Original Article

Spectral analysis of intraocular pressure pulse wave in ocular hypertensive and primary open angle glaucoma patients

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Context: In attempt to find an alternative way to determine conversion from ocular hypertension to primary open angle glaucoma (POAG) (besides visual field and optic disc changes), we analyzed intraocular pressure (IOP) pulse wave in spectral domain. **Aims:** The aim of this study was to test the potential differences in spectral content of IOP pulse wave between ocular hypertension and POAG patients, which could indicate conversion. **Settings and Design:** Cross-sectional study designed to test the differences in the spectral content of pressure pulse wave between nontreated ocular hypertensive and nontreated, freshly diagnosed POAG patients. **Methods:** The total of 40 eyes of 40 subjects was included: 20 previously untreated ocular hypertensive patients, and 20 previously untreated POAG patients. Continuous IOP measuring gained by dynamic contour tonometry was submitted to fast Fourier transform signal analysis and further statistical data processing. **Statistics Analysis Used:** Ocular and systemic characteristics of the tested subjects were compared by analysis of variance appropriate for this study design. A $P < 0.05$ was considered to be statistically significant. **Results:** Higher spectral components of the IOP pulse wave was discerned up to the fifth harmonic in both of the tested groups. No statistically significant differences were found in any of the tested harmonic amplitudes. **Conclusions:** There are no differences in the spectral content of IOP pulse wave between ocular hypertensive and primary open angle glaucoma patients which could be indicative for conversion.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.179719

Quick Response Code:

Key words: Glaucoma, intraocular pressure, spectral analysis

Glaucoma, an optic neuropathy characterized by recognizable patterns of optic disc and retinal nerve fiber damage, is still one of the leading causes of blindness worldwide.[1] Elevated intraocular pressure (IOP) represents the only modifiable risk factor for developing and progression of this disease.[2] However, estimations are that approximately 4–7% of the population over the age of 40 years have higher IOP values without detectable glaucomatous damage, a condition called ocular hypertension (OHT).[3] OHT is a leading risk factor for the development of primary open-angle glaucoma (POAG).[4] Whether and when to treat OHT patient remains one of the burning ophthalmological dilemmas, in spite of the results of numerous studies. Results to date have shown an approximate 50% reduction in the conversion from OHT to POAG, with a 20% reduction in IOP,[5] OHT treatment study demonstrated that medical treatment of people with IOP of 24 mmHg reduces the risk of the development of POAG by 60%.[6] Factors that predicted the development of POAG included older age, race (African-American), sex (male), larger vertical cup–disc ratio, larger horizontal cup–disc ratio, higher IOP, greater Humphrey visual field (VF) pattern standard deviation (PSD), heart disease, and thin cornea.[7]

A different insight into glaucoma pathophysiology was offered to the ophthalmological public 13 years ago,[8] when Evans *et al*. studied the differences between healthy subjects and glaucoma patients at the level of spectral content of IOP.

In attempt to find an alternative way to determine conversion from OHT to POAG (besides VF and optic disc changes), we analyzed IOP pulse wave in spectral domain. If repeating IOP pulse is determined as a periodic function, it can be evaluated in the frequency domain by the fast Fourier transform algorithm (FFT).[9] Rhythmical IOP alternations over time, defined by ocular and systemic hemodynamic can be determined with a dynamic contour tonometer (DCT), which accurately registers the pressure curve continuously, and gives values for ocular pulse amplitude (OPA), the difference of diastolic and systolic pressures.[10,11] The idea behind and practical value of this testing is to simply measure IOP continuously (for 10–20 s), submit it to spectral analysis and then, according to results, tell if the patient is converting to glaucoma, before visible changes in VF or optic disc appearance are noted.

The aim of this study was to test the hypothesis that there is a distinct difference in the spectral component of IOP pulse wave

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Manuscript received: 16.04.15; Revision accepted: 21.01.16

Cite this article as: Bozic MM, Dukic ML, Stojkovic MZ. Spectral analysis of intraocular pressure pulse wave in ocular hypertensive and primary open angle glaucoma patients. Indian J Ophthalmol 2016;64:114-7.

in ocular hypertensive and POAG patients that can be a regarded as a predictive factor for converting OHT into glaucoma.

Methods

The total of 40 eyes of 40 subjects was included in this cross-sectional study: 20 previously untreated ocular hypertensive patients (OHT group) and 20 newly diagnosed, previously untreated POAG group patients. Patients were examined for glaucoma, and all of them were tested during their first visit to the clinic before adequate treatment was given. The study was approved by the local Ethics Committee, and the informed consent according to the Declaration of Helsinki was obtained from each subject.

