RI in central retinal artery as assessed by CDI does not correspond to retinal vascular resistance

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Flow through a blood vessel is determined entirely by two factors: the pressure difference between the two ends of the vessel (ΔP) and vascular resistance (R). Resistance refers to the impedance or opposition to blood flow created by the amount of friction the blood encounters as it passes through the vessels and is related to blood viscosity (η), the length of blood vessels (l), and vessel radius (r) (for laminar, nonpulsatile fluid flow). The mathematical formula to determine blood flow (Q) through a vessel can be expressed by modifying Poiseuille’s law

\[ Q = \frac{\Delta P}{R} \quad \text{and} \quad R = \frac{8\eta l}{\pi r^4} \]

Because R cannot be measured by any direct means, it is of interest to establish other parameters reflecting vascular resistance. The resistive index (RI) is considered to reflect vascular resistance peripheral to the measuring location. RI is calculated using velocity data as assessed by color Doppler imaging (CDI). RI is derived from the characteristics of the spectral wave form as described by Pourcelot (20)

\[ RI = \frac{PSV - EDV}{PSV} \]

where PSV is peak systolic flow velocity and EDV is end-diastolic flow velocity. Pourcelot’s ratio tends to be independent of the Doppler angle (20). The values of RI can vary from 0 to 1, with higher numbers indicating greater vascular resistance.

Several studies indicate that measurement of resistive index is clinically useful in a variety of vascular beds. Resistive index has been used in evaluating renal transplant beds as a reliable indicator for assessing acute rejection (22). In cirrhosis (5, 13) and chronic viral hepatitis (5), hepatic arterial resistive index increases parallel to the severity of liver failure. Bolognesi et al. (2) demonstrated that in patients with cirrhosis, intrasplenic arterial resistive index correlates significantly with portal vein blood flow resistance. The usefulness of the ultrasonographic measurement of resistive index in ocular blood vessels is not fully understood. Several studies (4, 9, 21) indicate that in patients with ocular vascular disease resistive index is elevated compared with healthy controls. However, some concerns have been raised by relying solely on resistive index as a measure of distal vascular resistance in ocular vessels (12, 14).

The aim of the present study was to investigate the association between resistive index in the central retinal artery as assessed by CDI and retinal vascular resistance. Am J Physiol Heart Circ Physiol 280: H1442–H1447, 2001.—The aim of the present study was to investigate the association between ultrasound Doppler measurements of resistive index (RI) in the central retinal artery and retinal vascular resistance (R) assessed with laser Doppler velocimetry, vessel size measurement, and calculation of ocular perfusion pressure (PP) in healthy subjects. An increase in vascular resistance was induced by inhalation of 100% O2. During hyperoxia no significant changes in PP were observed. Mean flow velocity in main retinal veins was reduced by −27.5 ± 2.0%. The average decrease in diameter was −11.5 ± 1.0%. R, which was calculated as the ratio of PP to flow rate, increased by 97.6 ± 7.7%. RI increased as well, but the effect was much smaller (6.6 ± 2.2%). In addition, a negative correlation was found between baseline values of R and RI (r = −0.83). During hyperoxia R and RI were not associated. In conclusion, our data indicate that RI as assessed with color Doppler imaging in the central retinal artery is not an adequate measure of R.

In several ophthalmic diseases, such as diabetic retinopathy and glaucoma, changes in ocular blood flow are assumed to play an important pathogenic role (8, 27). Hence, there is considerable interest in noninvasive methods for the assessment of ocular blood flow in humans and a variety of innovative techniques have been realized.

