Subfoveal Choroidal Thickness and Cerebrospinal Fluid Pressure: The Beijing Eye Study 2011

Jost B. Jonas, Ningli Wang, Ya Xing Wang, Qi Sheng You, Diya Yang, Xiaobin Xie, Wen Bin Wei, and Liang Xu

1Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Science Key Lab, Beijing, China
2Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University of Heidelberg, Heidelberg, Germany
3Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing, China
4Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Correspondence: Liang Xu, Beijing Institute of Ophthalmology, 17 Hou-gou Lane, Chong Wen Men, 100005 Beijing, China; xlbio1@163.com.

JBJ and NW are joint first authors.

Submitted: September 27, 2013
Accepted: January 4, 2014


Purpose. The venous choroidal blood drains through the superior orbital vein into the intracranial cavernous sinus. The cerebrospinal fluid pressure (CSFP) may thus influence the choroidal venous blood pressure. Since volume and thickness of the choroid depend on its pressure, we tested the hypothesis whether the subfoveal choroidal thickness (SFCT) is associated with CSFP.

Methods. The population-based Beijing Eye Study 2011 included 3468 individuals. A detailed ophthalmic examination was performed including spectral-domain optical coherence tomography (SD-OCT) with enhanced depth imaging for measurement of SFCT. The CSFP was calculated as CSFP (mm Hg) = 0.44 × Body Mass Index (kg/m²) + 0.16 × Diastolic Blood Pressure (mm Hg) − 0.18 × Age (years) − 1.91.

Results. Mean calculated CSFP was 8.8 ± 3.7 mm Hg and mean SFCT was 254 ± 107 μm. In multivariate analysis, SFCT was significantly associated with higher CSFP (P = 0.009; standardized coefficient β: 0.08; regression coefficient B: 2.27) after adjusting for lower age (P < 0.001; β: −0.36; B: −3.99), shorter axial length (P < 0.001; β: −0.37; B: −35.7), lower body mass index (P = 0.02; β: −0.05; B: −1.51), and higher corneal curvature radius (P < 0.001; β: 0.10; B: 41.1). In univariate analysis, SFCT increased by 9.2 μm (95% confidence interval: 8.3, 10.1) for each mm Hg increase in CSFP. In a reverse manner, CSFP was significantly associated with thicker SFCT (P < 0.001; B: 0.007; β: 0.21), after adjusting for region of habitation (P < 0.001; B: −0.51; β: −5.22), higher levels of glucose (P = 0.02; B: 0.10; β: 0.04) and triglycerides (P < 0.001; B: 0.13; β: 0.09), higher intraocular pressure (P < 0.001; B: 0.17; β: 0.12), and thinner lens (P < 0.001; B: −2.39; β: −0.22).

Conclusions. Thicker subfoveal choroid was associated with higher CSFP after adjustment for age, axial length, body mass index, and corneal curvature radius. This association may explain thicker SFCT measurements in the morning than evening. It shows the importance of the CSFP for the physiology of the eye.

Keywords: subfoveal choroidal thickness, cerebrospinal fluid pressure, translamina cribrosa pressure difference, axial length, Beijing Eye Study

