Flicker Sensitivity and Cardiovascular Function in Healthy Middle-aged People

Alvin Eisner, PhD; John R. Samples, MD

Objective: To establish normative relations between measures of visual function and cardiovascular variables that are important for age-related disease, including various forms of glaucoma.

Methods: Foveal flicker sensitivities, resting blood pressures and heart rates, and intraocular pressures were measured in 18 individuals aged 40 to 68 years. All subjects had 20/20 or better visual acuity in the test eye and no evidence of eye disease or glaucoma suspicion on clinical evaluation and medical history. No subjects were using medication to lower blood pressure. Flicker sensitivity was measured by increasing the illuminance of a fully modulated 20-Hz test stimulus until flicker was perceived. Two test-background stimulus combinations were used: a 570-nm (“yellow”) test on a predominantly long-wavelength (“magenta”) background and a 580-nm (“yellow”) test on a 580-nm (“yellow”) background. The illuminance of the yellow background was dimmer than that typically used for short-wavelength automated perimetry, whereas the illuminance of the magenta background was greater.

Results: The 2 flicker sensitivity measures were distinguished by the strong dependence of the magenta background measure on the ratio of mean arterial blood pressure to heart rate. Log flicker sensitivity on this background generally could be modeled as a linear combination of age, intraocular pressure, and ratio of mean arterial blood pressure to heart rate. The optimal model accounted for 84% of the variance ($R^2=0.92$) from all but 2 outlying individuals. After age and intraocular pressure effects were partialed out, an increasing ratio of mean arterial blood pressure to heart rate was strongly associated with decreasing flicker sensitivity.

Conclusions: Reduced cardiovascular function impacts the ability of the normal visual system to adapt and regulate flicker sensitivity. Elevated intraocular pressure and increased age reduce flicker sensitivity relatively uniformly across a range of stimulus conditions. Because the ratio of mean arterial blood pressure to heart rate equals total peripheral vascular resistance multiplied by cardiac stroke volume, and because total peripheral resistance is determined largely at the arterioles, it is likely that even modest changes in arteriolar function are associated with measurable alterations of visual function.


There is increasing evidence that glaucoma often has a multifactorial etiology that does not depend solely on elevated intraocular pressure (IOP). Various aspects of cardiovascular dysfunction can be involved, perhaps especially for certain forms of glaucoma. Attempts to quantify relations between visual dysfunction and pathophysiologic compromise are complicated by the nature of the disease process itself, which frequently is characterized by high degrees of response variability within individual patients. Moreover, the IOPs of almost all patients with glaucoma have been altered by medical or surgical intervention. Topical medications to reduce IOP might have other local or systemic cardiovascular effects. In addition, many patients with glaucoma use medication to reduce blood pressure. The heterogeneity of glaucoma can be a complicating factor, even in the absence of any medication use. Thus, establishing quantitative relations between glucomatous change and physiologic variables is problematic.

To circumvent these problems and to quantify relations between visual function and physiologic variables that are important for glaucoma and other age-related disorders, it might be productive to evaluate healthy individuals. Tyler et al already have shown that IOP differences as little as 1 to 2 mm Hg may correspond to measurable differences in temporal resolution (ie, of flicker sensitivity) in healthy
SUBJECTS AND METHODS

SUBJECTS

Participants in this study were members of the 27-subject “normal control” group for 2 glaucoma studies. Subjects were assigned to this group only after Humphrey 30-2 visual fields were measured and optic nerve head photographs were taken and these clinical records were evaluated by 2 glaucoma specialists (including J.R.S.) masked from all other data. An ophthalmologist examined subjects’ maculas ophthalmoscopically.

Data were analyzed for the 18 subjects who had 20/20 or better Snellen acuity in their test eye and no worse than 20/25 Snellen acuity in their fellow eye and who were not using medication to reduce blood pressure or to remedy any other cardiovascular condition. Visual acuities were measured with subjects’ existing optical corrections or with no correction at all and thus did not necessarily represent best-corrected acuities. All subjects had 5 diopters or less of myopia and claimed medical histories that were negative for diabetes, ocular hypertension, and eye disease. All subjects had congenitally normal trichromatic color vision.

