Aging Affects the Retrobulbar Circulation Differently in Women and Men

Alon Harris, PhD; Mira Harris, MD; José Biller, MD; Hanna Garzozi, MD; Drora Zarfty, MD; Thomas A. Ciulla, MD; Bruce Martin, PhD

Background: While aging clearly has protean biological effects on every organ system, the differential effects of aging in women and men in the retrobulbar vasculature, to our knowledge, have never been investigated. Because glaucoma and age-related macular degeneration are closely linked to advanced age, we performed a cross-sectional study using color Doppler imaging of 4 retrobulbar vessels in both healthy women and men.

Objective: To define the influence of aging per se on ocular hemodynamics.

Methods: Women (n=73) and men (n=55), aged from 20 to 90 years, free of ocular and systemic disease, and with normal intraocular pressure, were recruited for this study. Postmenopausal women who were not receiving estrogen replacement therapy were also recruited. Studies involved color Doppler imaging analysis of the ophthalmic, central retinal, and nasal and temporal posterior ciliary arteries. Ophthalmic arterial peak systolic and end-diastolic velocities and a Pourcelot resistance index were determined for each vessel.

Results: In both sexes, ophthalmic arterial end-diastolic velocity decreased and the Pourcelot resistance index rose with advancing age (each P<.001); peak systolic velocity in the ophthalmic vessel was age-independent. In contrast, central retinal arterial flow velocities were unaffected by age in both sexes. In the posterior ciliary arteries, in men, flow velocities and the Pourcelot resistance index were independent of age. However, in women, end-diastolic velocity decreased with age in both the nasal and temporal posterior ciliary vessel (each P<.05); peak systolic velocity was constant; the Pourcelot resistance index in each ciliary artery rose with advancing age (each P<.05).

Conclusion: In healthy women and men, aging-induced changes in retrobulbar hemodynamics are comparable to alterations seen in patients with glaucoma or age-related macular degeneration, suggesting that vascular changes with senescence may contribute to increased risk for these diseases in older age.


Aging inevitably causes widespread physiological declines that reduce functional capacities and increase susceptibility to disease.1 These declines necessarily include many alterations within the eye. For example, aging reduces aqueous inflow and outflow,2 lessens the mobility of the ciliary muscle,3 decreases the optical performance of the eye,4 and slowly enlarges the cup and thins the neuroretinal rim.5,6 The result of these multiple effects of aging on the eye is to concentrate diseases such as cataract, glaucoma, and age-related macular degeneration (AMD) within older age groups.7 However, the specific link between a given aging-induced decline and disease initiation remains obscure for many ocular illnesses.

Both glaucoma and AMD are rare in younger persons and quite common in the seventh and eighth decades of life. Nevertheless, the mechanisms accounting for either of these illnesses at any age remain incompletely described, and the age-linked factors that increase disease risk in senescence remain unexplored. For example, although elevated intraocular pressure is clearly a major risk factor for glaucoma, many patients develop glaucomatous optic nerve head damage in normal or pharmacologically controlled intraocular pressure, and intraocular pressure itself is largely independent of age.8 Similarly, both the cause of AMD, and the age-dependent factors that influence this cause, remain poorly detailed.9 While investigators have traditionally believed that senescence of the retinal pigment epithelium leads to cellular engorgement and drusen formation,9 others postulate an alternative theory involving primary vascular changes in the choroid.10

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SUBJECTS AND METHODS

EXPERIMENTAL DESIGN

Healthy persons of both sexes, with no history of ocular illness or ocular trauma, were recruited for this study. Subjects did not have diabetes mellitus, heart disease, ocular or systemic hypertension, or cancer. None were taking topical or systemic medications or receiving hormonal therapy for any of these illnesses. Postmenopausal women were not receiving estrogen replacement therapy. Subjects signed informed consent to procedures that had been reviewed and approved by an institutional review board. All procedures conformed to the tenets of the Declaration of Helsinki. Subjects were studied on a single occasion in the laboratory.

EXPERIMENTAL MEASUREMENTS

Heart rate was measured by palpation of the radial pulse; blood pressure was measured using sphygmomanometry. Flow velocities in the retrobulbar vasculature were determined using color Doppler imaging.

Color Doppler imaging is an ultrasound technique that combines b-scan gray-scale imaging of tissue structure with colored representation of blood movement toward or away from the sensor based on Doppler shifted frequencies and pulsed-Doppler measurement of blood velocities. Blood velocities were measured in the ophthalmic, central retinal, and nasal and temporal posterior ciliary arteries.

