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Relationship of systemic blood pressure with ocular perfusion pressure and intraocular pressure of glaucoma patients in telemedical home monitoring

Authors' Contribution:
- A Study Design
- B Data Collection
- C Statistical Analysis
- D Data Interpretation
- E Manuscript Preparation
- F Literature Search
- G Funds Collection

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Summary

Background: We evaluated the relation of systemic blood pressure with intraday variations in ocular perfusion pressure and intraocular pressure in patients with primary open-angle glaucoma in a telemedical home monitoring scenario.

Material/Methods: In the project Teletonometry Mecklenburg-Vorpommern (TTMV) patients were equipped with a home monitoring system for 24-hour self-measurements of intraocular pressure and blood pressure for a period of six months. All measurements were transmitted via telephone modem to an electronic patient record. Ocular perfusion pressure (OPP) was automatically calculated from self-measurements of intraocular pressure (IOP), systolic (SBP) and diastolic blood pressure (DBP) using the equation: OPP=[2/3*(2/3*DBP+1/3*SBP)]–IOP. We present the temporal characteristics of 70 patients with primary open-angle glaucoma based on 3282 self-measurements.

Results: The diurnal ocular perfusion pressure trend showed four characteristic phases (7am – 12am, 12am – 6pm, 6pm – 10pm, and 10pm – 7am). Between 7am and 12am ocular perfusion pressure and simultaneously systolic and diastolic blood pressure were significantly depressed compared to all other phases ($p<0.05$) whereas intraocular pressure showed no significant shifting. Instead intraocular pressure was significantly depressed between 6pm and 10pm ($p<0.05$) where ocular perfusion pressure reached the highest intraday values.

Conclusions: We found that ocular perfusion pressure in patients with primary open-angle glaucoma showed remarkable circadian fluctuations. A significant decrease in the morning was associated with significantly depressed systolic and diastolic blood pressure levels. In addition we observed normal intraocular pressure values in the morning but a significant decrease in the evening which did not affect ocular perfusion pressure. These conclusions strengthen the evidence that systemic blood pressure fundamentally influences ocular circulation and consequently glaucoma progression.

key words: **glaucoma • ocular perfusion • homemonitoring • 24 h ambulatory blood pressure monitoring • intraocular pressure • selftonometry**

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Background

In 2002 glaucoma jumped from third to second place on the list of the leading causes of blindness globally, which is published by the World Health Organization [1,2]. Glaucoma is becoming increasingly important in the context of an ageing world population. It poses a considerable challenge to public health, because blindness and visual impairment caused by glaucoma are irreversible. As a chronic eye disease glaucoma leads to a loss of retinal ganglion cells over the years, which results in characteristic optic nerve damage and typical visual field defects. In the early stages of glaucoma the patients affected may not realize that they are in danger of losing their sight, usually they only notice the few symptoms of the gradual loss of vision when retinal nerve fibres are already irreversibly lost. To avoid this feasible prevention, effective diagnostics and appropriate treatment are required, but this can only be achieved, if we improve our general understanding of glaucoma: "The medical understanding of the nature of glaucoma has changed profoundly in the past few years and a precise comprehensive definition and diagnostic criteria are yet to be finalised [3]."

Main risk factors for glaucoma development and progression are age and genetic predisposition, both parameters without interventional potential [4]. The only parameter subject to treatment is intraocular pressure, which is also correlated to glaucoma. However, this is insufficient because we observe both: individuals with elevated intraocular pressure without glaucomatous retinal changes (ocular hypertension) and individuals with normal intraocular pressure, who develop glaucoma (normal tension glaucoma). Furthermore, there are patients who develop glaucoma progression despite optimal treatment with successful intraocular depression [5–7]. The first evidence for the role of vascular components in the pathogenesis of primary open-angle glaucoma was reported in 1953 [8] and several studies have followed in the last few years [9–15]. In 1993 Kaiser et. al. demanded that blood pressure be considered in glaucoma treatment [16]. The impact of blood pressure and ocular perfusion pressure on glaucoma has received greater attention as evidence mounts [17].

Material and Methods

Patients

In the home monitoring project Teletonometry Mecklenburg-Vorpommern (TTMV) 153 probands were selected to evaluate the benefits of innovative telemedical glaucoma management. Eligible probands were individuals aged 18 years or older who had any type of glaucoma, ocular hypertension or suspected glaucoma. The main exclusion criteria were: blepharospasm, extreme visual impairment or blindness, diseases of the anterior segment, allergic inflammation, intraocular inflammation in the past six months or acute glaucoma. During the 12-month monitoring period 24 probands had to quit the study due to job-related or health-impaired factors (e.g. relocation, shift working or hospital admission due to accidents). The data presented in this study is exclusively based on the measured values of 70 patients with primary open-angle glaucoma. 33 patients were female, 37 were male. The average age of all 70 patients was 60.3±9.6 (mean ±SD). All participants were volunteers and gave their written consent to take part in this study. Local ethics committee approval was obtained to carry out this study.