The criteria for establishing the diagnosis for OHT were IOP >21 mm Hg in one or both eyes in repeated tonometry (minimum 3), medium wide and open angle on gonioscopy, without data or any signs indicating the closing of the angle or secondary glaucoma, absence of glaucomatous defects on visual-field testing, normal appearance of the optic disc, and nerve fiber layer.

The criteria for establishing the diagnosis of the POAG were as follows: IOP readings over 21 mmHg in repeated tonometry (minimum 3), medium wide and open angle on gonioscopy, without data or any signs indicating the closing of the angle or secondary glaucoma, glaucomatous optic disc damage (cup/disc asymmetry between two eyes ≥0.2, neuroretinal rim thinning, notching, disk hemorrhage, or the nerve fiber layer defect), and/or characteristic VF defect.

Tested groups were matched for age, gender distribution, systemic blood pressure, and heart rate.

The exclusion criteria were any type of preceding ophthalmic surgery or disease, the use of antiglaucomatous medication and systemic antihypertensive medication. A comprehensive protocol was used for all subjects in the following order:

- Review of general and ophthalmological medical history;
- Best corrected visual acuity;
- Dynamic contour tonometry DCT, Pascal, Ziemer Ophthalmic System AG, Switzerland). Measurements were repeated until three recordings with a quality score Q of three or higher were obtained. The average recording time for all tested subjects was 12.8 ± 3.2 s;
- A slit lamp (Haag-Streit, Switzerland) with a calibrated Goldmann tonometer was used for Goldmann applanation tonometry (GAT). Fluorescein sodium 2% strips were used for the GAT measurements. Three measurements were taken for the mean IOP value. The DCT and GAT were performed with the patient sitting in an upright position at the slit lamp. The DCT was not biased by the GAT as it was the first reading performed;
- Central corneal thickness (CCT) measurement (Palm Scan AP 2000, Ophthalmic Ultrasound, 2007, Micro Medical Devices Inc., Calabasas, CA, 91302 USA) after instillation of one drop of 1.0% tetracaine. The pachymeter probe was placed on the center of the cornea over an undilated pupil, and the mean of three readings within a range of ±5 μm was calculated for each eye;
- Optic nerve head examination with Heidelberg scanning laser ophthalmoscope (HRT 2, Heidelberg Engineering, Heidelberg, Germany)
- Automated VF examination. All patients had a 24-2 full threshold or Swedish interactive threshold algorithm automated VF (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, California, USA). Only reliable fields with a fixation loss rate ≤33% and false positive and false negative rates ≤20% were included. To be eligible, glaucoma patients were required to have a glaucomatous field defect, defined as the presence of a glaucoma hemifield test (GHT) outside normal limits and a PSD with $P < 0.05$ in the worse eye and a normal GHT and PSD $P > 0.05$ in the fellow eye. Criteria for the definition of a normal field (OHT group) were the absence of one or more clusters of three or more neighboring locations showing sensitivity loss of >5 dB below the age-matched Humphrey normal database, or of a single location with a sensitivity loss >10 dB in each hemifield.

Data Wizard PC Software (version 1.3, Ziemer Ophthalmic System AG, Switzerland) was used for further data analysis. This software automatically registers, calculates, and stores the IOP, OPA values, heart pulse rate, and IOP reading time interval into a database. Continuous IOP measuring gained by DCT was then submitted to advanced FFT signal analysis and further statistical data processing. After Fourier transform was conducted, the amplitude of the first, second, third, fourth, and fifth harmonics was calculated. Oscillatory changes of IOP are periodical, with period that corresponds to the heart rate periodic. During the conducted measurements, it was observed that in about 95% of subject's heart rate ranges from 55 ppm to 90 ppm. Sampling period in DCT is $T_s = 0.01$ s, which means that every $T_s = 0.01$ s IOP measurements are taken. The value of the required IOP measurement time interval is determined in the following manner. First (fundamental) harmonic frequency, f_1, of periodically oscillatory IOP changes is calculated based on the DCT measurement data as , $f_1 = \frac{\text{heart beats per minute}}{60}\,(\text{Hz})$ where $T_1 = 1/f_1$ is the period. Spectral resolution is defined as a number of spectral components within a period of oscillatory IOP changes. In our study, the value of selected resolution is $\Delta f = \frac{f_1}{n} = \frac{f_1}{4}$ where $n = 4$ represents the number of spectral components according to the selected spectral resolution. If N is the number of points of IOP measurements required for spectral analysis, frequency of the spectral component in the frequency bandwidth which corresponds to the first harmonic value is $f_n = \frac{1}{NT_s} n = \frac{1}{N0.01} 4 = \frac{400}{N}\,(\text{Hz})$. Therefore, to calculate the first harmonic f_1 value, number of measuring points must be $N = \frac{400}{f_1}$. Taking into account minimum and maximum expected heart rates, the necessary length of the interval measurement is determined based on the following expressions:

