Fourier Analysis of the Envelope of the Ophthalmic Artery
Blood Flow Velocity
Age- and Blood Pressure–Related Impact

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Abstract—The harmonic content of the envelope waveform of the blood flow velocity in the ophthalmic artery was analyzed in aging and arterial hypertension. The case-control study enrolled 98 healthy men (age: 44.0±15.6 years), 100 healthy women (age: 44.5±19.1 years), which is group 1, and overall 199 hypertensive patients with increased systolic and diastolic blood pressure (in millimeters of mercury) before registration of the blood flow velocity using pulsed Doppler sonography. Group 2 was sufficiently treated (\(\leq 140/\leq 90\)), group 3 (\(>140/\leq 90\)) and group 5 (\(>140/\geq 90\)) were insufficiently treated, and group 4 (\(>140/\leq 90\)) and group 6 (\(>140/\geq 90\)) were untreated. Cronbach-\(\alpha\) reliability of the calculated spectral coefficient and SI (SI) was 0.88 and 0.93, respectively. In control subjects, the SI was influenced by age (men: 45.1%; women: 50.2%; \(P<0.001\) each) and in women additionally by mean arterial pressure (13.1%; \(P<0.001\)). The SI differed in subjects \(\geq 43\) years of age (men: 0.37±0.11; women: 0.26±0.08; \(P<0.001\) each) as compared with subjects \(\leq 43\) years of age (men: 0.60±0.18; women: 0.48±0.13). All of these changes were lacking for the resistance index. In both men and women with hypertension, the SI decreases, whereas the mean arterial pressure increases, but the resistance index did not change. The SI of the ophthalmic artery allows an assessment of the ocular circulation in consideration of age and arterial blood pressure in contrast to the resistance index. (Hypertension. 2007;50:1-2.)

Key Words: aging ■ arterial hypertension ■ blood flow velocity ■ fast Fourier transform ■ harmonic oscillation ■ resistance index ■ spectral index

Several parameters were used to explore differences in aging rates influenced by cardiovascular risk factors. The correlations of chronological age with arterial hypertension\(^1\) and of age with systolic blood pressure (SBP), cholesterol plasma concentration, and consumption of cigarettes\(^2\) were investigated.

It is well known that hemodynamic characteristics of the arterial system change in dependency on age and, eg, arterial hypertension. These characteristics may be analyzed by decomposition of the complex waveforms, which are induced by systolic cardiac output, the subsequently reflected wave from the vessel periphery, and the again-reflected wave from the aortic valve. The fast Fourier transform represents a mathematical approach for analysis, which is an optimized and refined algorithm\(^3\) based on the discrete Fourier transform. Respective examinations were performed in the cerebrovascular system,\(^4\) in the cardiovascular and respiratory system,\(^5\) and in other different vessel areas to measure the input impedance.\(^6,7\) Fourier coefficients of the first to tenth harmonic oscillations have been shown to differentiate between normal and pathological vessels,\(^8\) and already in small retinal vessels of young patients with arterial hypertension, the hemodynamics was shown impaired.\(^9\)

The goal of our study was to examine the usefulness of the harmonic content derived from the envelope waveform of the blood flow velocity of the ophthalmic artery (OA) as a parameter related to age and arterial hypertension. The ratio of the most meaningful oscillations of the harmonic content was compared with the resistance index (RI), which is broadly used as a marker of peripheral vascular resistance.

Methods

Participants
Participants were randomly selected from a population-based screening project for glaucoma, which is established at the Department of Ophthalmology, University of Erlangen. Subjects received a questionnaire requesting age, gender, height, weight, known cardiovascular risk factors (ie, arterial hypertension, diabetes, and smoking history), and cardiovascular events (ie, myocardial infarction, peripheral arterial disease, transient ischemic attack, and stroke). Cholesterol levels were not requested. Eyes were assessed by a full ophthalmologic examination with dilated pupils and a judgment of colored fundus images with respect to optic nerve and retinal diseases. Images were acquired using a nonmydriatic fundus camera (nonmyd-o45, Kowa).

The control group, group 1, consisted of 98 healthy men (age: 44.0±15.6 years) and 100 healthy women (age: 44.5±19.1 years)
without the inquired cardiovascular risk factors or cardiovascular events and without eye diseases, such as glaucoma or ocular hypertension. Subjects had a normal blood pressure (diastolic blood pressure [DBP]: \( \leq 90 \text{ mm Hg} \); SBP: \( \leq 140 \text{ mm Hg} \)) before registration of the blood flow velocity in OA using pulsed Doppler sonography.

