

Regulation of Subfoveal Choroidal Blood Flow in Age-Related Macular Degeneration

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PURPOSE. To assess the capability of the subfoveal choroidal circulation to regulate its blood flow in response to an acute increase in ocular perfusion pressure in the eyes of healthy elderly persons or of subjects with neovascular age-related macular degeneration (AMD).

METHODS. Changes of subfoveal choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBF) induced by isometric exercise were determined using laser Doppler flowmetry (LDF) in 19 young healthy volunteers (group 1), 24 elderly healthy volunteers with mild macular pigment distribution changes (group 2), and 23 subjects with subfoveal classic neovascularization caused by AMD (group 3).

RESULTS. Isometric exercise induced significant increases in mean ocular perfusion pressure (PPm) of $19.5\% \pm 4.9\%$, $20.2\% \pm 3.8\%$, and $23.2\% \pm 4.2\%$, for groups 1, 2, and 3, respectively (mean \pm 95% confidence interval). In groups 1 and 2, the increase in PPm did not induce significant changes in the mean values of the different LDF parameters. In group 3, however, ChBF increased significantly by $12.4\% \pm 5.0\%$. No significant correlations were found between age and the changes of each of the LDF parameters and of PPm at the end of squatting for the young and elderly healthy groups.

CONCLUSIONS. In response to an acute, moderate increase in PPm induced by isometric exercise, subfoveal choroidal blood flow behaves similarly in young and elderly healthy persons and is not significantly different from its value at rest. In contrast, in patients with neovascular AMD, this flow increases, indicating altered regulation in response to the increase in PPm. (*Invest Ophthalmol Vis Sci.* 2006;47:1581–1586) DOI:10.1167/iovs.05-0434

Alterations of blood flow in the subfoveal choroidal circulation and metabolic changes of the retinal pigment epithelium (RPE) have been suggested as important in the development of neovascular age-related macular degeneration (AMD). Hemodynamic studies by color Doppler^{1–4} and indocyanine green (ICG) angiography^{5–7} have suggested blood perfusion defects in aged and AMD eyes involving macular and other vascular regions of the fundus.

Choroidal blood flow changes affecting the metabolism of the adjacent external retinal layers lead either to the development of atrophic lesions or to subretinal neovascular lesions.¹ In addition to environmental influences (smoking, sunlight exposure, and nutritional factors), the risk factors for AMD are similar to those for cardiovascular diseases, such as hypertension, suggesting a vascular role in the development of AMD. Furthermore, vascular changes in the choroid have potentially deleterious effects on the RPE and, in addition to metabolic changes of the RPE caused by senescence, may induce the early clinical findings in AMD. A healthy RPE is necessary for the preservation of the choriocapillaries because RPE loss induces choriocapillary degeneration.^{8,9} This hypothesis appears to be supported by laser Doppler flowmetry (LDF) data demonstrating a significant decrease of choroidal blood flow with age¹⁰ and with the presence of AMD.¹¹ However, whether these LDF data indeed represent a decrease in choroidal blood flow or are caused by changes in the laser light-scattering properties of the sampled tissue is still a matter of debate.^{12,13} This scattering probably changes with age and with the presence of AMD.

An alternative and more robust approach to compare choroidal hemodynamics between normal and AMD eyes is to assess the capability of subfoveal choroidal blood flow to respond to a physiological stimulus, such as an increase in ocular perfusion pressure (PPm). In healthy volunteers, LDF subfoveal choroidal flow is largely constant in spite of increases in the PPm to 67% above the baseline value, when PPm is raised by means of isometric exercises.¹⁴ This approach provides data uninfluenced by potential changes in tissue light scattering assuming, legitimately, that isometric exercise itself does not modify this scattering.

The present work investigates the regulation of subfoveal choroidal blood flow in response to acute increases in PPm in the eyes of young and elderly healthy volunteers and in eyes with subfoveal choroidal neovascularization (CNV) caused by AMD. Our results indicate an impaired regulation of subfoveal choroidal blood flow during isometric exercise in patients with neovascular AMD.

MATERIALS AND METHODS

Subjects

LDF measurements were performed in one eye each of subjects, who were divided into three groups. Group 1 consisted of 19 healthy volunteers, ranging in age from 24 to 44 years (mean \pm SD, 33 ± 6 years). Group 2 consisted of 24 volunteers, ranging in age from 50 to 84 years (68 ± 10 years), who had mild age-related changes of the macular area, primarily macula pigment distribution changes. Group 3 consisted of 23 patients, ranging in age from 45 to 86 years (70 ± 12 years), who had classic subfoveal neovascularization. Slit lamp and fundusoscopic examination showed no other pathologic conditions than those mentioned.

In all volunteers and patients, the mean visual acuity (VA) was equal to or better than 1/10 (Snellen chart); in particular, group 3 expressed a mean VA of 0.58 ± 0.26 . LogMAR ranged from 0.22 to 1 logMAR units, sufficient to maintain fixation of the laser Doppler aiming beam.

