Study on the Correlation between OBF and Age Based on Analysis of Time Domain and Frequency Domain

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Abstract. Many studies indicate that the old people are prone to high blood pressure with the age growing. Elevated blood pressure can lead to the changes of hemodynamic parameters in the blood circulation system, and then cause abnormal changes in the physiological activities of the endothelium, heart and so on. These Characteristic of physiological rhythm reflect the changes of ocular blood pressure and ocular blood flow signals. Thus, we could study on the correlation between ocular blood flow (OBF) and age by analyzing the variety of age on hemodynamic. The paper sets out to fully examine the time domain and frequency domain relationship between OBF and age. Time domain: the paper introduces the thigh cuff method to produce sudden drops in arterial blood pressure (ABP) and study the evolution of the immediate OBF response with LSFG. The LSFG (Laser Speckle Flow graph) allows for quantitative estimation of blood flow in the optic nerve head (ONH), and it is the only noninvasive method that allows sufficient temporal resolution to measure these rapid changes. The paper studies on the relationship between time-domain parameter Kr(L) (The slope of DAR descending curve), Kr(R) (The slope of DAR up curve), Tr(L) (The amount of time it takes to the maximal BF or BP decrease), Tr(R) (The amount of time it takes to the maximal BF or BP increase) and age, respectively. Kr(R), Kr(R), Tr(R) are shown significantly influenced by age changing. Frequency domain: in the case of without any factor, the harmonic content of the envelope waveform of the blood flow velocity in the ophthalmic artery is analyzed in aging and OBF. Cronbach-α reliabilities of the calculated frequency coefficient (FC) and frequency index (FI) are 0.91 and 0.92, respectively. The FI of the ophthalmic artery allows an assessment of the ocular circulation in consideration of age and OBF. The order the age, the smaller the FC, FI in OBF.

Keywords. time parameters, harmonic index, OBF, OBP, age
1. Introduction

The possibility of the elderly people developed ocular vascular disease is gradually higher than young people. It is convinced that the elderly people have 5 times glaucoma risk higher than young people. The reason is that a series of physiological changes occur in the body of elderly people [1]. The volume of ocular blood flow, the elasticity of blood vessel wall, the function of ocular blood vessels and the regulation of blood pressure decreased in the changes of ophthalmic arterial system lead to elevated intraocular pressure (IOP), the ocular blood flow supply insufficiency in optic nerve or retina [2-4]. Now there is evidence that abnormal eye blood flow may be related to some people's disease. Tiny changes in IOP associated with each heartbeat are manifestations of the pulsation of intraocular vessels during the cardiac cycle. The IOP pulse wave has been used to assess the ocular vascular status in patients with glaucoma. A large number of studies have shown that compared with the control group, the amplitude of IOP pulse and pulse blood flow in glaucoma patients are decreased [5].

In systemic circulation, blood flow pulse wave has also been studied for more details. Many researches focus on the study of blood flow pulse waveform by Fourier analysis [6]. In short, this analysis uses the principle that all periodic functions, such as repetitive arterial pressure pulses, can be constructed by adding sine waveforms of different amplitudes and phases: Fourier analysis reduces this waveform or signal to the sine wave function composed of it. These functions are often shown by plotting the relationship between amplitude and frequency. In addition, compared with time domain waveform, the method can display waveform in frequency domain or frequency domain [7-10]. The fundamental frequency contains the spectral component of highest power. Thus, the fundamental frequency represents the information of heart-beat associated with the arterial pressure pulse. However, the time domain contains the amplitude information, which shows waveform changes on the time axis with image and intuitively clear. The purpose is to test the practicability of the harmonic content derived from the OBF envelope of the ophthalmic artery as a parameter. This parameter is related to the age in the frequency. The most significant oscillation ratio of harmonic content should be compared with the resistance index. This ratio is widely used as an indicator of peripheral vascular resistance. The transient blood flow changes as the variation of sudden BP which forms dynamic autoregulation in time domain. This pattern of change is known as an indicator of changes in blood pressure or intraocular pressure. The cuffs could be inflated and held at last for 1 min [11]. The paper study on the process of the dynamic autoregulation by time parameter, and analyses the relationship between OBF and age.

