Detection of Glaucoma based on the Analysis of Cardiovascular Signals

Andreas Voss[1], Katharina Witt[1], Eva Koch[2], Matthias Fuest[2], Niklas Plange[2]

[1]Department of Medical Engineering and Biotechnology, University of Applied Sciences Jena, Germany
[2]Department of Ophthalmology, University Hospital Aachen, Germany

Abstract

Especially vascular dysfunctions seem to play an important role in the development of glaucoma. The objective of this study was to investigate if the blood pressure regulation is impaired in glaucoma patients. Therefore, 30min ECG and continuous blood pressure were recorded from 10 healthy controls (CON) and 19 patients with glaucoma (GC). The time series of heart rate, systolic and diastolic blood pressure were extracted and analyzed applying univariate linear and nonlinear univariate and bivariate methods (symbolic dynamics and joint symbolic dynamics) to separate the groups. The index plvar2_Dia (symbolic dynamics) from diastolic blood pressure variability revealed high significant differences between GC and CON leading to a sensitivity of 90% and specificity of 80%. The combination of this parameter plvar2_Dia with SP101 (joint symbolic dynamics, coupling systolic blood pressure with heart rate) led to an increased specificity of 90% while the sensitivity was maintained at 90%.

Parameters from the symbolic dynamics were able to characterize the diastolic blood pressure and the coupling between heart rate and systolic blood pressure and separated the GC and CON. The changes in short term blood pressure regulation patterns and the coupling with heart rate are a sign of a vascular dysfunction. Therefore, this method might contribute to an improved and preterm diagnosis of glaucoma.

1. Introduction

Glaucoma is a disorder of the retina as well as optic nerve and is the leading cause of blindness and irreversible visual loss. It has been estimated that approximately one million people will have glaucoma in Germany. The most common types of glaucoma are high-tension and normal-tension glaucoma (NTG) as well as open-angle glaucoma (POWG) and the most important known risk factor of glaucoma is an increased intraocular pressure (IOP). In general, it is estimated that 50% of this risk factor are applies for glaucoma. However, it is known that another risk factor is the vascular dysregulation. This vascular dysregulation is changing blood regulation of retina and optic nerve which is caused by the disruption of blood flow and thereby associated with changes in autonomic regulations [1, 2].

In recent years, the importance of vascular regulation has increased for assessment of diagnosis glaucoma. It could be proven that changes of the eye are caused by vascular dysregulations and these are associated with disturbed autoregulation. Such vascular changes often occur systemically and they are not local limited on the vessels of the eye [3-5].

Therefore, systemic blood pressure variability (BPV) allows in combination with other markers of autonomic regulation (heart rate variability, marker of ischemia) another method for diagnosis of glaucoma. Methods of heart rate variability (HRV) and BPV based on nonlinear system theory and beat-to-beat dynamics have gained recent interest as they may reveal dedicated changes of autonomic regulations. There are various types of different fractal scaling measures, complexity measures, power law analysis, measures of symbolic dynamics, turbulence and acceleration/ deceleration of heart rate and blood pressure and have been studied in various patient populations [6-8].

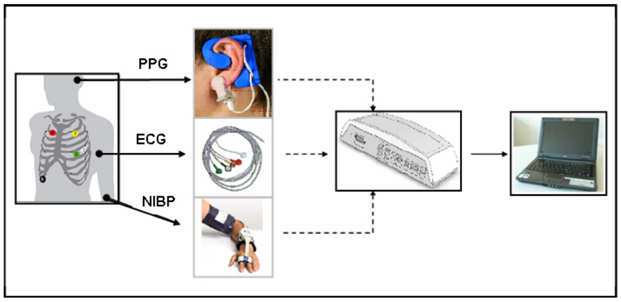
The aim of this study was to characterize the cardiovascular regulation in patients with glaucoma (GC) and healthy controls (CON) by analysing HRV, BPV and the coupling between these signals. As a consequence, it should be examined if vascular dysregulations accompany the development of glaucoma.

2. Material and methods

2.1. Measurement set up

The measuring device “Glaucoscreen” allows to record simultaneously and non-invasively multichannel biosignals such as ECG, continuous blood pressure (NIBP) and continuous volume pulse (PPG).

Figure 1. Measurement setup of Glaucoscreen.



NIBP was measured on the finger applying the non-invasive CNAP® OEM Module (CNSystems Medizintechnik AG, Austria) and the PPG was measured on the ear via a pulse sensor (Corscience GmbH & Co. KG).

2.2. Patients

In this first pilot study 19 patients with glaucoma (GC) and 10 healthy controls (CON) as a reference group were enrolled from the University Hospital Aachen, Department of Ophthalmology. Table 1 shows the patient characteristics of the study population. From all participants ECG, PPG and simultaneously the NIBP were continuously recorded over a period of 30 minutes.

Table 1. Characteristics of healthy controls (CON) and patients with glaucoma. * mean ± standard deviations

Parameters	**CON**	**GC**
number of patients	10	19
(male/female)	(5/5)	(10/9)
*age [years]**	65.20 ± 8.68	65.63 ± 8.48
*bmi [kg/m²]**	24.38 ± 3.78	26.05 ± 17.34

All recordings were performed under resting conditions (supine position, quiet environment and same location) and the study was approved by the Ethics Committee of University Hospital Aachen. The investigation fulfilled the recommendations of the Declaration of Helsinki.

2.3. Data preprocessing

From the raw data the time series of heart rate consisting of successive beat-to-beat intervals (BBI) and of systolic as well as diastolic blood pressure values were extracted.