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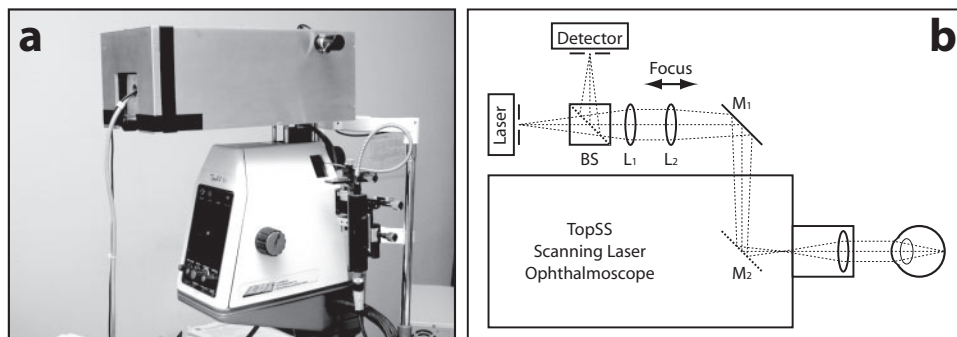


FIGURE 1. (a) Confocal laser Doppler flowmeter (LDF) module mounted on a topographic scanning system. (b) Schematic diagram of LDF inserted into the topographic scanning system. The light from a 670-nm laser diode is focused onto a 50- μm -diameter pinhole and passes through a beam splitter (BS), two lenses (L_1 and L_2), and a pair of mirrors (M_1) before it is reflected in the optical path of the topographic scanning system by a dichroic mirror (M_2).

Patients with diabetes, history of systemic hypertension with systemic medications, glaucoma under topical eye medication potentially affecting the regulation of blood flow, and patients with high ametropia were excluded.

All subjects received detailed explanations about the procedure, and all gave informed consent. This study followed the tenets of the Declaration of Helsinki and was approved by the institutional human experimentation committees of the Universities of Geneva and Cr eteil.

Subfoveal Choroidal Blood Flow

As previously described, a confocal LDF module (Fig. 1a) mounted on a topographic scanning system (TopSS; Laser Diagnostic Technologies, San Diego, CA) was used to measure subfoveal blood flow.¹⁵ Briefly, (Fig. 1b) the light from a 670-nm laser diode was focused on a 50- μm diameter pinhole and passed through a beam splitter (BS), two lenses (L_1 and L_2), and a pair of mirrors (M_1) before it was reflected into the optical path of the topographic scanning system by a dichroic mirror (M_2). Subjects were asked to fixate on this beam (1-mm diameter, 100 μW at the cornea). Light scattered from the focal plane of the laser beam at the fundus and exiting the subject's pupil followed an optical path identical to that of the incident beam up to the beam splitter (BS), where it was reflected toward a pinhole. This pinhole was optically conjugated to the pinhole in front of the laser source (confocal design). After the pinhole, the light was detected by an avalanche photodiode. The operator focused the probing beam at the fundus by adjusting the position of lens L_2 . Recording time was approximately 20 seconds.

The signal from the detector was fed into a computer (station Turbo; NeXT, Redwood City, CA) and was analyzed using custom-developed software. Choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBF, which is proportional to $\text{ChBVel} \times \text{ChBVol}$)

were obtained continuously and in real time at a rate of 21.5 Hz.^{16,17} In addition, the direct current (DC) level of the signal, which was proportional to the amount of detected light, was recorded. Portions of the recording with DC variations superior to 5% of the mean values and spikes associated with eye motions were removed, thereby minimizing potentials artifacts.

Experimental Protocol

Before the experiment, the pupil of the examined eye was dilated with 1% tropicamide (Ciba Vision, Basel, Switzerland). Systemic blood pressure was measured at rest with the subjects standing up and then squatting. The latter was performed as long as tolerated by the subjects to obtain a significant elevation of the systemic blood pressure. LDF parameters and blood pressure were intermittently measured at baseline, during squatting, and after recovery from squatting. Mean perfusion pressure (PPm) was defined as the mean arterial blood pressure in the ophthalmic artery (MOAP) minus the intraocular pressure (IOP). IOP was measured by Goldmann contact tonometry only at baseline, before LDF was started.

MOAP, which increases during isometric exercise,^{18,19} was assumed to be equal to two thirds of the mean arterial blood pressure (MABP). We calculated MABP as $\text{BP}_{\text{diast}} + \frac{1}{3}(\text{BP}_{\text{syst}} - \text{BP}_{\text{diast}})$. BP_{diast} and BP_{syst} are the brachial artery blood pressures during diastole and systole, respectively. In addition, an index of mean vascular resistance (Rm) was calculated as PPm/ChBF .