2. Methods

2.1. Participants
Participants were randomly selected from a project to achieve population-based screening among healthy people. The project was established at the department of Ophthalmology, Devers Eye Institute. Subjects received a questionnaire asking for age, gender, height, weight (considered to be a cardiovascular risk factor) and cardiovascular events. No need for cholesterol levels. The eyes were evaluated by the ophthalmic examination of pupil dilation and the judgment of optic nerve and retinal diseases by fundus color image. The images were taken with a non-crystalline fundus camera (Nonmyd-α45, Kowa). The subject were composed of 13 healthy men (Age: 44 ± 14.7 years) and 14 healthy women (Age: 44.5 ± 12.3) without acquiring cardiovascular risk factors or cardiovascular events. They did not suffer from any diseases, such as glaucoma or high intraocular pressure. Before LSFG was used to record the blood flow velocity of ophthalmic artery (OA), the blood pressure of subjects were recorded as normal parameters (DBP: < 90 mmHg; SBP: < 140 mmHg).

2.2. Procedure: time domain analysis
DAR is a transient blood flow (BF). The DAR can indicate the sudden blood pressure changes which are induced by altering either BP or intraocular pressure [12-14]. This research aims to test the relationship between OBF and age. The relationship can be gained by characterizing the DAR response.
in ONH. The ONH OBF is usually induced by the sudden drop of BP. In the experiment, the continuous BP data were recorded with Finometer Pro (FMS, The Netherlands). The ONH was monitored with LSFG. The cuffs were inflated and held on the pressure for 1 minute. After a 10 seconds ONH BF recording, the cuffs were released to cause a rapid BP drop in blood pressure (Ranging from 5 to 35 mmHg), resulting in a DAR response to ONH (Figure 1).

![Figure 1. The BF recording After 10 seconds of continuous ONH.](image)

The DAR could be picked up from BF signals which include: 1) Basal BF-before the cuff release; 2) ∆BFmax-maximal BF decreases from basal BF; 3) Kr(L)-the slope of DAR descending curve; 4) Kr(R)-the slope of DAR increasing curve; 5) Tr(L)-the amount of time to the maximal BF decrease; 6) Tr(R)-the amount time of the maximal BF decrease to the Basal BF.

The criteria for whether a test was included for analysis, depended on the quality of the BF recording during the test. If the subject had eye movement and/or many blinks during the recording, this caused missing data points or noise which made plotting the DAR curve impossible. This data was then excluded from further analysis. From the 27 subjects tested, nobody was excluded. Paired t-test was performed on 27 subjects to compare the mean value parameters of the differences between eyes. The subjects had whole data from 2 tests over the 2 visits. One repeated ANOVA measurement of several parameters (∆BFmax, Kr(L), Kr(R), Tr(L), Tr(R)) is performed to evaluate the repeatability between two different tests or individuals on this subset.

2.3. Statistical analysis

| Eye | Basal BF | ∆BF max (%) | Tr(R) | Kr(R) | Tr(L) | Kr(L) |
|-----|----------|-------------|-------|-------|-------|-------|
| OD  | 18.17 ± 2.8 | 23.6% ± 0.03% | 29.01 ± 1.54 | 0.66 ± 0.3 | 10.44 ± 1.34 | -0.75 ± 0.28 |
| OS  | 18.23 ± 2.1 | 23.6% ± 0.03% | 28.93 ± 1.17 | 0.65 ± 0.3 | 10.37 ± 1.26 | -0.75 ± 0.24 |
| P value | 0.64 | 0.78 | 0.5 | 0.5 | 0.66 | 0.58 |

| age | Basal BF | ∆BF max (%) | Tr(R) | Kr(R) | Tr(L) | Kr(L) |
|-----|----------|-------------|-------|-------|-------|-------|
| young subject (29-35) | 18.0 ± 3.5 | 22.8% ± 0.06% | 8.03 ± 1.96 | 0.94 ± 0.08 | 9.55 ± 1.29 | -0.94 ± 0.25 |
older subject (36-53) P value
17.9 ±3.7 0.58
22.8% ±0.06% 0.96
9.25 ±2.21 0.0358
0.31 ±0.15 P<0.01
9.49 ±1.39 P=0.87
-0.49 ±0.06 P<0.01

For determining of differences between OD (The right eye) and OS (The left eye), corresponding data are in Table 1, 2. Basal BF, ∆BFmax, Kr(L), Kr(R), Tr(L) and Tr(R) are not significantly different between OD and OS (P>0.05).