As a highly vascularized structure between the sclera and Bruch’s membrane, the choroid is composed of the choriocapillaris, the middle layer of medium-sized vessels (Sattler’s layer) and the outer layer with large vessels (Haller’s layer), melanocytes interposed between the vessels of Sattler’s layer and Haller’s layer, a NADPH-diaphorase–positive and nitric oxide synthase–positive ganglion cell plexus located mainly in the temporal–central portion, connective tissue, and other cellular elements. The choroid is primarily or secondarily involved in the pathogenesis of many diseases of the posterior segment of the eye, such as age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy, and myopic retinopathy. The arterial blood supply of the choroid occurs mainly through the short posterior ciliary arteries, and the choroid receives approximately 95% of the ophthalmic artery blood. The drainage of the venous blood is carried out through the vortex veins and the superior orbital vein, which joins the intracranial cavernous sinus within the compartment of the cerebrospinal fluid pressure (CSFP). Since the pressure in the draining part of a system of communicating tubes influences the pressure in the main part of the system, the CSFP may influence the choroidal venous blood pressure. Since the volume and thus the thickness of the choroid depend on its pressure, we tested the hypothesis whether the subfoveal choroidal thickness (SFCT) is associated with the CSFP. We used the enhanced depth imaging (EDI) mode of optical coherence tomography (OCT) as described by Spaide and colleagues to measure the choroidal thickness. We chose a population-based study design to avoid the potential bias due to referral-related selection of study participants. Since measurement of CSFP is
invasive, we estimated the CSFP from diastolic blood pressure, age, and body mass index, using a formula that was derived in a previous investigation on the relationship between these three parameters.\textsuperscript{15,13}

**METHODS**

The Beijing Eye Study\textsuperscript{14,15} is a population-based cross-sectional study in Northern China.\textsuperscript{16} The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants gave informed consent according to the Declaration of Helsinki. The study was carried out in five communities in an urban district in the North of Central Beijing and in three communities in a rural region south of Beijing. All subjects living in the communities and fulfilling the inclusion criterion of an age of $\geq 50$ years were eligible for the study. Of an eligible population of $4403$ individuals ($56.6\%$ women) participated in the eye examination. The study was divided into a rural part ($1633$ individuals ($56.6\%$ women) and an urban part ($1855$ ($52.9\%$) women; $1020$ ($55.6\%$) women). The mean age was $64.6 \pm 9.8$ years (median, $64$; range, $50$–$93$ years). The details of the Beijing Eye Study 2011 have been described recently.\textsuperscript{16}

All study participants underwent an interview with standardized questions on topics such as their family status, level of education, quality of life, known major systemic diseases, and quality of vision. Fasting blood samples were taken for measurement of blood lipids, glucose, and glycosylated hemoglobin HbA1c. Blood pressure was measured. Body height and weight and the circumference of the waist and hip were recorded. The ophthalmic examination included measurement of visual acuity with refractometry; tonometry; slit lamp examination of the anterior and posterior ocular segment; biometry of the right eyes (or of the left eyes if measurements of the right eye were not possible) (Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland); and digital photography of the cornea, lens (slit lamp digital camera Type BG-4; Topcon Medical Systems, Inc., Tokyo, Japan); retroilluminated lens photographs by Neitz CTR camera [Neitz Instruments Co., Tokyo, Japan]), macula, and optic disc (fundus camera CR6-15NM; Canon, Inc., Ota, Tokyo, Japan).

The SFCT was measured by using a spectral-domain OCT (SD-OCT) (wavelength: $870$ nm, Spectralis; Heidelberg Engineering Co., Heidelberg, Germany) with EDI modality after pupil dilation.\textsuperscript{17} Seven sections, each comprising $100$ averaged scans, were obtained in an angle of $5^\circ$ to $30^\circ$ rectangle centered onto the fovea. The horizontal section running through the center of the fovea was selected for further analysis. The SFCT was defined as the vertical distance from the hyperreflective line of the Bruch's membrane to the hyperreflective line of the inner surface of the sclera. The measurements were performed by using the Heidelberg Eye Explorer software (version 5.3.3.0; Heidelberg Engineering Co.). Only the right eye of each study participant was assessed.