In the case-control study group 1 was compared with 98 men and 101 women, who were subdivided into categories according to antihypertensive therapy and to their SBP and DBP (in millimeters of mercury). Group 2 was sufficiently treated (\( \leq 140/90 \)), groups 3 (\( >140 \leq 90 \)) and group 5 (\( >140/90 \)) were insufficiently treated, and group 4 (\( >140/90 \)) and group 6 (\( >140/90 \)) were untreated for increased blood pressure. The hypertensive groups had neither diabetes nor smoking history, myocardial infarction, peripheral arterial disease, transient ischemic attack, stroke, glaucoma, or ocular hypertension.

The study was conducted in accordance with the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The University of Erlangen-Nürnberg Clinical Investigation Ethics Committee gave its approval to the study protocol. Written informed consent was obtained from all of the subjects.

**Method**

**Procedure**

After a subject’s rest of 10 minutes, the arterial blood pressure was measured by an experienced observer 1 time on the supine subject at the brachial artery using a commercial automated sphygmomanometer according to the method of Riva-Rocci. The cuff size had a 14-cm width and a 50-cm length. Ingestion of the day of examination was not prohibited but was not done 1 hour before the beginning of the study. The mean arterial pressure (MAP) was calculated according to the following equation: MAP (in millimeters of mercury) = DBP + 1/3(SBP – DBP).

Subsequently, the blood flow velocity of OA was registered using pulsed Doppler sonography (Companion, Nicolet-EME). The 4-MHz transducer was placed temporal on the upper eyelid of the right closed eye, as described previously. Pupils were not pharmacologically dilated. Six measuring lengths of 10-second duration each were recorded under visual and acoustic check. Ultrasonic waves reached a mean depth of 41 ± 3 mm.

**Spectral Coefficient and Spectral Index**

The envelope waveform of the blood flow velocity is composed of different superimposed frequency components. Fast Fourier transform is an algorithm, which allows separation into single sinus waves according to their frequencies, amplitudes, and time periods. The oscillation amplitude of the separate signal components, ie, the first through fifth harmonic oscillation, is indicated by the power absolute values. Oscillation frequencies of the 5 harmonics considered share in their sum as power percentage values. Because absolute values are dependent on the blood flow velocity, which may further influence age-dependent calculations but not the relative values of the overall spectrum, power percentage values were chosen for further proceeding. The spectral coefficient (SC) was calculated from the power percentage values according to Eq 1 with \( n = 5 \) (the first through fifth harmonic oscillation). Power percentage values of each harmonic are designated by \( h_i \) and \( i \) indicates the numbering of the harmonics.

\[
SC = \frac{\sum_{i=1}^{n} i h_i}{(1+2+3+4+5)p_1}
\]

As shown in the Results, the third and the first harmonic possessed the highest explanatory power, which is why the ratio of their power percentage values was used for calculation of the spectral index (SI; Eq 2).

\[
SI = \frac{p_3}{p_1}
\]

**Calculation of the RI**

The RI was calculated according to the formula defined by Pouchot, which indicates the peak systolic velocity, and \( V_d \) representing the end diastolic velocity:

\[
RI = \frac{(V_s - V_d)}{V_s}
\]

**Statistical Analysis**

Analyses were performed using the SPSS software (release 13.0, SPSS Inc). The significance of mean values was estimated by the Mann-Whitney test for unpaired metric data. The partial correlation procedure considered Pearson’s coefficient. Two-way uni-ANOVA and multivariate 2-way ANOVA were applied for analyses in control subjects and across hypertensive groups, respectively. The SPSS function of curve estimation tested for the best-adjusted regression curve, and quadratic complement determined the minimum of asymmetrical parabolas (see the data supplement available at http://hyper.ahajournals.org). All of the values are expressed as mean ± SD. \( P < 0.05 \) was considered to be significant.

**Reliability of the Variables Derived From the Envelope Waveform**

Twelve healthy subjects were examined 2 times each at days 1 and 8, respectively, and 1 time after 6 weeks. Cronbach-\( \alpha \) at the 95% confidence interval was 0.88 for SC and 0.93 for SI. Thus, the intraclas correlation coefficients of reliability of the blood flow envelope velocity’s waveforms were within a very good range of reliability.