The ages of the 18 subjects ranged from 40 to 68 years (mean [SD], 56.0 [9.0] years); 11 subjects were women and 7 were men. Test eye IOPs ranged from 10 to 20 mm Hg and were distributed approximately uniformly, with a mean of 15.4 mm Hg. The highest IOP in a fellow eye was 22 mm Hg. Systolic blood pressures ranged from 92 to 170 mm Hg (mean [SD], 127.9 [20.3] mm Hg). Diastolic blood pressures ranged from 66 to 90 mm Hg (mean [SD], 79.7 [7.0] mm Hg). Heart rates ranged from 48 to 88 bpm (mean [SD], 71.9 [10.9] bpm). It is possible that some subjects had undiagnosed or borderline vascular hypertension. This is addressed empirically in the “Results” section.

This research was approved by the institutional review board of Legacy Health System, Portland, Ore. Written informed consent was obtained from all participants after explanation of the nature and possible consequences of the study.

APPARATUS

All flicker threshold measurements were made using a custom-built 2-channel, tungsten-halogen source Maxwellian view. (A Maxwellian view is a psychophysical testing device that allows visual stimuli to be focused on the retina while the light source for those retinal images is projected on the pupil of the eye.) A chinrest and rubber eye-piece facilitated proper subject alignment. The exit pupil of the apparatus was 1.21 mm in diameter. Thus, anatomical pupil size did not affect retinal illuminance.

STIMULI

Flicker threshold was measured for foveal vision using a fully modulated 20-Hz square wave test stimulus. The test stimulus was a 1° diameter disc superimposed on an 11° diameter background. Crosshairs with a 4° gap aided fixation. Flicker thresholds were measured for 2 test-background stimulus combinations. For one combination, the test stimulus was 570 nm and the background was provided by a Wratten 33 gelatin filter (Eastman Kodak Co, Rochester, NY) that passed light approximately metameric with 633 nm. The background illuminance was 3.8 log troland; about 1.5% of this illuminance was passed in short wavelengths, below 480 nm. For the other combination, both the test and the background were 580 nm, and the background illuminance was 2.6 log troland.

PROCEDURE

Psychophysical Testing

For each test-background combination, flicker sensitivity (ie, inverse threshold) was measured by raising the illuminance of the test stimulus in logarithmic steps until the subject reported detecting flicker. For the 570-nm/633-nm combination, flicker threshold was measured as a function of time after background-field onset. Mean thresholds were calculated from thresholds obtained 1 to 3 minutes after background-field onset, by which time flicker thresholds had already asymptoted. Test illuminances were raised in approximately 0.1 log unit steps at a rate that usually resulted in about 15 measurements per subject. Seven minutes of monocular dark adaptation preceded background-field onset. For the 580-nm/580-nm stimulus combination, mean thresholds were calculated from 4 threshold measurements obtained after subjects had viewed the 2.6 log troland 580-nm background for about 5 minutes for other purposes. Test illuminances were raised in approximately 0.06 log unit steps.

Physiologic Data Measurement

Intraocular pressures were measured using Goldmann applanation tonometry after conclusion of the Maxwellian view testing battery. Resting brachial blood pressures and heart rates were measured with a mercury sphygmomanometer and stethoscope before the start of psychophysical testing. Heart rates were computed from a 30-second measurement interval.

DATA ANALYSIS

All statistical analyses were conducted using statistical software (SYSTAT 6.0 for Windows; SPSS Inc, Chicago, Ill). All P values are for 2-sided tests.
crucial for minimal field loss and preservation of foveal function on conventional assessment (terms defined by Eisner et al13). Instabilities were associated with an increased ratio of mean arterial blood pressure to heart rate (MAP/HR), which was interpreted as evidence for small vessel disease within this select POAG subpopulation.12

If small blood vessel disease can lead to conspicuous visual dysfunction among patients with POAG and only minimal field loss, then perhaps less pronounced cardiovascular compromise can lead to detectable visual change in healthy people. A suitable population for examining such change would comprise middle-aged individuals who are old enough to have reduced cardiovascular function14 but young enough to have essentially normal visual processing in most cases.

The purpose of the present study was to establish quantitative relations between foveal visual function and physiologic variables, particularly cardiovascular variables, for healthy middle-aged individuals with normal vision. These individuals have relatively stable flicker sensitivities. Thus, the present study deals with mean sensitivities rather than with variability. The testing conditions are identical to those used for patients with POAG.12 These conditions cause a form of flicker response suppression,15 which can occur when the relation between test illuminance and flicker response becomes sufficiently nonlinear.16 The resultant amplification of small neurophysiological response changes into proportionately larger flicker sensitivity changes could account for the categorical association between flicker sensitivity instability and MAP/HRs for patients with POAG. It could also account for the quantitative relations between mean flicker sensitivity levels and MAP/HRs that are established by the present study for healthy individuals.