For the calculation of a formula to estimate the CSFP, we used the lumbar CSFP measurements obtained in a previous study on $74$ Han Chinese patients who consecutively underwent lumbar puncture for diagnosis and treatment of neurologic diseases.\textsuperscript{13} These included peripheral neuropathy, intracranial hypertension, spontaneous intracranial hypotension, cavernous sinus syndrome, meningitis, multiple sclerosis, unilateral ischemic optic neuropathy, unilateral optic neuritis, optic nerve atrophy, and head injury. The mean measured CSFP was $12.6 \pm 4.8$ mm Hg. Of the total group, we randomly formed a training group consisting of $32$ patients, and a test group including the remaining $42$ patients. A multivariate analysis in the training group showed that CSFP was best described by the following formula: $\text{CSFP (mm Hg)} = 0.44 \times \text{Body Mass Index (kg/m}^2) + 0.16 \times \text{Diastolic Blood Pressure (mm Hg)} - 0.18 \times \text{Age (years)} - 1.91$. The association between higher CSFP and younger age, higher body mass index and higher blood pressure had also been found in other investigations.\textsuperscript{18,19} We then applied the formula in the test group. In the latter, the measured lumbar CSFP ($12.6 \pm 4.8$ mm Hg) did not differ significantly ($P = 0.29$) from the calculated CSFP ($13.3 \pm 3.2$ mm Hg). The Durbin-Watson value was $2.08$. Values falling into the acceptable range of $1.5$ to $2.5$ indicate a nonsignificant autocorrelation for the residuals in the multiple regression models.\textsuperscript{20} The intraclass correlation coefficient was $0.71$. The Bland-Altman analysis revealed that $40$ of $42$ measurements were within the $95\%$ limits of agreement. If the test group was taken as training group, the algorithm to calculate the CSFP was as follows: $\text{CSFP (mm Hg)} = 0.85 \times \text{Body Mass Index (kg/m}^2) + 0.27 \times \text{Diastolic Blood Pressure (mm Hg)} - 0.08 \times \text{Age (years)} - 24.8$.

Exclusions for the present study were opacities of the optic media such as cataract, which prevented OCT imaging of the choroid, and insufficient quality of the OCT images for a reliable determination of the SFCF.

Statistical analysis was performed by using a commercially available statistical software package (SPSS for Windows, version 21.0; IBM-SPSS, Chicago, IL). In a first step, we examined the mean values (presented as mean $\pm$ standard deviation) of SFCT and CSFP. In a second step, we performed a univariate linear regression analysis with SFCT or CSFP as dependent parameter, and ocular and general parameters as independent parameters. In a third step, we performed a multivariate linear regression analysis with SFCT or CSFP as dependent parameter, and all those parameters as independent parameters that were significantly associated with SFCT in univariate analysis. We presented the $95\%$ confidence intervals (CIs). All $P$ values were two sided and were considered statistically significant when the values were less than $0.05$.

**RESULTS**

For the $3468$ participants, SFCT measurements and data on body mass index and blood pressure were available for $3230$ ($93.1\%$) subjects ($1815$ ($56.2\%$) women). The group of subjects without complete data on measurements of SFCT, body mass index, or blood pressure, as compared with the group of subjects with complete data, was significantly older ($69.6 \pm 9.8$ years vs. $64.3 \pm 9.6$ years; $P < 0.001$), had a higher diastolic blood pressure ($75.8 \pm 15.7$ mm Hg vs. $69.7 \pm 12.2$ mm Hg; $P < 0.001$), more myopic ($-1.72 \pm 4.60$ diopters [D] vs. $-0.17 \pm 1.96$ D; $P = 0.001$), and had a longer axial index, or blood pressure, as compared with the group of subjects with complete data, was significantly older ($69.6 \pm 10.9$ years vs. $64.3 \pm 9.6$ years; $P < 0.001$), had a higher diastolic blood pressure ($75.8 \pm 15.7$ mm Hg vs. $69.7 \pm 12.2$ mm Hg; $P < 0.001$), was more myopic ($-1.72 \pm 4.60$ diopters [D] vs. $-0.17 \pm 1.96$ D; $P = 0.001$), and had a longer axial length ($23.6 \pm 1.8$ mm vs. $23.2 \pm 1.1$ mm; $P = 0.03$). Both groups did not vary significantly in sex ($P = 0.08$) and body mass index ($P = 0.58$). The mean calculated CSFP in the group of subjects with SFCT measurements ($8.8 \pm 3.7$ mm Hg) and the group of excluded subjects without SFCT measurements ($8.2 \pm 4.3$ mm Hg) did not differ significantly ($P = 0.08$). Reasons why SD-OCT images for the measurement of the SFCT were not available in $238$ subjects were opacities of the optic media, such as cataract, in approximately $90$ subjects, and insufficient quality of the images for a reliable determination of the SFCT in approximately $148$ subjects.

