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EXTENDED REPORT

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Aim: To investigate the effect of systemic hypertension (SH) on the foveolar choroidal circulation in patients with age related macular degeneration (AMD).
Methods: This study included 163 study eyes with early AMD characteristics of 124 AMD patients. Study eyes had visual acuity of 20/40 or better, drusen ⩾63 μm, and/or RPE hypertrophy. 56 of the AMD patients had a history of SH and 47 of these patients were receiving antihypertensive medications. Laser Doppler flowmetry (Oculix) was used to assess relative choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBFlow) in the centre of the fovea of the study eyes. Differences in the mean haemodynamic parameters between groups of eyes were assessed using analysis of variance (ANOVA) and a test of linear trend, with adjustment for the correlation between eyes of the same patient.
Results: AMD patients with SH showed decreased ChBFlow in comparison with those without SH (ANOVA, p = 0.02). This association was maintained after adjustments for multiple factors (p = 0.04).
Conclusions: AMD patients with SH have lower ChBFlow than those without SH. This decrease in choroidal blood circulation may help explain the mechanism by which systemic hypertension may contribute to the progression of AMD and the development of choroidal neovascularisation.

Age related macular degeneration (AMD) is the leading cause of incurable blindness in the elderly population in industrialised countries.[1–3] Both local ocular and systemic vascular risk factors are thought to be associated with the development of this disease process.

Disturbances in the ocular circulation in AMD have been reported[4–10] and several histopathological studies have suggested decreased choroidal vascularity,[11–14] supporting the presence of haemodynamic abnormalities in this disease. We have previously reported that choroidal blood flow is significantly reduced in the patients with AMD and large drusen.[4] Furthermore, choroidal haemodynamic parameters progressively decreased with an increase in the severity of AMD features associated with risk for the development of choroidal neovascularisation (CNV).[5]

Association between AMD and systemic vascular factors, such as systemic hypertension, has been studied by many epidemiological studies. Some of the studies have shown an association,[15–21] while others, such as the Beaver Dam,[22] Colorado,[23] Blue Mountains,[24] London,[25] Oulu,[26] Rotterdam,[27] and some others have failed to establish an association. Results of the Macular Photocoagulation Study have shown that AMD patients with systemic hypertension (SH) responded less well to laser photocoagulation treatment suggesting that hypertension may have a deleterious effect on the disease process.[28]

In order further to explore the association between SH and AMD, we investigated the effect of SH on choroidal blood flow of AMD patients.

METHODS

This cross sectional study was carried out in a group of 124 AMD patients ranging in age from 51–86 years (mean 72 (SD 8) years). One hundred sixty three eyes of these patients met inclusion criteria for a study eye, which were early stages of AMD, visual acuity of 20/40 or better, good fixation, intraocular pressure (IOP) of 21 mm Hg or less, clear ocular media, pupillary dilation of 5 mm or more, and absence of other intraocular diseases. AMD patients with diabetes mellitus, high myopia (>7 dioptres), previous periorbital or ocular radiation, and previous treatment with macular toxic drugs did not qualify for this study. All study eyes had either drusen larger than 63 μm (62 eyes) or drusen ⩾63 μm with retinal pigment epithelium (RPE) hyperpigmentary changes present (101 eyes) and no evidence of CNV; 19 patients, however, had CNV in the fellow eye. These fellow eyes with CNV were not included in the blood flow measurements. Grading of drusen characteristics and RPE changes in the study eyes were performed according to the Complications of Age Related Macular Degeneration Trial protocol.

Fifty six AMD patients had a history of SH, as defined by the World Health Organization guidelines; 47 of these 56 were on chronic antihypertensive therapy. Among them 24 patients were taking a single drug, 17 were receiving a combination of two drugs, and six were taking three different medications. All characteristics of the patients with and without SH are summarised in table 1. The frequency distribution of the antihypertensive drugs can be found in table 2.

A detailed explanation of the study procedures was given to each study subject. All participants were asked to sign an appropriate consent form approved by the institutional review board of the University of Pennsylvania. The study was conducted in accord to HIPAA regulations. The tenets of the Declaration of Helsinki were observed.

