

## SCIENTIFIC CORRESPONDENCE

## Pulsatile ocular blood flow in asymmetric exudative age related macular degeneration

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**Abstract**

**Background/claims**—Decreased perfusion or increased vascular resistance of the choroidal vessels had been proposed as the vascular pathogenesis for age related macular degeneration (AMD). This study planned to answer the question whether pulsatile ocular blood flow (POBF) was different in patients with asymmetric exudative AMD between eyes with drusen, choroidal neovascularisation (CNV), or disciform scar.

**Methods**—37 patients with asymmetric exudative AMD were enrolled in this observational case series study. POBF were measured in both eyes of each subject. Eyes with high myopia, anisometropia, recent laser treatment, and glaucoma were excluded.

**Results**—After adjusting for ocular perfusion pressure, intraocular pressure, and pulse rate, multivariate regression analysis with generalised estimating equation showed POBF was significantly higher in eyes with CNV (1217 (SD 476)  $\mu\text{l}/\text{min}$ ) than the contralateral eyes with drusen (1028 (385)  $\mu\text{l}/\text{min}$ ) ( $p = 0.024$ ). Eyes with disciform scar had lower POBF than the contralateral eyes with drusen (999 (262)  $\mu\text{l}/\text{min}$  and 1278 (341)  $\mu\text{l}/\text{min}$ , respectively,  $p < 0.001$ ). There was no significant correlation between the POBF and the lesion size of the CNV.

**Conclusion**—The POBF in eyes with drusen was lower than their fellow eyes with CNV, but higher than their fellow eyes with disciform scar. This finding suggests that haemodynamic differences between fellow eyes in individuals are relevant to the development of CNV and the formation of disciform scar. Further studies on the follow up patients might shed light on the pathogenesis of exudative AMD.

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and egg” question for primary RPE degeneration or choroidal perfusion defects,<sup>2</sup> the haemodynamic role of the choroid is becoming more clear. In two studies of colour Doppler imaging of the retrobulbar vessels in patients of AMD, increased vascular resistance or reduced blood flow velocity of the short posterior ciliary arteries had been suggested to be related to the formation of AMD<sup>3</sup> or exclusively non-exudative AMD,<sup>4</sup> respectively. The change of choroidal perfusion was unknown for exudative AMD. Nevertheless, among the risks of fellow eyes to develop choroidal neovascularisation (CNV), patients with definite systemic hypertension had 50% chance of developing of CNV in 5 years compared with only 33% in patients without hypertension.<sup>5</sup> Haemodynamic change in the choroid might still have a role in exudative AMD.

Among the tools for ocular blood flow studies, pulsatile ocular blood flow (POBF) is a non-invasive, inexpensive one, and has good acute test-retest reproducibility.<sup>6-9</sup> This technique derives blood flow measurements from the continuous intraocular pressure (IOP) recording and deducts the pulsatile blood flow from pressure-volume relation. Although controversy exists on the exact components of pulsatile blood flow to the total ocular blood flow,<sup>10,11</sup> POBF has been measured in patients with normal tension glaucoma<sup>12,13</sup> and in diabetics,<sup>14</sup> and has revealed significant changes in their disease states. POBF is mainly determined by the choroidal circulation and the contribution of the retinal circulation is almost negligible. As the CNV derives the blood supply mainly from the choroid, an investigation of the POBF might reveal the ocular haemodynamics in eyes with AMD. Recently, Mori *et al* studied the POBF in patients with exudative AMD and found that the POBF of affected eyes were lower than that in the eyes with non-exudative AMD and age matched controls.<sup>15</sup> However, the disease activity of the CNV—for example, disciform scar or active CNV, was unknown.

The aim of this study was to investigate ocular blood perfusion by means of POBF in subjects with exudative AMD. Patients with exudative AMD with asymmetric retinal pathology in their fellow eyes—namely, drusen, CNV and disciform scar, were selected for this study so that the relation between potential disturbances in ocular blood flow could be investigated.

