The Influence of Sex Difference in Measurements with the Langham Ocular Blood Flow System

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Purpose: To assess sex difference and parameters possibly accounting for such a difference in healthy subjects evaluated by means of the Langham Ocular Blood Flow (OBF) System.

Methods: Pulse amplitude of intraocular pressure (IOP) and pulsatile ocular blood flow (POBF) as measured with the Langham OBF System were assessed in 86 healthy men and 69 healthy women.

Results: Compared to men, women showed higher POBF (mean ± SD: 722.6 ± 152.8 versus 647.8 ± 164.9 μL/min; $P = .0056$) and pulse amplitude (mean ± SD: 2.3 ± 0.7 versus 2.0 ± 0.6 mm Hg; $P = .0043$) values. Sex difference was still significant after correcting for age, refraction, blood pressure, IOP, and pulse rate. Pulse amplitude correlated negatively with pulse rate, and POBF correlated negatively with IOP. Women had higher readings in pulse amplitude and POBF, even after correcting for age, refraction, IOP, blood pressure, and pulse rate.

Conclusions: While using the Langham OBF System, one needs to be aware of sex difference that is independent of other hemodynamic parameters. How the observed difference in POBF is related to ocular blood flow, and how it might influence the preponderance of various ocular diseases in men or women remains to be clarified. **Jpn J Ophthalmol 2001; 45:528–532** © 2001 Japanese Ophthalmological Society

Key Words: Blood flow, choroid, hemodynamics, sex difference.

Introduction

Ocular blood flow abnormalities have been reported in several ocular diseases, such as age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, myopia, and glaucoma.[1–14] In recent years, there has been increasing interest in the quantitative assessment of ocular blood flow in patients with such diseases, as well as in healthy subjects.[8,15–17]

Among various techniques, the pulsatile ocular blood flow (POBF) assessment by means of the Langham Ocular Blood Flow (OBF) System[18] is frequently used. It is claimed that this technique derives blood flow measurements from a pressure/volume relationship,[19] permitting an evaluation of the pulsatile component of ocular blood flow, which is thought to account for 50%[20] to 80%[21,22] of total ocular blood flow. It has been suggested that the pulsatile component of ocular blood flow is a reliable parameter for the evaluation of choroidal circulation.[21] More recent studies seem to confirm the validity of the OBF system as a relative measure of pulsatile choroidal blood flow.[23,24]

The POBF may be affected by certain ocular diseases, such as glaucoma,[25,26] as well as by extraocular diseases, such as carotid stenosis.[27] Moreover, POBF changes may be related to age,[28] heart rate,[29] axial length and scleral rigidity,[30] as well as change in body posture.[26]

Several studies have shown that some systemic circulatory parameters may be different between men and women,[31–33] including ocular blood flow parameters.[34,35] The prevalence of ocular diseases such as age-related macular degeneration,[36] myopia,[37] and glaucoma[38] is different in men and women. Therefore, and because such differences may be related to different ocular circulatory conditions, it seems relevant to study the sex difference in ocular blood flow. The authors of previous studies describing ocular blood flow differences measured in male and female

Received: December 14, 2000

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Jpn J Ophthalmol 45, 528–532 (2001)

Published by Elsevier Science Inc.

0021-5155/01/$–see front matter
PII S0021-5155(01)00367-7

subjects by the Langham OBF System postulated[34,35] an influence of heart rate on their results, but did not provide statistical evidence for their hypothesis. Therefore, a detailed evaluation of the difference in ocular blood flow parameters between healthy men and women as measured by the Langham OBF System, as well as an analysis of potential factors possibly accounting for such a difference was performed in the present study.

Materials and Methods

Subjects between 16 and 78 years of age were recruited for the present study. The protocol had been approved by the institutional ethics committee, and each subject signed an informed consent form prior to any examination. Subjects were screened for systemic and ocular diseases. Age and sex were recorded. A detailed medical history was obtained. Subjects with a history of diabetes, high levels of blood lipids, systemic circulatory diseases, drug abuse, alcohol drinking, and smoking habits were excluded. Further exclusion criteria were ocular diseases, such as glaucoma and retinal vascular illness, and any eye-related surgery or medication.

