Ocular Blood Flow Velocity in Age-related Macular Degeneration

Ephraim Friedman, MD,[1] Sara Krupsky, MD,[1] Anne Marie Lane, MPH,[1] Setsuko S. Oak,[2] Eric S. Friedman, MD,[1] Kathleen Egan, MPH,[1] Evangelos S. Gragoudas, MD[1]

Background: Changes in the structure of the ocular blood vessels associated with age-related macular degeneration (AMD) have been described in some detail, but comparatively little is known of the concomitant circulatory changes. The goal of this study is to evaluate changes in the ocular circulation that may be associated with AMD.

Methods: Ocular blood flow velocities and vessel pulsatilities were measured in volunteers with and without AMD using a color Doppler imaging unit. Spectral analyses were recorded from the ophthalmic artery, central retinal artery and vein, the temporal and nasal short posterior ciliary arteries, and the four vortex veins.

Results: Adjusting for age, pulsatility indices of all arteries were higher in subjects with AMD (central retinal artery [$P = 0.02$]; temporal and nasal short posterior ciliary arteries [$P = 0.06$ and 0.002, respectively]; and ophthalmic artery [$P = 0.24$]). End-diastolic blood flow velocity of the short posterior ciliary arteries tended to decrease in the presence of AMD.

Conclusions: The combination of increased pulsatility and decreased velocity of the short posterior ciliary arteries, observed in the presence of AMD, are interpreted as evidence of increased vascular resistance. The clinical signs of AMD may be related to degradation of the metabolic transport function of the retinal pigment epithelium, resulting from impaired choroidal perfusion. *Ophthalmology 1995;102:640–646*

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in Western countries.[1] The cause of the disorder is unknown, and we can neither prevent its development nor arrest its progression. Laser photocoagulation is effective for only a small fraction of patients, and vision is impaired often despite or because of treatment. The effectiveness of dietary supplementation with vitamins or minerals is unproven.

There is evidence that the flow of blood in the choroid of eyes with AMD is impaired,[2–4] but neither the nature nor the cause of this impairment has been established. This study was part of a series designed to test the hypothesis that AMD is the result of an increase in the resistance of the choroid caused by a decrease in the compliance of the sclera and the choroidal vessels.[5–9] To evaluate differences in ocular circulation between AMD and non-AMD eyes, blood flow velocity was measured and vessel pulsatility calculated with the use of color Doppler imaging (CDI).

Color Doppler imaging produces a color-code image of moving blood superimposed on a real-time gray-scale ultrasonic image. The Doppler effect is used to detect

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[1] Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston.

[2] Boston University School of Medicine, Boston.

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Reprint requests to Ephraim Friedman, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

moving blood and is expressed as a shift in frequency of transmitted sound waves. Correcting for the direction of the blood column, the Doppler shift is translated to velocity of the erythrocytes.

Changes in the resistance of a vascular bed affect the velocity of blood flow as well as the shape of the waveform. Pulsatility, the hydraulic response of a vessel and its bed to an approaching pulse wave is a function of the compliance of the vessel wall and the resistance of its capillary bed. The pulsatility index (sometimes called the resistive index) is derived from the ratio of diastolic to systolic velocities. It is less dependent than measures of absolute velocities on the Doppler angle, machine settings, and physiologic conditions such as hypotension or hypertension, and mainly reflects variations in the vascular state. While there are several indices in use, Pourcelot's ratio is the most suitable for the low resistance vessels located in the eye.[10]

Color Doppler imaging has been used to study vascular disorders throughout the body as an alternative to more invasive procedures. It also has been used to study blood flow in the eye and orbit and in ocular tumors.[11,12] In this report, we present results of a retrospective study of CDI-measured vascular changes in relation to the presence or absence of AMD. To our knowledge, this is the first published report involving the use of CDI in studying AMD.

Methods

Identification of Study Subjects

Patients from the Retina, Vision Rehabilitation, and General Eye Services of the Massachusetts Eye and Ear Infirmary, and volunteers from the Infirmary were enrolled in the study. Only one eye of each subject was included. All patients with AMD were classified according to the clinical manifestations of the disorder, including visual acuity. Eyes with retinal or choroidal disorders other than AMD or with indefinite signs of AMD (numerous hard drusen, retinal pigment epithelial [RPE] atrophy), were excluded from analyses. The study eye was selected randomly in subjects without AMD when both eyes were classified as eligible for the study, and in patients with AMD when both eyes were diagnosed with the same type of AMD. For patients who received diagnoses with both soft drusen and exudative AMD, the eye with exudative disease was chosen as the study eye.