$$N_{\min} = \frac{400}{f_{1,\max}} = \frac{400}{90 ppm/60} = 267 \Rightarrow \Lambda_{\min} = 267 \times 0.01 = 2.67\,(\text{s})$$

$$N_{\max} = \frac{400}{f_{1,\min}} = \frac{400}{55 ppm/60} = 436 \Rightarrow \Lambda_{\max} = 436 \times 0.01 = 4.36\,(\text{s})$$

Where $\Lambda_{\min}$ and $\Lambda_{\max}$ represent minimally required and maximally sufficient measuring time intervals. The next step

in the analysis of measurement results is their smoothing. This helps to avoid irregularities that result from the measurement process, such as micromovements of DCT piezoresistive sensor and movements of the eye. The Savitzky–Golay method of data smoothing was chosen because this method essentially performs a local polynomial regression of degree *k*, in a series of values of at least *k* + 1 points which are treated as being equally spaced in the series to determine the smoothed value for each point.[12] Polynomials of the second and third order have been used in our study. The number of points of smoothing window was around 30. The main advantage of this approach is that it tends to preserve features of the distribution such as relative maxima, minima, and width, which are usually flattened by other adjacent averaging techniques.

The normality of distribution of the study variables in particular groups was assessed with the Shapiro–Wilk test. Methods of descriptive (arithmetical mean, standard deviation) and analytical statistics (analysis of variance) were used to analyze the data and evaluate the significance of the difference. $P < 0.05$ was considered statistically significant.

Results

Demographic information, measured ocular parameters, heart rate, and blood pressure for all tested subjects are given in Table 1.

There was no significant difference between the tested groups in IOP values measured both with DCT and GAT.

OHT group had significantly thinner corneas on ultrasound pachymetry ($P = 0.04$).

There was no statistical significance in the OPA values between the OHT and POAG group ($P = 0.8$).

Table 1: Demographics, ocular and systemic characteristics of tested subjects

	OHT group	POAG group	*P* value ANOVA
Mean age (year±SD)	60.05±7.59	63.35±10.93	0.27
Sex (% female)	14 (70%)	12 (60%)	
Mean GAT (mmHg±SD)	24.14±4.1	26.27±5.09	0.08
Mean DCT (mmHg±SD)	25.98±6.11	27.13±4.13	0.2
Mean CCT (μ±SD)	562.4±32.21	571.3±32.4	0.04
Heart rate (beats/min)	74.25±8.9	75.12±9.4	0.2
Mean arterial pressure (mmHg)	127±7.33	130±9.45	0.3
OPA (mmHg±SD)	4±1.39	4.1±1.25	0.8

GAT: Goldmann Applanation Tonometry, DCT: Dynamic Contour Tonometry, CCT: Central Corneal Thickness, IOP: Intraocular Pressure, OPA: Ocular Pulse Amplitude

The results of the spectral analysis of IOP are shown in Table 2 and Fig. 1.