A color Doppler imaging system (Siemens Quantum 2000; Siemens Quantum, Issaquah, Wash) with a 7.5-MHz linear probe was used. Samples of pulsed-Doppler signal from within a 0.2 × 0.2-mm sample volume were analyzed to calculate blood velocities. In each vessel, peak systolic (PSV) and end-diastolic (EDV) velocities were determined, and a Pourcelot resistance index (PSV-EDV)/PSV was calculated.11,12 The ophthalmic artery is localized approximately 25 mm behind the globe, while the central retinal vessel is detected within the anterior portion of the optic nerve about 3 mm behind the surface of the optic disc. Typically, neither the ophthalmic nor the central retinal arteries require angle corrections. The nasal and temporal short posterior ciliary arteries are detected immediately nasal and temporal to the optic nerve head shadow, at a depth similar to the central retinal artery.

Because of their small size, it is not always possible to resolve individual posterior ciliary vessels, although the velocity spectra from these arteries are easily distinguished from the ophthalmic or central retinal artery.11-13,17,18 Angle corrections were performed in measurements from the posterior ciliary vessels. During testing, subjects reclined in a chair as acoustic coupling gel was placed over a closed right eye and the probe gently positioned. After identification of the appropriate vessel, the sample volume was placed in the center of the vessel, the angle of incidence was selected, and several seconds of Doppler waveform were recorded.

STATISTICAL ANALYSIS

The dependence of flow velocities on age was determined by using least-squares linear regression, with $P<.05$ regarded as statistically significant for the slope of the best-fit line.

RESULTS

EXPERIMENTAL SUBJECTS

The subject characteristics (mean age, age distribution, age range, and arterial blood pressure) are listed in Table 1. Diastolic blood pressure did not correlate with age in either sex; systolic blood pressure correlated with age only in women ($r=0.35$, $P<.01$).

COLOR DOPPLER IMAGING

Ophthalmic Artery

The ophthalmic arterial PSV was uncorrelated with age in either sex (Table 2). In contrast, EDV decreased with age in both sexes (each $P<.001$; Table 2). Estimates based on the coefficient of determination ($r^2$) suggest that 30% of the population variation in ophthalmic arterial EDV arises from aging effects in women, and 12% of that variation is caused by age in men (Table 2). Because EDV decreased with age in both sexes at constant PSV, the derived Pourcelot resistance index rose steadily with age in both sexes (each $P<.001$; Table 2 and Figure 1). Coefficient of determination ($r^2$) analysis again found substantial contributions...
from age to the population variation in the ophthalmic artery Pourcelot resistance index, the estimate proportion being 26% in men and 50% in women (Table 2).

Central Retinal Artery

In contrast to results seen in the ophthalmic artery, in neither sex were PSV, EDV, or Pourcelot resistance index in the central retinal artery dependent on age (Table 2 and Figure 2).

Nasal and Temporal Short Posterior Ciliary Arteries

A third pattern of response, distinct from results observed in the ophthalmic and central retinal arteries, was seen in the nasal and temporal short posterior ciliary arteries. In these vessels, men showed no correlation of any Doppler index with age (Table 2 and Figure 3). In contrast, in women, EDV in each posterior ciliary artery decreased with advancing age (each \( P < .05 \), Table 2). In addition, the Pourcelot resistance indexes in both the nasal and temporal posterior ciliary arteries rose with increasing age (Table 2 and Figure 3).

COMMENT

In this cross-sectional study, we found that ophthalmic arterial EDV decreased with advancing age at constant PSV, producing a rise in the Pourcelot resistance index in both sexes. In contrast, no effects of senescence were noted on flow velocities measured in the central retinal artery. Finally, in the nasal and temporal short posterior ciliary arteries, both sexes showed different responses with advancing age. In men, flow velocities in these small arteries were independent of age. In contrast, in women not receiving estrogen replacement therapy, older age was

Table 1. Subjects’ Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 55)</th>
<th>Women (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44 ± 18</td>
<td>47 ± 20</td>
</tr>
<tr>
<td>Age range, y</td>
<td>23-77</td>
<td>20-90</td>
</tr>
<tr>
<td>Age distribution in years, No. of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>30-39</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>40-49</td>
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<td>8</td>
</tr>
<tr>
<td>50-59</td>
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<td>7</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>≥70</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
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</tr>
<tr>
<td>Systolic</td>
<td>121 ± 11</td>
<td>116 ± 18</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 ± 10</td>
<td>70 ± 10</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (± SD), unless otherwise indicated.