**Results**

**Determination of the SI**

The first 5 oscillations of the harmonic content were examined for their explanatory power. In male and female control subjects (Figure 1), the power percentage values of the third and the first harmonics achieved both the steepest gradients over age and the greatest squared coefficients of determination, \( R^2 \), which is why their ratio was considered for definition of the SI.

**Dependent Variables in Normotension**

In male and female control subjects, the dependent variables SC, SI, and RI, as well as their covariates age, SBP, MAP, DBP, and heart rate (HR) achieved Gaussian distribution (data not shown). Age, RI, SBP, and HR were not significantly different between men and women, but SC (\( P = 0.008 \)), SI (\( P < 0.001 \)), MAP (\( P = 0.041 \)), and DBP (\( P = 0.015 \); Table 1, left) were significant.

![Figure 1](http://hyper.ahajournals.org). Power percentage values of the first through fifth harmonic oscillations of the OA in dependency on age in men (M) and in women (F). In both genders, the highest explanatory power that is the steepest gradient (\( b \)) and the highest square regression coefficient (\( R^2 \)) were found for the first and the third harmonic oscillations (H).
Partial correlations are depicted in Table S1. Overall, in men, SI correlated with age and, in women, with both age and MAP, but RI did not.

The uni-ANOVA procedure using age, SBP, DBP, and HR as covariates revealed that only age displayed a relative statistical weight to the variation observed in SI (men: 45.1%, P < 0.001; in women: 50.2%, P < 0.001). SC was influenced significantly by age (men: 53.4%; women: 57.3%; P < 0.001 each) and HR (men: 10.9%; women: 11.7%; P < 0.001). In men, the relative statistical weight of DBP, which only contributes to RI, was 8.1% (P = 0.006). In women, there was no significant influence of the covariates on RI.

If submitting MAP and HR to uni-ANOVA, none of the covariates influenced RI significantly in men and women. SC and SI were not under the control of MAP in men but were in women (SC: 11.2%, P = 0.006; SI: 13.1%, P < 0.001). In contrast to the equation for men, the resulting equation for women additionally included the MAP.

(4) \[ \text{SI} = 0.84 - 0.008 \times \text{age} \]

(5) \[ \text{SI} = 1.05 - 0.005 \times \text{age} - 0.005 \times \text{MAP} \]

Linearity between age and SI was checked (please see Figure S1).

For determination of differences between younger and older subjects, the median age in men and women (43 years each) was calculated. Corresponding data are depicted in Table 1 (at right). In the older group, SI was significantly lower in men and women as compared with younger subjects, but SBP, MAP, and DBP were clearly different between age groups only in women. Within the respective age groups, SI was significantly decreased in women as compared with men. In the younger age group, SBP, MAP, and DBP of men were increased, but in the older group, only mean age was decreased in comparison with the respective data of women.

In summary, the present study has found that, in normotensive subjects, a defined SI derived from the envelope waveform of the blood flow velocity in the OA shows differences in dependency on age, with lower SI values in older subjects, and between men and women, with lower SI values in women. These changes were lacking for RI. In men, SI was inversely dependent on age and, in women, on both age and MAP. With increasing values for MAP, SI was influenced by MAP also in men, whereas RI became dependent only on age in women. Furthermore, in normotensive control subjects, SI was positively correlated with RI but, of note, RI did not change with increasing MAP, whereas SI decreased.

SI in Arterial Hypertension

Because of the different sample sizes of the different blood pressure groups, it is recommended to interpret the results of SI within hypertensive groups always in comparison with RI. As shown in Figure 2 and Tables 2 and 3, SI but not RI was decreased in subjects with hypertension. A solely increased SBP was associated with a significantly decreased SI in men and in women. This effect was further intensified if the diastolic blood pressure was increased (Figure 2).

