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Nocturnal blood pressure in primary open-angle glaucoma

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ABSTRACT.

Purpose: **To evaluate the nocturnal blood pressure (BP) dipping-pattern in patients with manifest primary open-angle glaucoma (POAG) and to find possible associations with the severity of visual field damage.**

Methods: **A number of 314 patients suffering from POAG were consecutively enrolled in this cross-sectional hospital-based study. Each patient had diurnal intraocular pressure (IOP) measurements, 24-hr BP monitoring and computerized perimetry with the Humphrey 30-2 SITA Standard program. Inclusion criteria were a mean IOP of less than 15 mmHg with fluctuations of less than 5 mmHg and a visual acuity of at least 20/40. One eye was randomly selected. Based on the night–day BP ratio, a mean arterial nocturnal BP drop of less than 10% was considered as non-dipping, between 10% and 20% as physiological dipping and of more than 20% as over-dipping.**

Results: **Glaucoma patients with daytime systemic normotension on the average had more visual field loss in the over-dipper group (MD = − 16.6 dB, IQR = −18.9 to −2.7 dB) than glaucoma patients with daytime systemic hypertension, who had less visual field defects in the over-dipper group (MD = −3.9 dB, IQR = −6.2 to −1.9 dB) (p = 0.004). This result was also found taking age, glaucoma duration, visual acuity, gender, systemic and topical medication as covariates into account.**

Conclusions: **To judge the nocturnal BP situation of an individual patient, it is important to do this in relation to the daytime BP level. Twenty-four-hour BP evaluation might be important for all patients with POAG, as nocturnal BP could be a modifiable risk factor for glaucoma severity and progression.**

Key words: 24-hr ambulatory blood pressure – nocturnal blood pressure dipping – nocturnal safety range – ocular perfusion pressure – open-angle glaucoma – systemic hypertension – visual field severity

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Introduction

Glaucoma represents a multifactorial optic neuropathy characterized by nerve fibre layer defects that lead to the typical glaucomatous cupping and thinning of the rim of the optic nerve head as well as characteristic visual field defects in cases that are already more advanced. Many risk factors for the development and progression of primary open-angle glaucoma (POAG) have been identified of which intraocular pressure (IOP) is considered the most important modifiable one (Collaborative 1998; Heijl et al. 2002; Kass et al. 2002). Vascular factors are another important group of risk factors. They can lead to hypoperfusion of the optic nerve head and thus may play an important role in the pathogenesis and progression of POAG (Phelps & Corbett 1985; Hayreh 1997; Anderson 1999; Drance 2001; Huck et al. 2014). Among those factors, arterial blood pressure (BP) and its association with glaucoma and IOP have been studied thoroughly in large epidemiological surveys. Recent studies (Choi et al. 2006, 2007, 2013; Leske et al. 2007; Sung et al. 2009; De Moraes et al. 2012; Costa et al. 2014) have shown that low or fluctuating ocular perfusion pressures (OPPs) represent a major risk factor for the prevalence, incidence and progression of glaucoma. Most of these studies based their results on one or more daytime BP readings and on IOP readings at a specific time of day. With the development and availability of ambulatory BP monitoring, it is possible to study BP continuously during day and night, during activity and sleep and thus to get a better assessment of the actual BP situation of the individual patient.

The purpose of this study was to assess the nocturnal BP dipping-pattern in patients with manifest POAG, to find possible associations with the severity of visual field damage and to define a safe nocturnal perfusion pressure range in which the probability of further progression is low.

Methods

In this cross-sectional study, we investigated the 24-hr ambulatory BP pattern and nocturnal BP dipping behaviour of 314 consecutive patients with open-angle glaucoma of Caucasian origin. For analysis, one eye was randomly selected. A number of 147 patients suffered from high-pressure glaucoma (HPG) and 167 from normal pressure glaucoma (NPG).