The mean age in the population of the present study was $64.3 \pm 9.6$ years (median: $63$ years; range, $50$ to $93$ years), the mean refractive error (spherical equivalent) was $-0.17 \pm 1.96$ D (median: $0.25$ D; range, $-20.0$ to $+7.00$ D), and mean axial length was $23.2 \pm 1.1$ mm (median: $23.13$ mm; range, $18.96$-
TABLE 1. Associations Between Subfoveal Choroidal Thickness and Systemic and Ocular Parameters (Univariate Analysis)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P Value</th>
<th>Standardized Regression Coefficient B</th>
<th>Regression Coefficient B</th>
<th>95% Confidence Intervals of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated cerebrospinal fluid pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>9.19</td>
<td>8.25, 10.1</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>-0.44</td>
<td>-4.86</td>
<td>-5.20, -4.51</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban/rural region of habitation</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body height, cm</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>1.14</td>
<td>0.69, 1.59</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>&lt;0.001</td>
<td>0.12</td>
<td>1.14</td>
<td>0.85, 1.46</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>2.45</td>
<td>1.49, 3.41</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.15</td>
<td>1.28</td>
<td>0.98, 1.58</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose concentration, mM</td>
<td>0.01</td>
<td>0.05</td>
<td>3.47</td>
<td>0.79, 6.16</td>
</tr>
<tr>
<td>Blood cholesterol concentration, mM</td>
<td>0.03</td>
<td>0.04</td>
<td>4.03</td>
<td>0.39, 7.66</td>
</tr>
<tr>
<td>Blood concentration of high-density lipoproteins, mM</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood concentration of low-density lipoproteins, mM</td>
<td>0.052</td>
<td>0.04</td>
<td>4.63</td>
<td>-0.04, 9.30</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>-0.35</td>
<td>-3.38</td>
<td>-3.70, -3.06</td>
</tr>
<tr>
<td>Refractive error, D</td>
<td>&lt;0.001</td>
<td>-0.29</td>
<td>15.6</td>
<td>13.8, 17.5</td>
</tr>
<tr>
<td>Anterior corneal curvature radius, mm</td>
<td>&lt;0.001</td>
<td>-0.10</td>
<td>-4.35</td>
<td>-5.81, -2.84</td>
</tr>
<tr>
<td>Anterior chamber depth, mm</td>
<td>&lt;0.001</td>
<td>-0.09</td>
<td>-19.3</td>
<td>-27.0, -11.6</td>
</tr>
<tr>
<td>Lens thickness, mm</td>
<td>&lt;0.001</td>
<td>-0.07</td>
<td>-21.2</td>
<td>-32.7, -9.7</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>2.59</td>
<td>1.24, 3.95</td>
</tr>
</tbody>
</table>

30.88 mm). This study group was almost identical to the group of subjects examined in a previous investigation on the SFCT without taking into account the CSFP.16

Mean calculated CSFP was 8.8 ± 3.7 mm Hg (median: 8.8 mm Hg) and mean SFCT was 254 ± 107 μm (median: 252 μm; range: 8–854 μm).

