The Relationship of Intraocular Pressure with Age, Systolic Blood Pressure, and Central Corneal Thickness in an Asian Population

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PURPOSE. To describe the distribution of intraocular pressure (IOP) and its cross-sectional relationship to age, systolic blood pressure (sBP), and central corneal thickness (CCT) in an Asian population.

METHODS. This was a population-based, cross-sectional study of 3280 Malay subjects (78.7% response) aged 40 to 80 years residing in Singapore. The participants had a standardized interview, examination, and ocular imaging at a centralized study clinic. IOP was measured with Goldmann applanation tonometry (GAT) before pupil dilation, CCT measurements were obtained with an ultrasound pachymeter, and sBP was taken with participants seated after 5 minutes of rest with an automatic blood pressure monitor.

RESULTS. IOP increased with age to the sixth decade, after which a decrease in IOP was seen with further increase in age, resulting in an inverted U pattern. sBP increased linearly with age whereas CCT decreased linearly with age. In regression analysis, models, age, CCT, and sBP were all significant determinants of IOP (P < 0.001 for all three). In younger persons aged 40 to 59 years, both CCT and sBP were positively associated with IOP (P < 0.001 for both), but in older persons of 60 to 80 years, only age and sBP had a positive association with of IOP (P = 0.001 for age, P < 0.001 for sBP).

CONCLUSIONS. Age, CCT and sBP are significant determinants of IOP in persons aged 40 to 80 years, with CCT being a more important determinant in younger persons. The opposing effects of age-specific changes in sBP and CCT interact to lead to a relatively flat profile of IOP with age, possibly with a subtle a relatively flat profile of IOP with age, possibly with an inverted U-shaped relationship. (Invest Ophthalmol Vis Sci. 2009;50:4097–4102) DOI:10.1167/iovs.08-2822

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Intraocular pressure (IOP) is the key modifiable risk factor for glaucoma, and understanding its distribution with age is important for definition of “normal values.” In this regard, previous population-based studies in Caucasians have generally reported a positive correlation between increasing age and IOP.1–5 In contrast, an inverse relationship of age and IOP has been reported in Japanese populations.6–8 The reasons for this apparent discrepancy are unclear.

To understand the relationship of IOP with age, we considered two factors that together influence IOP: systolic blood pressure (sBP) and central corneal thickness (CCT).9 Population studies have consistently found a positive correlation between sBP and IOP in Caucasian,10,11 black,12 Japanese,8,13 and Chinese populations.14–15 The relationship between age and CCT has also been investigated, but with more conflicting results. For example, results of studies conducted in Caucasians and blacks have suggested that CCT is independent of the effect of age,16 but reports of studies of Asian people indicate that CCT decreases with age.17–19 Furthermore, the Beijing Eye Study did not find age to be significantly associated with CCT.20 The Ocular Hypertension Treatment Study was a large prospective effort that found that CCT is a prognostic factor for glaucomatous progression in patients with ocular hypertension.21 The authors concluded that individuals who have decreased CCT are more likely to progress to glaucoma. Furthermore, CCT has been reported to be influenced by factors such as age, sex, race and tonometric measurements, all of which would have an influence on the IOP recorded.19,22,23

It is clear that the influence of age, CCT, and sBP on IOP is complex and cannot be examined in isolation. We therefore sought to investigate these interrelationships in a population-based study among Malay adults in Singapore. We hypothesize that increasing sBP and decreasing CCT with age are important influences driving the distribution of IOP with age.

METHODS

Study Population

The Singapore Malay Eye Study was a population-based cross-sectional study of 3280 Malay subjects residing in Singapore that was conducted between August 2004 and June 2006.24,25 In brief, an age-stratified random sampling procedure was used to select Malay people aged 40 to 80 years living in the South-Western part of Singapore. From 4168 persons eligible to participate, 3280 were examined (response rate of 78.7%).25 Nonparticipants were older (28.9% vs. 22.2% were 70–80 years, comparing nonparticipants and participants; P < 0.001) but did not differ by sex (52.4% vs. 52.0% were females, P = 0.82) or possession of telephone in their homes (64.6% vs. 63.7% owned telephones, P = 0.63).