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The pathogenesis of age related macular degeneration (AMD) remained speculative. Retinal pigment epithelium (RPE) senescence, genetic defects, and primary ocular perfusion abnormalities had been proposed in the pathogenesis for AMD.<sup>1</sup> Although it is a “chicken

## Materials and methods

### PATIENTS AND DEFINITION

Study subjects were eligible for inclusion if they had at least one eye with exudative macular degeneration. Fundus lesion was defined accordingly. Eyes with drusen were defined as being in categories II and III of the Age-Related Eye Disease Study<sup>16</sup>—the presence of more than 15 small hard drusen, one or more intermediate drusen, one or more large drusen, or pigment abnormalities in the two discs diameter of the centre of the macula. The definition of CNV was evidence of leakage on fluorescein angiography from classic or occult CNV. If the CNV was combined with fibrous components, they should be less than 25% of the total lesion. Other lesion components of CNV may include thick blood and serous pigment epithelium detachment. Scar was classified as white fibrous tissue with blocked fluorescence and/or staining on angiography. If disciform scar lesion was accompanied by CNV, the leaking CNV must be no more than 25% of the entire lesion. Scar lesions that comprised more or equal to 25% of CNV but less than 75% were defined as CNV/disciform scar, and were not included in this study. For the design of the study to compare the fellow eyes in the same individuals, only those subjects with asymmetric exudative AMD in their fellow eyes were included—that is, the disease status of AMD (drusen, CNV, or disciform scar) in the fellow eyes of the same individuals were different from each other.

Study subjects were excluded if they had a history of glaucoma, diabetic retinopathy, arterial or venous occlusive disease, optic neuropathy, macular dystrophies, retinal detachment, or ocular inflammatory diseases. Subjects with a history of laser treatment for CNV within 1 year, previous uneventful cataract surgeries in one or both eyes within 1 year,<sup>17</sup> or vitreoretinal surgeries for any causes were also excluded. Other exclusion criteria were high myopia defined as more than 6 dioptres in at least one eye, marked anisometropia of more than 4 dioptres, or difference in axial length between the fellow eyes of more than 2 mm.

Eligible subjects underwent assessment of refraction, best corrected visual acuity with Snellen visual acuity chart, slit lamp biomicroscopy, axial length, fundus photography, and fluorescein angiography.

### POBF MEASUREMENTS

All patients were measured for POBF by an experienced examiner who was masked to the diagnosis. IOP and pulse amplitude (PA) were

measured in both eyes with an OBF Tonometer (Ocular Blood Flow Ltd, Wiltshire, UK) using software version 16.2. The software identifies five pressure pulses out of a longer train of pulses that are closest to each other in beat to beat variation over 10–14 second interval. These five pulses are then averaged and used to calculate the PA. The pulse volume (PV) and POBF were also calculated from five pulses using previously described theory and methods.<sup>9</sup>

The POBF measurement was conducted with the patient in a sitting position, with the OBF probe mounted on a slit lamp microscope and following instillation of topical anaesthetics (0.5% proxymetacaine (proparacaine)). The same examiner using the same OBF tonometer made all measurements. Blood pressure was measured by sphygmomanometry with the patient in the sitting position. The mean blood pressure (MBP) was calculated as diastolic blood pressure plus one third of the systolic minus the diastolic blood pressure. The ocular perfusion pressure (OPP) was calculated as two thirds MBP minus IOP.<sup>18</sup>

### STATISTICAL ANALYSIS

The paired Student's *t* test was used to assess the differences in POBF and PA between the fellow eyes in the same subject. To adjust the effects of IOP, OPP, and pulse rate on POBF and PA, multivariate logistic regression analysis was performed, using OBF parameters as the dependent variable, and disease status of the study eyes, IOP, OPP and pulse rate as independent variables. In addition, to include both eyes of AMD patients in our regression analysis, the generalised estimation equation<sup>19</sup> was used to account for the correlation between the fellow eyes. Statistical significance was set at *p* < 0.05.