RESULTS

This section is divided into 2 parts. In the first, a model is developed to relate physiologic variables to the flicker sensitivities obtained for a 570-nm test superimposed on a 3.8 log troland = 633-nm background (flicker sensitivity[570/633]). In the second, these same flicker sensitivities are compared with the flicker sensitivities obtained for a more typical test background combination, a 580-nm test superimposed on a 2.6 log troland 580-nm background (flicker sensitivity[580/580]). Estimated MAP is calculated as \( \frac{2}{3} \) diastolic blood pressure17 + \( \frac{1}{3} \) (systolic blood pressure).17

MODEL FOR FLICKER SENSITIVITY(570/633) DATA

Figure 1 is a graph of log flicker sensitivity(570/633) vs MAP/HR. The reduction of flicker sensitivity(570/633) with increasing MAP/HR is significant (Spearman \( r = -0.51, P = .03 \)) and extends across the entire age range (40-68 years). Neither MAP nor HR was significantly correlated with flicker sensitivity(570/633).

The MAP/HR is not likely to be the only factor related to flicker sensitivity(570/633). Flicker sensitivity (570/633) decreases significantly with age (Spearman

\[ r = -0.50, P = .03 \].) Intraocular pressure by itself is not significantly correlated with flicker sensitivity(570/633) but is expected to be an important factor nevertheless.11 Multivariate regression techniques could help assess effects of these 3 variables: MAP/HR, age, and IOP.

To assess appropriately the significance of a multilinear regression that relates age, IOP, and MAP/HR to flicker sensitivity(570/633), outlying data from 2 subjects first must be dealt with via transformation or exclusion. One of these 2 subjects is a 65-year-old man whose data are at the lower right-hand corner of Figure 1. The departure of his data from the continuum corresponds to the profound reductions of flicker sensitivity (570/633) that sometimes occur off the low end of the continuum for elderly individuals15 or glaucomatous patients.13 His data must be excluded from any parametric analysis. The other subject is a 41-year-old woman whose flicker sensitivity(570/633) is 3.95 log degrees/µW and whose MAP/HR is 1.03 mm Hg/bpm. No reasonable transformation can bring her data in line with the other subjects’ data. This person was 1 of 2 with a first-degree family history of glaucoma. She had a separate first-degree family history of diabetes. Her test eye IOP equaled the highest of any subject, 20 mm Hg. Thus, it is prudent to exclude this subject’s data from parametric analyses. Inclusion of her data would not alter any of this study’s conclusions, although numerical estimates would differ.

After exclusion of the 2 outliers, the multilinear regression on age, IOP, and MAP/HR accounts for 82% of the variance for log flicker sensitivity(570/633). The regression equation is:

\[
\begin{align*}
\log \text{flicker sensitivity}(570/633) &= 6.096 - 0.0124[\text{age}] - 0.0306[\text{IOP}] - 0.5990[\text{MAP/HR}] \\
&= 6.096 - 0.0124[\text{age}] - 0.0306[\text{IOP}] - 0.5990[\text{MAP/HR}] \\
\end{align*}
\]

Although none of the standardized full or partial residual error distributions differ significantly from a standardized normal distribution (1-sample Kolmogorov-Smirnov test), some of the partial residuals seem to be moderately skewed.

To reduce skewness, age and MAP/HR can be transformed to reflect the likelihood that effects of these 2 vari-
which is highly significant (F3,12 = 20.81, P \leq .0001). Each of the 4 regression coefficients—the intercept and 3 partial slopes—is significantly different from zero. The P values for the exp(age/40), IOP, and exp(MAP/HR) residuals after effects of age and intraocular pressure were partialed out using the multilinear regression model of equation 2. IOP indicates intraocular pressure; MAP/HR, ratio of mean arterial blood pressure to heart rate.