Flow through a blood vessel is determined entirely by two factors: the pressure difference between the two ends of the vessel (ΔP) and vascular resistance (R). Resistance refers to the impedance or opposition to blood flow created by the amount of friction the blood encounters as it passes through the vessels and is related to blood viscosity (η), the length of blood vessels (l), and vessel radius (r) (for laminar, nonpulsatile fluid flow). The mathematical formula to determine blood flow (Q) through a vessel can be expressed by modifying Poiseuille’s law

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\[ Q = \frac{\Delta P}{R} \quad \text{and} \quad R = \frac{8\eta l}{\pi r^4} \]
inal artery as assessed with CDI and vascular resistance assessed with laser Doppler velocimetry (LDV), retinal vessel size measurement, and calculation of ocular perfusion pressure. An increase in vascular resistance in the retina was induced by inhalation of 100% O₂. Oxygen is known to be a potent vasoconstrictor in many circulatory beds, including the retinal circulation (23).

METHODS

Subjects

After approval from the Ethics Committee of Vienna University School of Medicine was obtained, 11 healthy male nonsmoking volunteers were studied (age range: 21–32 yr, mean ± SD: 26.3 ± 3.9 yr). The nature of the study was explained and all subjects gave written consent to participate. All volunteers passed a prestudy screening during the 4 wk before the first study day, which included a physical examination and medical history, 12-lead electrocardiogram, and an ophthalmic examination. Inclusion criteria were normal findings in the screening examinations and ametropia of <3 diopters.

Experimental Design

All subjects were asked to refrain from alcohol and caffeine for at least 12 h before the trial day. After the subjects were given a 20-min resting period in a sitting position, baseline measurements of blood flow velocities in central retinal artery (CDI), retinal venous blood velocity by LDV, retinal venous diameter (Zeiss retinal vessel analyzer), intraocular pressure (IOP) (applanation tonometry), blood pressure, and pulse rate were obtained. Thereafter, an inhalation period of 100% oxygen was scheduled for 25 min. Oxygen (100%) (gases for human use, AGA; Vienna, Austria) was delivered through a partially expanded reservoir bag at atmospheric pressure. For gas delivery a two-valve system with a mouth piece was used. During the last 15 min of this breathing period, IOP and hemodynamic measurements were performed again. In all subjects the same sequence was used to assess ocular hemodynamics: CDI, LDV, Zeiss retinal vessel analyzer (RVA), IOP, and CDI. Retrobulbar flow velocity in the central retinal artery was measured at the beginning and the end of the measurement cycle to exclude time dependence of oxygen-induced retinal vasoconstriction. All examinations were performed by the same operator with the subjects in a sitting position. To evaluate intraobserver reproducibility, two separate baseline measurements of resistance index were performed. Heart rate and real time electrocardiogram were monitored until return to baseline values.

Methods Of Evaluation

CDI of the central retinal artery. The CDI examinations were performed using an Acuson 128 XP/10 Color Doppler Ultrasound device (Mountain View, CA). We used a combined transducer with 7.0 MHz for the B-mode (intensity: 40 mW/cm²) and 5.0 MHz for the pulsed Doppler (intensity: 25 mW/cm²). The depth of penetration of the ultrasound was set at 40 mm. The probe was placed on the closed upper eyelid following the application of contact jelly (methylcellulose 2%). To minimize the exertion of pressure on the globe, the examiner supported his hand on the subject’s forehead. Measurements of central retinal artery blood flow velocities were performed within the less echogenic optic nerve shadow, ~1- to 2-mm posterior to the globe. PSV and EDV were determined (16). From these parameters resistive index and mean flow velocity (MFV = integral of the Doppler curve/duration of the cardiac cycle) were calculated.

Systemic hemodynamics. Mean brachial artery blood pressures (MBABP) were measured on the upper arm by an automated oscillometric device. Pulse rate was automatically recorded from a finger pulse-oxygenymeter (HP-CMS patient monitor, Hewlett-Packard; Palo Alto, CA).

Measurement of IOP. A slit-lamp mounted Goldmann applanation tonometer was used to measure IOP. Before each measurement, one drop of 0.4% benoxinate hydrochloride combined with 0.25% fluorescein sodium was used for local anesthesia of the cornea.