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethics approval was obtained from the Singapore Eye Research Institute (SERI) Institutional Review Board.
Study Measurements

Participants underwent a comprehensive systemic and ocular examination. Relevant portions of the examination are presented here. A slit lamp examination (BQ-900; Haag-Streit, Koeniz, Switzerland) was performed before and after pharmacological dilation of the pupil. IOP was measured using a Goldmann applanation tonometer (GAT; Haag-Streit) before pupil dilation. A single drop of topical anesthesia (amethocaine hydrochloride 0.5%) was instilled into the inferior conjunctival sac, and a dry strip of fluorescein was used to stain the cornea. Care was taken to ensure that just enough fluorescein was used to make the tonometry prism visible. One reading was taken from each eye. If the IOP reading was greater than 21 mm Hg, a repeat reading was taken and the second reading was used for analysis.

Five CCT measurements were obtained from each eye with an ultrasound pachymeter (Advent, Mentor O & O, Norwell, MA), and the median reading was recorded. As there was good correlation between the measurements in both eyes, only the readings from the right eye were used for analysis.

Systolic and diastolic blood pressures were measured with an automatic blood pressure monitor (Dinamap model Pro Series DP110XR-WV, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI) using a standardized protocol. Blood pressure was measured with participants seated after 5 minutes of rest; this was measured twice, each 5 minutes apart. A third measurement was made if the blood pressures differed by more than 10 mm Hg in systolic and 5 mm Hg in diastolic readings. The mean of the two closest readings was then taken as the blood pressure of that individual.

Height was measured in centimeters using a wall-mounted measuring tape. Weight was measured in kilograms using a digital scale (SECA, model 782 2321009; Vogel & Halke, Hamburg, Germany). Body mass index (BMI) was calculated as kilograms divided by height in square meters. A detailed interviewer-administered questionnaire was used to collect information about medical history (e.g., hypertension, diabetes), cigarette smoking (defined as current, past and never), and other variables. Nonfasting venous blood samples were drawn and used to assess serum glucose. Diabetes mellitus was defined as nonfasting glucose ≥11.1 mM, use of diabetic medication or self reported history of diabetes. Refraction was measured using standardized subjective refraction techniques and if that technique was unavailable, autorefraction measurements were used instead.

Statistical Analysis

Statistical analysis was performed using SPSS (version 13.0, SPSS Inc., Chicago, IL). Mean IOP was calculated for quartiles of CCT and sBP for all persons and in younger (40–59 years) and older (60–80 years) age groups. Analysis of variance was used to test differences in mean IOP between quartile groups of CCT and sBP across the age groups. Multiple linear regression models were used to assess the change in IOP with 1-year increase in age, 1-mm Hg increase in sBP, and 1-μm increase in CCT separately and jointly. Additional adjustement was made in the final multivariable models for sex, spherical refraction, diabetes, BMI, and cigarette smoking status. For linear regression, we present both the nonstandardized and standardized coefficients. The absolute magnitude of the standardized regression coefficient indicates the relative importance of a factor as a predictor of IOP.

RESULTS

Data from 3280 persons were available for analyses, but results are presented for right eyes only (n = 3263 with right IOP data), as very similar results were obtained when the analysis was repeated for left eyes (n = 3265 for left IOP data).

Figure 1 shows the distribution of IOP, which increased with age from the fifth to sixth decades, after which the IOP appeared to show a slight decrease with increasing age. sBP was positively correlated with age and CCT negatively, as illustrated in Figures 2 and 3. Table 1 shows the mean IOP in...
The positive associations between IOP with higher measurements of both CCT and sBP were apparent in all persons, and in both younger and older age groups (P < 0.001).