## Results

Thirty seven patients with asymmetric AMD between their fellow eyes were consecutively enrolled. They were categorised into three groups (Table 1). Group 1 included 21 patients with drusen in only one eye and CNV in the contralateral eye, group 2 included nine patients with disciform scar in one eye and drusen in the other eye, and group 3 included seven patients with CNV in one eye and disciform scar in the other eye. Table 1 shows the baseline clinic data of the three groups. No statistically differences in age, sex, or blood pressure were observed between subjects in the three groups. The differences of spherical equivalence between the fellow eyes in the three groups were all less than 3 dioptres. For

Table 1 Demographic data of the patients

Characteristics	Group 1 Drusen/CNV	Group 2 Drusen/scar	Group 3 CNV/scar	<i>p</i> Value
Number of the patients	21	9	7	—
Age (years, mean (SD))	74.4 (6.1)	74.6 (3.8)	76.9 (3.2)	0.271
Sex (M/F)	18/3	6/3	7/0	0.177
Systolic blood pressure (mm Hg, mean (SD))	141.1 (16.0)	131.4 (19.5)	138.3 (19.4)	0.507
Diastolic blood pressure (mm Hg, mean (SD))	77.9 (15.8)	75.1 (6.7)	76.7 (5.2)	0.892
Mean blood pressure (mm Hg, mean (SD))	98.9 (14.2)	93.9 (9.9)	97.2 (7.1)	0.668
Refractive difference (dioptre, mean (SD))	0.64 (1.42)	0.46 (0.58)	0.83 (1.6)	0.897

Table 2 Mean values of IOP, OPP, POBF, and PA of the AMD patients with asymmetric AMD (n = 37)

	IOP (mm Hg)	OPP (mm Hg)	POBF ( $\mu\text{l}/\text{min}$ )	PA (mm Hg)
<b>Group 1 (n = 21)</b>				
Drusen	14.5 (2.8)	50.5 (7.9)	1028.0 (384.8)	2.9 (1.1)
CNV	13.0 (3.0)	52.0 (7.5)	1216.7 (475.7)	2.9 (0.9)
	p=0.04	p=0.04	p<0.001 p=0.024*	p=0.840 p=0.564*
<b>Group 2 (n = 9)</b>				
Drusen	15.4 (3.2)	47.1 (8.4)	1278.0 (340.6)	3.6 (1.0)
Disciform scar	14.5 (4.3)	48.0 (8.5)	998.6 (261.6)	2.9 (0.9)
	p=0.264	p=0.399	p<0.001 p<0.001*	p=0.007 p<0.001*
<b>Group 3 (n = 7)</b>				
CNV	11.9 (3.3)	52.8 (4.4)	1359.9 (166.5)	3.2 (0.8)
Disciform scar	14.1 (4.0)	50.3 (5.1)	1122.4 (249.2)	3.1 (0.9)
	p=0.134	p=0.135	p=0.040 p=0.318*	p=0.489 p=0.082*

IOP = intraocular pressure, OPP = ocular perfusion pressure, POBF = pulsatile ocular blood flow, PA = pulse amplitude.

\*p Value adjusted for IOP, OPP, and pulse rate.

previous eye surgeries, two patients in group 1 (9.5%), three in group 2 (33%), and another three (42%) in group 3 had cataract extraction and intraocular lens implantation more than 1 year earlier. Of these eight patients, only one patient in group 1 had cataract surgery in the eye with CNV, and other patients had bilateral cataract surgeries.

Table 2 shows mean value of IOP, OPP, POBF, and PA in the three groups, and Figure 1 shows the individual POBF values plotted in these groups. The IOP and OPP showed no significant difference between the fellow eyes in groups 2 and 3 ( $p > 0.05$ ), but marginal significant difference ( $p = 0.04$ ) between the eyes with CNV and drusen in group 1. Although PA of the two eyes is not significantly different in group 1, the final value of POBF turned out to be significantly different ( $p < 0.001$ ). To adjust the differential effects of IOP, OPP, and heart rate on POBF between the fellow eyes, we then used multivariate logistic regression analysis to compare the POBF between the fellow eyes while controlling the IOP, OPP, and heart rate at the same level. Eyes with CNV in group 1 still had significantly higher POBF than their fellow eyes with drusen only ( $p = 0.024$ ). Eyes with disciform scars in group 2 had significantly lower POBF ( $p < 0.001$ ) and PA ( $p < 0.001$ ) than their contralateral eyes with drusen. The mean lesion size of all eyes with CNV (n = 28) was 6.6 (SD 5.0) disc area (DA), and in eyes with disciform scar (n = 16) it was 8.4 (4.6) DA. The correlation of POBF with the lesion size of the CNV ( $\gamma = -0.072$ ,  $p = 0.732$ ) or with the disciform scar ( $\gamma = 0.215$ ,  $p = 0.425$ ) was not statistically significant.