Color Doppler imaging was performed on subjects 50 years of age and older. A total of 50 patients with AMD were examined. Twenty-two (44%) were male and 28 (56%) were female (median age, 75 years; range, 50–87 years). Twenty-three eyes were diagnosed with the exudative form of the disease (RPE detachments or choroidal neovascular membranes). The remaining 27 eyes were classified as having soft drusen, without exudative changes.

Eyes of 74 subjects without AMD, who ranged in age from 50 to 86 years, were examined. The median age of controls was 70 years. There were 30 (40.5%) males and 44 (59.5%) females in this group.

Patients with the following conditions were excluded from the study: optic nerve disease (neuropathy, atrophy, papilledema); conditions limiting view of fundus (vitreous hemorrhage, cataract, epiretinal membrane); ocular surgery, excluding cataract and laser surgery; degenerative myopia; active posterior intraocular inflammatory disease; use of steroidal eye medications; vasoproliferative retinopathies (other than AMD); retinal detachment; macular edema; and macular dystrophy.

Data Collection

Approval of the Massachusetts Eye and Ear Infirmary Human Studies Committee and written informed consent were obtained before initiating all procedures. Ocular and medical histories were obtained from study subjects or medical record review. Ocular examination, visual acuity testing, and measures of intraocular and systemic blood pressure were completed for most subjects.

All color Doppler studies were performed by a single ophthalmologist (SK). Every effort was made to mask the ophthalmologist to the disease status of study subjects. The Q2000V CDI unit (Siemens-Quantum, Issaquah, WA) with a 7.5-MHz phased linear array transducer was used for all CDI studies. The probe was applied to the closed eyelid coated with sterile ophthalmic methyl-cellulose coupling gel, and horizontal scans were taken of the eye and orbit. The vessels were identified on the real-time, gray-scale image, the cursor was aligned with the colored pixels within the vessels, and pulsed Doppler spectral analyses were performed. Mean peak systolic and end-diastolic velocities were measured (in centimeters per second) and pulsatility was calculated using Pourcelot's ratio (PR) (PR = [systolic velocity − diastolic velocity]/systolic velocity) for each of the following vessels: ophthalmic, central retinal, temporal, and nasal short posterior ciliary arteries; central retinal vein; and superotemporal, superonasal, inferotemporal, and inferonasal vortex veins. The central retinal arteries and veins were studied within the optic nerve shadow; the short posterior ciliary arteries were studied nasal and temporal to the optic nerve, as close to the globe as possible; the ophthalmic artery signal was studied nasal or temporal to the optic nerve, as far posterior as possible. The vortex veins were identified by flow coursing obliquely through the sclera, directed away from the probe, posterior to the equator, in the oblique axes, nasally and temporally, superiorly and inferiorly (Fig 1).

Data Analyses

Analysis of variance was performed to test for statistically significant effects of age and AMD status on mean peak systolic velocity, mean end-diastolic velocity, and Pourcelot's ratio. Logistic regression techniques were used to further investigate associations between AMD and vessel-specific measures of ocular blood flow to control for confounding effects of other variables on AMD status and pulsatility. Pulsatility for each vessel was entered into a model with age and sex as covariates and AMD as the