Patients were admitted for a one-day routine glaucoma workup that included

(1) A detailed medical history including all ocular and systemic medications the patient was taking. Patients were using their medication as usual.
(2) A complete and detailed ophthalmic examination, including a complete glaucoma workup.
(3) Measurements of diurnal IOP were taken at 1, 4, 7 and 10 pm in a sitting position at the slitlamp with a Goldmann tonometer, at midnight in a supine position using a Perkins tonometer and at 7 am again in a sitting position at the slitlamp.
(4) Twenty-four-hour BP was monitored with a portable device from Bosch & Sohn GmbH, Jungingen, Germany. Daytime measurements were taken from 7 am to 10 pm every 15 min and night-time measurements from 10 pm to 7 am every 30 min (The Scientific Committee 1990). All patients had the same in-hospital routine. Meals were served from 7:30 to 8:30 am, 12:00 to 12:45 pm, 15:00 to 15:45 pm and 5:45 to 6:45 pm. After the last IOP measurement at 10 pm, patients were asked to go to bed and to possibly turn off the light.
(5) The Humphrey 30-2 SITA Standard program (Zeiss Humphrey Systems, Dublin, CA, USA) was used for computerized perimetry. All patients were experienced in visual field testing. Reliability criteria were false-positive errors of < 15% and a fixation loss of < 20%. Otherwise, the visual field testing was repeated.

The following criteria were used for establishing the diagnosis of HPG and NPG:

(1)High-pressure glaucoma (HPG): a history of untreated IOP of more than 21 mmHg, a normal anterior chamber with an open angle on gonioscopic examination, an optic nerve head with typical glaucomatous appearance and corresponding nerve fibre layer defects or typical visual field defects, no other ophthalmic or systemic causes for visual field defects.
(2)Normal pressure glaucoma (NPG): a history of untreated IOP equal or less than 21 mmHg, otherwise the same criteria applied as for HPG.

Definition of normal and elevated arterial BP on 24-hr BP readings

According to the guidelines of the European Society of Hypertension and Cardiology, normal BP on 24-hr BP readings is defined as daytime systolic/diastolic BP means of <135/85 mmHg and night-time SBP/DBP of <120/70 mmHg. Elevated BP otherwise (Mancia et al. 2014).

Definition of non-dippers, physiological dippers and over-dippers

The drop from daytime mean arterial BP (MAP) to night-time MAP in per cent is referred to as night-time BP dip. It is calculated as: 100 − (nocturnal averaged MAP*100/diurnal averaged MAP). According to the guidelines of the European Society of Hypertension and Cardiology (Mancia et al. 2014), patients with a nocturnal MAP reduction of <10% are classified as non-dippers, those with a reduction between 10% and 20% as physiological or normal dippers and those with a reduction of more than 20% as over-dippers or extreme dippers.

Mean arterial BP (MAP) is defined as the average pressure throughout the cardiac cycle and represents the perfusion pressure of an individual (Oblouck 1987). It is calculated as: MAP = diastolic BP + 1/3 (systolic BP − diastolic BP) (Cywinski 1980).

Ocular perfusion pressure is usually calculated for the upright position using the formula OPP = 2/3 MAP − IOP and for the supine position as OPP = MAP − IOP (Costa et al. 2014).

Further inclusion criteria:
(1) Best-corrected visual acuity > 20/40
(2) Mean IOP < 15 mmHg
(3) IOP fluctuation < 5 mmHg
(4) Age > 40 years

The study was approved by the ethics committee of the Medical Faculty of the Technische Universität Dresden, Germany. Each participant signed an informed consent form, and all procedures were in accordance with the Declaration of Helsinki.

Statistical analysis

Normally distributed variables are presented as the mean ± SD and categorical variables as frequencies. Data given as percentages were calculated afterwards.

To investigate the main parameters mean deviation (MD) and pattern standard deviation (PSD) by analysis of variance (ANOVA), these non-normally distributed variables were transformed by a Box–Cox transformation into a normal distribution in order to be able to search for influencing factors. The influence of covariates such as age, reported duration of glaucoma, visual acuity, gender and the application of systemic and local medications were evaluated separately in an ANCOVA. As *post hoc* test, the SIDAK test was used. The covariate-adjusted retransformed mean values and the 95% confidence intervals were given.

Categorical variables were investigated by cross-tables and chi-square tests. A two-tailed p value less than

Table 1. Patient demographics.

	Normotensive	Hypertensive	p Value
Number of patients	112	202	
Age (years)	64.9 ± 9.7	68.4 ± 8.8	0.002
Gender (m/f)	33/79	80/122	0.086
BCVA (logMAR)	0.063 ± 0.088	0.077 ± 0.100	0.186
SE (D)	−1.1 ± 2.5	−0.7 ± 2.4	0.167
CCT (μm)	538.9 ± 37.7	533.2 ± 52.3	0.324
IOP (mmHg)	12.1 ± 1.7	12.1 ± 1.8	0.862
Duration of disease (years)	10.3 ± 7.8	9.8 ± 8.1	0.619
HPG/NPG	52/60	95/107	0.919

BCVA = best-corrected visual acuity (BCVA), logMAR = logarithm of the minimal angle of resolution, SE = spherical equivalent, D = diopters, CCT = central corneal thickness, IOP = intraocular pressure, HPG/NPG = high-pressure glaucoma/normal pressure glaucoma.