### Discussion

Our results showed that the POBF was different between the fellow eyes of the individuals with asymmetric exudative AMD. These results were in agreement with those studies that suggest choroidal blood flow abnormalities in AMD patients.

Friedman *et al*<sup>20</sup> proposed that as a result of lipoidal infiltration of the sclera and Bruch's membrane in eyes with AMD, the eyes become increasingly rigid and non-compliant. Using colour Doppler imaging, Friedman *et al*<sup>3</sup>

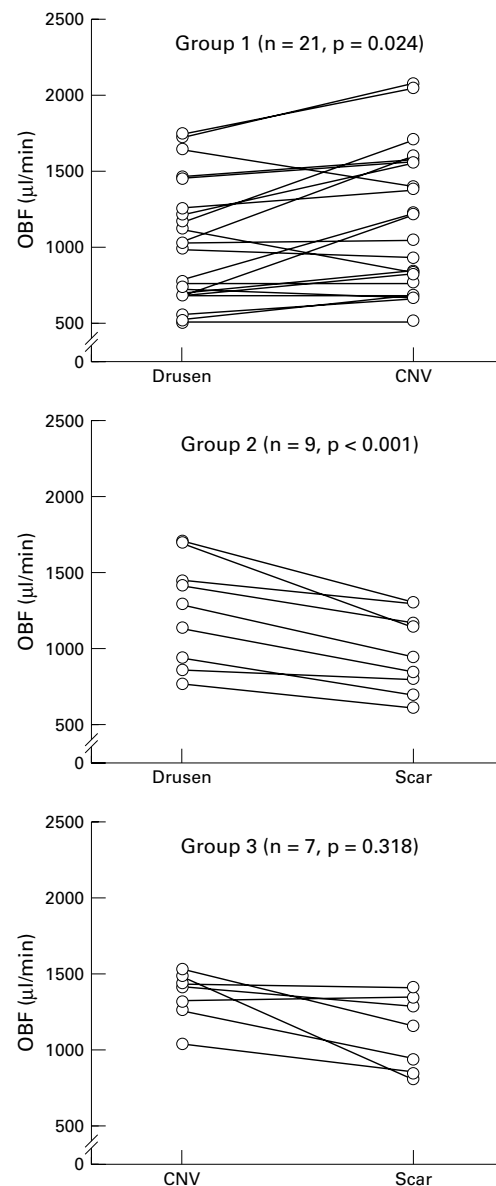


Figure 1 Pulsatile ocular blood flow in three groups of patients with asymmetric exudative AMD. Two circles connected by a straight line in each group represent a single subject with different diagnosis in his eyes.

found decreased velocity and increased pulsatility in arteries that perfused the eye of AMD. These findings, which were interpreted as elevated venous pressure and increased resistance of choroidal vessels, were correlated in a separate study analysing the morphometric difference between the eyes of AMD and age matched normal controls.<sup>21</sup> In that study, Spraul *et al*<sup>21</sup> found increased total luminal area of peripheral choroidal vessels and decreased density of choroidal vessels in the macular area in eyes with AMD, which could explain the above findings.

In a study comparing the foveolar choroidal circulation between subjects with non-exudative AMD and normal controls, Grunwald *et al*<sup>22</sup> found decreased choroidal blood flow in subjects with AMD but a tendency towards an increase in flow pulsatility in AMD. In our study, pulsatility and the calculated

blood flow difference was noted between different disease statuses in individuals with asymmetric exudative AMD. Because the calculated OPP was not different between the two eyes in a single subject, we speculated that the discrepancy in POBF might originate in a more distal part—for example, the retrobulbar vessels or the eye wall itself.

At least two possibilities could explain this asymmetric pulsation. One is that there may be an asymmetric scleral rigidity more pronounced in the eyes of CNV in group 1 and drusen in group 2. Although it was depicted by Friedman *et al*<sup>20</sup> that scleral rigidity increased in patients with AMD compared to the age matched normal controls, it was unknown in his study how scleral rigidity was affected in different stages of maculopathy. However, as stated in that article, most of the AMD patients had both eyes affected and were frequently asymmetrical in severity. Yet, the mean scleral rigidity between the right and left eyes in patients with AMD was very much the same.<sup>20</sup> In addition, as the choroidal blood could act as vascular buffering that decreases the scleral rigidity,<sup>23 24</sup> it is unlikely that the more infiltrated scleral walls in eyes with disciform scar, and thus with less buffering effect, are less rigid than their fellow eyes with drusen. A long term follow up of the eyes with CNV might help us to understand the scleral rigidity change when the CNV began to cicatrise.