All patients underwent full eye examination including stereo 30° colour fundus photography in both eyes. Fundus photographs were graded in a masked fashion by the Fundus Photography Reading Center of the University of Pennsylvania.

Foveolar choroidal blood flow was assessed by the laser Doppler flowmetry (LDF) (Oculix, Inc, Berwyn, PA, USA),

Abbreviations: AMD, age related macular degeneration; ANOVA, analysis of variance; BP, blood pressure; ChBFlow, choroidal blood flow; ChBVel, choroidal blood velocity; ChBVol, choroidal blood volume; CNV, choroidal neovascularisation; LDF, laser Doppler flowmetry; RBCs, red blood cells; RE, retina section; RPE, retinal pigment epithelium; SH, systemic hypertension

Table 1 Characteristics of AMD patients with and without systemic hypertension (SH)

	AMD patients with SH (n = 56)	AMD patients without SH (n = 68)	
	Mean (SE)	Mean (SE)	p Value
Age (years)	73.8 (1.02)	70.2 (1.02)	0.02*
Systolic blood pressure (mm Hg)	149.5 (3.22)	134.1 (2.21)	0.002*
Diastolic blood pressure (mm Hg)	78.3 (2.05)	74.2 (1.31)	0.10*
Mean blood pressure (mm Hg)	102.0 (2.25)	94.2 (1.44)	0.004*
Intraocular pressure (mm Hg)	15.6 (0.47)	14.4 (0.31)	0.04‡
Perfusion pressure (mm Hg)	52.4 (1.48)	48.6 (0.99)	0.03‡
Refractive error (dioptres)	1.10 (0.34)	0.62 (0.25)	0.25‡
Male/female ratio	24/32	34/34	0.47†
Current smoking status (yes/no)	2/54	8/60	0.11†

*From two sample *t* test.
†From Fisher's exact test.
‡From generalised estimating equations (GEE) to adjust for the correlation in measurements between both eyes of the same subject.

after pupillary dilatation with tropicamide 1% (Alcon, Fort Worth, TX, USA) and phenylephrine hydrochloride 10% (Sanofi Winthrop, New York, NY, USA). This non-invasive technique provides measurements of relative choroidal blood velocity (ChBVel), volume (ChBVol) and flow (ChBFlow). Choroidal blood velocity is proportional to the mean velocity of the red blood cells (RBCs) within the volume sampled by the laser light; choroidal blood volume is proportional to the number of RBCs. Both of these measurements are independent. Choroidal blood flow is calculated by the instrument from these two parameters according to the following formula: ChBFlow = Constant × ChBVel × ChBVol.[29] Measurements obtained in this fashion from the centre of the foveola correspond mainly to blood flow in the choriocapillaries.[30]

While the subjects were seated in a darkened room, a diode laser beam (670 nm) with a 20 mW intensity and diameter of 200 μm was delivered to the eye through a fundus camera (model TRC; Topcon, Tokyo, Japan). Subjects were asked to fixate on the probing laser beam to obtain measurements in the centre of the fovea. The light scattered back was electronically analysed, allowing us to measure flow mainly in the choriocapillaris.[30] Proper fixation was controlled thorough the fundus camera. This was achieved through illumination of the posterior retinal area of 30° in diameter with an additional light (wavelength of 570 nm) with a retinal irradiance of approximately 0.03 mW/cm^2. A detailed description of the technique has been published before.[30–33]

In each study eye, three continuous 30 second measurements of the choroidal circulation were obtained. Only those parts of the recordings that showed stable haemodynamic parameters were selected for analysis. On average, about 12 seconds of measurements were analysed in each study eye.