Study design

This study was designed as an observational study in two groups, conducted at the University Eye Hospital in Greifswald, Germany. Probands were recruited at the hospital itself, at ophthalmologic practices and through the media. They were randomly assigned in a 1:1 ratio to one of two groups. The first group underwent 6 months of telemedical home monitoring followed by 6 months conventional glaucoma management, whilst the second group started with 6 months conventional glaucoma management followed by 6 months of telemedical home monitoring. All probands were examined at the beginning, after 6 months and at the end of the study using all glaucoma relevant diagnostics.

Study assessments

All patients were equipped with devices for telemedical home monitoring. For a period of 6 months they performed self-measurements of intraocular pressure and blood pressure at home and subsequently transmitted the data via a telemedical interface to a server in the hospital. The data was stored in electronic patient records, which were accessed by the ophthalmologists using a web frontend [18,19].

After extensive personal instruction in device handling the probands installed the devices at home and measured intraocular pressure with the Ocuton S (EPSa GmbH, Saalfeld, Germany), a self-tonometer using the Goldmann applanation principle, and blood pressure with the boso medicus PC (Bosch + Sohn GmbH u. Co. KG, Jungningen, Germany). We handed out a measuring schedule, that instructed the probands to check blood pressure and intraocular pressure in the morning and evening once a week and in addition to perform 24-hour profiles every 4 weeks. The majority of the probands decided to perform even more measurements than requested. The electronic patient record automatically calculated ocular perfusion pressure using the equation:

$$OPP = \frac{2}{3} \cdot \left(\frac{2}{3} \cdot DBP + \frac{1}{3} \cdot SBP \right) - IOP$$

where:
OPP – ocular perfusion pressure,
DBP – diastolic blood pressure,
SBP – systolic blood pressure,
IOP – intraocular pressure.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests showed no normal distribution of the data, so we analyzed significance using the non-parametric Mann-Whitney and Waller-Duncan tests. All reported P values are two-sided. Statistical analysis was performed with the software SPSS.

Results

All 70 patients with primary open-angle glaucoma performed a total number of 3282 self-measurements at home and

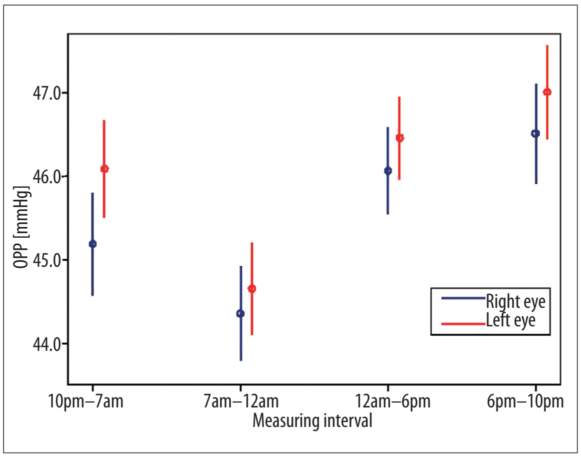

Figure 1. Characteristic phases in diurnal variation of ocular perfusion pressure (OPP) in 70 patients with primary open-angle glaucoma (n=3282 self-measurements). Between 7am and 12am ocular perfusion pressure was significantly depressed compared to all other phases (p<0.05). Indicated is the mean OPP with 95% confidence intervals.

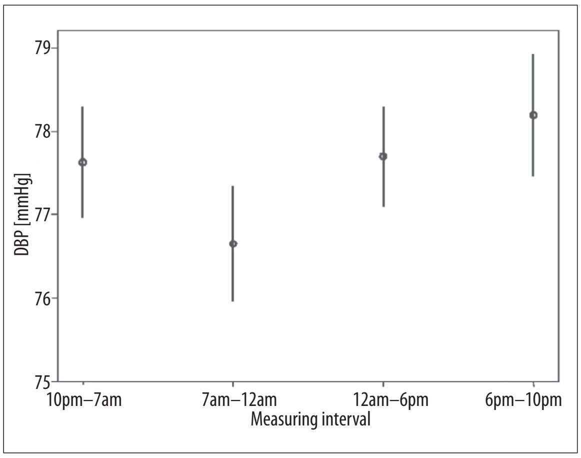

Figure 2. Characteristic phases in diurnal variation of diastolic blood pressure (DBP) in 70 patients with primary open-angle glaucoma (n=3282 self-measurements). Between 7am and 12am diastolic blood pressure was significantly depressed compared to all other phases (p<0.05). Indicated is the mean diastolic blood pressure with 95% confidence intervals.