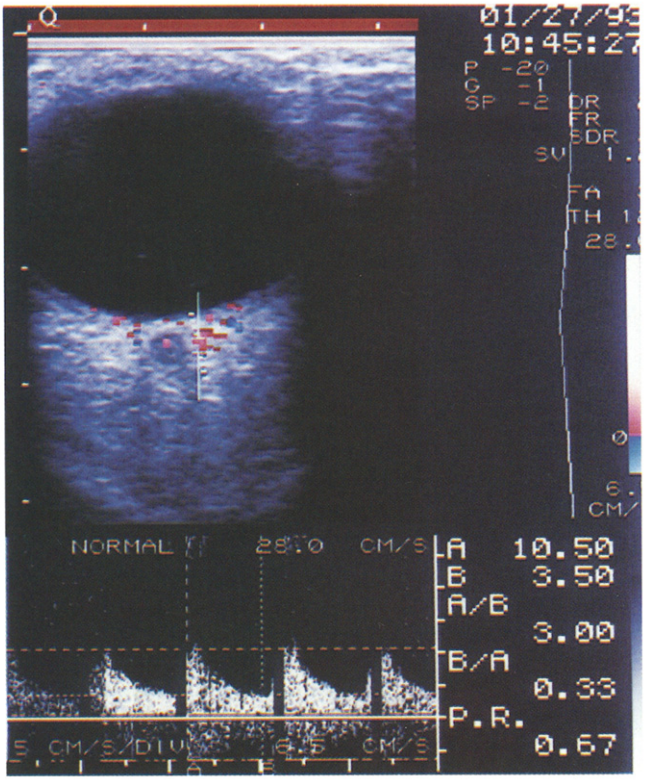

Figure 1. Color Doppler image and waveform of the temporal short posterior ciliary artery of a 64-year-old subject. Red pixels = flow toward the probe; blue pixels = flow away from the probe. The cursor is positioned over the vessel which is adjacent to the optic nerve shadow. A = peak systolic velocity in cm/sec; B = end-diastolic velocity. P.R. = Pourcelot's ratio.

dependent variable. Pulsatility was categorized into tertiles (low, moderate, and high) for these analyses. Systemic systolic and diastolic blood pressure measures, pulse pressure (the difference between systemic systolic and diastolic pressures), intraocular pressure, and history of smoking and hypertension were evaluated as covariates using this same logistic regression model.

Results

Reliability Studies

Before initiating the CDI study of patients with AMD, a study was completed to determine the reliability of measures obtained using CDI. A randomly chosen eye of hospital employees without ocular pathology and the unaffected eye of patients with uveal melanoma were used for the study.

The examination was performed in a masked fashion by two experienced sonographers. The second group of measurements was made immediately after the first group of measurements for each subject. To limit the length of the ultrasound studies, only three to four vessels were measured per session (some of the hospital employees participated in multiple sessions). These included the central retinal artery, central retinal vein, ophthalmic artery, ophthalmic vein, temporal short posterior ciliary artery, nasal short posterior ciliary artery, superonasal vortex vein, inferonasal vortex vein, superotemporal vortex vein, and inferotemporal vortex vein.

Reproducibility of pulsatility measures (Pourcelot's ratio) was evaluated using a paired Student's t test to determine whether the mean difference between sonographers' measures was equal to zero. Table 1 presents results of the study. Differences between the number attempted and the number measured reflect difficulties encountered either in locating or in measuring individual vessels. As shown, a larger percentage of veins than arteries were attempted but not measured. However, among those vessels

Table 1. Interreader Reliability of Pourcelot's Ratio

Vessel	No. of Attempts	Sonographer 1		Sonographer 2				
		No.	Mean	No.	Mean	No.	Mean Difference	P
Central retinal vein	15	15	0.334	13	0.350	13	−0.006	0.85
Ophthalamic artery	15	15	0.633	15	0.639	15	−0.006	0.87
Nasal short posterior ciliary artery	10	10	0.641	10	0.627	10	0.014	0.77
Inferonasal vortex vein	10	5	0.302	8	0.333	5	0.020	0.88
Superonasal vortex vein	15	10	0.278	13	0.244	10	0.023	0.42
Temporal short posterior ciliary artery	10	10	0.609	10	0.648	10	−0.039	0.38
Inferotemporal vortex vein	10	8	0.297	7	0.251	7	0.051	0.44
Central retinal artery	10	10	0.717	10	0.659	10	0.058	0.20
Superotemporal vortex vein	10	7	0.232	10	0.274	7	−0.060	0.19
Superior ophthalmic vein	10	6	0.321	2	0.175	1	0.070	—

that were measured in duplicate, no statistically significant differences could be detected between sonographers.

These results, though based on small numbers, suggest that arterial blood flow can be identified and measured with high reliability. They also point to the difficulties in obtaining reliable venous data.

Age-related Macular Degeneration Studies

As demonstrated in Figure 2, systolic and diastolic velocities tended to be lower in patients with AMD across all age groups. Differences were statistically significant for diastolic velocities for the temporal short ciliary artery ($P = 0.01$) and central retinal artery ($P = 0.006$), and for systolic velocities for the central retinal artery ($P = 0.03$).