In univariate analysis, SFCT was significantly (all P < 0.05) associated with higher CSFP (Fig.), younger age, male sex, urban region, taller body height, higher body weight, higher body mass index, longer waist circumference, higher diastolic blood pressure, and higher blood concentration of glucose and cholesterol, and with the ocular parameters of shorter axial length, refractive error, steeper anterior corneal curvature, flatter anterior chamber depth, thinner lens, and higher intraocular pressure (Table 1). The univariate analysis of the association between SFCT and CSFP showed that for each mm Hg increase in CSFP, the SFCT increased by 9.2 mm (95% CI: 8.3, 10.1) (Fig.). The SFCT was not significantly (all P ≥ 0.20) associated with systolic blood pressure, higher pulse, level of education, and blood concentration of high-density lipoproteins (Table 1).

In a first step of the multivariate analysis, we adjusted the SFCT for those parameters for which the value of the regression coefficient was higher than 0.20 (i.e., age, axial length, region of habitation, CSFP), and for body mass index as parameter combining body height and body weight. It revealed that SFCT remained significantly associated with higher CSFP (P = 0.005), younger age (P < 0.001), shorter axial length (P < 0.001), and lower body mass index (P = 0.03), while region of habitation was no longer significantly associated (P = 0.56). We then included the remaining ocular variables into the list of independent parameters. We dropped intraocular pressure, since it was no longer significantly associated with SFCT (P = 0.35), we dropped anterior chamber depth owing to an inflation variance factor of 2.1 (indicating a high collinearity), and we dropped lens thickness. We arrived at a model in which SFCT was significantly associated with higher CSFP after adjusting for lower age, shorter axial length, lower body mass index, and higher corneal curvature radius (Table 2). If age was dropped, since age was included in the formula to calculate CSFP, SFCT was associated with higher CSFP, shorter axial length, lower body mass index, and longer corneal curvature radius.

The calculated SFCT showed a Gaussian distribution curve (Kolmogorov-Smirnov test; P = 0.75). In multivariate analysis, as also shown in a previous study,21 CSFP was significantly (all P < 0.005) associated with urban region, higher blood concentrations of glucose and triglycerides, higher intraocular pressure, and thinner lens. Adding SFCT showed that CSFP was significantly associated with thicker SFCT (P < 0.001) after adjusting for the region of habitation, higher levels of glucose and triglycerides, higher intraocular pressure, and thinner lens (Table 3).

If we took the second algorithm for calculation of the CSFP (CSFP [mm Hg] = 0.85 × Body Mass Index [kg/m²] + 0.27 × Diastolic Blood Pressure [mm Hg] – 0.08 × Age [years] – 24.8), similar results were obtained: SFCT was significantly associated with higher CSFP (P = 0.009) after adjusting for lower age, shorter axial length, lower body mass index, and higher corneal curvature radius (Table 2). If age was dropped, since age was included in the formula to calculate CSFP, the SFCT was associated with higher CSFP, shorter axial length, lower body mass index, and longer corneal curvature radius (Table 2).

DISCUSSION

Using data of body mass index, diastolic blood pressure, and age for the estimation of CSFP, our population-based study showed that the subfoveal choroid in a general population was associated with a higher CSFP. After adjustment for younger age, shorter axial length, lower body mass index, and higher corneal curvature radius, SFCT increased significantly with higher CSFP. In univariate analysis, SFCT increased by 9.2 μm for each mm Hg increase in CSFP. In a reverse manner, CSFP was significantly associated with thicker SFCT after adjusting for the region of habitation, blood concentrations of glucose and triglycerides, intraocular pressure, and lens thickness.

In the univariate analysis, both SFCT and CSFP were significantly associated with younger age. The relationship
between thicker choroid and younger age, as also shown in other studies.\textsuperscript{22,25} may perhaps be explained by an age-related loss in choroidal tissue. The relationship between higher estimated CSFP and younger age, as also found in other studies, may be parallel to the age-related decline in intraocular pressure.\textsuperscript{24,25} It corresponds to the trilateral associations between thicker choroid and younger age, as also shown in other studies. While the reasons for this discrepancy have not been fully explored yet, one may speculate that the more marked and the more rapid changes in systolic blood pressure are reflected faster in changes in CSFP, while SFCT may react more slowly and may thus be influenced mainly or only by the diastolic blood pressure value.