Calculation of mean retinal perfusion pressure. Mean retinal perfusion pressure (PP) in the supine position is the following: PP = mean ophthalmic artery blood pressure (MOABP) – IOP. Robinson et al. (25) explored the relationship between MOABP (measured using Baillart ophthalmodynamometry) and the MBABP during isotemic exercises and found the following relation: MOABP = % MBABP. We then calculated PP as % MBABP – IOP. The factor % accounts for the drop in blood pressure between the brachial and ophthalmic artery while the subject is in a sitting position.

Measurement of centerline red blood cell velocity using bidirectional LDV. The principle of red blood cell velocity measurement by LDV is based on the optical Doppler effect. Laser light, which is scattered by moving erythrocytes, is shifted in frequency. This frequency shift is proportional to the blood flow velocity in the retinal vessel. The maximum Doppler shift corresponds to the centerline erythrocyte velocity (Vmax) (24). In the present study, we used a fundus camera-based system with a single mode laser diode at a center wavelength of 670 nm (Oculix Sarl; Arbaz, Switzerland). The Doppler shift power spectra were recorded simultaneously for two directions of the scattered light. The scattered light was detected in the image plane of the fundus camera. This scattering plane can be rotated and adjusted in alignment with the direction of Vmax, which enables absolute velocity measurements.

From Vmax, mean blood velocity in retinal vessels (Vmean) may be calculated as Vmean = Vmax/1.6. This relation has been found by experiments for blood flowing in glass tubes with a diameter in the range of those measured in our study (7, 17). With the use of this relation, mean velocities in retinal arteries and retinal veins can be obtained. LDV provides a reliable and reproducible technique for retinal blood velocity measurement (24).

In the present study, Vmean was determined for each major retinal vein draining into the optic disk. An average Vmean was calculated as the average blood velocity of all measured veins of a subject. All measurement locations were within one to two disk diameters from the center of the optic disk.

Diameter measurements using Zeiss RVA. The vessels diameters at the same measurement locations (D) were determined from retinal images recorded with a new fundus camera-based system. The Zeiss RVA is a commercially available system which comprises a fundus camera (Zeiss FF 450; Jena, Germany), a video camera, a real time monitor, and a personal computer with an analyzing software for the accurate determination of retinal arterial and venous diameters (1). Every second, a maximum of 25 readings of vessel diameter can be obtained. For this purpose, the fundus is imaged onto the charge-coupled device chip of the video camera. The consecutive fundus images are digitized by using a frame grabber. In addition, the fundus image can be inspected on the real-time monitor and, if necessary, stored on a video
recorder. Evaluation of the retinal vessel diameters can either be done online or offline from the recorded videotapes. Because of the absorbing properties of hemoglobin, each blood vessel has a specific transmittance profile. Measurement of retinal vessel diameters is based on adaptive algorithms by using these specific profiles. Whenever a specific vessel profile is recognized, the RVA is able to follow this vessel as long as it appears within the measurement window. This means that the system is able to automatically correct for alterations in luminance as induced for instance by slight eye movements. If the requirements for the assessment of retinal vessel diameters are not fulfilled anymore, as it occurs during blinks, the system automatically stops the measurement of vessel diameter. As soon as an adequate fundus image is achieved again, measurement of vessel diameters restarts automatically. Our previous data indicates excellent reproducibility of measurements with the Zeiss RVA. With this system changes between 3% and 5% in retinal vessel diameters can be detected (19). In the present study, a mean diameter of all retinal vein diameters was calculated as

$$D = \sum_{i=1}^{n} D_i/n$$

Calculation of blood flow. Blood flow through an individual retinal vein was calculated as

$$Q_i = V_{mean,i} \times \pi \times D_i^2/4$$

Total retinal blood flow was obtained using the equation

$$Q = \sum_{i=1}^{n} V_{mean,i} \times \pi \times D_i^2/4$$

The number of veins that were used for calculation of total retinal blood flow varied between 4 and 6 depending on the individual retinal angioarchitecture.