Subjects were excluded if they had a history of systemic disease, any chronic systemic medication (especially α-adrenergic blockers, nicotinic acid, calcium-channel blockers, or other vasoactive drugs), drug or alcohol abuse. Further exclusion criteria were a best-corrected visual acuity worse than 20/25, ametropia with spherical equivalent ≤3 or >3 diopters, an applanatory intraocular pressure (IOP) of and above 20 mm Hg, or any pathological finding upon ophthalmologic examinations, including slit-lamp biomicroscopy and indirect fundoscopy.

All subjects underwent blood pressure (BP) measurement in the sitting position. Subjects relaxed in the reception area for at least 15 minutes prior to any BP measurement. The BP was evaluated by means of a mercury sphygmomanometer, with a standard adult cuff. One arm was exposed, and kept free from constricting clothing. During the BP measurements, the cuff was placed around the arm, approximately at heart level. The BP was evaluated by multiple measurements at 2-minute intervals, 2 to 3 times in each subject. Subjects with a high variation (>5 mm Hg) between measurements were excluded from the study. The systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurements were averaged for the entire experimental period. The mean blood pressure (MBP) was calculated according to the formula: $MBP = DBP + 1/3 \times (SBP - DBP)$.

The POBF assessment was performed by means of the Langham OBF System (OBF Labs, Malmesbury, Wiltshire, UK; software version 8.3). Basic fundamentals of this system have been described elsewhere.[20,22,39–41] Briefly, it is thought that the pulsatile component of choroidal circulation is calculated from the ocular pulse measured by an applanation pneumotonometer. During systole, a quantity of blood (bolus) enters the choroidal circulation, causing a change in IOP proportional to its volume. The pulsatile blood flow is calculated from the pulse amplitude. A pneumotonometer transmits IOP change signals recorded over a period of 15–20 seconds to a computer that automatically selects five pulses of equivalent amplitude. The POBF values are calculated after taking into account the heart rate and a standard value for scleral rigidity.[20,22,39–41] This instrument provides data with reasonable reproducibility.[42]

All OBF measurements were done by the same observer (MG). The POBF testing was conducted in the sitting position, with the pneumotonometer probe mounted on a slit-lamp microscope, following the instillation of a topical anesthetic (oxybuprocaine 0.4%). One randomly selected eye was tested in each subject. Measurements were all taken between 10 am and 12 pm in order to reduce the potential influence of circadian changes.

The OBF software automatically calculated and stored in the database the IOP, pulse amplitude, pulse rate, and POBF values recorded over a maximum period of 20 seconds. If during this time, five pulses of equivalent amplitude could not be recorded, the test was automatically interrupted and the recorded measurements were classified as of poor reliability by the computer software. Such measurements were excluded from further analysis.

From 324 subjects originally recruited for the present study, 50 (15.43%) were excluded on the basis of medical history revealing a relevant pathological condition or chronic medication intake; 43 (13.27%) subjects were excluded because of a refraction error ≥3 diopters (spherical equivalent); 33 (10.19%) subjects were excluded because they had an IOP ≥21 mm Hg on applanation tonometry; 23 (7.1%) subjects were excluded because they had an elevated systemic BP (SBP >140 or DBP >90); and 20 (6.17%) subjects were excluded from the statistical analysis because their results were classified as of poor reliability by the OBF software. As a result, 86 men (mean age ± SD: 44.1 ± 14.1 years) and 69 women (mean age ± SD: 44.4±15.6 years) were included in the analysis.

Differences between men and women in age, refraction, IOP, BP, pulse rate, POBF values, and

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pulse amplitude were analyzed by means of the Student *t*-test for unpaired variables. Furthermore, the differences in POBF values and pulse amplitude between male and female subjects were determined in a model of analysis of covariance (ANCOVA), with age, MBP, refraction, IOP, and pulse rate as changing covariates. The relationship between the ocular blood flow parameters (POBF and pulse amplitude) and sex, age, refraction, MBP, IOP, and pulse rate was analyzed by means of Pearson's linear correlation factors as well as in a least squares regression model (multiple regression), where the partial correlations, the correlation between a given predictive variable and the dependent variable after correcting for all other influences, were scrutinized. *P*-values $<.05$ were considered statistically significant.