### Table 1. Statistical Data of the Control Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men (n=98)</th>
<th>Women (n=100)</th>
<th>Men (n=49)</th>
<th>Women (n=51)</th>
<th>Men (n=49)</th>
<th>Women (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.0±15.6</td>
<td>44.5±19.1‡‡</td>
<td>30.9±6.7</td>
<td>28.2±7.2†‡</td>
<td>57.1±10.1§</td>
<td>61.5±10.9§</td>
</tr>
<tr>
<td>Age range, y</td>
<td>20 to 83</td>
<td>20 to 83</td>
<td>20 to 43</td>
<td>20 to 43</td>
<td>44 to 83</td>
<td>44 to 83</td>
</tr>
<tr>
<td>SC</td>
<td>15.6±1.3</td>
<td>15.1±1.4†‡</td>
<td>16.5±0.9</td>
<td>16.2±0.7†‡</td>
<td>14.7±1.1§</td>
<td>14.0±1.0§†</td>
</tr>
<tr>
<td>SI</td>
<td>0.48±0.19</td>
<td>0.37±0.15*‡</td>
<td>0.60±0.18</td>
<td>0.48±0.13*</td>
<td>0.37±0.11§</td>
<td>0.26±0.08*§</td>
</tr>
<tr>
<td>RI</td>
<td>0.68±0.07</td>
<td>0.68±0.06‡</td>
<td>0.69±0.07</td>
<td>0.69±0.06‡</td>
<td>0.67±0.08§</td>
<td>0.70±0.08‡§</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.0±10.7</td>
<td>120.6±10.7‡</td>
<td>120.7±10.4</td>
<td>115.8±9.2†</td>
<td>123.4±11.0§</td>
<td>125.5±10.1§</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>90.0±8.1</td>
<td>87.6±8.2‡</td>
<td>89.0±7.1</td>
<td>84.3±7.3†‡</td>
<td>91.4±8.8§</td>
<td>91.1±7.7§</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>73.9±7.8</td>
<td>71.2±7.6†‡</td>
<td>72.4±6.6</td>
<td>68.5±6.8‡</td>
<td>75.4±8.7‡</td>
<td>73.9±7.6§</td>
</tr>
<tr>
<td>HR, s⁻¹</td>
<td>68.0±11.9</td>
<td>69.6±9.8‡‡</td>
<td>66.8±11.8</td>
<td>70.3±10.9‡</td>
<td>69.2±11.9§</td>
<td>68.9±8.7†§</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise specified.
Significant changes between men and women: *P<0.001; †0.001<P<0.05; ‡Not significant.
Significant changes between age groups: §P<0.001; ‡0.001<P<0.05; ¶Not significant.

![Figure 2](http://hyper.ahajournals.org/). The SI in dependency on arterial hypertension. The SI but not the RI was decreased in hypertensive subjects. The thick line within the box marks the median; the lower and the upper boundaries of the box indicate the 25th and 75th percentile, respectively. Whiskers below and above the box indicate the 10th and 90th percentiles, respectively. The circles and the single asterisk label extreme values.
pressure was also increased. Overall, in both men and women, SI
decreases, whereas MAP increases over the hypertensive
groups, but RI did not change. Also, in the hypertensive groups,
women had significantly lower SI values than men, but RI
values were not different between men and women. Gender-
related differences of MAP over the hypertensive groups were
only weakly significant in groups 1 and 3, and differences of age
were only weakly significant in group 3.

RI and SI as dependent variables were submitted to
multivariate ANOVA. Normotensive, solely systolic hyper-
tensive, and combined systolic and diastolic hypertensive
groups were defined as fixed factors and age and HR as
covariates. This model produced equally observed covariance
matrices of the dependent variables across groups and equal
error variances across cells only after RI and SI were log
transformed and if analysis was performed broken according
to gender. Additional fragmentation of groups according to
treatment status without log transformation of RI and SI did
not provide valid test conditions. In men, only age (40.9%;
P<0.001) and affiliation to blood pressure group (4.2%;
P=0.017) contributed to the logarithm of SI, but log(RI) was
not affected significantly. In women, age (35.4%; P<0.001),
HR (2.6%; P=0.023), and group affiliation (7.9%; P<0.001)
influenced log(SI), whereas only age (4.4%; P=0.003) con-
tributed to log(RI). Taken together, our results revealed that,
in subjects with arterial hypertension, the SI was decreased
but not the RI.

Additional patient characteristics are available from in
Table S2. Figure 3 shows sample envelope waveform of the
blood flow velocity in the OA in women of different ages and
with normal or increased blood pressure, respectively.