Calculation of vascular resistance. Vascular resistance was calculated as the ratio of mean retinal PP and Q: $R = PP/Q$.

Data Analysis

Statistical analysis was done with CSS Statistica for Windows (Statsoft; Tulsa, CA). MFV and resistive index in the ophthalmic artery during hyperoxia were calculated as the mean between the two values measured. The effects of 100% $O_2$ breathing on retinal outcome parameters are expressed as percent change from baseline ($\Delta\%$). Data are presented as means ± SE. Statistical significance of the intervention-induced effects was assessed by Wilcoxon matched pairs test. The association between retinal hemodynamic parameters was investigated using linear regression analysis. A $P$ value <0.05 was considered significant. The intraobserver reproducibility of CDI measurements was quantified with intra-class correlation coefficients (12) and coefficients of variation.

RESULTS

Systemic Hemodynamics and IOP

The values of systemic blood pressure, pulse rate, and IOP at baseline and during 100% $O_2$ breathing are shown in Table 1. Systemic hyperoxia did not affect these parameters.

Retrolubar Hemodynamic Measurements Using CDI

Figure 1, top, shows the individual hyperoxia-induced changes in MFV and resistive index. The reduction in MFV in the central retinal artery during hyperoxia was $-25.4 \pm 4.9\% \ (P = 0.004 \ vs. \ baseline)$. Resistive index slightly increased by $6.6 \pm 2.2\% \ (P = 0.04 \ vs. \ baseline)$. However, an increase in resistive index was not observed in all subjects (Table 2).

$V_{mean}$ as Measured by LDV and Retinal Venous Diameter by Using RVA

Hyperoxia-induced changes in $V_{mean}$ and diameter in all 11 subjects are shown in Fig. 1, bottom. Average $V_{mean}$ in main retinal veins during hyperoxia was reduced by $-27.5 \pm 2.0\%$ compared with baseline ($P < 0.001$). The average decrease in retinal venous diameter was $-11.5 \pm 1.0\% \ (P < 0.001 \ vs. \ baseline)$.

Blood Flow and Vascular Resistance

During pure oxygen breathing retinal blood flow decreased significantly ($-42.8 \pm 2.0\%, \ P < 0.001$). This effect was observed in all retinal veins under study. Total retinal venous flow rates in all subjects are presented in Table 3. As expected 100% $O_2$ breathing induced a pronounced increase of vascular resistance in the retina ($97.6 \pm 7.7\%, \ P = 0.003 \ vs. \ baseline$). Individual hyperoxia-induced percent changes in vascular resistance are shown in Table 2.

Comparison of Outcomes

A negative correlation was found between baseline values of vascular resistance and resistive index ($r = -0.83, \ P = 0.0016$, Fig. 2). During pure oxygen breathing, however, vascular resistance and resis-

Table 1. Effects of 100% $O_2$ breathing on systemic hemodynamics and intraocular pressure

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CDI</th>
<th>100% $O_2$</th>
<th>Baseline</th>
<th>CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV</td>
<td></td>
<td></td>
<td>LDV</td>
<td></td>
</tr>
<tr>
<td>Mean brachial artery pressure, mmHg</td>
<td>79±3</td>
<td>79±2</td>
<td>81±2</td>
<td>81±3</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>116±3</td>
<td>117±2</td>
<td>117±2</td>
<td>118±2</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>60±3</td>
<td>59±2</td>
<td>62±4</td>
<td>62±3</td>
<td></td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>63±3</td>
<td>61±2</td>
<td>60±2</td>
<td>59±2</td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure, mmHg</td>
<td>16±3</td>
<td>15±3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean retinal perfusion pressure, mmHg</td>
<td>37±2</td>
<td>37±2</td>
<td>39±2</td>
<td>39±2</td>
<td></td>
</tr>
</tbody>
</table>

Results are means ± SE; $n = 11$ male volunteers. Systemic hemodynamics are shown twice: during laser Doppler velocity (LDV) measurements and during color Doppler imaging (CDI) measurements.
tive index were not associated ($r = -0.32$, $P = 0.33$, data not shown). Similarly, the percent change of resistive index was not significantly correlated with the percent change of vascular resistance ($r = 0.4$, $P = 0.25$; Fig. 3, top).