Statistical Analysis

Intragroup differences between the mean values of all the measured parameters at rest and at end of exercise were tested by Student's

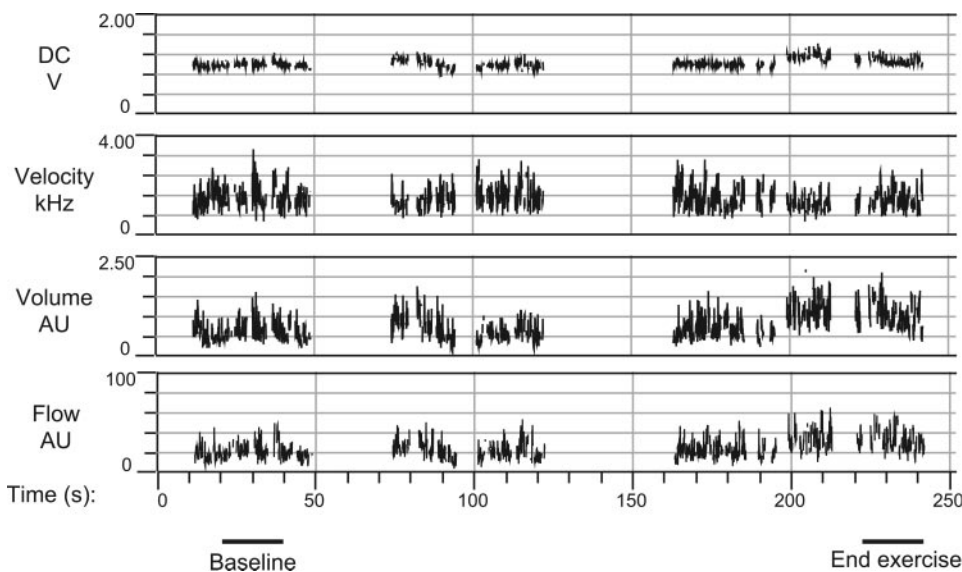


FIGURE 2. Typical online recording of the LDF parameters (DC, ChBVel, ChBVol, and ChBF) at baseline and under 240-second isometric exercise. In this subject, squatting induced a 37% increase in PPm (from 35 to 48 mm Hg). The resultant 29% ChBF increase resulted from a 40% increase of the ChBVol parameter. ChBVel was decreased by 8%. ChBVel, ChBVol, and ChBF values were obtained by averaging the corresponding data over 20 seconds of baseline and over the end of squatting. Brachial artery blood pressure was measured during the recording segments, indicated by a horizontal line (Baseline and End exercise bars). DC variation in the analyzed sections was inferior to 5%.

TABLE 1. Percentage Changes of Ppm, Laser Doppler Flowmeter Parameters, and Rm Responses to Isometric Exercise in All Groups

	Group I < 45	Group II > 45	Group III, AMD
N	19	24	23
PPm	19.5 ± 4.9*	20.2 ± 3.8*	23.2 ± 4.2*
ChBVel	3.0 ± 3.8	5.7 ± 9.1	7.3 ± 7.1
ChBVOL	-1.3 ± 3.8	-2.9 ± 7.1	6.7 ± 7.0
ChBF	0.9 ± 1.5	0.5 ± 1.8	12.4 ± 5.0*†
Rm	18.6 ± 5.1*	19.8 ± 4.4*	10.2 ± 4.3*‡

Values are mean ± 95% CI. Changes in ChBF and Rm were found to be significantly different between groups 2 and 3.

* $P < 0.05$; paired t test.

† $P < 0.0001$ for ChBF.

‡ $P = 0.002$ for Rm.

paired t test. Changes in all parameters were expressed as percentage of the value at rest: $100 \times (\text{value at end exercise} - \text{value at rest}) / \text{value at rest}$. Intergroup differences in the mean changes of all measured parameters at the end of exercise were tested by ANOVA (independent factor group; dependent variables; changes of PP_m, ChBVel, ChBVOL, and ChBF). Plots show mean values ± 95% confidence intervals and linear trend lines as calculated by least-squares regression (correlation coefficients, R and P values were reported if significant).

RESULTS

A representative set of recordings of DC, ChBVel, ChBVOL, and ChBF obtained in one subject in group 3 while at rest and during 3 minutes of squatting is shown in Figure 2. In this subject, squatting induced a 37% increase in PP_m (from 35 to 48 mm Hg). The resultant 29% ChBF increase was the result of a 40% increase of the ChBVOL parameter, suggesting insufficient resistance changes during squatting. ChBVel decreased by 8%. LDF signals were recorded with a time constant of 0.047

second and were displayed with a time constant of 0.186 second. ChBVel, ChBVOL, and ChBF values were obtained by averaging the corresponding data over 20 seconds of baseline and over the end of squatting. Brachial artery blood pressure was measured during the recording segments and was indicated by a horizontal line.

Changes in all LDF parameters at the end of exercise are listed in Table 1 and are shown in Figure 3 for the three groups. Squatting induced a significant increase in mean PPm that was similar in all groups. This increase amounted to 19.5% ± 4.9%, 20.2% ± 3.8%, and 23.2% ± 4.2% for groups 1, 2, and 3, respectively. At the end of squatting, the LDF parameters in group 1 (3.0% ± 3.8% for ChBVel; -1.3% ± 3.8% for ChBVOL; and 0.9% ± 1.5% for ChBF) and group 2 (5.7% ± 9.1% for ChBVel; -2.9% ± 7.1% for ChBVOL; and 0.5% ± 1.8% for ChBF) were not significantly different from baseline but were the consequence of a significant increase in Rm by 18.6% ± 5.1% and 19.8% ± 4.4% for group 1 and group 2, respectively. No statistically significant differences were found in the changes in mean values of the LDF parameters between groups 1 and 2. In contrast, in group 3 patients, ChBF significantly increased at the end of squatting by 12.4% ± 5.0%. Rm increased by 10.2% ± 4.3%. Changes in ChBF and Rm were found to be significantly different between group 2 and group 3 (Table 1; $P < 0.0001$ for ChBF; $P = 0.002$ for Rm). The change in ChBVOL tended to be larger in group 3 than in group 2 ($P = 0.054$).