**Discussion**

**Impact of Oscillation Analysis**

Transformation of experimental data from the time domain into
the frequency domain by fast Fourier transform provides
information about dynamic mechanical properties of the
vascular system. Smaller arteries are characterized by a
higher resistance than large arteries and, therefore, represent

### Table 2: Statistical Data of Hypertensive Groups

<table>
<thead>
<tr>
<th>SBP/DBP, mm Hg</th>
<th>Sex</th>
<th>RI</th>
<th>SI</th>
<th>MAP, mm Hg</th>
<th>Age, y</th>
<th>n</th>
<th>RI</th>
<th>SI</th>
<th>MAP, mm Hg</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 1: ≤140/≤90, no medication</td>
<td>Men</td>
<td>0.68±0.07</td>
<td>0.48±0.19</td>
<td>90.0±8.1</td>
<td>44.0±15.6</td>
<td>98</td>
<td>0.256</td>
<td>&lt;0.001</td>
<td>0.041</td>
<td>0.913</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.69±0.07</td>
<td>0.37±0.15</td>
<td>87.6±8.2</td>
<td>44.5±19.1</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr 2: &gt;140/≤90, with medication</td>
<td>Men</td>
<td>0.67±0.08</td>
<td>0.37±0.15</td>
<td>93.7±10.1</td>
<td>58.5±11.6</td>
<td>10</td>
<td>0.978</td>
<td>0.005</td>
<td>0.892</td>
<td>0.216</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.68±0.07</td>
<td>0.26±0.07</td>
<td>94.1±8.0</td>
<td>65.4±10.3</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr 3: &gt;140/&lt;90, no medication</td>
<td>Men</td>
<td>0.69±0.06</td>
<td>0.36±0.14</td>
<td>106.2±4.3</td>
<td>55.1±16.3</td>
<td>41</td>
<td>0.368</td>
<td>&lt;0.001</td>
<td>0.029</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.71±0.07</td>
<td>0.23±0.07</td>
<td>108.1±4.7</td>
<td>63.6±12.5</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr 4: &gt;140/&lt;90, with medication</td>
<td>Men</td>
<td>0.69±0.03</td>
<td>0.34±0.08</td>
<td>108.8±2.0</td>
<td>54.9±16.2</td>
<td>7</td>
<td>0.757</td>
<td>0.047</td>
<td>0.852</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.70±0.11</td>
<td>0.25±0.11</td>
<td>109.5±6.0</td>
<td>67.4±9.3</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr 5: &gt;140/&gt;90, no medication</td>
<td>Men</td>
<td>0.67±0.06</td>
<td>0.29±0.07</td>
<td>119.5±9.9</td>
<td>60.2±13.4</td>
<td>14</td>
<td>0.112</td>
<td>&lt;0.001</td>
<td>0.341</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.70±0.09</td>
<td>0.19±0.07</td>
<td>122.4±9.9</td>
<td>64.9±11.3</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr 6: &gt;140/&gt;90, with medication</td>
<td>Men</td>
<td>0.67±0.07</td>
<td>0.29±0.10</td>
<td>124.9±12.4</td>
<td>62.7±11.6</td>
<td>26</td>
<td>0.157</td>
<td>0.005</td>
<td>0.277</td>
<td>0.253</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.71±0.11</td>
<td>0.20±0.08</td>
<td>119.3±6.1</td>
<td>67.4±9.4</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD.

### Table 3: P Values of Differences Between Hypertensive Groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 2 vs Gr 1</td>
<td>0.759</td>
<td>0.531</td>
</tr>
<tr>
<td>Gr 3 vs Gr 1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 4 vs Gr 1</td>
<td>0.817</td>
<td>0.557</td>
</tr>
<tr>
<td>Gr 5 vs Gr 1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 5 vs Gr 3</td>
<td>0.536</td>
<td>0.278</td>
</tr>
<tr>
<td>Gr 6 vs Gr 1</td>
<td>0.909</td>
<td>0.873</td>
</tr>
<tr>
<td>Gr 6 vs Gr 2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 6 vs Gr 4</td>
<td>0.598</td>
<td>0.686</td>
</tr>
<tr>
<td>Gr 6 vs Gr 5</td>
<td>0.158</td>
<td>0.788</td>
</tr>
<tr>
<td></td>
<td>0.475</td>
<td>0.411</td>
</tr>
<tr>
<td></td>
<td>0.986</td>
<td>0.325</td>
</tr>
<tr>
<td></td>
<td>0.590</td>
<td>0.911</td>
</tr>
<tr>
<td></td>
<td>0.856</td>
<td>0.610</td>
</tr>
</tbody>
</table>

Gr indicates group.
the major source of wave reflections. The definite contour of the envelope waveform is composed of primary waves (generated by contraction of the left ventricle) and secondary reflected waves, which interfere with the primary ones. Endothelial dysfunction may result in an increase in the tone of small arteries that would reduce oscillatory compliance. Experimental data indicate that aging alters endothelium-dependent relaxation in arteries, and loss of the oscillatory waveform represents an early and consistent finding with aging and hypertension. 