Another explanation for our findings is that the pulsatile components of the choroidal blood flow are dynamically influenced during the development of exudative AMD. From our study, eyes with CNV had more POBF than the contralateral eyes with drusen while eyes with drusen had higher POBF than their contralateral eyes with disciform scar. The disciform scar in the macula might replace multiple active CNV, disorganise the central choriocapillaris-Bruch's membrane complex, and damage the outer retina.<sup>25</sup> After burnout of the active vascularisation episode, these effects might decrease the need and supply of the choroidal blood vessels compared to their relatively well preserved, perfused contralateral eyes with drusen, while in eyes with CNV the active neovascularisation may attract more choroidal blood flow to the affected eyes than their contralateral eyes.

Whether the increased POBF leads to the development of CNV or vice versa is unknown. In a study using the laser interferometric method, Schmetterer *et al*<sup>26</sup> showed that topical fundus pulsation was lower inside the classic CNV than outside the membrane. The authors attributed this observation to changes in fundus layer or local choroidal perfusion abnormalities. The OBF tonometer measured a more global pulsation than the laser interferometer and might reflect more generalised choroidal perfusion abnormalities. Although there was delayed regional choroidal perfusion in some AMD patients,<sup>27</sup> our study indicated that in an active stage of CNV infiltration and exudation, the total choroidal blood flow might increase compared to the contralateral eyes with drusen. And, as the pulsatile components

of blood flow is delivered during systole,<sup>11</sup> an increased haemodynamic stress to the already thickened and defective Bruch's membrane in the systolic phase, especially the macular area which had larger pulsation than the periphery,<sup>28</sup> might have some association with the development of CNV.

Compared to other tools of measurements of choroidal blood flow, the extrapolation of the pneumatic ocular pulse measurement to the blood volume had some inherent defects.<sup>16</sup> In addition to the applied assumptions, the components of pulsatile blood flow to the total blood flow is unclear and ranges from 50% to 80%.<sup>10 11</sup> The POBF measurement also suffered from a high interindividual variation and moderate reliability of 70% when tested one day apart.<sup>9</sup> Some factors, such as age,<sup>29</sup> sex,<sup>7 30</sup> blood pressure,<sup>23 31</sup> and blood viscosity<sup>32</sup> may affect the POBF measurement. To keep these to the minimum, we compared the POBF between the fellow eyes with different disease states in the same individual instead of comparing groups of patients with or without exudative AMD.<sup>15</sup> By this, we can control those systemic factors which may affect the POBF measurement. Yet, our results should be interpreted carefully because they might be true only in a subgroup of patients with exudative AMD. Meanwhile, although we tried to follow the stringent definition of CNV and disciform scar from fluorescein angiography and colour fundus photographs, some of the patients had leaking disciform scar as described by Haas *et al*.<sup>33</sup> The type II disciform scar with leaking border beyond the arcades. Two patients in group 3 had these big leaking disciform scars and small classic CNV in their fellow eyes. These two patients both had higher PA in their eyes with disciform scar. This might explain the insignificant difference in POBF change in group 3.

Long term follow up and periodic measurements of POBF in patients with AMD may clarify the relation between the onset and regression of CNV. We are now studying the colour Doppler imaging and POBF simultaneously in patients with asymmetric exudative AMD. We hope that the correlation of these two measurements might help us to understand the haemodynamic role of the choroid in exudative AMD.

In conclusion, this study disclosed different changes in the pulsatile choroidal circulation in patients with asymmetric exudative AMD. The POBF in eyes with drusen was lower than in eyes with CNV, but higher than in eyes with disciform scar. This finding has lent some support to the vascular pathogenesis of exudative AMD. Although it is not possible to determine whether this change in pulsatile blood flow is causative or secondary to exudative AMD, further studies on the follow up patients, combined with colour Doppler imaging, might shed some light to the pathogenesis of this blinding eye disease.

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