ANOVA pointed out a significant intergroup difference ($P = 0.00003$) in flow parameter changes induced by squatting, and further post hoc comparison with Tukey honest significant difference test (Sjotvoll-Stoline) indicated that the ChBF increase was significantly larger in group 3 than in groups 1 and 2 ($P < 0.001$).

Figure 4 shows plots of the changes in ChBF as a function of the PPm changes for the three groups (linear fits and 95% confidence intervals). No correlation was found between these two parameters in the groups of young and elderly healthy

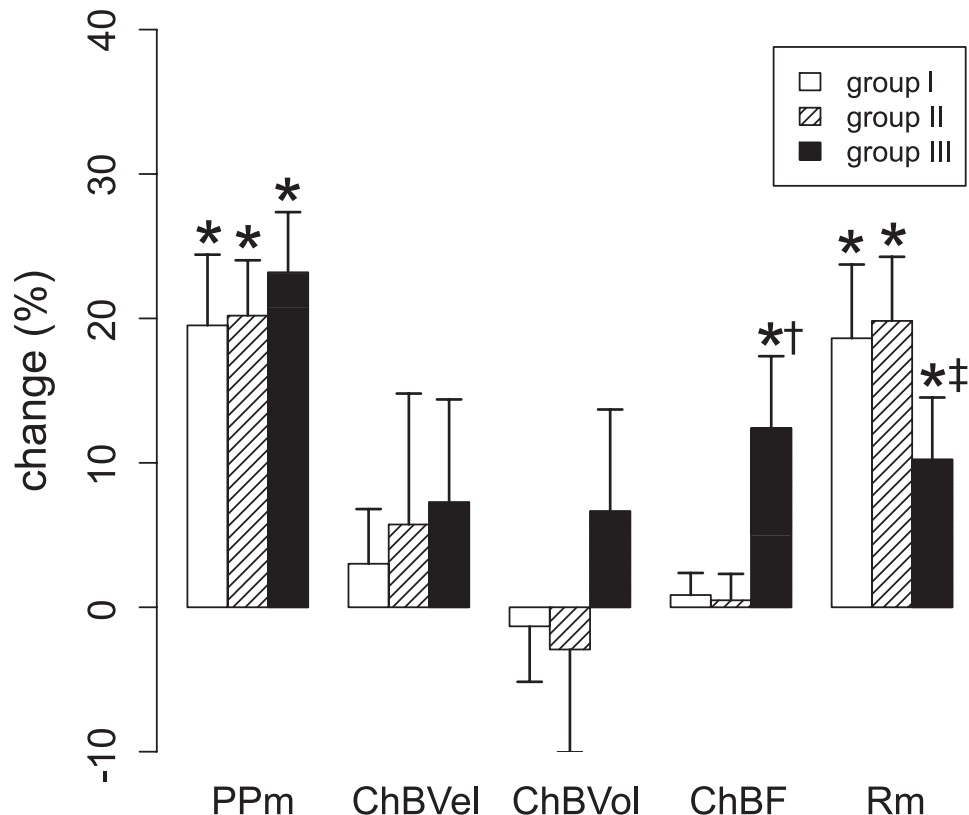


FIGURE 3. Mean percentage changes of LDF parameters PPm, ChBVel, ChBVOL, ChBF, and Rm at the end of squatting, for all groups (*paired t test; $P < 0.05$). Squatting induced a significant increase in mean PPm that was similar in all groups. At the end of squatting, the LDF parameters in groups 1 and 2 were not significantly different from those at baseline. In contrast, in group 3, the ChBF parameter significantly increased at the end of squatting. Changes in ChBF and Rm were significantly different between groups 2 and 3 (†ChBF, $P < 0.0001$; ‡Rm, $P = 0.002$).