Conversely, vessel pulsatility, as measured by Pourcelot's ratio, was higher in patients with AMD than in subjects without the disorder (Fig 3). Controlling for age, statistically significant differences were observed for the central retinal artery ($P = 0.02$) and nasal short posterior ciliary artery ($P = 0.002$). Due to the paucity of venous data and to the lack of meaningful differences in velocities or pulsatility between subjects with and those without AMD further exploration of the relation between AMD status and the venous circulation was not completed.

Results of logistic regression suggest that AMD is associated with changes in arterial pulsatilities, adjusting for the effects of age and sex (Table 2). Subjects whose pulsatility measures were in the upper tertile for the temporal short ciliary artery and central retinal artery were approximately three times as likely to have AMD than those in the lowest tertile. The magnitude of the pulsatility effect in the nasal short ciliary artery was larger; subjects with pulsatility measures in the upper tertile were 11 times more likely to have AMD than those in the lowest tertile, and odds ratios increased monotonically with increasing pulsatility. However, given sparse data, confidence intervals were wide and results were statistically significant only for the highest categories in the nasal short ciliary artery ($P = 0.001$) and central retinal artery ($P = 0.036$).

Other variables examined as covariates in the regression model, including intraocular pressure, systemic systolic and diastolic blood pressure, pulse pressure (the difference between systemic systolic and diastolic blood pressure), and history of smoking and hypertension, were not significantly associated with AMD status.

Discussion

This study demonstrates that the pulsatility of the arteries which perfuse the eye (central retinal artery, temporal short ciliary artery, and nasal short ciliary artery) is higher in patients with AMD than in age-matched controls. While aware that caution must be exercised in extrapolating from velocity and pulsatility data to inferences of resistance and effective blood flow,[13,14] we believe that higher pulsatility, combined with lower end diastolic velocity, is evidence of an increase in the resistance of the short posterior ciliary arteries.[14,15] This increased resistance may be a result of a decrease in compliance of the choroidal vessels as well as a decrease in their caliber or increase in their tortuosity.

The results of this study are incorporated in a hemodynamic model of the pathogenesis of AMD (Fig 4) which postulates that the disorder is caused by a progressive decrease in the compliance of the sclera and choroidal vessels, leading to an increase in the resistance of the choroid to the flow of blood. It is proposed that this process is initiated by the deposition of lipid in the sclera[16,17] and Bruch membrane,[18] and that it results in decreased perfusion, higher intravascular pressure, or a combination of the two. The coefficient of scleral rigidity of patients with AMD has been found to be higher than that of age-matched controls.[6] The reports of delayed angiographic transit of fluorescein[2,4] and indocyanine green[3,19] in AMD support the suggestion that choroidal perfusion is compromised in AMD, and the dilated arteries demonstrated with indocyanine green[19–21] and the presence of phlebosclerosis in AMD[22,23] are consistent with a pressure in the choroidal vessels which is higher than normal in AMD.

While early versions of this hypothesis[5] attributed the disorder to venous obstruction, the results of this study suggest that it is the resistance of the choroidal arteries which is primarily affected in AMD. The current model also differs from earlier versions in reflecting the recent hypotheses of Bird and colleagues that emphasized the potential role played by the progressive infiltration of Bruch membrane with lipid.[2,18] The lipids in Bruch membrane may be a manifestation of the same systemic process responsible for the deposition of lipid in the sclera[17] and choroid,[24] or they may represent the residuum of the vast quantities of discs synthesized by the photoreceptor inner segments which the RPE must digest and eliminate into a progressively impaired choroidal circulation. It is postulated that these lipids contribute to the development of drusen, RPE atrophy and neovascularization, which characterize the disorder clinically (Fig 4).

There is a consensus that the crucial lesion in AMD involves the RPE[25–27] and that choroidal blood flow is delayed,[2–4] but the causal relations have not been established.[5–27] Light damage, aging, and a variety of dietary deficiencies have been invoked as possible primary causes of RPE failure in AMD with secondary atrophy of the choroid.[25–27] The hemodynamic model proposes the decompensation of the RPE to be the result of impairment of its capacity to transport fluid and metabolites against progressively unfavorable hydrostatic and osmotic gradients, respectively.

