responses.

Several previous publications[4, 5] have reported that the human choroid can maintain constant blood flow in response to changes in perfusion pressure. This response is mediated by adjustments in vascular resistance.

In normal subjects, choroidal blood flow is maintained constant for acute increases of up to 67 % of perfusion pressure produced by isometric exercise[5]. This regulatory response most probably protects the choroidal vasculature and prevents ischemia when perfusion pressure decreases and overperfusion and macular swelling when perfusion pressure increases.

We report here a study of the autoregulatory response of the choroidal circulation in AMD patients and age matched controls.

METHODS

This cross-sectional study compared changes in choroidal blood flow in response to perfusion pressure changes caused by isometric exercises in patients with AMD and controls. Measurements were performed in one study eye of seventeen AMD patients and nineteen age matched controls (if both eyes were eligible, only one was randomly selected). AMD eyes studied had pathologic features that matched those of the AREDS Classification [6] Categories 1 through 3, with typical AMD features such as drusen and retinal pigment epithelium (RPE) changes and no evidence of choroidal neovascularisation (CNV) or central geographic atrophy. Eyes with intraocular conditions other than AMD were excluded from the study. Eyes of controls had no intraocular pathology. Inclusion criteria for all study eyes were: visual acuity of 20/40 or better, clear ocular media, excellent fixation, which insured measurements of choroidal blood flow in the center of the fovea, pupillary dilatation of 5 mm or more, refraction error less than ± 7 diopters and intraocular pressure (IOP) of less or equal to 21 mm Hg. Subject's characteristics are summarized in Table 1.

A standard ocular exam with visual acuity, IOP measurements and slit lamp examination was conducted in all subjects. Ophthalmoscopic examination was carried out after pupillary dilation with tropicamide 1% (Alcon, Fort Worth, TX) and phenylephrine hydrochloride

10% (Sanofi Winthrop, New York, NY). All subjects were provided with detailed explanations of the study protocol and were asked to sign an appropriate informed and HIPAA consent forms approved by the human experimental committee of the University of Pennsylvania. The tenets of the Declaration of Helsinki were followed.

We employed a Laser Doppler Flowmeter (Oculix instrument) to measure relative choroidal blood velocity (ChBVel), volume (ChBVol) and flow (ChBFlow) in the foveola of the study eyes. The choroidal blood flow measurements obtained in this way reflect the flow in the choriocapillaris. Choroidal blood velocity and volume are proportional to the mean velocity of the red blood cells and the number of the red blood cells, respectively, within the volume sampled by the laser light. Unlike ChBVel and ChBVol, blood flow is not an independent parameter and is calculated by the instrument according to the following formula: ChBFlow = Constant × ChBVel × ChBVol[7]. A detailed description of this method can be found in several publications[8-11]. The beam of a 670 nm diode laser with a diameter of 200 μm and an intensity at the cornea of 20 micro Watts was delivered to the retina through a fundus camera (model TRC, Topcon, Tokyo, Japan). Measurements of foveolar choroidal blood flow were obtained by asking subjects to fixate on the probing laser beam. A 30° area of the posterior retina was continuously illuminated at a wavelength of 570 nm with a retinal irradiance of approximately 0.03 mW/cm^2, which allowed for constant monitoring of the laser position on the foveola by the examiner. Measurements were conducted in a darkened room. We recorded a baseline measurement of 30 seconds duration. This was followed by a continuous recording of 3 minutes of isometric exercises and 2 minutes of post-exercise (resting) phase. Isometric exercises consisted of steadily squeezing a handgrip in each hand for the duration of all 3 minutes. Subjects were instructed to continuously fixate on the probing laser beam from the beginning to the end of the recordings.

Measurements of blood pressure were obtained during the choroidal blood flow measurements. One or more measurements were obtained each minute during exercise. Brachial artery systolic and diastolic blood pressures (BP_s and BP_d, respectively) were determined by sphygmomanometry (Accutorr 1A, Datascope, Paramus, NJ). For calculation of mean arterial pressure (MAP) and perfusion pressure (PP) we used the following formulas:

$$MAP = BP_{\mathrm{d}} + 1/3\,(BP_{\mathrm{s}} - BP_{\mathrm{d}})$$

$$PP = 2/3 BP_{\mathrm{m}} - IOP$$

Blood flow data were analyzed in a masked fashion with software that was specifically developed for the analysis of Doppler signals from ocular tissues using a NeXT computer[10]. We selected only those parts of the recordings that were consistently stable for ChBVel, ChBVol, ChBFlow, and the DC parameter.