Discussion

Spectral analysis methods are relatively new in use in ophthalmology, especially in glaucoma and anterior segment diagnostics.[13,14] In this study, we determined and compared the harmonic components of IOP in subjects with untreated OHT and newly diagnosed, untreated POAG patients. The results of previous studies[14-16] have shown that IOP pulse can readily be analyzed in the frequency domain, but the results of spectral analysis of these studies differ significantly. Using pneumatonometer for gaining continuous IOP measurements, Evans *et al*.[8] successfully determined the IOP pulse's higher spectral components by FFT up to the fourth harmonic. The results of Evans study indicated that previously untreated glaucoma patients had lower power in the second, third, and the fourth harmonics, when compared to healthy subjects. Furthermore, this study found no difference in the pulse amplitude, pulse volume, and the pulsatile ocular blood flow among tested groups. More recent study,[15] in which more sophisticated method of spectral analysis of continuous IOP measurement was used, showed that previously untreated POAG patients with high IOP levels had higher amplitudes of the first, second, and the third harmonic. Based on limited sample size analysis, no distinct difference in the spectral component of IOP pulse wave in healthy subjects and subjects suffering from different glaucoma types was found. In their study, Asejczyk-Widlicka *et al*.[16] considered the ratio of the spectral harmonic amplitude of the IOP pulse wave and that of the first harmonic, offering a more objective form of spectral analysis. This cross-sectional study included much more subjects (296), none of them were on any kind of systemic medications, but a substantial number of them were taking local antiglaucoma medications, which probably influenced final results. Spectral content up to the 6th harmonic of the pressure pulse wave was considered. The conclusion of this study is that using spectral analysis technique which takes into account the nonstationary character of the DCT signals one can distinguish healthy eye from those suspected for glaucoma, since that was the only analysis that showed statistically significant difference, whereas GAT IOP, DCT IOP, and OPA changes in heart rate and CCT did not. Even if we assume that taking local antiglaucomatous therapy did not affect the results of the spectral analysis conducted, the question is how justifiable is to use such a complex analysis in cases where it is already clinically apparent that a person has glaucoma.

To simplify the interpretation of the spectral analysis results, and give it a tangible ophthalmological meaning, we have to highlight the fact that the pressure pulse that we have analyzed is not directly the pressure of the eye's internal vasculature. More important than the pressure change within the intraocular

Table 2: Mean actual spectral components of the IOP pulse in OHT and POAG group

Group	First harmonic	Second harmonic	Third harmonic	Forth harmonic	Fifth harmonic
OHT (mmHg±SD)	1.685±0.63	0.468±0.24	0.165±0.1	0.089±0.07	0.062±0.02
POAG (mmHg±SD)	1.677±0.62	0.394±0.26	0.147±0.13	0.099±0.05	0.079±0.07
P value (analysis of variance)	1	0.3	0.6	0.6	0.2

IOP: Intraocular Pressure, SD: Standard deviation, OHT: Ocular hypertension, POAG: Primary open angle glaucoma

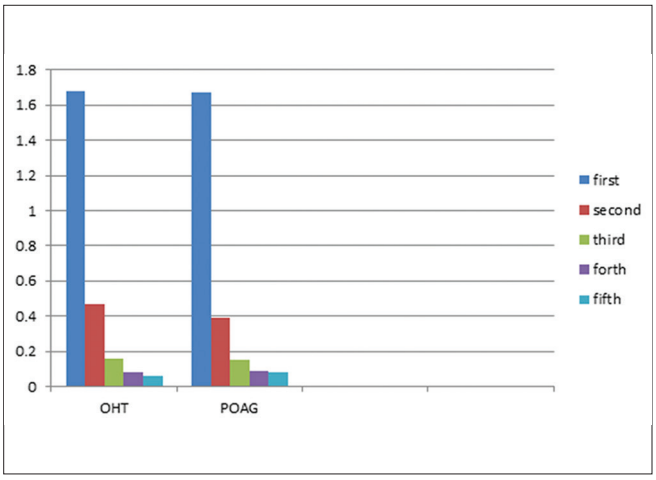

Figure 1: Amplitude spectra

blood vessel is its volume change. Although the pulsation initially originates from the intraocular vessels, they are very dependent on the elasticity of the ocular coat. We could not account for this confounder in our study, so this could be one of the limiting factors. Some of the authors stress out that a single IOP measurement is just an error-prone snapshot of a widely varying physiologic parameter.[17,18] Furthermore, one of the important factors correlated to measures of the IOP pulse wave is heart rate. The higher the heart rate, the lower the pulse amplitude, pulse volume, and pulsatile ocular blood flow, but with groups matched for heart rate, this factor is eliminated. As stated in the conclusion of previous studies,[19,20] our results imply that systemic factors must not be ignored when utilizing the IOP pulse wave as a measure of ocular blood flow.

Conclusion

Our study was done in attempt to disclose the complexity of IOP pulse wave and especially its possible specificities in different glaucoma types. We failed to prove any differences in spectral content of IOP pulse wave in ocular hypertensive and POAG patients. In spite of that spectral analysis of IOP, pulse wave is a relatively new diagnostic opportunity by which we can emphasize a different perspective of glaucoma pathogenesis, especially the vasogenic origin of some of glaucoma subtypes. Unfortunately, according to results of our study, this method cannot be of much use in predicting conversion from OHT to POAG.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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