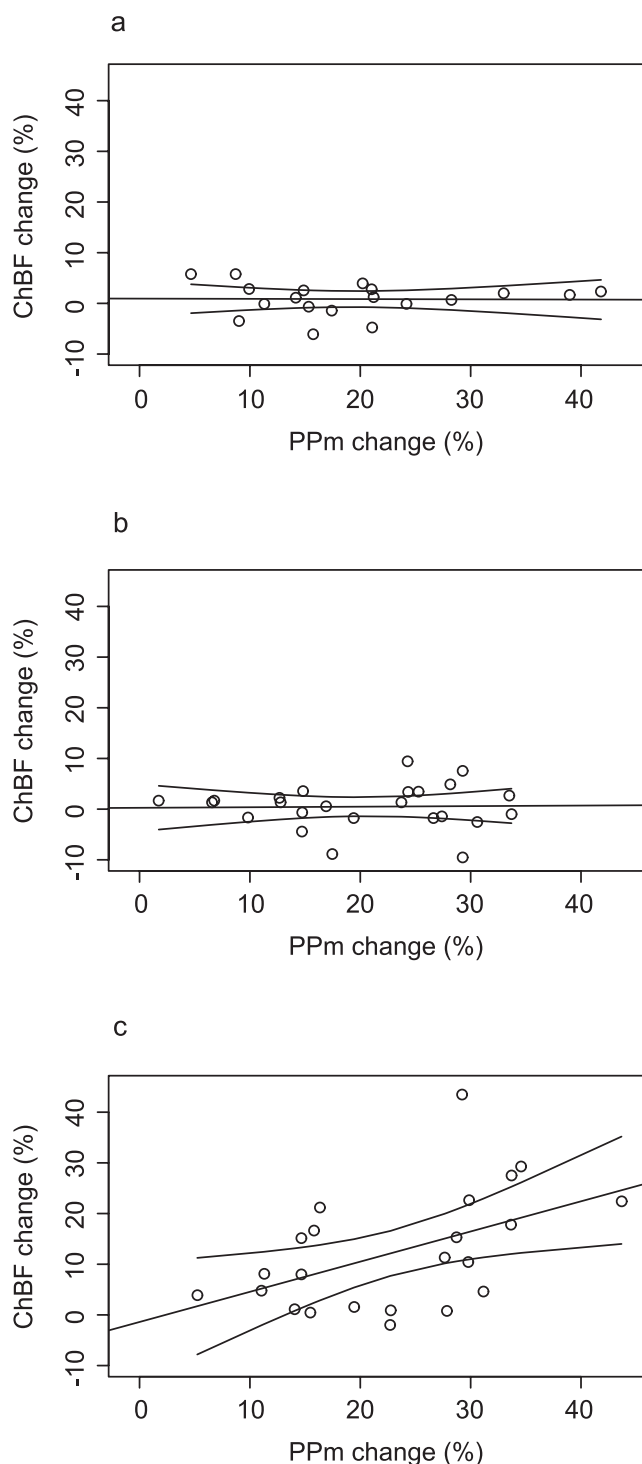


FIGURE 4. Percentage changes in ChBF as a function of PPm for the three groups (linear fits and 95% confidence intervals). Similar PPm increases for all groups were obtained; two-tailed independent Student's *t* test, \pm 95% confidence interval). For the groups of (a) young and (b) elderly healthy persons, no correlation was found between these two parameters. (c) For the AMD group, linear correlation provided significant values ($R = 0.6$; $P = 0.016$).

persons. For the AMD group, a linear correlation provided a significant R of 0.6 and a P of 0.016.

Figure 5 shows the percentage changes of the LDF parameters and PPm relative to the baseline values according to age at the end of squatting for the young and elderly healthy

persons. No significant correlations between age and responses of the different parameters were found. Similarly, no correlation between age and Rm changes were observed.

DISCUSSION

The purpose of this work was to examine the regulation of choroidal blood flow in the subfoveal region in response to an acute increase of systemic blood pressure in eyes with senile changes of the choroidal vasculature or with subfoveal neovascularization. The results of our study indicate that acute elevation of the ocular perfusion pressure by 20% to 23% induced by isometric exercise does not induce a significant change of subfoveal choroidal blood flow in elderly subjects with early macular changes. Thus, the regulation of subfoveal choroidal blood flow during moderate increases in PPm induced by isometric exercise seems to be preserved in elderly persons. The finding that for such moderate increases in PPm the choroidal circulation regulates its blood flow normally is not surprising given that the perfusion pressure can be increased by as much as 67% in healthy young volunteers before a breakdown of the regulation is observed.¹⁴ However, even with an average increase by 23% in PPm, ChBF in eyes of patients with subfoveal neovascularization (group 3) increased significantly during squatting, as revealed by the significant correlation between PPm and ChBF changes and the statistically significant increase of ChBF in these eyes (Figs. 3 and 4).

The measured increase of ChBF in the subretinal neovascular tissue during isometric exercise results, most probably, from an insufficient increase in vascular resistance either within this immature neovascular bed or within the underlying choroidal vasculature, or both. Therefore, overperfusion of neovascular tissue should occur during increases in perfusion pressure.

Vascular resistance depends mainly on the contractile state of the smooth muscle of the arterioles irrigating the neovascular tissue and, presumably, of the pericytes of the capillary network.²⁰ Changes in vascular resistance during isometric exercise can occur along the ciliary arteries, the choroidal terminal arterioles, or the capillaries within the neovascular tissue because, during isometric exercise, blood pressure in the ophthalmic artery increases in parallel with that in the brachial artery.¹⁹ In calculating the values of PPm at the end of exercise, we used IOP values measured at baseline. Based on previous data¹⁸ showing that a 30% increase in PPm induces an increase in IOP of approximately 4 mm Hg, our calculation of PPm overestimated the actual PPm. Taking into account that the PPm in our experiments was increased by only 20%, we calculated that the actual PPm at the end of the experiment should have been lower than the actual PPm by less than 7%. This slight difference was not expected to alter the conclusions of this study, particularly the finding of a dysregulation of ChBF within the neovascular tissue in group 3.