To insure that we selected portions of choroidal blood flow recordings that represent peak blood pressure changes, we chose stable parts of last 30 seconds of the isometric exercise phase and the last 30 seconds of resting phase.

Changes in circulatory parameters from baseline during the isometric exercise and the resting phases were calculated and compared between AMD patients and control subjects by non-paired, two-tailed, t-test. The linear slope for the relationship between circulatory changes and PP changes was calculated and compared between AMD patients and control subjects by linear regression analysis. Findings with $P<0.05$ were considered to be statistically significant. All circulatory measurements are shown in arbitrary units (AU).

RESULTS

Table 1 shows characteristics of AMD patients and control subjects. No significant differences were observed between these two groups.

During isometric exercise mean systolic BP increased by 32.6 ± 5.20 mmHg (Mean ± SE) in the AMD group and by 35.7 ± 4.93 mmHg in the control group, mean diastolic BP increased by 15.1 ± 2.81 mmHg and 20.2 ± 5.22 mmHg, respectively, and mean PP increased by 13.8 ±2.32 mmHg and 16.9 ± 2.99 mmHg, respectively. The difference between the mean blood pressure changes in the two groups was not statistically significant for systolic BP ($P = 0.61$), diastolic BP ($P = 0.40$), and PP ($P = 0.42$).

When mean ChBVel and ChBVol data were compared between AMD patients and controls at baseline no statistically significant differences were observed for these two choroidal blood flow parameters (P=0.38 and P=0.19, respectively). Mean ChBFlow, however, was lower in the AMD group 7.51 ± 0.77 (SE) than in the control group (9.59 ± 0.73), and this difference was of borderline statistical significance (P=0.06), which is in accord with our previous findings[1-,3]. During isometric exercise phase, no statistically significant changes in mean choroidal blood flow parameters from baseline were observed in the AMD group or in the control group. When the two groups were compared, there were no statistically significant differences between the mean changes from baseline for ChBVel, ChBVol or ChBFlow during isometric exercise phase (Table 2) or during the resting phase following the end of the isometric exercise.

Analysis of the linear relationships between perfusion pressure (PP) change and change in each of the three choroidal circulation parameters during isometric exercise showed no statistically significant linear relationship between change in PP and change in choroid blood flow. Also no statistically significant difference in slope was detected between the AMD patients and the control group (data not shown).

DISCUSSION

Our results show no statistically significant differences in the changes of ChBVel, ChBVol or ChBFlow between control subjects and AMD patients during acute increases in PP of about 20%. This suggests that there is no autoregulatory abnormality in AMD eyes within this range of PP increase.

Since we detected no statistically significant difference in changes in ChBFlow between the two groups, it is important to assess what statistical power we have to detect such differences. We estimate that we have 8% power to detect the observed difference (0.28 vs. 0.67) in ChBFlow change from baseline during isometric exercises between the two groups (type I error of 0.05).

Results of Riva et al. showed that in normal eyes there is an efficient regulatory mechanism that can keep choroidal blood flow unchanged for acute increases in PP for up to 67%[5]. These larger increases in PP were obtained through squatting isometric exercise. Because our AMD population is elderly we did not perform squatting experiments, which are difficult at a more advanced age. In this study we chose hand grip squeezing exercises because they are easier to perform in an elderly population. Furthermore, handgrip exercises have a smaller detrimental effect on the ability to fixate on a laser target than squatting. This is important because good fixation is necessary for appropriate measurements of the choroidal foveolar circulation. We are fully aware that the range of pressure increase in our study is modest. Therefore, we can only conclude on flow changes that may occur within this limited range of increases in BP and we cannot make any comments on the full range of the autoregulatory response. Additional studies are needed to investigate the autoregulatory response for larger perfusion pressure increases in AMD patients.