transmitted the data to the electronic patient record, which then calculated ocular perfusion pressure automatically from the submitted values. We analyzed intraday variations of ocular perfusion pressure and determined four characteristic phases: 7am – 12am, 12am – 6pm, 6pm – 10pm, 10pm – 7am [20]. Between 7am and 12am ocular perfusion pressure (Figure 1) and simultaneously systolic and diastolic blood pressure were significantly depressed (Figure 2) compared to all other phases (p<0.05) whereas intraocular pressure showed no significant shifting (Figure 3). Instead intraocular pressure was significantly depressed between 6pm and 10pm (p<0.05) where ocular perfusion pressure reached the highest intraday values (Figures 1, 3). Systolic blood pressure was significantly lowered from 7am – 12am (p<0.05) and significantly increased from 12am – 6pm (Figure 4).

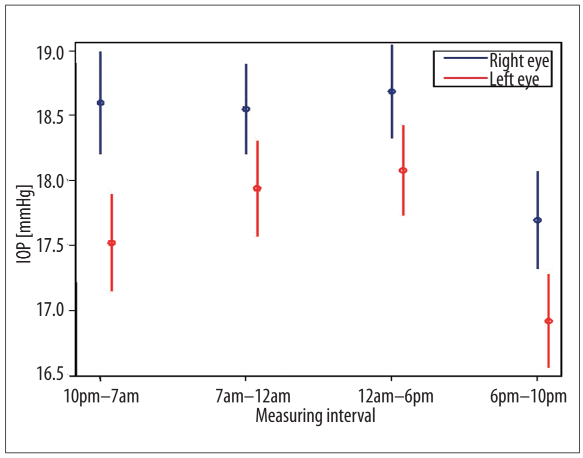

Figure 3. Characteristic phases in diurnal variation of intraocular pressure (IOP) in 70 patients with primary open-angle glaucoma (n=3282 self-measurements). Intraocular pressure showed no significant shifting between 7am and 12am while ocular perfusion pressure was significantly depressed (p<0.05) in the same time interval. Instead intraocular pressure decreased significantly between 6pm and 10pm (p<0.05) without affecting ocular perfusion pressure. Indicated is the mean IOP with 95% confidence intervals.

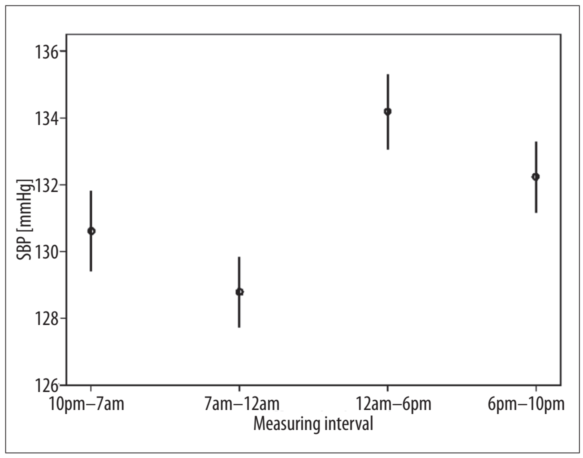

Figure 4. Characteristic phases in diurnal variation of systolic blood pressure (SBP) in 70 patients with primary open-angle glaucoma (n=3282 self-measurements). Systolic blood pressure was significantly lowered from 7am – 12am (p<0.05) and significantly increased from 12am – 6pm (p<0.05). Indicated is the mean systolic blood pressure with 95% confidence intervals.

Discussion

The vascular role in glaucoma pathophysiology has been studied intensely, but the etiology of primary open-angle glaucoma still remains unclear and relations between riskfactors appear to be controversial. Newer studies conclude that ocular perfusion pressure is strongly associated with glaucoma especially in persons with hypertension and hypertensive therapy [21]. Thus we have to reconsider the general impact of this diagnostic parameter as well as its relation to intraocular pressure. A recently published review provides a detailed and extensive overview of several