The adaptation of choroidal vascular resistance is achieved through a mechanism involving either the sympathetic nervous system²¹⁻²³ or the release of vasoconstricting substances by the vascular endothelium^{24,25}; the former affects the contraction of the smooth muscle of choroidal arterioles, and the latter affects either the smooth muscle of the arterioles or the contractile state of pericytes surrounding the capillaries.²⁰

Aging causes loss of neurons and adrenergic nerve terminations in various human systems, including the choroidal circulation.²⁶ Furthermore, this process induces morphologic changes of the walls of choroidal arterioles, leading to stiffening¹⁻³ or to alterations of the vascular endothelium of these vessels. The decrease in sympathetic innervation and vascular stiffening could have a detrimental effect on the regulatory

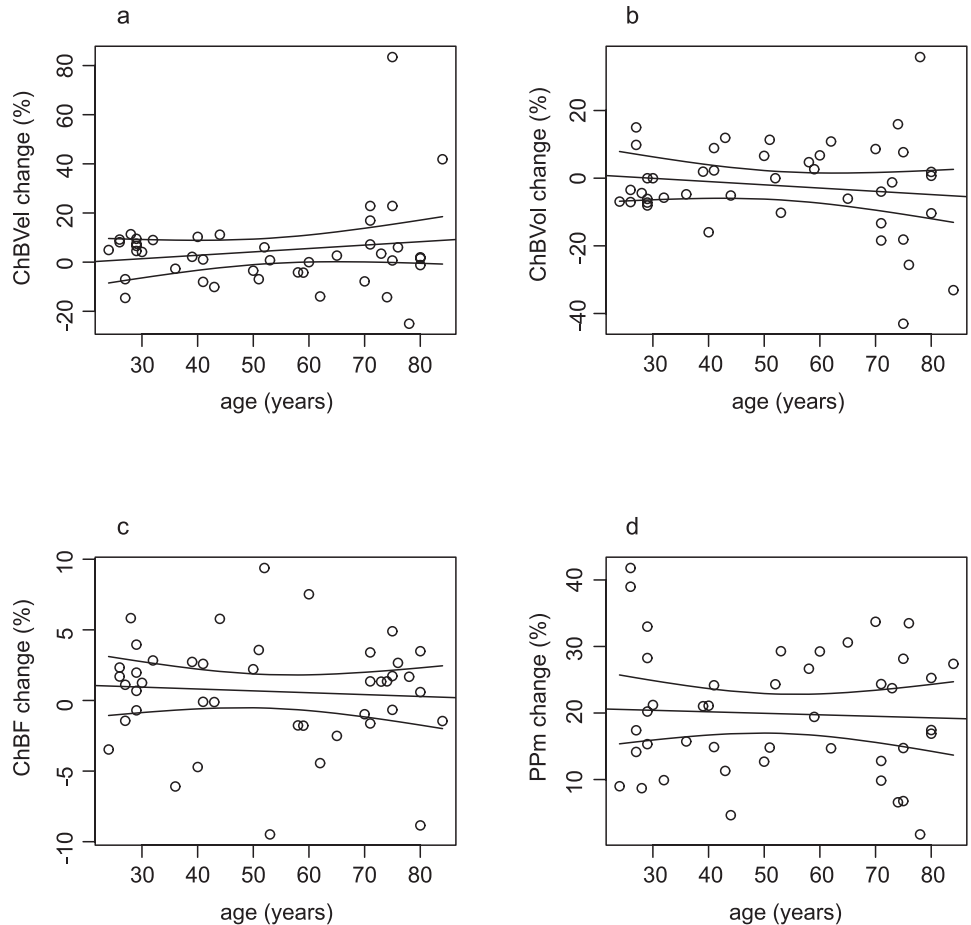


FIGURE 5. Percentage changes at the end of squatting, of the LDF (a-c) parameters, and of PPM (d) relative to the baseline values according to age for all groups (linear fits and 95% confidence intervals). No significant correlations were found between age and response to different parameters.

capability of the choroidal arterioles. In addition, morphologic and functional changes in the vascular endothelium of choroidal vessels could alter the release of vasoactive substances and could diminish the regulatory capability of these vessels.

The lack of significant correlations between age and the change in each LDF parameter assessed at the end of squatting does not exclude that such age-induced alterations take place in the subjects of group 2. Either these morphologic and functional changes were not severe enough to affect the choroidal blood flow regulation in eyes with mild related macular changes or the increase of PPM was too small to bring in evidence of an altered regulation. Although in our study squatting was maintained as long as physically possible, it was not possible to reach PPM values in our patients as high as those achieved in previous studies performed in young, trained subjects.¹⁴

Abnormal regulation was observed in the subfoveal area, including the neovascular tissue, for increases of the PPM in group 3 similar to those reached in group 2. Because the LDF signal in the subfoveal and parafoveal areas is dominated by the choroidal circulation^{16,27} with little contribution from the retinal capillary bed, our data suggest choroidal dysregulation in the patients in group 3.