Variables accelerate at relatively high values. The resulting regression equation becomes:

\[
\log \text{flicker sensitivity}(570/633) = 5.769 - 0.1298 \text{exp(age/40)} - 0.0311 \text{IOP} - 0.1561 \text{exp(MAP/HR)}
\]

This equation accounts for 84% of the variance (R = 0.92), which is highly significant (F3,12 = 20.81, P \leq .0001). Each of the 4 regression coefficients—the intercept and 3 partial slopes—is significantly different from zero. The P values for the exp(age/40), IOP, and exp(MAP/HR) slope coefficients and their corresponding partial correlations are P = .0005, P = .0010, and P = .0002, respectively. Each factor makes a comparably important contribution to the regression. The standardized slope coefficients are −0.56, −0.54, and −0.66, respectively. Increasing any of these factors reduces sensitivity.

Had the MAP/HR term been omitted from the model, only 47% of the variance would have been accounted for and the IOP contribution would have been considered nonsignificant. Had the model retained 3 factors but MAP not been divided by HR (ie, had the model contained age, IOP, and either MAP or HR terms as factors), then neither IOP nor either cardiovascular factor would have been considered significant. Had the model been expanded to 4 factors, the separate MAP and HR terms each would have been considered to be highly significant and to contribute with approximately equal weight to the regression. However, the contributions would have been of opposite sign and the coefficient of determination would have increased only slightly, from 84% to about 86%. These results collectively support the appropriateness of the 3-factor model with a single MAP/HR term.

**Figure 2** displays the fit of this 3-factor regression model to the flicker sensitivity(570/633) data. The ordinate represents the log flicker sensitivity(570/633) data, and the abscissa represents the values output by the model using equation 2. All the nonoutlying data lie within a linear cluster.

To examine the relation between MAP/HR and flicker sensitivity(570/633) directly, effects of age and IOP were partialed out using the reduced-skewness multilinear regression model of equation 2. The relation between the log flicker sensitivity(570/633) residuals and exp(MAP/HR) residuals is shown in **Figure 3**. The best-fitting straight line accounts for 70% of the residual variance (\(r^2 = −0.83\)). The inflection at mean residual levels in Figure 3 could be caused by any of several factors: (1) incomplete specification of physiologic variables, (2) a fundamental nonlinearity, (3) relations among the variables, or (4) chance. None of these possibilities alters the fact that 70% of the residual variance is accounted for or that the parent 3-factor regression model accounts for 84% of the flicker sensitivity(570/633) variance.

In fact, the various P values calculated for the regression model are not materially affected by transformations that exacerbate rather than reduce residual skewness or by omission of any individual data points. Even omission of pairs of data points would not change the model; the worst-case P value for the exp(MAP/HR) slope becomes .0064. When data are omitted from the 2 subjects whose diastolic blood pressure was 90 mm Hg and the 4 additional subjects whose systolic blood pressure was 140 mm Hg or greater, the coefficient of determination increases from 84% to 95% and all 3 factors remain highly significant. Thus, the model is robust and is not aided disproportionately by any subjects who might have undiagnosed or borderline high blood pressure.

The model also seems to be essentially complete given the available data. Adding terms such as ocular perfusion pressure (estimated as 1/3 MAP – IOP)\(^{18,19}\) or pulse pressure (defined as systolic minus diastolic blood pressure) scarcely affects the model. Substituting these terms substantially degrades the model.

**COMPARISON OF FLICKER SENSITIVITY(570/633) AND FLICKER SENSITIVITY(580/580) DATA**

Three different analyses show that flicker sensitivity(570/633) is distinguished from flicker sensitivity(580/580) largely by its extra dependence on MAP/HR. The net conclusion is that the 2 different flicker sensitivities share a common set of determining factors but that flicker sensitivity(570/633) depends additionally on MAP/HR.
The first analysis concerns an alternative regression model for flicker sensitivity (570/633). This model contains 2 factors: flicker sensitivity (580/580) and exp(MAP/HR). The least-squares linear combination of log flicker sensitivity (580/580) and exp(MAP/HR) accounts for 74% of the log flicker sensitivity (570/633) variance (R = 0.86, same 2 outliers excluded). The P values for log flicker sensitivity (580/580) and exp(MAP/HR) slope coefficients are \(P = .0006\) and \(P = .0099\), respectively. Much of the remaining variability is derived from 2 subjects whose flicker sensitivity (570/633) data are low at the bottom end of the continuum in Figure 2. When data from these 2 additional subjects are excluded, 89% of the variance is accounted for.