The Uni-ANOVA procedure using Basal BF, ∆BFmax, Kr(L), Kr(R), Tr(L), Tr(R) as covariates revealed that Kr(R), Kr(L), Tr(R) revealed a relative statistical weight to the variation observed in age (Subject: 61.7%, p<0.05). Basal BF, ∆BFmax and Tr(L) have no significant influence on the covariates in age.

Figure 2. Measured Kr(R) and age relationship during acute BP drop.

Kr(R) and age were plotted in Figure 2. The Kr(R) and age were fitted to a polynomial function to describe the static relationship between age (x) and Kr(R):

$$\text{Kr}(R) = 4.8 \times 10^4 x^2 - 5.5 \times 10^4 x + 1 \{P < 0.05, r = 0.96\} \quad (1)$$

Tr(R) and age were plotted in Figure 3. The Tr(R) and age were fitted to a polynomial function to describe the static relationship between age (x) and Tr(R):

$$\text{Tr}(R) = 0.11 \times 10^8 x^2 + 7 \{P < 0.05, r = 0.94\} \quad (2)$$

Figure 3. Measured Tr(R) and age relationship during acute BP drop.

Figure 4. Measured Kr(L) and age relationship during acute BP drop.
Kr(L) and age were plotted in Figure 4. The Kr(L) and age were fitted to a polynomial function to describe the static relationship between age (x) and Kr(L):

\[
Kr(L) = -0.5 \times 10^4 x^2 + 0.6 \times 10^2 x - 1.3 \quad (P < 0.05, r = 0.89)
\]  

(3)

Figure 2, Figure 3, Figure 4. Kr(R), Tr(R), Kr(L) were estimated from experimental data. Each parameter is a nonlinear function of age. Figure 2: relationship between Kr(R) and age; Figure 3: relationship between Tr(R) and age; Figure 4: relationship between Kr(L) and age. Kr(R) has a nonlinear relationship with age, which decreases when age increases. The Tr(R), Kr(L) have also a nonlinear relationship with age, which increases as the age increases. It indicates that the different physiological activity becomes weak with age growing. However, it can’t analyze the frequency band of physiological activity. Thus, we used the frequency domain analysis to solve this problem.

2.4. **Frequency domain analysis**

After 10 minutes of rest, the arterial blood pressure of subjects in supine position of brachial artery was measured by an experienced observer through a commercial automatic sphygmomanometer. The cuffs are 14cm wide by 50cm long. The intake was permitted during the daytime examination. However, the ingestion was forbidden 10 minutes before the start of the research. The mean arterial pressure (MAP) is calculated according to the following formula:

\[
MAP = DBP + \frac{1}{3} (SBP - DBP)
\]  

(4)

The BF velocity of OA was recorded by employing LSFG (A laser speckle flowgraphy device was used to measure the BF in ONH).

2.5. **Frequency coefficient and frequency index**

The envelope waveform of BF velocity consists of several superimposed frequency. Fast Fourier transform (FFT) is an algorithm that allows the separation of a single sinusoid based on frequency, amplitude, and time period. The oscillation amplitude of the independent signal component is represented by the absolute value of power as the first to fifth harmonic oscillation. The oscillation frequency of the five harmonics is considered as a percentage of their sum as a percentage of power. Because the absolute value depends on the blood flow velocity, it may also affect the age-related calculation. Nevertheless, it will not affect the relative value and power percentage ratio of the whole spectrum. The absolute value which depends on the blood flow velocity were chosen for making further efforts to process. The FC is calculated according to the power percentage (PP) ratio of Formula 1, \( n = 5 \) (1st to 5th harmonic oscillation). The PP value of every harmonic is specified by HI, and i indicates the harmonic number.

\[
FC = \frac{\sum_{i=1}^{n} a_i p_i}{\sum_{i=1}^{n} a_i} = \frac{1* p_1 + 2* p_2 + 3* p_3 + 4* p_4 + 5* p_5}{1+2+3+4+5}
\]  

(5)

The results show that the third harmonic and the 1st harmonic have the highest credibility. That is why the power ratio of the 3rd harmonic and the first harmonic are used to calculate the frequency index (FI) in Eq 6.