Choroidal dysregulation in AMD patients in group 3 could suggest a failure of adaptation of the choroidal vascular resistance, in contrast to what occurred in the subjects of group 2. However, subfoveal neovascularization was expected to scatter the laser light because it usually expresses an irregular, multilayer, interconnecting pattern of capillaries associated with larger irrigating arterioles, draining venules and fibroblastic tissue.²⁸ This scatter may be the dominant component of

the LDF signal, which would preclude conclusions about choroidal dysregulation.

Within the subfoveal abnormal neovascular bed, alteration of the autonomic system innervating the arterioles irrigating the choroidal neovascular network has not been demonstrated, in contrast to the existence of immature features of the capillaries. The new vessels in the choroid, as do those in the retina,²⁹ express immature fenestrated endothelial cells, inadequate numbers of pericytes, diminished pericyte coverage of the endothelial cells,³⁰ and inadequate sites of contact between endothelial cell and pericyte membranes.³¹ Pericytes express contracting smooth muscle α -actin. Based on the behavior of pericytes in culture, under the effect of contracting or relaxing factors, pericytes can contract or relax to modify capillary diameter.³²⁻³⁵ In addition, electron light microscopy of freshly isolated rat retinas demonstrates capillary relaxation in response to carbonic anhydrase blockers.^{36,37} These findings suggest that pericytes act as capillary diameter regulators within the retinal microvasculature. Assuming that pericytes of the subfoveal new vessels exhibited similar behavior within the neovascular network, altered contraction capability of capillary pericytes could have affected the vascular resistance response of newly formed capillaries of group 3 eyes to increases of the PPM, resulting in an overperfusion in the neovascular tissue during isometric exercise. Altered vascular resistance within the neovascular tissue in eyes with neovascular AMD has already been revealed under normal conditions of perfusion pressure when fundus pulsation amplitudes, measured from healthy retinal areas adjacent to CNV, are compared with those obtained from areas associated with CNV.³⁸

In conclusion, assessment of subfoveal choroidal blood flow regulation in healthy and diseased human eyes has provided, for the first time, evidence that acute, moderate elevations of systemic blood pressure induced by isometric exercises do not affect regulation in elderly subjects. Indeed, in elderly subjects, ChBF remained constant in response to increases in PPM by at least 20%. In contrast, similar elevations of PPM induced blood flow increases within the neovascular tissue in eyes with AMD-related subfoveal neovascularization. This effect was caused, most probably, by the inability of the new vessels to increase their flow resistance during isometric exercise. Such blood flow increase is expected to induce an overperfusion of neovascular tissue, which may lead to increased exudation and bleeding, a potentially threatening condition for macular function.