The second analysis concerns regression models for flicker sensitivity (580/580). Exp(MAP/HR) is not a significant factor for any candidate regression model of flicker sensitivity (580/580), whereas IOP and exp(age/40) would be considered significant even for the 2-factor model that contains no cardiovascular variables (\(P = .016\) and \(P = .002\), respectively; same 2 original outliers excluded). The linear combination of IOP and exp(age/40) obtained for this 2-factor model of flicker sensitivity (580/580) correlates almost perfectly (\(r = 0.99\)) with the linear combination of IOP and exp(age/40) obtained for the 3-factor model of flicker sensitivity (570/633). Moreover, the ratios of the IOP to exp(age/40) regression coefficients do not differ significantly among the various models.

The third analysis directly concerns the difference of the 2 log flicker sensitivities, which can be evaluated nonparametrically without reliance on any regression model or exclusion of outlying data. A drawback is that this analysis is retrospective and limited to 1 factor. Nevertheless, it provides further evidence that the 2 flicker sensitivities are contrasted by their dissimilar dependence on MAP/HR.

The difference of the 2 log flicker sensitivities (log flicker sensitivity [570/633] – log flicker sensitivity [580/580]) is shown in Figure 4, top, as a function of MAP/HR. For 7 subjects, this difference is virtually identical; the data for these 7 subjects all lie within 0.025 log units of each other. These subjects’ data are separated from the other 11 subjects’ data by 2 horizontal broken lines, which are positioned \(\pm 3\) SD from the mean log flicker sensitivity difference for the 7 subjects. Figure 4, bottom, plots log flicker sensitivity (570/633) vs log flicker sensitivity (580/580) directly. A least-squares best-fit straight line is drawn through these 7 subjects’ data. The slope of this line is 45.7°.

As seen in Figure 4, top, people for whom the 2 types of flicker sensitivities are mutually proportional (ie, whose data are represented by circles) have lower MAP/HRs than those whose data are not mutually proportional (\(P = .002\), Mann-Whitney U test). As seen in Figure 4, bottom, they also have higher flicker sensitivities (570/633) (\(P = .03\)). The between-group difference for flicker sensitivity (580/580) is not significant (\(P = .26\)). At low overall flicker sensitivity levels, flicker sensitivity (570/633) can be viewed as elevated slightly relative to flicker sensitivity (580/580). This suggests that the MAP/HR factor is related either statistically or functionally to at least 1 other factor determining flicker sensitivity. None of the full or partial correlations among the 3 factors identified in equation 2—age, IOP, and MAP/HR—are statistically significant.

The data in Figure 4, top, suggest that the MAP/HR factor begins to affect the 2 flicker sensitivities differentially at values of about 1.25 mm Hg/bpm. This would correspond to a MAP of about 90 mm Hg for a 72-bpm HR. For reference, the MAP for a systolic/diastolic blood pressure reading of 120/80 would be 93.3 mm Hg.

The results imply that flicker sensitivity depends substantially on cardiovascular function for certain combinations of visual stimulus parameters. Flicker sensitivity seems to depend on 2 main sets of factors: one that applies relatively uniformly for a range of stimulus conditions and another that is more stimulus dependent. The former set involves age and IOP. The latter involves cardiovascular variables that in all likelihood affect response and adaptation properties responsible for regulating flicker sensitivity. The alternative possibility is that 20-Hz foveal flicker sensitivity can be mediated by 2 separate “channels,” only one of which is materially affected by changes of cardiovascular function. This is the less plausible alternative. It offers no mechanism to account
for the gross instabilities of flicker sensitivity that often occur when patients with high blood pressure and POAG are tested under the same stimulus conditions used for the present study.12

Flicker sensitivity has been shown previously to depend inversely on IOP.11,20 and there are numerous studies21,22 concerning flicker sensitivity in ocular hypertension or glaucoma. The relation of visual function to cardiovascular function has been studied much less, although vascular hypertension is a more common condition23,24 and a major public health problem. The flicker response instability—high blood pressure relations that were reported by Eisner et al12 for a subpopulation of patients with POAG probably depended on the use of a test-background stimulus combination that amplified effects of small blood vessel disease on visual adaptation. Profound reductions of flicker sensitivity likewise seem to be stimulus dependent,12,33 as in Figure 4, bottom.