Mean flow velocity as measured with CDI did not correlate directly with $V_{mean}$ ($r = 0.52$, $P = 0.1$, data not shown) at baseline, but an association was observed during 100% $O_2$ breathing ($r = 0.72$, $P = 0.013$, data not shown). Percent changes of both parameters during hyperoxia correlated as well ($r = 0.7$, $P = 0.024$; Fig. 3, bottom).

**Intraobserver Reproducibility**

Short-term intraobserver variability in determining MFV and resistive index were estimated from repeated baseline measurements. The coefficients of variation were 3.0% for resistive index and 5.7% for MFV. The intraclass correlation coefficient $\kappa$ was 0.88 (RI) and 0.73 (MFV), respectively.

**DISCUSSION**

In the present study we observed a pronounced decrease in retinal blood flow during inhalation of 100% oxygen. This is in keeping with a variety of previous studies by using either the same technique as in the present study (10, 23), the blue field entoptic technique (6, 30), or confocal scanning laser Doppler flowmetry (31). In the present study retinal blood flow decreased by $\sim 40\%$. Because neither blood pressure nor IOP were significantly affected, retinal vascular resistance increased almost twofold.

The main result of the present study is that this increase in retinal vascular resistance was not adequately reflected from the measurements in resistive index. Whereas 100% oxygen breathing caused a significant increase in resistive index, this increase was $<7\%$. This is in the same order as observed in previous studies (28) and indicates that resistive index underestimates the effect of systemic hyperoxia on retinal vascular resistance more than 10-fold. Our reproducibility data ensure that this results is not a consequence of low test/retest variability with CDI.

**Table 2. Individual hyperoxia-induced percent changes in vascular resistance and resistive index**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Vascular resistance</th>
<th>Resistive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>114.2</td>
<td>14.7</td>
</tr>
<tr>
<td>2</td>
<td>112.1</td>
<td>10.6</td>
</tr>
<tr>
<td>3</td>
<td>72.2</td>
<td>12.3</td>
</tr>
<tr>
<td>4</td>
<td>108.7</td>
<td>9.4</td>
</tr>
<tr>
<td>5</td>
<td>128.6</td>
<td>15.4</td>
</tr>
<tr>
<td>6</td>
<td>133.9</td>
<td>-4.0</td>
</tr>
<tr>
<td>7</td>
<td>105.4</td>
<td>11.2</td>
</tr>
<tr>
<td>8</td>
<td>52.0</td>
<td>-3.8</td>
</tr>
<tr>
<td>9</td>
<td>79.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>10</td>
<td>74.7</td>
<td>3.3</td>
</tr>
<tr>
<td>11</td>
<td>92.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Means $\pm$ SE</td>
<td>97.6 $\pm$ 7.7</td>
<td>6.6 $\pm$ 2.2</td>
</tr>
</tbody>
</table>