Table 2. Age Dependence of Retrobulbar Arterial Flow Velocities*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r )</td>
<td>( P )</td>
</tr>
<tr>
<td>Ophthalmic Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>End-diastolic velocity</td>
<td>-0.35 .008</td>
<td>-0.55 .001</td>
</tr>
<tr>
<td>Pourcelot resistance index</td>
<td>+0.51 .001</td>
<td>+0.71 .001</td>
</tr>
<tr>
<td>Central Retinal Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>End-diastolic velocity</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>Pourcelot resistance index</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>Temporal Short Posterior Ciliary Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>End-diastolic velocity</td>
<td>. . . NS</td>
<td>-0.22 .049</td>
</tr>
<tr>
<td>Pourcelot resistance index</td>
<td>. . . NS</td>
<td>+0.26 .03</td>
</tr>
<tr>
<td>Nasal Short Posterior Ciliary Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity</td>
<td>. . . NS</td>
<td>. . . NS</td>
</tr>
<tr>
<td>End-diastolic velocity</td>
<td>. . . NS</td>
<td>-0.35 .005</td>
</tr>
<tr>
<td>Pourcelot resistance index</td>
<td>. . . NS</td>
<td>+0.35 .005</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable; NS, not significant.
sociated with a reduced EDV, constant PSV, and an el-

evated Pourcelot resistance index in both short posterior
ciliary vessels.

Noninvasive color Doppler imaging measurements
necessarily involve indirect signal interpretation.20 Never-
theless, a number of in vitro and in vivo comparisons of
Doppler flow velocities with direct measurements of total
blood flow and vascular resistance have resulted in con-
sensus interpretations of selected aspects of Doppler in-
formation.20-22 Specifically, reduced EDV at constant PSV,
resulting in increased Pourcelot resistance index, has been
shown in both anesthetized dogs and in in vitro cardio-
vascular models to result from elevated vascular resis-
tance downstream from the arterial measurement site.20-22

Aging, via reductions in growth hormone and in-
sulinlike growth factors, increases vascular resistance by
an absolute loss of arterioles, reduction of distensibility
within the remaining vessels, and compromise of endo-
thelium-dependent vascular relaxant mechanisms.23,24 Pre-
vious whole-population studies consistently find age-
linked flow velocity reductions and Pourcelot resistance
index elevations in the short posterior ciliary arteri-
es.17,18 Comparable retrobulbar hemodynamic changes
are found in patients with glaucoma and AMD.10,11 In this
study, analogous results were restricted to women. Be-
cause the women in this study were not receiving estro-
gen replacement therapy, it is possible that declining es-

estrogen levels with age contributed to these results.

Women, more than men, lose cerebral vasoreactivity with
age25; estrogen replacement therapy blunts this loss of
responsivity25 and mitigates age-linked changes in arte-
rial structure and distensibility.26 However, the current
cross-sectional results are indirect and preliminary: di-
rect comparisons of women receiving and not receiving

![Figure 2](image-url) Central retinal arterial Pourcelot resistance index in women and men as a function of age. In both sexes, the Pourcelot resistance index was independent of age.

![Figure 3](image-url) Nasal posterior ciliary arterial Pourcelot resistance index in women and men as a function of age. In women, the Pourcelot resistance index rose with advancing age ($P = .005$). In men, there was no correlation of the Pourcelot resistance index with age.
estrogen replacement therapy will be required to fully define the role that estrogen may play in the regulation of ocular hemodynamics and in the prevention or mitigation of ocular disease.

Studies of both normal-tension and primary open-angle glaucoma, and of AMD, characteristically find reduced flow velocities and increased ophthalmic arterial Poucrelot resistance indexes.\(^1\)\(^-\)\(^1\)\(^3\)\(^-\)\(^1\)\(^7\)\(^-\)\(^1\)\(^9\) While previous aging studies emphasize changes in PSV or EDV in the ophthalmic artery, at an unchanged Poucrelot resistance index, our results find reductions in ophthalmic arterial EDV and increases in the Poucrelot resistance index with advancing age in both sexes. Analogous vascular resistance rises in the ophthalmic arterial watershed are found in aging rats.\(^1\)\(^5\)\(^-\)\(^1\)\(^7\)\(^-\)\(^1\)\(^9\) The similar effects of aging and disease, independent of sex, suggest that increased vascular resistance distal to the ophthalmic artery occurring as a normal consequence of aging could be one factor predisposing to glaucoma and/or AMD in older age groups.

While we found evidence for rising resistance distal to the ophthalmic artery, flow velocities in the central retinal retinal artery were independent of age in both sexes in our study. Other studies have found variously that aging and atherosclerosis render the monkey retina susceptible to ischemia.\(^1\)\(^0\)\(^-\)\(^1\)\(^0\)\(^-\)\(^1\)\(^9\)\(^-\)\(^2\)\(^0\)\(^-\)\(^2\)\(^1\) Our results, obtained from healthy individuals free from systemic or ocular hypertension, suggest that the effect of aging per se on central retinal arterial hemodynamics is small. It is unclear why aging-induced increases in the Poucrelot resistance index, so apparent in the ophthalmic artery, are absent in the central retinal vessel.

In summary, because our results were obtained from a healthy cohort characterized by normal intraocular and systemic arterial pressure, they capture the effects of uncomplicated aging on retrobulbar hemodynamics in both sexes. Our findings imply that vascular factors may play a role in the increased susceptibility to glaucoma and AMD seen in both sexes in senescence.

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REFERENCES