Results

The characteristics of the study groups are given in Table 1. There were no statistically significant differences between men and women in age, refraction, IOP, and pulse rate, but women had a statistically significantly lower systemic BP than men (SBP, DBP, and MBP), as well as higher POBF and pulse amplitude values.

After correcting for age, refraction, MBP, IOP, and pulse rate in an analysis of covariance model, the observed differences between the sexes were still significant for pulse amplitude ($F = 7.28$; $P = .0077$) as well as for POBF ($F = 7.79$; $P = .0059$).

Pulse amplitude correlated statistically significantly with pulse rate ($R^2 = 0.06$; $P = .004$). No significant correlations were found between pulse amplitude and age ($R^2 < 0.001$; $P = .99$), refraction ($R^2 = 0.008$; $P = .26$), MBP ($R^2 = 0.006$; $P = .34$), or IOP ($R^2 = 0.002$; $P = .56$).

The POBF correlated statistically significantly with IOP ($R^2 = 0.12$; $P < .0001$). No significant correlations were found between POBF and age ($R^2 = 0.009$; $P = .23$), refraction ($R^2 = 0.015$; $P = .12$), MBP ($R^2 = 0.012$; $P = .16$), or pulse rate ($R^2 = 0.005$; $P = .38$).

A multiple regression analysis between pulse amplitude and sex, age, refraction, MBP, IOP, and pulse rate disclosed a statistically significant model ($R^2 = 0.12$; $P = .006$). Partial correlations disclosed a higher pulse amplitude for women ($P = .008$) and a lower pulse amplitude in subjects with higher heart rate ($P = .003$).

A multiple regression analysis between POBF and sex, age, refraction, MBP, IOP, and pulse rate disclosed a statistically significant model ($R^2 = 0.19$; $P < .0001$). Partial correlations disclosed higher POBF readings for women ($P = .006$), and lower POBF readings in subjects with higher IOP ($P < .0001$).

Table 1. Characteristics (Mean ± SD) of the Study Groups

Characteristics	Men (n = 86)	Women (n = 69)	*P*-Values
Age	44.1 ± 14.1	44.4 ± 15.6	.89
Refraction	0.07 ± 0.98	0.05 ± 0.97	.92
Systolic BP	122.7 ± 11.2	114.4 ± 12.33	<.0001
Diastolic BP	78.0 ± 7.7	74.9 ± 8.7	.017
Mean BP	92.9 ± 7.9	88.0 ± 8.9	.0004
IOP	16.1 ± 2.2	15.9 ± 2.4	.52
Pulse rate	74.6 ± 9.5	73.4 ± 8.8	.62
POBF	647.8 ± 164.9	722.6 ± 152.8	.0043
Pulse amplitude	2.0 ± 0.6	2.3 ± 0.7	.0056

BP: systemic blood pressure, IOP: intraocular pressure, POBF: pulsatile ocular blood flow.

Discussion

Studies investigating ocular hemodynamics are influenced by several variables that assume a critical relevance when measurements of different subjects are compared. Using analysis of variance and uni- as well as multivariate regression analysis models, we demonstrated that, independent of age, refraction, IOP, BP, and pulse rate, women have higher POBF and pulse amplitude values as measured by the Langham OBF system.