As previously suggested,[20,28] the vulnerability of the macular region of the choroid may be related to the higher arterial (and venous) pressures in the posterior pole. The consequences of a pathologic increase in intravascular pressure caused by an increase in resistance are most likely to be manifest in that part of a vascular bed which is characterized by high pressures. The tendency of the abnormal arteries visualized with indocyanine green to be located in the posterior pole of eyes with AMD[19] may be attributable to the same phenomenon.

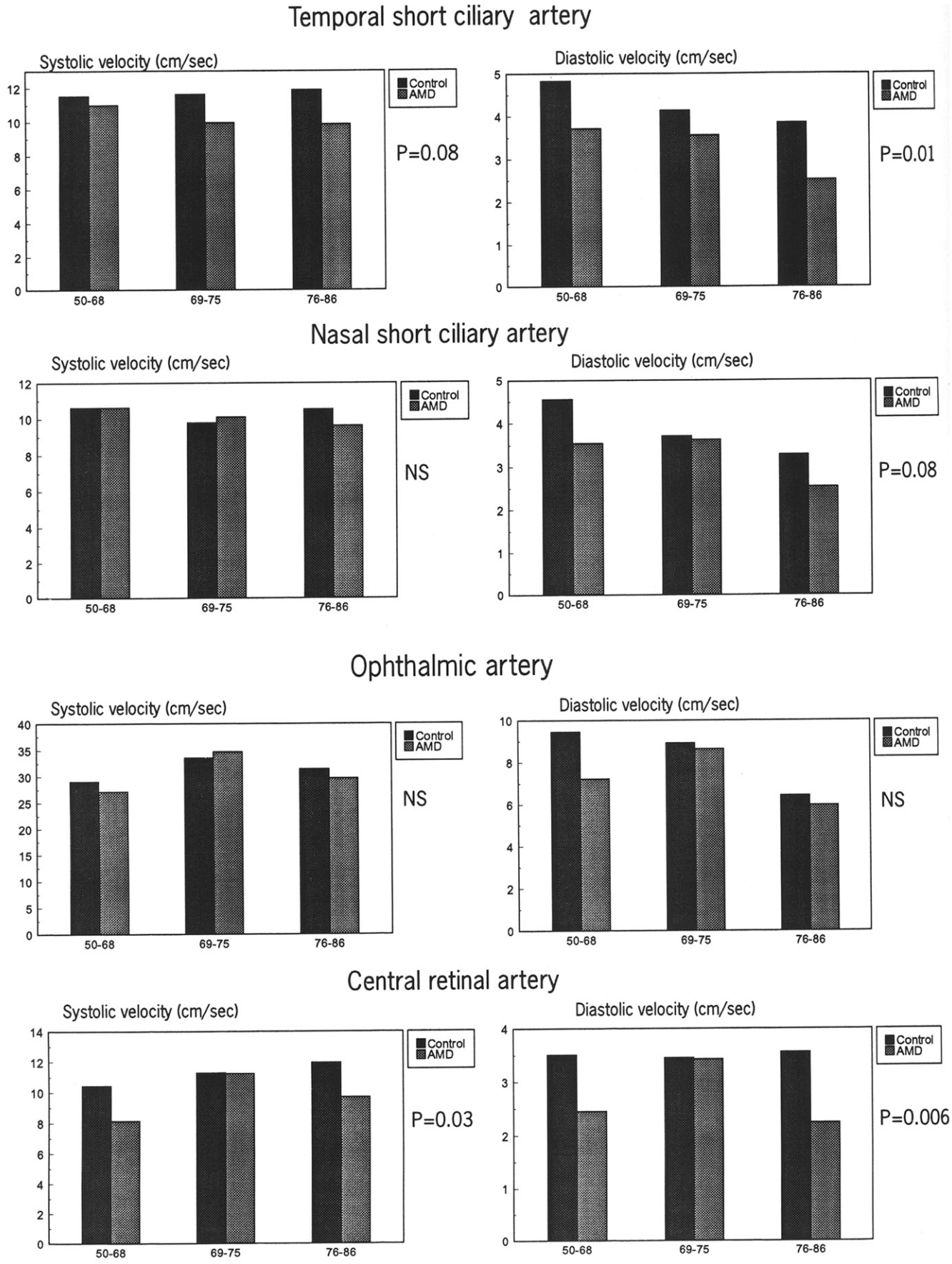

Figure 2. Velocity as a function of age and age-related macular degeneration status. Ophthalmic and central retinal arteries are on the left and temporal and nasal short posterior ciliary arteries are on the right.