A masked observer analysed these data on a NeXT computer with software specifically developed for analysis of Doppler signals from ocular tissues.[31] Brachial artery systolic and diastolic blood pressures (BP_s and BP_d, respectively) were determined by sphygmomanometry (Accutorr 1A, Datascope, Paramus, NJ, USA) immediately after blood flow measurements. The mean brachial artery pressure (BP_m) was calculated according to the following formula:

$$BP_m = BP_d + 1/3(BP_s - BP_d)$$

Based on the mean values of systemic blood pressure, we divided all AMD patients (with and without SH) into four groups based on the four quartiles of mean blood pressure: group 1 had mean blood pressure values that ranged from 62–88 mm Hg; group 2 had values from 88.1–96 mm Hg; group 3 values ranged from 96.1–106 mm Hg and group 4 had values within 106.1–144 mm Hg.

To assess the reproducibility of the blood flow data, we calculated a coefficient of variability (CV) for each study eye derived from three subsequent measurements. CV was calculated using the following formula: CV = (SD/mean) ×100. Average CV of all eyes was 10.3% (SD 7.2%) for ChBFlow.

The average of three replicates of each haemodynamic parameter was used in the data analysis. Differences in the mean haemodynamic parameters between AMD patients with and without SH were assessed using analysis of variance (ANOVA). For patients with both eyes eligible, measures from both eyes were included in the analysis, and their correlation was adjusted by using the generalised estimating equations (GEE) and executed by using PROC GENMOD (SAS version 8.2, SAS, Cary, NC, USA). We specified an exchangeable working correlation structure to describe the correlation in haemodynamic parameters between the two

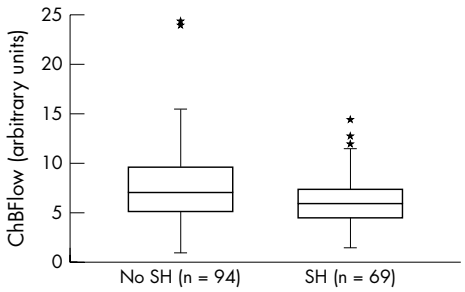

Figure 1 Relative foveolar choroidal blood flow (ChBFlowl) in arbitrary units (AU) for eyes with and without systemic hypertension. Each box plot shows the upper extreme (excluding outliers), upper quartile, median, lower quartile, and lower extreme (excluding outliers). The outliers are shown as circles outside the box. There is a statistically significant difference in choroidal blood flow between both groups (p = 0.02).

Table 2 Frequency distribution of antihypertensive drugs in patients with systemic hypertension (n = 56 patients)*

Antihypertensive drugs	No (%)†
β blockers	20 (35.7)
Diuretics	15 (26.8)
ACE inhibitors	13 (23.2)
Calcium channel blockers	13 (23.2)
Angiotensin receptor blockers	9 (16.1)
Centrally acting antihypertensives	1 (1.79)
Others	5 (8.9)

*Nine hypertensive patients did not take any antihypertensive drugs.
†Some patients received more than one type of antihypertensive drug.

Table 3 Comparison of blood flow parameters between eyes with hypertension (SH) and no hypertension (no SH)

	No SH (n = 94 eyes)	SH (n = 69 eyes)		
	Mean (SE)	Mean (SE)	% Difference	Univariate model analysis p value*
ChBVel (AU)	0.39 (0.01)	0.37 (0.01)	−4.5%	0.23
ChBVol (AU)	0.24 (0.01)	0.22 (0.01)	−11.1%	0.11
ChBFlow (AU)	8.0 (0.4)	6.7 (0.3)	−16.7%	0.02

*The generalised estimating equations (GEE) approach was used to adjust for the correlation in measurements between both eyes of the same subject.

eyes of the same subject. This procedure corrects for the correlations between the measurements in the two eyes of the same subject and allows the inclusion of all measured eyes in the analysis of the results of the study.

To investigate the association between choroidal blood flow parameters and mean blood pressure, a linear trend test was performed comparing ChBVel, ChBVol, and ChBFlow among the four groups of AMD patients with increasing mean blood pressure as defined above. The association was examined both by univariate and multivariate analysis. Age, sex, current smoking status, and IOP were included in the multivariate model since they were found to be significantly associated with haemodynamic parameters from the univariate analysis. The multivariate model also includes AMD severity (three levels) because it was associated with decrease in the haemodynamic parameters, as reported in our previous publication.[5] Two sided probability values less than 0.05 were considered statistically significant.