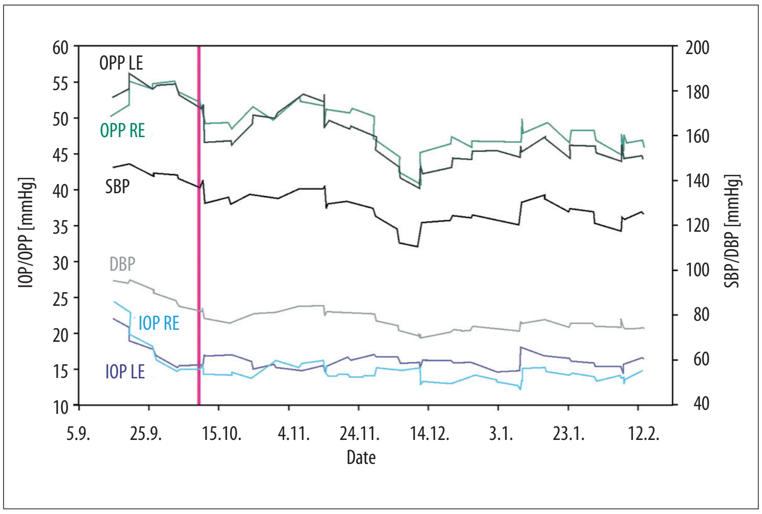

Figure 5. Clinical case report of a female 56 year old patient with primary open-angle glaucoma and systemic hypertension. Diagrammatic overview of the dynamic of intraocular pressure (IOP), ocular perfusion pressure (OPP), systolic (SBP) and diastolic (DBP) blood pressure based on 77 self-measurements during a period of six months home monitoring (all lines show moving average smoothed series). The red line indicates the date when both the ophthalmologist and the general practitioner modified glaucoma medication (topical clonidine was replaced by latanoprost) and respectively hypertensive therapy (angiotensin II receptor antagonist was added to initial combination of ACE-inhibitor, diuretic and calcium ion antagonist). This reduced intraocular pressure and blood pressure successfully, whereas the resulting decrease of ocular perfusion pressure remained unnoticed.

milestone glaucoma studies [5]. The authors not only confirmed the role of ocular perfusion pressure as an important risk factor for the development and progression of glaucoma but furthermore pointed out that this parameter perfectly combines the vascular and mechanical components of glaucoma.

Since there is no feasible method to measure ocular perfusion pressure directly we investigated the approximated value calculated from home monitoring self-measurements of blood pressure and intraocular pressure. This framework demonstrated how easily ocular perfusion pressure can be obtained; nevertheless this important parameter has not yet been included continuously in large studies or clinical routine. Although self-tonometry is not yet common, we were able to observe several benefits for glaucoma patients: 24-hour profiles without hospital admission [22], completed diurnal documentation without office hours related gaps [22], optimized healthcare management for elderly patients in remote areas [23], positive health economics evaluation [24], and finally it opened new ways to analyze the relation of intraocular pressure, blood pressure and ocular perfusion pressure. The results of this study are not only important for ophthalmologists who still focus on intraocular pressure [4] and morphological or functional changes as treatment relevant parameters without regarding systemic blood pressure. We now have strong evidence that the glaucomatous effects of intraocular pressure depend on the characteristics of systemic blood pressure. In Figure 5 we present a clinical case report of a female patient, whose glaucoma medication was modified by her ophthalmologist while at the same time the general practitioner changed her hypertensive therapy, neither informed the other of the new treatment regime. They both regarded their intervention as successful because the patient's intraocular pressure and blood pressure were lowered to appropriate levels. However both were unaware that as a result patient's ocular perfusion pressure dropped under 45 mmHg, a level that increases the risk of glaucomatous damage progression [11,17]. This report illustrates that glaucoma is a systemic disease which requires interdisciplinary cross-sectional treatment. Consequently hypertensive therapy has to be adapted to ocular circulation in glaucoma patients to reduce the risk of morphologic damage.

Our study has some limitations. Ocular perfusion pressure (OPP) was not measured directly instead it was calculated by taking mean arterial blood pressure and subtracting intraocular pressure (IOP). Since perfusion pressure is defined as the difference between arterial and venous pressure, and in the eye venous pressure is slightly higher than or even equal to IOP, for practical purposes the calculated OPP is a good approximation to quantify vascular changes [25,26]. Furthermore it was reported that the self-tonometer Ocuton S tended to over- or underestimate IOP compared to the gold standard Goldmann applanation tonometry (GAT) even though it uses the GAT principle to measure IOP [27,28]. However measurement accuracy of the self-tonometer was already improved after the implementation of a new firmware [29].

Conclusions

Our findings strengthen the evidence that blood pressure may contribute to optic disc damage in glaucoma patients. Still future research is needed to demonstrate how glaucoma patients may benefit from telemedical home monitoring in terms of slowing or even stopping morphological changes and glaucoma progression. Since glaucoma progresses slowly over several years this would require a long-lasting study setup. This would probably answer the question how strong perfusion pressure is as prognostic factor. Further efforts will have to be spent on improving the usability and reliability of the self-tonometer to advance measuring accuracy.

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Conflicts of interest

None.

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