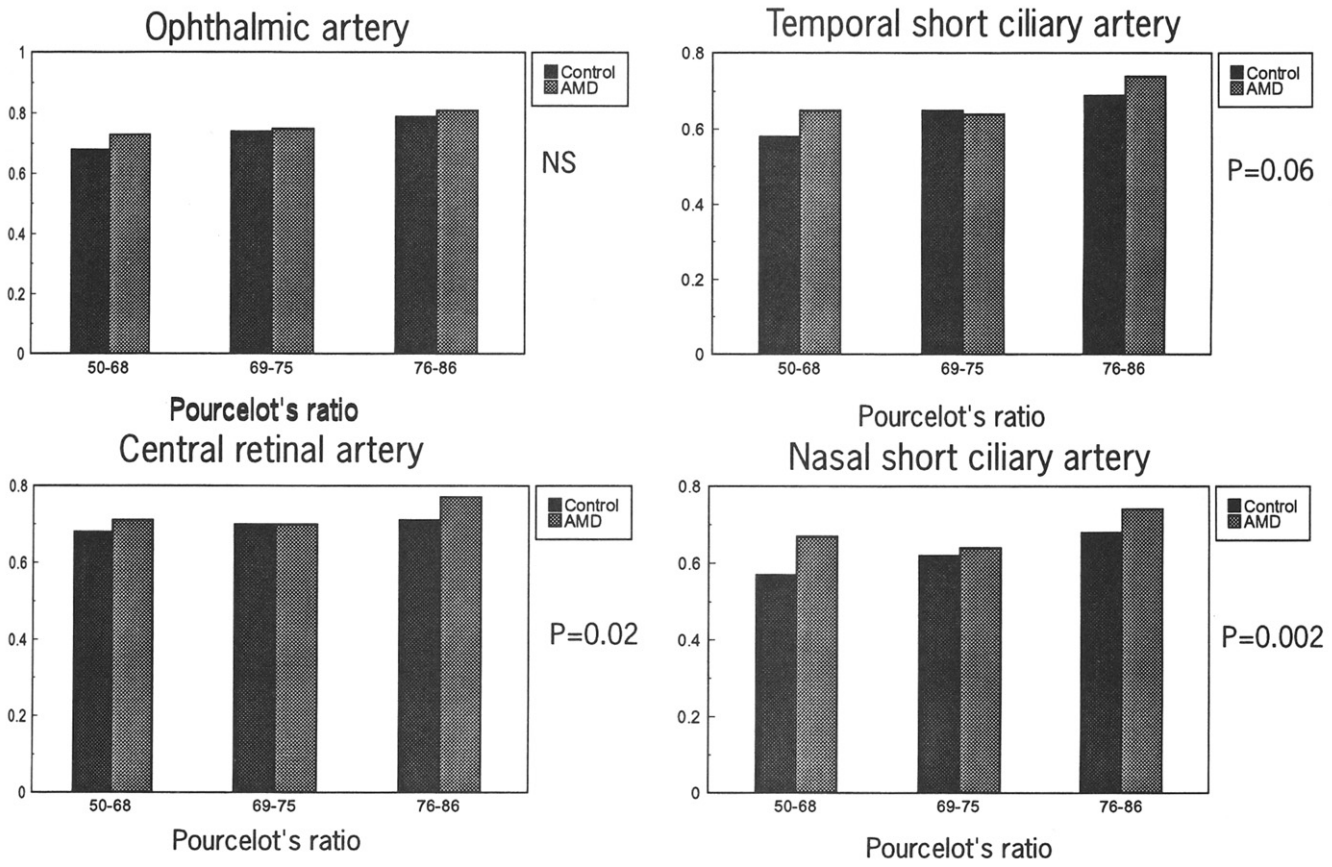

Figure 3. Pulsatility as a function of age and age-related macular degeneration status.