0.05 was considered statistically significant. Analyses were performed using the statistical software packages SPSS (version 21 for Windows; SPSS Inc., Chicago, IL, USA).

Results

Glaucoma patients with systemic normotension, untreated or treated, were younger than patients with uncontrolled arterial hypertension. There were no statistically significant differences regarding gender ratio, visual acuity, spherical refractive error, central corneal thickness, IOP, the duration of the disease and the distribution between HPG/NPG between systemic normotensives and hypertensives (Table 1). There was no difference in BP parameters between systemic normotensive HPG and NPG patients as well as between systemic hypertensive HPG and NPG patients (Table 2). The distribution of the three dipping groups in daytime normal BP and high BP patients was statistically significantly different ($p = 0.030$; Fig. 1).

Systemic normotensive patients with a nocturnal overdipping on the average had more visual field loss (MD = − 16.6 dB, IQR = −18.9 to −2.7 dB) than overdippers in the systemic hypertensive group (MD = −3.9 dB, IQR = −6.2 to −1.9 dB) ($p = 0.004$; Figs 2 and 3). The same was true looking at patients with HPG and NPG separately (Table 3). This result was also seen taking the covariates age, glaucoma duration, visual acuity, and gender into account and when controlling for possible effects of systemic and topical medication. To investigate these influencing factors, MD and PSD were transformed into a normal distribution (Table 3). Regarding systolic dipping, as preferred in internal medicine, or diastolic dipping, the overdippers on average always had more visual field loss in daytime normal BP patients with glaucoma and less visual field loss in daytime high BP patients with glaucoma.

With a stepwise change of MAP limits, we evaluated a range of nocturnal MAPs between 65 and 90 mmHg which showed 70% of visual fields with a MD of better than −6 dB. This was statistically highly significant ($p = 0.006$). This range would lead to an approximate, calculated nocturnal OPP range between 50 and 75 mmHg (supine OPP = MAP − IOP; mean IOP had to be 15 mmHg).

A number of 112 (36%) of the entire group were normotensive on mean daytime 24-hr BP measurements (Table 2), 57 (18% of the whole sample) without BP lowering medication and 55 (18% of the whole sample) with BP lowering medication. A number of 202 (64%) of the patients with glaucoma were hypertensive on mean daytime 24-hr BP measurements (Table 2), 81 (26% of the whole sample) were not treated and 121 (39% of the whole sample) were treated insufficiently. Only 57 (18%) of the patients with glaucoma had normal daytime BP without medication. There was no difference in the distribution of BP treatment ($p = 0.075$) or the evening dosage of BP lowering medications ($p = 0.346$) between treated normotensives and hypertensive glaucoma patients or between the three dipping groups ($p = 0.101$).

Table 2. Blood pressure and heart rate in daytime systemic normotensive and hypertensive patients with HPG and NPG.

	SBP	DBP	MAP	HR	PP
Normotensives $n = 112$					
Day time-all	125.3 ± 7.2	75.3 ± 5.1	91.9 ± 4.8	68.5 ± 7.6	49.9 ± 7.1
HPG	126.7 ± 7.2	76.1 ± 5.3	92.9 ± 5.0	69.3 ± 9.1	50.6 ± 6.9
NPG	124.0 ± 7.0	74.6 ± 4.9	91.0 ± 4.5	67.7 ± 6.1	49.4 ± 7.2
p Value	0.047	0.131	0.041	0.273	0.358
Night time-all	112.7 ± 12.3	66.1 ± 7.0	80.8 ± 8.1	60.7 ± 7.5	46.6 ± 8.5
HPG	114.4 ± 14.0	67.5 ± 7.7	82.3 ± 9.2	61.6 ± 8.4	46.9 ± 9.3
NPG	111.2 ± 10.6	64.9 ± 6.1	79.5 ± 6.9	60.0 ± 6.5	46.3 ± 7.7
p Value	0.163	0.051	0.071	0.268	0.669
Hypertensives $n = 202$					
Day time-all	148.5 ± 11.8	85.4 ± 7.6	106.3 ± 8.0	68.8 ± 7.8	63.1 ± 9.5
HPG	149.7 ± 12.0	86.5 ± 7.6	107.4 ± 8.2	68.7 ± 7.8	63.2 ± 9.3
NPG	147.4 ± 11.5	84.4 ± 7.4	105.3 ± 7.7	68.9 ± 7.8	63.0 ± 9.7
p Value	0.179	0.046	0.056	0.807	0.934
Night time-all	129.3 ± 16.3	73.1 ± 9.4	90.9 ± 10.9	62.1 ± 7.2	56.2 ± 10.8
HPG	129.1 ± 16.1	72.9 ± 9.7	90.7 ± 11.1	61.7 ± 7.4	56.2 ± 10.2
NPG	129.4 ± 16.6	73.3 ± 9.1	91.1 ± 10.8	63.1 ± 7.1	56.1 ± 11.4
p Value	0.889	0.753	0.787	0.505	0.950