Then, ectopic beats and disturbance or artefacts were detected and replaced by interpolated "normal" beats by applying an adaptive filter to generate normal-to-normal beat time series (NN).

HRV and BPV standard parameters were calculated from time and frequency domain according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [9].

2.4. Symbolic Dynamics (SD)

Symbolic dynamics is a nonlinear method which describes the global short- and long term dynamics of beat-to-beat variability on the basis of symbolization. Methods of nonlinear symbolic dynamics analysis [7, 9] have been shown to be sufficient for the investigation of complex systems and describe dynamic aspects within time series. The method applied in this study (there are different approaches for deriving symbolic dynamics from a time series) is described in detail elsewhere [7], and in the following, only a brief introduction is given. The NN beat to beat interval time series are converted into an alphabet of four predefined symbols (0, 1, 2, and 3) [10] according to the transformation rules based on consecutive comparison of successive beat-to-beat intervals. The symbols "0" and "2" reflect slight deviations (increase or decrease) from the mean NN interval, and the symbols "1" and "3" reflect stronger deviations (increase or decrease over the mean NN interval and in addition over a predefined limit). Then, the symbol strings are transformed into word series where each word consists of three successive symbols. This leads to a range of 64 different word types (000, 001, ..., 333). Then, we estimate from the word distribution the probability of occurrence (pWxxx) of each word type (xxx = 000, 001, ..., 333) within NN interval time series.

The index plvar2_dia is a measure of proportion of low-variability patterns within the diastolic BPV time series (<2 mmHg) over six heart cycles.

2.5. Joint Symbolic Dynamics (JSD)

The method of Joint Symbolic Dynamics (JSD) [7] was applied to quantify the short-term bivariate nonlinear behaviour of CVC. JSD transforms BBI and systolic BPV (SYS) time series into symbol sequences of different words w according to the transformation rules using an alphabet A={0,1}. Thereby, symbol '1' represents increasing values and symbol '0' decreasing and unchanged values applying a threshold level equal to zero. Afterwards, short patterns (words of length 3) were formed (k=64). Following indices were estimated:

- Normalized probability occurrences of bivariate word type combinations (JSD1-JSD64) 'xxx' of BBI and simultaneous 'yyy' of SYS (e.g. BBI001/SYS101) within an 8x8 word distribution density matrix W,
- Sum of each row (combinations with equal BBI word: BBIxxx) and the sum of each column (combinations with equal SYS word: SYSyyy) and

• Sums of diagonals within W: SumSym - symmetric word types (including baroreflex patterns) and SumDiam - diametric word types.

The index SP101 is the sum of the measures of couplings between SYS and HRV.

2.6. Statistics

The analysis was performed on the basis of the HRV/BPV indices (time- and frequency domain, methods from nonlinear dynamics). The nonparametric Mann-Whitney U-test was applied for statistical analysis to figure out univariate significant parameters ($p<0.001$) differentiating between patients with glaucoma and healthy controls. With the most univariate and multivariate significant parameters the stepwise discriminant function analysis was performed to calculate the specific sensitivity, specificity and the area under the receiver operating characteristics – ROC curve (AUC).

3. Results

Considering the discrimination between patients with glaucoma and healthy controls measures from SD and JSD revealed high univariate significances. Table 2 shows the mean values and standard deviations of the most significant indices after discriminant function analysis.

Table 2. Statistical analysis – significant parameters (** means $p < 0.001$) for discriminating between GC and CON including mean value ± standard deviation of the indices.

Index	p	CON	GC
plvar2_Dia	**	0.67 ± 0.24	0.23 ± 0.16
SP101	**	0.08 ± 0.04	0.14 ± 0.03

The index from SD decreased in patients with glaucoma, whereas the index SP101 of JSD increased in this group (Figure 2).

Only some linear indices from HRV and BPV analysis showed significances. However, these indices could not contribute for the discrimination between GC and CON in the same level as SD.

4. Discussion

Previous studies have shown that reduced heart rate variability [11, 12] and increased blood pressure variability [13, 14] are associated with glaucoma. Thus changes in HRV and BPV are assigning to an impaired autonomic regulation.

The disadvantages of these studies are the measurement of discontinuous blood pressure and only linear methods of HRV analysis were used.

In this study we have shown that especially nonlinear methods (SD, JSD) could be play an important role for the detection of changes in the autonomic regulation in glaucoma.

The combination of HRV and BPV analyses provides a sensitivity of nearly 90% (89.5%), a specificity of 90% and an AUC of 98.4%. Therefore, we speculate that the calculation of these both indices from BPV and HRV could be used in future in medical devices for a screening of glaucoma.

However, there are two limitations. First of all in this study is only a small number of patients included. Then we did not yet consider the influence of treatments.

For the validation of the results a larger number of patients have be enrolled. Therefore, we started a validation study with planned 100 enrolled patients. In this study we plan also to investigate if we can discriminate between NTG and POWG.

5. Conclusion

The results of this study show that the application of multivariate data analysis from ECG and NIBP might contribute to an improved and preterm diagnosis of glaucoma. Especially nonlinear indices from symbolic dynamics were able to characterize the diastolic blood pressure impairment in GC and the coupling between heart rate and systolic blood pressure to differentiate between healthy controls and patients with glaucoma. These alterations in blood pressure variability and coupling with heart rate suggests a modified autonomic regulation due to a vascular dysfunction.

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Address for correspondence.

Prof. Dr. A. Voss
University of Applied Sciences Jena, Germany
Department of Medical Engineering and Biotechnology
Carl-Zeiss-Promenade 2
07745 Jena
andreas.voss@fh-jena.de, Phone: 03641-205625