**Table 3. Individual hyperoxia-induced changes in total retinal blood flow rate**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Total Retinal Blood Flow Rate, $\mu l/min$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>39.7</td>
</tr>
<tr>
<td>2</td>
<td>32.0</td>
</tr>
<tr>
<td>3</td>
<td>31.3</td>
</tr>
<tr>
<td>4</td>
<td>30.8</td>
</tr>
<tr>
<td>5</td>
<td>22.3</td>
</tr>
<tr>
<td>6</td>
<td>35.6</td>
</tr>
<tr>
<td>7</td>
<td>32.6</td>
</tr>
<tr>
<td>8</td>
<td>49.5</td>
</tr>
<tr>
<td>9</td>
<td>42.1</td>
</tr>
<tr>
<td>10</td>
<td>25.5</td>
</tr>
<tr>
<td>11</td>
<td>34.6</td>
</tr>
<tr>
<td>Means $\pm$ SE</td>
<td>34.1 $\pm$ 2.3</td>
</tr>
</tbody>
</table>
A variety of previous experiments focused on the relation between vascular resistance and resistive index. In vitro (11, 29) and in vivo studies in renal (18) and brachial arteries (15) show a close correlation between resistive index and vascular resistance. However, more recently a study investigating the uterine artery in sheep found that it is the impedance that determines resistive index (26). The impedance is not only a factor that accounts for vascular resistance but also for vascular compliance (C). Vascular compliance, however, is defined as $C = \frac{dV}{dP}$, where $dV$ is a change in vascular volume and $dP$ is a change in pressure. These results were confirmed in an in vitro perfusion model in which compliance and resistance could be varied independently (3). This study has shown that in general resistance and compliance interact to alter resistive index and that only at high vascular compliance resistive index is an adequate measure of vascular resistance.

In the present study, systemic hyperoxia induced a pronounced decrease in retinal blood flow and retinal diameters. Obviously this will alter the elastic properties of the retinal vessels and consequently vascular compliance. During pronounced retinal vasoconstriction, retinal vascular compliance will decrease significantly resulting in a nonresistance-related decrease in retinal resistive index. Hence, we propose that during systemic hyperoxia, resistive index is affected by two counteracting factors: the increase in vascular resistance and the decrease in vascular compliance. This leads to an underestimation of the effect of 100% oxygen breathing on vascular resistance when resistive index is used.

A comparison of our data obtained in the central retinal artery and from retinal veins indicates that vasoconstriction occurs to some extent in the extraocular part of the central retinal artery. Reductions in mean flow velocity as observed in the central retinal artery and retinal venous branches were in the same order and showed some degree of correlation. By contrast, retinal blood flow was decreased to a higher degree. The only explanation for these data is significant vasoconstriction in the extraocular part of the central retinal artery. Hence, our results also establish a good example that velocity changes as assessed in retrobulbar vessels cannot be extrapolated to changes in blood flow.

The evidence for vasoconstriction of the central retinal artery is also related to an important limitation of the present study. PP was calculated from brachial artery blood pressure and IOP, because direct measurement of retinal PP is not possible in humans. Vasoconstriction of the artery supplying the retina indicates that even this “large” vessel acts as a resistance vessel during 100% oxygen breathing. This will lead to a pressure loss at the level of the central retinal artery and consequently to a slightly smaller PP as calculated in the present study.

The calculation of $V_{\text{mean}}$ from $V_{\text{max}}$ is a limitation in determining retinal blood flow using the LDV technique. Currently LDV of retinal vessels only allows for the measurement of the maximum blood velocity, and quantitative information on the blood velocity profile is...
not available. Hence, some assumptions on the distribution of blood velocities across the vessel diameter have to be made. The use of $V_{mean} = V_{max}/1.6$ is derived from in vitro studies in glass tubes and has been successfully applied to studies in the retinal circulation (24). To estimate the possible error introduced by using the factor 1.6, we recalculated our data by using the slightly different profiles (factors of 1.5 and 1.7). It turns out that the error introduced by changing this factor is small ($\pm 6\%$) when hyperoxia conditions and baseline conditions are compared. Hence, this does not account for the differences observed between $R$ and resistive index.

Interestingly, we observed a negative correlation between baseline resistive index and baseline vascular resistance in the present study. Whether this indicates that baseline resistive index is mainly a measure of vascular compliance remains to be established. However, the number of subjects in the present study ($n = 11$) is very small for a cross-sectional comparison, and data in a larger study population are necessary to confirm our observation. Nevertheless, our data question cross-sectional comparisons in retinal vascular resistance between patients with ocular disease and healthy controls by relying on resistive index.

In conclusion, the data of the present study indicate that resistive index is not a valid indicator of vascular resistance in the retina.

We are indebted to Acuson for the loan of the ultrasound Doppler device.

REFERENCES