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

(6)

2.6. **Statistical analysis**

MATLAB software was used for analysis. The mean was gained by Mann Whitney test of unmatched measurement data. The partial correlation method includes Pearson coefficient. In this study, Uni-ANOVA was used to analyze healthy subjects. The curve estimation function of MATLAB was used
to test the most suitable adjusted regression curve. Then, the minimum value of asymmetric parabola is determined by quadratic complement function.

2.7. Reliability of the variables derived
The 27 healthy subjects were measured twice every 1-8 days and once every 6 weeks. Cronbach-α was 0.91 for FC and 0.93 for FI at the 95% confidence interval. Therefore, the reliability of the intra class correlation coefficient obtained from the envelope waveform of BF velocity is reasonable.

2.8. Determination of the FI
Figure 5 shows the credibility of the first oscillation to check the harmonic content. The power percentage ratio of the third and first harmonics shows the steepest gradient with age and the largest coefficient of determination $R^2$, which is why their ratios are used to define the parameter FI.

\[ \text{Figure 5. The power percentage of the 1st to 5th harmonic oscillation of OA varies with age.} \]

Figure 5 shows the power percentage ratio changes of the 1st through 5th harmonic oscillation of the OA. These changes are age-related. Among the two genders, the 1st and 3rd harmonic oscillations have the best credibility, i.e. steepest gradient and maximum square regression coefficient in Figure 6.

\[ \text{Figure 6. The highest credibility in the first and the third harmonic oscillations.} \]

In order to determine the difference between the young and the old, the median age of the person (43 years) was calculated. The corresponding curve are shown in Figure 6. In the elderly group, the FI of subjects was significantly lower than that of young subjects.

\[ \text{Figure 7. Time domain analysis.} \]
In conclusion, the study finds that in subjects with normal blood pressure, the definition FI based on OA blood flow velocity envelope waveform showed age-dependent difference, while the FI value of the elderly subjects was lower.

This study comes to a conclusion that FC of the first 5 harmonics is not suitable to be calculated independently of the age in Figure 7, because the percentage of FC is related to the blood flow velocity, and the blood flow velocity decreases with the increase of age (The first harmonic and the third harmonic). The 5 speaks of the harmonic represent 5 physiological activity, the frequency domain analysis does a deeper research compared to time domain analysis.

3. Conclusion
The paper studies on the relationship between OBF and age in time domain and frequency domain. In time domain: Kr(R), Tr(R) and Kr(L) were estimated by analyzing experimental data. Each variable value is a nonlinear function of age. Kr(R) has an inversely-proportional relationship with age, which decreases when age increases. Tr(R), Kr(L) has also a positive proportional relation with age, which increases when age increases. It indicates that the OBF auto regulation decreases gradually with age increasing. We could observe the shape of the signal intuitively clear. However, the signal can’t be described accurately with limited parameters. So, we used the frequency domain analysis to solve this problem. In frequency domain: The 5 peaks of the harmonic represent 5 physiological activities, and the frequency domain analysis does much deeper research compared to time domain analysis. FC of the first 5 harmonics is not suitable to be calculated independently of age because the percentage of FC is related to blood flow velocity. However, the percentages of FI are independent of blood flow velocity, which is why their percentages of power are used to calculate the frequency index. It also indicates that the order the age, the more the FI, the less the OBF at a health level. In a word, the macro conclusion of the time domain analysis and the frequency domain analysis is consistent.

4. Ethics statement
This research is authorized by the Fourth Affiliated Hospital of Harbin Medical University Clinical Trials.

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