The postulated increase in vascular resistance has more benign consequences to the tissue perfused by the central retinal artery than by the short posterior ciliary arteries. This may be attributable to the relatively greater percentage increase in the pulsatility of the short ciliary arteries in comparison to the retinal arteries with AMD (Fig 3). A more plausible explanation is that, because of their low permeability, there is net filtration from the retinal capillaries only if the mean transmural pressure difference is higher than the plasma oncotic pressure. Due to the high permeability of the choriocapillaris, on the other hand, a relatively low transmural hydrostatic pressure difference causes net filtration.[29]

In summary, the pulsatility of the ocular vessels increases with AMD. This increased pulsatility combined,

Table 2. Logistic Regression of Vessel Pulsatility on Age-related Macular Degeneration Status

Variable	OR*	95% CI	P
Pourcelot's ratio—nasal short posterior ciliary artery			
Low	1.0		
Moderate	3.2	0.89–11.8	0.072
High	11.4	2.7–48.4	0.001
Pourcelot's ratio—temporal short posterior ciliary artery			
Low	1.0		
Moderate	0.755	0.25–2.3	0.621
High	2.6	0.78–8.7	0.116
Pourcelot's ratio—central retinal artery			
Low	1.0		
Moderate	2.9	0.92–9.0	0.068
High	3.4	1.1–10.8	0.036

* Model includes terms for age and sex.

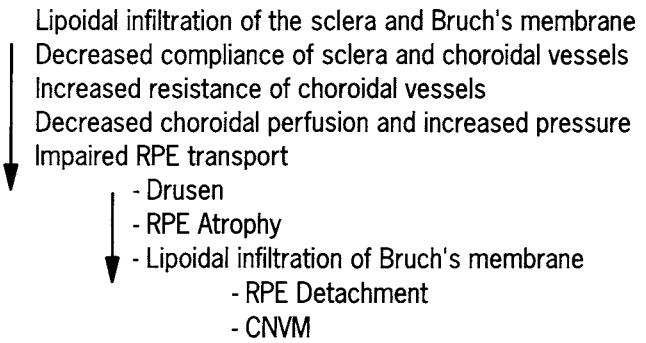

Figure 4. Literature references for each step in proposed sequence are cited in the discussion.

in the case of the short posterior ciliary arteries, with a decrease in blood flow velocity suggests that the resistance of choroidal vasculature is increased. These observations have been incorporated into a hemodynamic model of the pathogenesis of AMD which is consistent with the clinical picture of AMD, its histopathology, natural history, epidemiology, and risk factors.[5,6,30]

The simplest and most direct way of testing the validity of this model is to assess the impact of decreasing the resistance of the choroidal vasculature on the progress of AMD. There is no current method of increasing the caliber of the compromised choriocapillaries, but it may be possible to increase the compliance of the choroidal vessels by surgically thinning the sclera. The long-term solution to this disorder may lie in dietary restriction of lipids.[31]