References

- Friedman E. The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. *Am J Ophthalmol*. 2000;130:658-663.
- Friedman E, Krupsky S, Lane AM, et al. Ocular blood flow velocity in age-related macular degeneration. *Ophthalmology*. 1995;102:640-646.
- Friedman E. A hemodynamic model of the pathogenesis of age-related macular degeneration. *Am J Ophthalmol*. 1997;124:677-682.
- Ciulla TA, Harris A, Chung HS, et al. Color Doppler imaging discloses reduced ocular blood flow velocities in non-exudative age-related macular degeneration. *Am J Ophthalmol*. 1999;128:75-80.
- Ross RD, Barofsky JM, Cohen G, Baber WB, Palao SW, Gitter KA. Presumed macular choroidal watershed vascular filling, choroidal neovascularization, and systemic vascular disease in patients with age-related macular degeneration. *Am J Ophthalmol*. 1998;125:71-80.
- Ciulla TA, Harris A, Danis RP. Presumed macular choroidal watershed vascular filling, choroidal neovascularization, and systemic vascular disease in patients with age-related macular degeneration. *Am J Ophthalmol*. 1998;126:153-155.
- Ciulla TA, Harris A, Chung HS, et al. Choroidal perfusion perturbations in non-neovascular age-related macular degeneration. *Br J Ophthalmol*. 2002;86:209-213.
- Takeuchi M, Itagaki T, Takahashi K, Ohkuma H, Uyama M. Changes in the intermediate stage of retinal degeneration after intravitreal injection of ornithine. *Nippon Ganka Gakkai Zasshi*. 1993;97:17-28.
- Del Priore LV, Kaplan HJ, Hornbeck R, Jones Z, Swinn M. Retinal pigment epithelial debridement as a model for the pathogenesis and treatment of macular degeneration. *Am J Ophthalmol*. 1996;122:629-643.
- Grunwald JE, Hariprasad SM, DuPont J. Effect of aging on foveolar choroidal circulation. *Arch Ophthalmol*. 1998;116:150-154.
- Grunwald JE, Hariprasad SM, DuPont J, et al. Foveolar choroidal blood flow in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1998;39:385-390.
- Riva CE, Petrig BL. Laser Doppler techniques in ophthalmology: basic, diagnostic and surgical aspects. In: Fankhauser F, Kwasniewska S, eds. *Lasers in Ophthalmology*. The Hague, The Netherlands: Kugler Publications; 2003:51-59.
- Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Choroidal blood flow in AMD. *Invest Ophthalmol Vis Sci*. 1998;39:2201-2202.
- Riva CE, Titze P, Hero M, Movaffaghy A, Petrig BL. Choroidal blood flow during isometric exercises. *Invest Ophthalmol Vis Sci*. 1997;38:2338-2343.
- Petrig BL, Riva CE, Lorenz B, Movaffaghy A, Harbarth UP, Dreher AW. Confocal laser Doppler system for measurements of blood velocity in retinal vessels and flow in the optic nerve through the undilated pupil. *Laser and Light*. 1998;8:137-142.
- Riva CE, Cranston SD, Grunwald JE, Petrig BL. Choroidal blood flow in the foveal region of the human ocular fundus. *Invest Ophthalmol Vis Sci*. 1994;35:4273-4281.
- Petrig BL, Riva CE. Optic nerve head laser Doppler flowmetry: principles and computer analysis. In: Kaiser HJ, Flammer J, Hendrickson P, eds. *Ocular Blood Flow: Glaucoma Meeting 1995*. Basel, Switzerland: Karger Basel Publications; 1996:120-127.
- Movaffaghy A, Chamot SR, Petrig BL, Riva CE. Blood flow in the human optic nerve head during isometric exercise. *Exp Eye Res*. 1998;67:561-568.
- Robinson F, Riva CE, Grunwald JE, Petrig BL, Sinclair SH. Retinal blood flow autoregulation in response to an acute increase in blood pressure. *Invest Ophthalmol Vis Sci*. 1986;27:722-726.
- Haefliger IO, Zschauer A, Anderson DR. Relaxation of retinal pericyte contractile tone through the nitric oxide-cyclic guanosine monophosphate pathway. *Invest Ophthalmol Vis Sci*. 1995;35:991-997.
- Alm A, Bill A. The effect of stimulation of the cervical sympathetic chain on retinal oxygen tension and on uveal, retinal and cerebral blood flow in cats. *Acta Physiol Scand*. 1973;88:84-96.
- Alm A. The effect of sympathetic stimulation on blood flow through the uvea, retina, and optic nerve in monkeys (*Macaca inus*). *Exp Eye Res*. 1977;25:19-24.
- Ernest JT. The effect of systolic hypertension on rhesus monkey eyes after ocular sympathectomy. *Am J Ophthalmol*. 1977;84:341-344.
- Pournaras CJ. Autoregulation of ocular blood flow. In: Kaiser HJ, Flammer J, Hendrickson P, eds. *Ocular Blood Flow: Glaucoma Meeting 1995*. Basel, Switzerland: Karger Basel Publications; 1996:40-50.
- Haefliger IO, Meyer P, Flammer J, Lüscher TF. The vascular endothelium as a regulator of the ocular circulation: a new concept in ophthalmology? *Surv Ophthalmol*. 1994;39:123-132.
- Nuzzi R, Finazzo C, Grignolo FM. Modifications de l'innervation adrénergique de la choroïde pendant la sénescence. *J Fr Ophtalmol*. 1996;19:89-96.
- Polska E, Luksch A, Ehrlich P, Sieder A, Schmetterer L. Measurements in the peripheral retina using LDF and laser interferometry are mainly influenced by the choroidal circulation. *Curr Eye Res*. 2002;24:318-323.
- Grossniklaus HE, Green WR. Choroidal neovascularization. *Am J Ophthalmol*. 2004;137:496-503.
- Miller H, Miller B, Zonis S, Nir I. Diabetic neovascularization: permeability and ultrastructure. *Invest Ophthalmol Vis Sci*. 1984;25:1338-1342.
- Sarks JP, Sarks SH, Killingsworth MC. Morphology of early choroidal neovascularisation in age-related macular degeneration: correlation with activity. *Eye*. 1997;11:515-522.
- Ishibashi T, Inomata H, Sakamoto T, Ryan SJ. Pericytes of newly formed vessels in experimental subretinal neovascularization. *Arch Ophthalmol*. 1995;113:227-231.
- Chen Q, Anderson DR. Effect of CO₂ on intracellular pH and contraction of retinal capillary pericytes. *Invest Ophthalmol Vis Sci*. 1997;38:643-651.
- Das A, Frank RN, Weber ML, Kennedy A, Reidy CA, Mancini MA. ATP causes retinal pericytes to contract in vitro. *Exp Eye Res*. 1988;46:349-362.
- Haefliger IO, Anderson DR. Oxygen modulation of guanylate cyclase-mediated retinal pericyte relaxations with 3-morpholino-sydnonimine and atrial natriuretic peptide. *Invest Ophthalmol Vis Sci*. 1997;38:1563-1568.
- Matsugi T, Chen Q, Anderson DR. Adenosine-induced relaxation of cultured bovine retinal pericytes. *Invest Ophthalmol Vis Sci*. 1997;38:2695-2701.
- Reber F, Gersch U, Funk RH. Blockers of carbonic anhydrase can cause increase of retinal capillary diameter, decrease of extracellular and increase of intracellular pH in rat retinal organ culture. *Graefes Arch Clin Exp Ophthalmol*. 2003;241:140-148.
- Schonfelder U, Hofer A, Paul M, Funk RH. In situ observation of living pericytes in rat retinal capillaries. *Microvasc Res*. 1998;56:22-29.
- Schmetterer L, Kruger A, Findl O, Breiteneder H, Eichler HG, Wolzt M. Topical fundus pulsation measurements in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:160-163.