Different frequency fractions of the envelope waveform of the blood flow velocity possess different input resistances, meaning that individual oscillations of the harmonic content are exposed to different wave resistances, which are induced by both the peripheral reflections and the vessel elasticity. In this context, the power of the first 5 harmonics <10 Hz is well known and, therefore, was used for further considerations.

Influence of Gender

The results for RI are consistent with those of other studies, which have shown that both age and blood pressure are not effective to RI in the OA. In our study, the contradictory results seen for SI and RI may be explained by the different compliance and reflection effects, which were considered by the differing definitions of the 2 indices.

It is known that, in older subjects, the late systolic peak without a diastolic wave induces a high-input resistance in the range of the first harmonic, and, after a steep decline between 2 and 3 Hz, it raises again from 4 Hz. In contrast, in younger people without a systolic peak but with a diastolic wave, the first harmonic achieved a lower value with a decrease of the impedance minimum at ~2 Hz.

We have considered the SC of the first 5 harmonics less suitable for calculations independent from age, because the percentage values of SI were not related to the blood flow velocity, which changes with aging. For this reason, SI was preferred for further calculations.

Influence of Age

An earlier method has analyzed the ratio of the height of 2 peaks during cardiac systole in the supraorbital artery. The first peak of this measurement method is related to the sum of both the ejected and the reflected waves from the site of measurement. The second peak is composed of the reflected wave from the lower body minus end-diastolic pressure. Thus, these 2 peaks are considered related to the first harmonic and to a multiple of the first harmonic, respectively. The mean ratio of these 2 peaks was found to decrease from 20 to 50 years and to be significantly lower in females than in males.

The gender gap of SI may be explained by the described significant differences between aortic compliance in males and females during reproductive years and, dependent on age, by the differing arterial diameter, which seems to be influenced by gender, and by the vascular resistance corrected for the body surface, which was higher in women than in men. It was reported that women in the fourth decade had a lower MAP than men, which was adjusted by the end of the seventh decade. Also, in the present study, MAP in the younger group was significantly different between gender but not in the older group. These results are in line with the greater arterial distensibility until menstruation.

Influence of Blood Pressure

Changes of harmonics of the blood flow velocity with arterial hypertension and age were described previously. Fourier analysis of the middle cerebral artery considered changes of the single sinus waves from the mean value but did not define the ratio of the most powerful harmonics over age, in contrast to our proceeding. Nevertheless, the results revealed that the amplitude of the respective harmonic divided by the mean value of the blood flow velocity particularly of the first 3 harmonics was increased in patients with hypertension compared with healthy control subjects. Furthermore, in patients with hypertension, the first harmonic was increased more strongly than the third harmonic oscillation. Keeping in mind that the first harmonic mirrors the maximum velocity during systole and that it depends on the vascular resistance, which is increased in arterial hypertension, the percentage of the first harmonic amplitude increases according to the rising blood flow velocity. This effect is suggested to be larger than changes of the subsequent harmonics with the consequence of a decreased SI. The cited study assumed that constricted arterioles in the distal vasculature were responsible for the increased Fourier coefficients in arterial hypertension. This approach may not be excluded for our results.

Other Age-Related Clinical Parameters

Several clinical parameters exist, which change with increasing age, ie, the peak flow attained a correlation coefficient of 0.272 in men and 0.227 in women. If peak flow was combined with the clinical variables SBP, plasma urea nitrogen, cholesterol, and alkaline phosphatase, the correlation with age increased to 0.77.

Figure 3. Sample envelope waveform of the blood flow velocity in the OA in women (f) of different ages having normal or increased blood pressure, respectively. Y axes, including waveforms, have been adapted using InfranView 3.97 (Wiener Neustadt) to visualize adequate proportions.
in women.\textsuperscript{2} Physiological tests of the eye, such as visual accommodation and visual reaction time, achieved a maximum correlation with age of 0.166.\textsuperscript{30} In comparison, in our study, the coefficient of correlation for SI with age (at least 0.671) attained highly significant values so that this single parameter converged to the coefficient of combined tests.