These findings fit with clinical studies on circadian variations in SFCT, since the CSFP shows profound circadian changes due to the hydrostatic differences between the supine position and the sitting or standing position. Chakraborty and colleagues\textsuperscript{27} have investigated the pattern of diurnal variations in choroidal thickness and other ocular biometric parameters during 2 consecutive days. These authors have found that the choroid is thicker at night and thinnest in the morning, with a mean amplitude of change in choroidal thickness of 29 μm. Usui and colleagues\textsuperscript{28} have examined 38 eyes of 19 healthy volunteers and measured the SFCT every 3 hours over a 24-hour period. They have found that the SFCT is thickest (291 ± 111 μm) at 3 AM in the early morning, and that it is thinnest at 6 PM (272 ± 104 μm). In 32 of 38 eyes, the SFCT was thickest between 3 AM and 9 AM, and it was thinnest between 3 PM and 9 PM in 27 of 38 eyes. In an investigation by Tan et al.,\textsuperscript{29} 12 healthy volunteers underwent sequential ocular imaging on 2 separate days at five fixed, 2-hour time intervals, starting at 9 AM. They have observed a characteristic diurnal pattern in choroidal thickness, with the highest mean choroid thickness detected at 9:00 AM (the earliest measurement point) with a mean SFCT of 372 μm and a continuous decrease in SFCT over the subsequent time points to a low of 340 μm at 5 PM. These diurnal changes in the SFCT are usually accompanied by opposed changes in axial length. Accordingly, previous studies have shown an increase in optical axial length in the morning and a decrease in the evening.\textsuperscript{30} In a similar manner, experimental studies have revealed circadian rhythms in axial length, choroidal thickness, and intraocular pressure, for example, in chickens and in primates such as the common marmoset. Nickla and colleagues\textsuperscript{31} have examined 14 marmosets by tonometry and high-frequency A-scan ultrasonography to measure the ocular dimensions. The authors have observed

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardized Regression Coefficient β</th>
<th>Regression Coefficient B</th>
<th>95% Confidence Intervals of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>First algorithm (CSFP [mm Hg] = 0.44 × Body Mass Index [kg/m²] + 0.16 × Diastolic Blood Pressure [mm Hg] - 0.18 × Age [y] - 1.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated cerebrospinal fluid pressure, mm Hg</td>
<td>0.009</td>
<td>0.08</td>
<td>2.27</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>-0.36</td>
<td>-3.99</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>-0.37</td>
<td>-3.57</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.02</td>
<td>-0.05</td>
<td>-1.51</td>
</tr>
<tr>
<td>Corneal curvature radius, mm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>41.1</td>
</tr>
<tr>
<td>After dropping of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated cerebrospinal fluid pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>12.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>&lt;0.001</td>
<td>-0.23</td>
<td>-6.4</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>-0.37</td>
<td>-36.0</td>
</tr>
<tr>
<td>Corneal curvature radius, mm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>41.5</td>
</tr>
<tr>
<td>Second algorithm (CSFP [mm Hg] = 0.85 × Body Mass Index [kg/m²] + 0.27 × Diastolic Blood Pressure [mm Hg] - 0.08 × Age [y] - 24.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated cerebrospinal fluid pressure, mm Hg</td>
<td>0.009</td>
<td>0.07</td>
<td>1.34</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>-0.39</td>
<td>-4.29</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>-0.37</td>
<td>-35.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.02</td>
<td>-0.06</td>
<td>-1.66</td>
</tr>
<tr>
<td>Corneal curvature radius, mm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>41.1</td>
</tr>
<tr>
<td>After dropping of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated cerebrospinal fluid pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.30</td>
<td>5.81</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>&lt;0.001</td>
<td>-0.18</td>
<td>-4.9</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>-0.39</td>
<td>-37.7</td>
</tr>
<tr>
<td>Corneal curvature radius, mm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>43.7</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardized Regression Coefficient β</th>
<th>Regression Coefficient B</th>
<th>95% Confidence Intervals of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subfoveal choroidal thickness, μm</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.007</td>
</tr>
<tr>
<td>Rural/urban region of habitation</td>
<td>&lt;0.001</td>
<td>-0.31</td>
<td>-2.32</td>
</tr>
<tr>
<td>Blood glucose concentration, mM</td>
<td>0.02</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>Blood triglyceride concentration, mM</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>0.13</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>&lt;0.001</td>
<td>0.12</td>
<td>0.17</td>
</tr>
<tr>
<td>Lens thickness, mm</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>-2.39</td>
</tr>
</tbody>
</table>
that the choroid thickens during the night and thins during the
day at all ages measured.