Studies dealing with sex difference in blood flow are scarce. Duvernoy et al[33] found that women have a higher blood flow in myocardium compared to men. Gur and Gur[31] as well as Daniel et al[32] showed that women have higher cerebral blood flow than men. There are also some observations regarding sex differences in ocular blood flow. Fontana et al,[35] in a large study collecting POBF measurements from more than 1500 subjects, found that POBF values were approximately 18% higher in women than in men, and postulated that part of this difference may be attributed to the higher heart rate found in women in their study. A similar influence was postulated by Yang et al,[34] who found that women had significantly higher POBF values compared to men, as well as higher pulse rates. However, the difference in pulse rate did not account for the entire differences between men and women in a multiple regression analysis model in the study from Fontana et al,[35] which is consistent with the present findings. The POBF values and the differences between the sexes found in the present study were comparable to those reported in previous studies in normal subjects.[34,35]

In the present study, no differences were found between men and women in pulse rate, but pulse amplitude correlated significantly with heart rate. The difference in pulse amplitude between men and women persisted after correcting for pulse rate. Furthermore, no influence of pulse rate on POBF was observed. Therefore, the sex difference in POBF values cannot be attributed to this variable. Finally, in a multiple regression model, pulse rate did not influence the POBF values. Consequently, pulse rate, although affecting pulse amplitude in ocular blood flow measurements by means of the Langham OBF System, does not entirely account for differences found between men and women in pulse amplitude and POBF.

The influence of further factors was addressed in multiple regression analysis models. Women in the present cohort had a significantly lower systemic BP than men. However, the BP influenced neither POBF nor pulse amplitude values in a multiple regression model, and the difference between men and women was independent of systemic BP in a covariance analysis model. The POBF was influenced by IOP, which was expected from earlier studies.[35,43] Higher IOP values were accompanied by lower POBF values. However, the IOP values of the subjects included in the study were in the normal range, and there was no statistically significant difference between men and women with regard to this parameter. Furthermore, IOP did not account for differences found between men and women in pulse amplitude and POBF in the statistical models applied. Consequently, the sex differences in POBF and pulse amplitude values cannot be attributed to IOP or systemic BP.

In contrast to earlier studies, we found no correlation between POBF and ametropia, possibly because, compared to previous investigations,[35,44] the range in refractive error was less marked in our study, Furthermore, age did not influence the readings in POBF in our study. However, the relationship found between POBF and age in earlier studies may be due to the influence of systemic BP. Previous studies either had not investigated the influence of systemic BP at all,[35] or had included subjects with high BP readings.[28] In our study, we excluded not only subjects treated for systemic hypertension, but also any individual with a high systemic BP reading during the selection of the subjects, because such individuals might not be aware of their high systemic BP condition. We had to consider an altered vascular system in such individuals (they were referred to their physician). The fact that the correlation between POBF and age was independent of the level of BP readings[28] cannot account for potential alteration in the vascular system induced by an unknown high BP condition. This peculiar fact may account for the differences found with regard to the influence of age on POBF between the current evaluation and earlier assessments.

To the best of our knowledge, the present study represents the most detailed statistical analysis of the sources of the differences between female and male subjects when assessed by means of the Langham OBF System, underlining the independence of such a difference from other measured hemodynamic parameters. An influence of the hormonal status on the choroidal circulation has been suggested as a possible reason for a higher POBF in healthy female subjects as assessed with the Langham OBF System, although the influence of hormones still needs to be clarified.[45] Furthermore, how the observed difference in POBF might influence the preponderance of various ocular diseases in men or women remains unclear. It is remarkable that similar differences between sexes have not been observed in studies using other noninvasive methods assessing choroidal blood flow,[46,47] although, admittedly, the pulsatility of choroidal blood flow has not been analyzed with regard to sex differences in these investigations. Indeed, the differences between male and female subjects described in the present study apply only to the pulsatile part of the choroidal blood flow. It must be stressed that the implications of the present results are, at least partly, also methodological. Indeed, because scleral rigidity might influence POBF measurements with the Langham OBF System, the present findings might not relate only to choroidal blood flow, although recent studies seem to substantiate the validity of data obtained with this device.[23,24] Furthermore, although it might be debatable how much measurements with this device relate to choroidal blood flow, it is widely used, especially for scientific studies. Consequently, it is important for those scientists who use this device to be aware of possible pitfalls during the measurements.

Supported by a grant of the Swiss National Foundation (32-059094.99).

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