**Limitations**

First, we did not consider the duration of arterial hypertension and, thus, a possible long-term damage of the vessel wall. Second, the source of hypertension was not distinguished. Isolated systolic hypertension appears to result from an increased stroke volume and/or aortic stiffness, whereas an increased peripheral vascular resistance underlies essential hypertension.\textsuperscript{31} Thus, the mechanisms influencing our measurement results may be different between the hypertensive groups.

Third, systemic blood pressure was measured in the brachial artery and does not necessarily reflect the local pressure in the OA. Because an amplification of the blood pressure to the periphery has been described,\textsuperscript{27} it may be possible that the envelope waveform of the blood flow velocity may be influenced by this amplification.

**Conclusions**

We suggest that the SI may be a better indicator of abnormalities of choroidal vessels in arterial hypertension than the RI, however, without the possibility to localize the cause for changes in perfusion. First, the RI regards just 2 measurement points of the envelope waveform, whereas the SC is composed of information from the whole envelope waveform. Second, the SI was shown to be superior to the RI because of its high significance in age and arterial blood pressure, which represent the commonly approved factors that influence the local vessel properties.

**Perspectives**

The analysis method used in this study may be helpful to identify an impaired perfusion of the OA in arterial hypertension independent from age. The described approach may also be applied to the arteries of other organs, i.e., the kidney. Furthermore, future research may clarify the impact of different types of arterial hypertension and their pathophysiological changes for the relation of the harmonic content of the envelope waveform of the blood flow velocity to each other.

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**Disclosures**

None.

**References**

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Fourier Analysis of the Envelope of the Ophthalmic Artery Blood Flow Velocity – Age- and Blood Pressure-Related Impact

Georg Michelson, Joanna Harazny, Rainer Berendes, Thomas Fiermann, Simone Wärntges

ONLINE DATA SUPPLEMENT

Additional characteristics of patients
The characteristics of hypertensive groups were added as far as not listed in table 2A (table S2).

Additional results
Both a high $R^2$ (men: 0.540; women: 0.648) and significant equation coefficients were found for the square regression of SI over age (figure S1). If the influence of MAP in women was disregarded the respective equations of SI for men (6) and for women (7) were:

$$SI = 1.25 - 0.028 \times \text{age} + 0.00021 \times (\text{age})^2$$  \hspace{1cm} (6)

$$SI = 0.88 - 0.018 \times \text{age} + 0.00012 \times (\text{age})^2$$  \hspace{1cm} (7)

The square regression was also valid for the first and the third harmonic oscillation. $R^2$ of the first harmonic was 0.523 (men) and 0.698 (women). Respective values of the third harmonic were 0.448 (men) and 0.500 (women). In men the resulting calculable minimum of SI was achieved at the age of 66.7 years (SI = 0.319) and in women at 75.0 years (SI = 0.204).
However, samples at least of men at older age were rare and thus, may have influenced curve progression. Altogether, a larger number of subjects is required for determination of a universal equation over all age groups.
FIGURE LEGEND