Previous reports have shown that ChBFlow in patients with dry AMD is significantly lower than that of age-matched controls, and ChBFlow progressively decreases with increases in severity of the AMD[1-3]. However, our current study shows that the regulatory response to a moderate systemic BP increase seems to be largely unaffected by the disease process. Our results are different from those of Pournaras et al.[12], who showed that acute elevations of PP of up to 23% caused significant increases in ChBFlow in eyes of AMD patients with subfoveal CNV in the study eye[12]. Our data however, are not in contradiction from the report of Pournaras et al. They performed their study in patients with CNV whereas we excluded patients with CNV in the study eye.

We chose to perform our study in eyes without CNV because eyes with CNV usually have decreased visual acuity and poor fixation. In addition, we were interested in the physiologic response of the choroidal choriocapillaries and not the response of the abnormal choroidal neovascular vessels. The discrepancy between our results and those of Pournaras et al.[12] suggests indeed that choroidal neovascular vessels do not have much autoregulatory capacity, and therefore, increases of perfusion pressure of about 20% cause a similar increase in choroidal blood flow.

Foveolar Laser Doppler Flowmetry measurements are probably dependent on the scattering properties of the tissues measured. Possibly, AMD pathological changes in the fovea could affect the circulatory measurements obtained with this technique. Because in this study we have investigated quick flow responses in time to changes in blood pressure, this issue may be of less importance. Any effects that changes in the scattering properties caused AMD pathology could have on our blood flow measurements would probably not greatly affect our measurement of a rapid response to changing blood pressure.

Two previous studies have reported abnormal choroidal blood flow autoregulation in diabetic retinopathy and chronic inactive central serous chorioretinopathy[13,14]. In both of these studies, choroidal blood flow increased significantly with increases in PP Interestingly, both of these diseases show abnormalities of the autonomic sympathetic nervous system, which is known to play an important role in regulating choroidal circulatory vasoconstriction. There is no evidence that the autonomic nervous system is affected by the AMD disease process and that may explain the absence of autoregulatory abnormality in AMD eyes.

Finally, we would like to mention that we have used phenylephrine to dilate the pupils in our study and it is possible that this may have an effect on autoregulatory responses. Because both controls and AMD participants received the same medications this would probably not preclude us from detecting differences in the responses between the two groups.

CONCLUSION

Our results suggest that the response of the choroidal circulation to this type of isometric exercise does not seem to be affected in AMD eyes without CNV. Further studies are needed to investigate whether disturbances in choroidal autoregulation in response to larger increases in perfusion pressure are present in AMD.

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Table 1

Characteristics of AMD patients and control subjects.

Characteristic features	AMD (n=17)	Controls (n=19)	P-value*
Age in years (Mean ± SE)	68.3 ± 2.1	64.7 ± 1.9	0.21
Gender (% of males)	10 (58.8%)	7 (36.8%)	0.32
Race (% of white)	17 (100%)	18 (94.7%)	1.00
Current smoking (Yes %)	0 (0%)	1 (5.26%)	1.00
Hypertension (Yes %)	7 (41.2%)	9 (47.4%)	0.75
Regular aspirin intake (%)	9 (52.9%)	8 (42.1%)	0.74
Multi-vitamin taking (%)	14 (82.4%)	12 (63.2%)	0.27
Systolic BP, mmHg (Mean ± SE)	138.1 ± 5.0	130.3 ± 3.6	0.21
Diastolic BP, mmHg (Mean ± SE)	72.7 ± 2.2	75.6 ± 2.5	0.39
IOP, mmHg (Mean ± SE)	12.9 ± 0.4	13.0 ± 0.8	0.95
PP, mmHg (Mean ± SE)	49.0 ± 1.9	48.5 ± 1.9	0.85

Table 2

Comparison of circulatory changes from baseline between AMD patients ar controls. Results shown as Mean (SE) in Arbitrary Units.

		Baseline	Change from baseline	
			Isometric exercise	**Rest**
ChBVol	AMD patients	0.23 (0.02)	−0.01 (0.02)	−0.00 (0.01)
	Controls	0.29 (0.02)	0.00 (0.02)	−0.01 (0.01)
	P-value	0.19	0.63	0.68