Table 2 gives the nonstandardized and standardized regression coefficients and probabilities of the null hypothesis for two regression models of age only (model 1) and of age, CCT, and sBP (model 2). In model 1, with age as the single factor, age had no significant correlation with IOP in all persons. In model 2 with age, sBP, and CCT as factors, all three were significant in all persons (P < 0.001). In younger persons 40 to 59 years of age, both CCT and sBP were significant determinants of IOP (P < 0.001 for both), but in older persons (60 to 80 years), age and sBP, but not CCT, were significant determinants of IOP (P = 0.001 for age, P < 0.001 for sBP). On excluding patients taking antihypertensive medication (model 6), we found that sBP remained positively associated with IOP (P < 0.001) even after adjusting for systemic and ocular parameters. Hence, systemic antihypertensive medications do not appear to have a direct influence on IOP. The absolute magnitude of the standardized regression coefficient indicates the relative importance of a factor as a predictor of IOP. Thus, in all persons, sBP was the most important determinant, followed by CCT. In younger persons, CCT was a more important determinant of IOP than age.

Data show linear regression model of IOP.
Model 1 adjusts for age only.
Model 2 adjusts for age and sBP.
Model 3 adjusts for age and CCT.
Model 4 adjusts for age, sBP, and CCT.
Model 5 adjusts for age, sBP, CCT, sex, spherical equivalent refraction, diabetes, and smoking.
Model 6 adjusts for age, sBP, CCT, sex, spherical equivalent refraction, diabetes, and smoking, but excludes subjects in treatment with antihypertensive medication.
In Table 3, after further adjustments for sex, spherical equivalent refraction, diabetes, and smoking, the relationship of IOP with age, CCT, and sBP remained significant in all persons without a known diagnosis of glaucoma \((P < 0.001\) for age, CCT, and sBP). In contrast, in individuals with glaucoma, age, CCT, and sBP were all not significant associations with IOP \((P > 0.05\), except for age). There was a linear regression coefficient of 0.144 for CCT in persons with glaucoma and 0.016 in persons without glaucoma, and a linear regression coefficient of 0.033 for sBP in persons with and without glaucoma. Association of IOP with age, however, was different, with positive correlation of IOP with age in persons without glaucoma, and nonsignificant association of IOP with age in persons with glaucoma.

### DISCUSSION

The main findings of the study are the following: First, IOP shows a trend toward a subtle inverted U-shape relationship with increasing age in Asian Malays, although the observed decrease in IOP with increasing age was only a mean difference of \(< 0.5 \text{ mm Hg}\). Second, sBP shows a positive relationship, but CCT an inverse relationship with increasing age. Thus, the opposing effects of sBP and CCT with age may determine the tendency toward the relatively flat profile of IOP with age. Third, in younger persons, CCT was a more important determinant of IOP measurement than age.

Our cross-sectional study provides insights into the distribution of IOP with age reported in previous Asian studies. A longitudinal study in Japan\(^{26}\) analyzed the IOP changes in young and middle-aged, healthy subjects. The authors reported a decrease in IOP over a 10 year period in healthy middle aged Japanese subjects. A similar negative association of IOP with age was found in a more recent study of over 7000 healthy Japanese subjects.\(^{36}\) Furthermore, a downward trend of IOP with increasing age was reported in cross-sectional studies conducted by Nomura et al.\(^{37}\) and Shiose.\(^{7}\) A reduction of 1 mm Hg in men and 0.5 mm Hg in women between the third and eighth decade was reported by Nomura et al.\(^{37}\) Similarly, Shiose found a decrease of 1 mm Hg in all subjects between the same two decades. In contrast, the Barbados Eye and Egna-Neumarkt studies both found IOP to increase with age, reflecting that the effect of age remains a strong and persistent effect in IOP in Caucasian and black eyes.\(^{5,8}\) However, on adjustment for confounders such as sex, diabetes, hypertension, myopia, and BMI, the same two studies demonstrated a similar trend that was seen in the Japanese and our studies, that is IOP decreases with age. The IOP difference among the age groups in our study was noted to be not as great as other aforementioned epidemiologic studies. The reason for this is unclear and direct comparison with other studies is limited by differences in study design, sampling strategies, methodology of IOP measurement and variations in participant characteristics.