Figure S1

Squared regression of the spectral index and its power percent values of the third and the first harmonic over age. The small number of men older than 70 yrs was included in the regression analysis. In men the spectral index achieved its minimum at the age of 66.7 years (SI = 0.319) and in women at 75.0 years (SI = 0.204).
Table S1. Partial correlations in the control group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controlled for</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SC</td>
<td>SI</td>
<td>RI</td>
<td>SC</td>
<td>SI</td>
<td>RI</td>
</tr>
<tr>
<td>Age</td>
<td>SBP, DBP, HR</td>
<td>-0.731*</td>
<td>-0.671*</td>
<td>0.027‡</td>
<td>-0.757*</td>
<td>-0.709*</td>
<td>0.100‡</td>
</tr>
<tr>
<td>Age</td>
<td>MAP, HR</td>
<td>-0.731*</td>
<td>-0.675*</td>
<td>0.003‡</td>
<td>-0.765*</td>
<td>-0.721*</td>
<td>0.115‡</td>
</tr>
<tr>
<td>SBP</td>
<td>Age, HR</td>
<td>-0.136‡</td>
<td>-0.045‡</td>
<td>-0.136‡</td>
<td>-0.294†</td>
<td>-0.339†</td>
<td>-0.013‡</td>
</tr>
<tr>
<td>MAP</td>
<td>Age, HR</td>
<td>-0.128‡</td>
<td>-0.088‡</td>
<td>-0.128‡</td>
<td>-0.334†</td>
<td>-0.363*</td>
<td>-0.038‡</td>
</tr>
<tr>
<td>DBP</td>
<td>Age, HR</td>
<td>-0.104‡</td>
<td>-0.106‡</td>
<td>-0.104‡</td>
<td>-0.325†</td>
<td>-0.340†</td>
<td>-0.051‡</td>
</tr>
<tr>
<td>HR</td>
<td>Age, SBP, DBP</td>
<td>0.331†</td>
<td>0.103‡</td>
<td>0.080‡</td>
<td>0.341†</td>
<td>-0.177‡</td>
<td>0.186‡</td>
</tr>
<tr>
<td>HR</td>
<td>Age, MAP</td>
<td>0.332*</td>
<td>0.101‡</td>
<td>0.070‡</td>
<td>0.343†</td>
<td>-0.179‡</td>
<td>0.189‡</td>
</tr>
<tr>
<td>RI</td>
<td>Age, SBP, DBP, HR</td>
<td>0.458*</td>
<td>0.296†</td>
<td></td>
<td>0.417†</td>
<td>0.387†</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>Age, MAP, HR</td>
<td>0.432*</td>
<td>0.304†</td>
<td></td>
<td>0.417*</td>
<td>0.385*</td>
<td></td>
</tr>
</tbody>
</table>

SC, spectral coefficient; SI, spectral index; RI, resistance index; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; HR, heart rate; *p≤0.001; †0.001<p≤0.05; ‡not significant.
<table>
<thead>
<tr>
<th>Hypertensive patients</th>
<th>SC</th>
<th>SBP [mmHg]</th>
<th>DBP [mmHg]</th>
<th>HR [s⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: ≤ 140/ ≤ 90 with medication</td>
<td>Men (n = 10)</td>
<td>14.6±1.6</td>
<td>126.4±12.7</td>
<td>77.3±9.2</td>
</tr>
<tr>
<td></td>
<td>Women (n = 15)</td>
<td>13.6±1.0</td>
<td>127.7±10.6</td>
<td>77.3±8.4</td>
</tr>
<tr>
<td>Group 3: &gt; 140/ &lt; 90 no medication</td>
<td>Men (n = 41)</td>
<td>14.7±1.2</td>
<td>153.5±15.1</td>
<td>82.5±6.1</td>
</tr>
<tr>
<td></td>
<td>Women (n = 34)</td>
<td>13.7±0.8</td>
<td>156.5±14.4</td>
<td>83.9±6.0</td>
</tr>
<tr>
<td>Group 4: &gt; 140/ &lt; 90 with medication</td>
<td>Men (n = 7)</td>
<td>14.6±1.2</td>
<td>149.1±7.3</td>
<td>88.6±1.8</td>
</tr>
<tr>
<td></td>
<td>Women (n = 17)</td>
<td>13.7±1.0</td>
<td>157.3±15.2</td>
<td>85.6±2.9</td>
</tr>
<tr>
<td>Group 5: &gt; 140/ &gt; 90 no medication</td>
<td>Men (n = 14)</td>
<td>14.0±1.0</td>
<td>163.4±17.1</td>
<td>97.6±6.9</td>
</tr>
<tr>
<td></td>
<td>Women (n = 20)</td>
<td>13.5±0.8</td>
<td>173.1±18.4</td>
<td>97.0±7.9</td>
</tr>
<tr>
<td>Group 6: &gt; 140/ &gt; 90 with medication</td>
<td>Men (n = 26)</td>
<td>13.8±1.1</td>
<td>173.8±19.5</td>
<td>100.4±11.6</td>
</tr>
<tr>
<td></td>
<td>Women (n = 15)</td>
<td>13.4±0.8</td>
<td>170.3±14.7</td>
<td>93.7±77.9</td>
</tr>
</tbody>
</table>

SC, spectral coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Data given as mean ± SD.
Figure S1

Men

Women

Power Percent values [%]

Age [yrs]

Spectral index

3. Harmonic

1. Harmonic

Men

R² = 0.540

R² = 0.448

R² = 0.523

Women

R² = 0.648

R² = 0.500

R² = 0.698