In the present study, a regression model is developed to relate a particular measure of log flicker sensitivity to a linear combination of IOP with transformed age and MAP/HR variables. The regression model is given by equation 2. An alternative form of this model is obtained by exponentiating each side of equation 2. This yields a product of functional terms regarding age, IOP, MAP/HR, and a proportionality constant, \( c_0 \):

\[
\text{flicker sensitivity}(570/633) = [c_0] [f_1(\text{age})] [f_2(\text{IOP})] [f_3(\text{MAP/HR})]
\]

In this form, the model can be interpreted to mean that 3 distinct classes of factors are predominantly responsible for the flicker sensitivity differences in healthy middle-aged individuals. An increase in any of these factors reduces flicker sensitivity.

The age factor may encompass a variety of component subfactors and thus may affect response at multiple sites or via multiple mechanisms. The age factor could include the loss of optic nerve fibers that occurs in the absence of pathology,25,28 but that might heighten the effects of any additional glaucoma-induced optic nerve loss.

The IOP factor probably is the same one that most investigators assess when they use flicker sensitivity to evaluate glaucoma-related dysfunction. A widely held view is that elevated IOP causes compression of ganglion cell axons at the lamina cribrosa.27 Elevated IOP or reduced MAP each results in lowered ocular perfusion pressure,18,32 but this seems to be relatively inconsequential in healthy middle-aged individuals.

Because the MAP/HR factor is the most dependent on test-background stimulus combination, it is the factor most related to visual adaptation. Thus, the MAP/HR factor probably reflects cardiovascular differences involving the eye,28 where flicker response suppression occurs13,16,29 and where flicker sensitivity seems to be regulated as a function of background.30-32 Because MAP/HR equals total peripheral vascular resistance multiplied by cardiac stroke volume,14,37 the MAP/HR factor could depend directly on either or both of these variables or their correlates. Alternatively, it could reflect the action of an underlying substance or process that helps maintain a degree of reciprocity among the various multiplicative factors that together determine blood pressure. This latter possibility is consistent with the high proportion of variance accounted for by the model.

Only one extreme possibility, that increased stroke volume alone reduces visual function, seems inherently implausible. Pulse pressure, which is approximated by the ratio of cardiac stroke volume to arterial compliance,14,17 was not a major factor empirically.

All the viable possibilities suggest that visual adaptation is affected conjointly with or directly by increased arteriolar resistance. Increased arteriolar resistance is the main factor that would raise total peripheral vascular resistance14,17 and also resting blood pressure in middle-aged individuals.14,17 Had a reduction of flicker sensitivity(570/633) with elevated vascular resistance been caused by sympathetic stimulation, HR would have been expected to increase concomitantly.19,37 However, it did not. Moreover, the retinal circulation is thought to be unresponsive to autonomic stimulation.34 In contrast, intraocular arterioles could be affected along with systemic cardiovascular change as in overt hypertensive retinopathy,25,35,36 although the ocular circulation itself contributes only minimally to total peripheral resistance.

Based on the literature concerning the relation of flicker stimulation to blood flow in normal human27,38 and animal34,39-41 eyes, arterial compromise would have the potential to affect flicker sensitivity by altering the retinal circulation’s ability to autoregulate.19,42 However, it is not known how spatially localized autoregulation can be, or whether flickering stimuli at psychophysical threshold can elicit autoregulation. Moreover, cardiovascular effects were significant only for the more adaptationally taxing of the 2 test-background stimulus combinations. This suggests that any hypothetical autoregulatory effects, whether induced by flicker or otherwise, become apparent mainly when neural response capabilities approach their effective limits. Flicker-induced blood flow increases are not restricted to the retina but may be even greater at the optic nerve head.39,41

How might the strictly neural aspects of visual adaptation be affected (ie, burdened or altered) by inadequate blood flow? By failing to keep up with metabolic demand, inadequate blood flow would be expected to shrink neuronal response ranges, thereby exacerbating response nonlinearity under taxing adaptation conditions, thus enhancing flicker response suppression.16 If there were hypoxia or ischemia sufficient to alter levels of neurochemicals such as glutamate or nitric oxide,43-45 then adaptation processes involving complex neural networks and multiple time courses16,36 could be affected in ways not entirely predictable.47,48 Primary open-angle glaucoma seems to be accompanied by excessive intraocular levels of glutamate,49,50 and nitric oxide.51,52 Nitric oxide is thought to be an important substance for the regulation of systemic blood pressure.53

This article documents strong relations between standard clinical measures and appropriately chosen visual function tests. These tests have the practical advantage of being administered foveally. The underlying relations may be important for a variety of age-related diseases, including glaucoma.
REFERENCES