RESULTS

Table 1 summarises the characteristics of AMD patients enrolled in the study with and without SH. Both groups were well matched for sex, smoking status, refractive error, and male/female ratio. There was a small but statistically significant difference in average age of about 3 years and in average IOP of about 1 mm Hg between the two groups. Not surprisingly there was also a significant difference in systolic blood pressure, mean blood pressure, and perfusion pressure between the two groups.

Comparisons of choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBFlow) for AMD subjects with and without SH are summarised in table 3. Average ChBFlow was 8.0 (0.4) arbitrary units (AU) in non-hypertensive AMD patients and 6.7 (0.3) AU in AMD patients with SH (fig 1). The difference between both groups was statistically significant (p = 0.02) and corresponded to a decrease in ChBFlow flow of 16.7% in patients with SH. This difference was statistically significant after adjustments for age, sex, current smoking status, IOP, and severity of AMD (p = 0.04). There was no statistically significant difference in ChBVel (p = 0.23) and ChBVol (p = 0.11) between the two groups.

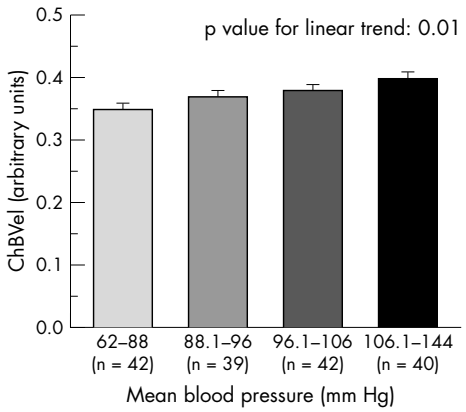

Figure 2 Relative choroidal blood velocity (ChBVel) in arbitrary units (AU) for AMD patients divided into four groups in accordance with the values of their blood pressures. p Value for linear trend is 0.01.

An analysis of the haemodynamic parameters was carried out to assess the potential effect of antihypertensive medications on the choroidal blood flow. No significant difference was observed in any of the haemodynamic parameters between hypertensive patients that received an antihypertensive therapy and those that were not treated. Although the number of patients receiving each type of antihypertensive medication was relatively small, we also found no large effect of any particular type of medication on choroidal blood flow parameters.

A statistically significant increase in ChBVel was found with an increase in the mean blood pressure (p = 0.01; table 4, fig 2) when a test of linear trend was performed to compare choroidal blood flow parameters among the four groups of AMD patients with increasing mean blood pressure. This trend was significant (p = 0.02) after adjustments for age, sex, IOP, and current smoking status and severity of AMD were performed. There was no association between ChBVol or ChBFlow and mean blood pressure values (p = 0.93 and 0.20 respectively, table 4).

No statistically significant differences in choroidal haemodynamic parameters were detected between hypertensive patients that were receiving hypertensive therapy and those who were not receiving such treatment. Also, no statistically significant differences were observed between the different types of antihypertensive medication. However, these analyses were based on a small number of patients.

DISCUSSION

Our results show that choroidal blood flow is 16.7% lower in AMD patients with a history of SH than in AMD patients without SH. This difference in ChBFlow is statistically significant (p = 0.02) and remains statistically significant after adjustments for age, sex, current smoking status, IOP, and severity of AMD (p = 0.04).

We have previously reported that ChBFlow is reduced in AMD patients[4] and the reduction becomes more marked with increasing AMD severity.[5] The results of this study suggest that within the population of AMD patients that have reduced choroidal blood flow, those with SH seem to have an even lower blood flow.

Because systemic hypertension has been shown by some studies to be associated with an increased risk for CNV development[15] and a decreased efficacy of laser treatment,[28] the presence of lower choroidal blood flow in AMD patients with SH suggests the possibility that an ischaemic mechanism may have a role in the aetiology of this disease.