References

1. Cullinan TR. The epidemiology of blindness. In: Miller S, ed. Clinical Ophthalmology. Bristol: Wright, 1987; Chap. 23.
2. Pauleikhoff D, Chen JC, Chisholm IH, Bird AC. Choroidal perfusion abnormality with age-related Bruch's membrane change. Am J Ophthalmol 1990;109:211–17.
3. Pruñte C, Niesel P. Quantification of choroidal blood-flow paramentrs using indocyanine green video-fluorescence angiography and statistical picture analysis. Graefes Arch Clin Exp Ophthalmol 1988;226:55–8.
4. Boker T, Fang T, Steinmetz R. Refractive error and choroidal perfusion characteristics inpatients with choroidal neovascularization and age-related macular degeneration. Ger J Ophthalmol 1993;2:10–13.
5. Friedamn E. Scleral rigidity, venous obstruction, and age-related macular degeneration: a working hypothesis. In: BenEzra D, Ryan SJ, Glaser BM, Murphy RP, eds. Ocular Circulation and Neovascularization Dordrecht: Martinus Nijhoff/Dr W Junk, 1987;197–204. (Doc Ophthalmol Proc Ser;50).
6. Friedman E, Ivry M, Ebert E, et al. Increased scleral rigidity and age-related macular degeneration. Ophthalmology 1989;96:104–8.
7. Friedman E, Smith TR, Kuwabara T. Senile choroidal vascular patterns and drusen. Arch Ophthalmol 1963;69:200–30.
8. Friedman E, Smith TR. Symposium: macular diseases. Pathogenesis. Senile changes of the choriocapillaris of the posterior pole. Trans Am Acad Ophthalmol Otolaryngol 1965;69:652–61.
9. Friedman E, van Buskirk E, Feneberg E, et al. Pathogenesis of senile disciform degeneration of the macula. In: Acta Concilium Ophthalmologicum (Mexico), 1975; vol. 1, 454–8.
10. Powis RL, Schwartz RA. Practical Doppler ultrasound for the Clinician. Baltimore: Williams & Wilkins, 1991, 187.
11. Lieb WE, Cohen SM, Merton DA, et al. Color Doppler imaging of the eye and orbit. Technique and normal vascular anatomy. Arch Ophthalmol 1991;109:527–31.
12. Guthoff RF, Berger RW, Winkler P, et al. Doppler ultrasonography of malignant melanomas of the uvea. Arch Ophthalmol 1991;109:537–41.
13. Hayreh SS. Discussion, 303–5. of: Flaharty PM, Sergott RC, Lieb WE, et al. Optic nerve sheath decompression may improve blood flow in anterior ischemic optic neuropathy. Ophthalmology 1993;100:297–305.
14. Trible JR, Sergott RC, Spaeth GL, et al. Trabeculectomy is associated with retrobulbar hemodynamic changes. A color Doppler analysis. Ophthalmology 1994;101:340–51.
15. Flaharty PM, Sergott RC, Lieb WE, et al. Optic nerve sheath decompression may improve blood flow in anterior ischemic optic neuropathy. Ophthalmology 1993;100:297–305.
16. Friedenwald JS. Contribution to the theory and practice of tonometry. Am J Ophthalmol 1937;20:985–1024.
17. Broekhuyse RM. The lipid composition of aging sclera and cornea. Ophthalmologica 1975;171:82–5.
18. Sheraidah G, Steinmetz R, Maguire J, et al. Correlation between lipids extracted from Bruch's membrane and age. Ophthalmology 1993;100:47–51.
19. Bischoff PM, Flower RW. Ten years experience with choroidal angiography using indocyanine green dye: a new routine examination or an epilogue? Doc Ophthalmol 1985;60: 235–91.
20. Bischoff PM, Flower RW. High blood pressure in choroidal arteries as a possible pathogenetic mechanism in senile macular degeneration [letter]. Am J Ophthalmol 1983;96: 398–9.
21. Monés J, Guyer DR, Krupsky S, et al. Indocyanine green diacritical videoangiography. In: Albert DM, Jakobiec FA, eds. Principles and Practice of Ophthalmology: Clinical Practice. Vol. 2. Philadelphia: WB Saunders, 1994; Chap. 52.
22. Friedman E. Central serous choroidopathy: pathogenesis and treatment. In: Brockhurst RJ, Boruchoff SA, Hutchinson BT, Lessell S, eds. Controversy in Ophthalmology. Philadelphia: WB Saunders, 1977;706–9.
23. Moschowitz E. Studies in phlebosclerosis. VI. The immunity from phlebosclerosis in the coronary vein. Am J Cardiol 1964;13:495–7.
24. Friedman E, Smith TR. Clinical and pathological study of choroidal lipid globules. Arch Ophthalmol 1966;75:334–6.
25. Eagle RC Jr. Mechanism of maculopathy. Ophthalmology 1984;91:613–25.
26. Young RW. Pathophysiology of age-related macular degeneration. Surv Ophthalmol 1987;31:291–306.
27. Tso MOM. Pathogenetic factors of aging macular degeneration. Ophthalmology 1985;92:628–35.
28. Potts AM. An hypothesis on macular disease. Trans Am Acad Ophthalmol Otolaryngol 1966;70:1058–62.
29. Bill A. Circulation in the eye. In: Renkin EM, Michel CC, eds. The Cardiovascular System. Vol. IV, Pt. 2 of: Handbook of Physiology: Critical, Comprehensive Presentation of Physiological Knowledge and Concepts. Bethesda: American Physiological Society, 1984; Chap. 22.
30. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. Arch Ophthalmol 1992;110:1701–8.
31. Blankenhorn DH, Kramsch DM. Reversal of atherosis and sclerosis. The two components of atherosclerosis. Circulation 1989;79:1–7.