Interestingly, the amount of macular edema in patients
showed similar diurnal changes as described for choroidal
thickness. Paques and colleagues\textsuperscript{32} have examined patients
with macular edema due to central retinal vein occlusion and
observed a significantly thicker macular edema at 7 AM than at
7 PM, parallel to changes in visual acuity. Similar observations
have been reported by Gupta et al.\textsuperscript{33} These findings pointing to
an increased pressure in the central retinal vein in the morning
as compared to the evening may be explained by the
assumption that the pressure in the central retinal vein
depends on the CSFP , since the vein passes through the optic
nerve cerebrospinal fluid space and drains into the intracranial
cavernous sinus. Both findings, the diurnal changes in the SFCT
and the diurnal changes in the amount of macular edema, suggest the CSFP may play a role in the physiology of the eye,
in particular for the pressure and thus the thickness of the
choroid, as well as for the pressure in the central retinal vein.

In a previous study, the reproducibility of the SFCT
measurements has been tested by comparing the SFCT
measurements obtained by grader 1 and by grader 2.\textsuperscript{17} The
mean difference between both measurements is 3.1 \pm 13.1
\mu m (95\% CI: 0.0, 24.0), and the Bland-Altman plot shows that
1.9\% (61/3233) of the points are located outside the 95\% limits
of agreement. For the assessment of the intra-observer
reproducibility, 21 eyes of 21 healthy subjects were scanned
10 times with 1-minute breaks between each examination. The
intraclass coefficient was 1.00 and the mean coefficient of
variation was 0.85\% \pm 1.48\%. The results of the present
investigation on the use of the CSFP formula with respect to
the SFCT in the Beijing Eye Study correspond with those of a
recent study on the population of the Central India Eye and
Medical Study, the translamina cribrosa pressure difference,
but not intraocular pressure, is significantly associated with
open-angle glaucoma but not with angle-closure glaucoma,
while the intraocular pressure, but not the translamina cribrosa
pressure difference, is significantly associated with angle-
closure glaucoma but not with open-closure glaucoma.\textsuperscript{34}

A major assumption of this article was that CSFP can be
assessed by a formula based on the three parameters of
diastolic blood pressure, age, and body mass index. This
formula was arrived at by using data from an observational
study on patients undergoing lumbar puncture for neurologic
diseases, which eventually were not felt to have influenced the
CSFP. Since inclusion of invasive lumbar CSFP measurements
into the design of a population-based study is not acceptable,
one may plan for a prospective study in which the association
between SFCT and CSFP is directly tested. In such an
investigation, diurnal measurements of diastolic blood pressure
could be compared with diurnal measurements of SFCT, or the
association between SFCT and CSFP could be addressed by
examining subjects at different body postures (with different
CSFPs). The question may arise, however, whether an
association between relatively small diurnal changes in SFCT,
or posture-dependent changes in SFCT, and corresponding
changes in diastolic blood pressure (the two other determin-
ants in the CSFP formula, i.e., age and body mass index, are
constant) can be found. One may also take into account that
blood pressure can show rapid changes, while one may assume
that the SFCT may change relatively slowly. Another model to
assess the postulated association between SFCT and CSFP may
be a condition with chronically elevated CSFP such as in
idiopathic intracranial hypertension. In such a study, patients
would undergo OCT for measurement of the SFCT at baseline
and again after a therapeutically induced reduction in CSFP.