The preliminary work of Ross *et al*[34] showing that CNV often develops in close proximity to choroidal watershed vascular filling zones, supports the hypothesis that ischaemia may have a role in the development of CNV. These choroidal

Table 4 Association between blood flow parameters and mean blood pressure in all study eyes

Blood flow parameters	Mean blood pressure (mm Hg) 62–88 (n = 42 eyes) Mean (SE)	88.1–96 (n = 39 eyes) Mean (SE)	96.1–106 (n = 42 eyes) Mean (SE)	106.1–144 (n = 40 eyes) Mean (SE)	Linear trend test (p value)
ChBVel (AU)	0.35 (0.01)	0.37 (0.01)	0.38 (0.01)	0.40 (0.01)	0.01
ChBVol (AU)	0.22 (0.01)	0.25 (0.03)	0.23 (0.01)	0.23 (0.01)	0.93
ChBFlow (AU)	6.70 (0.52)	7.93 (0.82)	7.36 (0.42)	7.68 (0.45)	0.20

watershed zones, which are the last places to fill with indocyanine dye during the early angiography phases, are the areas most prone to develop ischaemia and hypoxia in case of a decrease in choroidal blood flow.

The results of this study show an association between SH and decreased choroidal blood flow. From this association, however, we cannot establish a causal relation between SH and decrease in blood flow. Our previous study showing decrease in flow with increasing AMD severity and risk of development of CNV,[5] however, suggests that decrease in flow may have a role in the development of CNV.

In our current study, we did not detect any significant differences in blood flow parameters between SH patients who were taking antihypertensive medications and those who were not taking such medications. We cannot reach any strong conclusions regarding this issue, however, because the number of SH patients who did not receive treatment was small (nine patients).

A significant direct association was observed between mean blood pressure and ChBVel among all AMD patients included in our study. ChBVel progressively increased with an increase in mean blood pressure values (table 4, fig 2). No significant changes in ChBVol or ChBFlow were observed with increase in mean blood pressure. Possibly, an increase in ChBVel without a change in ChBFlow may occur if erythrocytes move faster through constricted choriocapillaris.

Interestingly, no such associations between ChBVel and arterial blood pressure have been reported in previous studies in individuals with normal eye examination, with and without SH.[35–37] Possibly, this association found in our current study may be characteristic of AMD patients. Such a significant association could be due to abnormal auto-regulatory responses caused perhaps by histopathological changes known to occur in AMD such as decrease in density and diameter of the macular choriocapillaris[38] and narrowing of the lumen and loss of the cellularity of choriocapillaris.[14]

The consequences of a faster blood flow through the choriocapillaris are not clear. Possibly, an increased velocity could negatively affect the exchange between the capillary blood and the tissues. This issue needs to be further investigated.

Although the studies mentioned above have not found any correlations between ChBVel and systemic blood pressure in individuals with normal eye examination, Polak *et al* reported small increases in mean flow velocity in the posterior cilliary arteries with increases in mean arterial blood pressure (3.5% per 10 mm Hg) using colour Doppler imaging.[39] These measurements, however, represent retrobulbar haemodynamics and may not reflect what happens in the choroidal circulation.

Okanouchi *et al*, using indocyanine green leucocyte angiography in a rabbit model, showed that acute hypertension induced by intravenous injection of angiotensin II caused increased choroidal leucocyte velocity.[40] This, however, was an acute experiment that may not represent the changes that may occur under chronically elevated blood pressures.

The fact that we found a significantly lower blood flow in patients with a history of SH but did not detect a significant correlation between actual blood pressure and blood flow is somewhat puzzling. This seeming discrepancy suggests that the history of SH or the presence of high systemic blood pressure in the past may produce chronic effects on the choroidal vasculature that may have a larger effect on flow than the actual blood pressure detected at the time of flow measurements. This may be related to our finding that systemic hypertension was very well controlled in the majority of the patients in this study, and the actual values of blood pressure in most cases were within the normal limits at the time of the flow measurements.

In conclusion, our current study suggests that choroidal blood flow in AMD patients with systemic hypertension is about 16.7% lower than that of patients without systemic hypertension. Because more advanced AMD pathology is associated with lower choroidal blood flow, a further decrease in flow of 16.7% associated with systemic hypertension may help explain the mechanism by which systemic hypertension may contribute to the progression of AMD and the development of CNV.

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