In this study we demonstrate results similar to those previously reported from other studies showing a positive association between CCT and IOP measurements.\(^{16,19,31}\) However, it has also been reported that even though there is a clear positive association of CCT and IOP measurements, its influence is not particularly large.\(^{16,18}\) It is clear that these physiological changes are dynamic and will certainly influence IOP measurements.

There are two likely factors that would have an effect on the IOP readings attained in our study. First, the method used to measure IOP—that is, noncontact versus contact tonometry. It has been reported that GAT can result in a notably higher recorded IOP reading of up to 0.71 mm Hg with a 10-\mu m increase in CCT when compared with the noncontact method.\(^{32,33}\) In addition to this, the second of two IOP readings was taken for analysis in the study, if the first IOP reading was greater than 21 mm Hg. This protocol may be a cause of measurement bias. Second, the effect of the biomechanics of the eye, in particular corneal hysteresis, was not measured in this study.

Corneal hysteresis is an emerging important clinical parameter that may influence IOP measurements.\(^{34,35}\) Recent work conducted on ex vivo human corneal buttons has demonstrated a correlated increase in corneal stiffness with increasing age.\(^{36}\) Changes in corneal hysteresis with increasing age may contribute to the observations in our study.

sBP was the most interesting and significant determinant for IOP for all persons, and also when stratified into younger and older persons. This confirms the importance of sBP on IOP in several population-based studies.\(^{2,5,10,12,14,15,17,57}\) With aging, the mean sBP increases in white persons and black persons, and there is an associated increase in IOP. In contrast, IOP decreased in our subjects, despite an increase in sBP with age, which is a similar observation reported in studies conducted in Japan and Korea.\(^{7,40}\) It is possible that systemic hypertension has an indirect effect on IOP in physiological and pathologic terms based on the overall sympathetic tone of hypertensive individuals, atherosclerotic changes,\(^{41}\) and elevated renin-angiotensin levels.\(^{42}\) All these systemic factors could influence local IOP by affecting episcleral venous pressure, which regulates aqueous humor outflow across the trabecular meshwork into Schlemm’s canal.\(^{43,44}\) However, these changes do not seem to explain the possible difference in IOP trend found in Asian eyes. Certainly, the relationship between IOP and sBP is an intriguing one, and it is far from clear in our study whether there is a direct cause-and-effect relationship.
This question should be investigated in a longitudinal study. Taken together, however, the results show that an increase in sBP is associated with an increase in IOP. Thus, the overall consequence of the perceived opposing effects of increasing sBP and decreasing CCT with age is the generation of a relatively flat IOP profile in our population.

The major limitation of the study is that these data are cross-sectional; therefore, we cannot presume longitudinal changes in terms of IOP with age and the other parameters, CCT and sBP. Adjustment for use of antihypertensive medication, however, had no measurable effect on the results seen. Furthermore, an important limitation is that the blood pressure measurement was performed at one time point in the study. An average of multiple readings taken at different times would more accurately reflect the true blood pressure level. Finally, GAT was the only method used to measure IOP despite other available techniques which have been reported to have different relationships with CCT.5,46

In conclusion, both CCT and sBP are positively associated with measured IOP level across the age range of the people in our study. However, with increasing age, mean sBP increases and mean CCT decreases. The opposing net effects of age-specific differences between these two variables seem to lead to a relatively flat IOP profile with age. These results highlight the importance of understanding age-related patterns and trends of CCT and blood pressure in different populations when considering IOP measurements in epidemiologic and clinical studies.

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