Potential limitations of our study should be mentioned.
First, the whole statistical analysis depended on the formula to
calculate the CSFP. This formula was developed in a pilot study

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scatterplot.png}
\caption{Scatterplot showing the correlation between estimated cerebrospinal fluid pressure and subfoveal choroidal thickness in the Beijing Eye Study 2011 ($P < 0.001$; correlation coefficient $r = 0.32$; equation of the regression line: Subfoveal Choroidal Thickness [\mu m] = 9.2 \times \text{Estimated Cerebrospinal Fluid Pressure (mm Hg)} + 175).}
\end{figure}
that included a relatively small number of subjects. These subjects had a clinical reason to undergo lumbar puncture, so that they were not normal subjects. Although the final neurologic diagnosis made it unlikely that the underlying neurologic condition had influenced the CSFP, one has to keep in mind that the participants were not randomly selected normal subjects. One may also consider that the estimation of CSFP was derived from a multivariate formula incorporating body mass index, diastolic blood pressure, and age. The mathematical result of this formula was termed CSFP. Although this calculated CSFP value was primarily the result of a mathematical equation, it correlated well with invasively measured CSFP values in the independent test group in the pilot study. The unknown general validity of the equation to estimate the CSFP may however be the most important limiting factor of our study. In view of this weakness in the study design, one may however also take into account that it would not have been possible to measure the CSFP in a population-based study. Second, as in any prevalence study, nonparticipation may be a major concern. The Beijing Eye Study 2011 had a reasonable response rate of 78.8%; however, differences between participants and nonparticipants could have led to a selection artifact. Third, blood pressure, as part of the formula to calculate CSFP and the SFCT, was measured only once, so that diurnal and situation-dependent variations may have influenced the measurements and statistical analysis.

Fourth, the participants of our study underwent the OCT examinations at various times of the day. Since these examinations were performed in a randomized manner with respect to when they were performed, it is unlikely that the reported dependence of the choroidal thickness measurement on the time of day introduced a bias into our study. It will have increased the inaccuracy or noise in the measurements, leading to a reduced statistical power of the measured parameters. Despite this weakness, however, the association between SFCT and CSFP was statistically significant so that this limitation of the study may serve to strengthen the results and conclusions. If we had documented the time of day when the OCT images were taken, we would have had the possibility to assess a change in the SFCT dependent on the time of day that the OCT images were taken, and to look for a parallel change in the estimated CSFP. Fifth, as with any population-based study, our investigation included all eligible and participating subjects from the study region. Therefore, also patients with diseases, such as disorders of the optic nerve and macula, were included, although these diseases may have affected the choroidal thickness, either in the sense of a thickening or in the sense of a thinning. Future studies may address whether these diseases show a different association between SFCT and CSFP.

In conclusion, thicker subfoveal choroid was associated with higher CSFP after adjustment for age, axial length, body mass index, and corneal curvature radius. This association may explain thicker SFCT values in the morning than evening. It shows the importance of the CSFP for the physiology of the eye.

Acknowledgments

Supported by National Natural Science Foundation of China Grant 81770890 and National Key Technology R&D Program of the Ministry of Science and Technology Grants 2012BAH05F05 and 2013BAH19F04. The sponsor or funding organization had no role in the design or conduct of this research. The authors alone are responsible for the content and writing of the paper.

Disclosure: J.B. Jonas, None; N. Wang, None; Y.X. Wang, None; Q.S. You, None; D. Yang, None; X. Xie, None; W.B. Wei, None; L. Xu, None

References