HPG = high-pressure glaucoma, NPG = normal pressure glaucoma, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, PP = pulse pressure; p value for comparison HPG and NPG.

Discussion

In this study, the BP of patients with manifest POAG was assessed during 24 hr, and possible associations with the severity of visual field damage were investigated.

In glaucoma patients with arterial normotension, untreated or treated, over-dippers had on average more visual field loss compared to over-dippers in the arterial hypertension group, who had the least visual field loss. It seems that the nocturnal perfusion pressure is insufficient in the first group and reaches an optimal range in the second group.

To maintain a constant ocular perfusion during changes in BP or IOP, an intact blood flow autoregulation is needed. It has been shown that optic nerve head blood flow is autoregulated (Pillunat et al. 1997). Measurements of optic nerve head function with visually evoked cortical potentials during stepwise IOP elevation in patients with glaucoma showed an impairment of the autoregulatory capacity of the optic nerve head (Pillunat et al. 1985, 1987) compared with healthy subjects. It has been shown (Strandgaard et al. 1973, 1976) that arterial hypertension also modifies autoregulation, probably as a consequence of artheriosclerotic microangiopathy. Therefore, long-standing hypertension or unphysiological nocturnal BP dipping-patterns in systemic normotensive patients with glaucoma might indicate a compromised peripheral vascular capacity and an impaired autoregulation of the optic nerve head circulation. Twenty-four-hour BP monitoring might be an additional suitable diagnostic tool to detect autoregulative disorders.

In many important epidemiological studies (Tielsch et al. 1995; Bonomi et al. 2000; Leske et al. 2008), it has

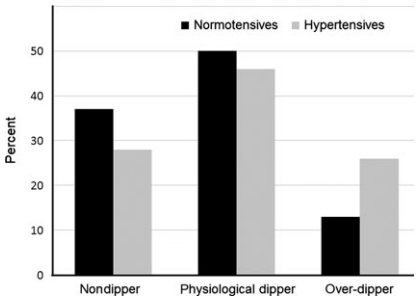

Fig. 1. Distribution of non-dippers, physiological dippers and over-dippers in systemic normotensive and hypertensive patients with open-angle glaucoma. The difference of the distribution was statistically significant ($p = 0.030$).

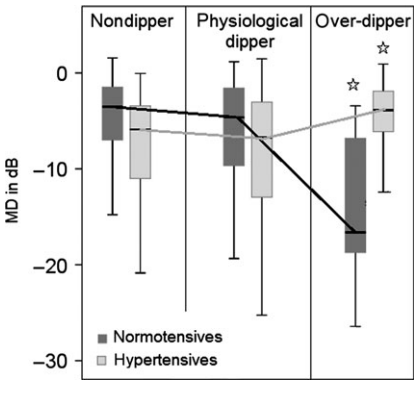

Fig. 2. Median MD (mean deviation) and interquartile ranges in the three dipping groups of systemic normotensive and hypertensive patients with open-angle glaucoma. Significances are marked with asterisks.

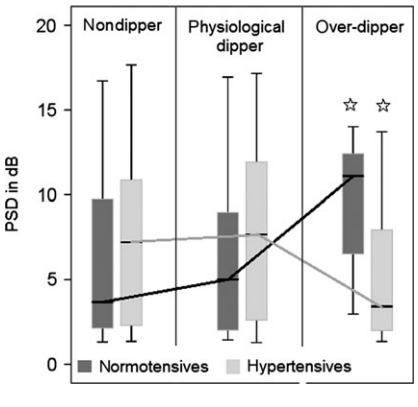

Fig. 3. Median PSD (pattern standard deviation) and interquartile ranges in the three dipping groups of systemic normotensive and hypertensive patients with open-angle glaucoma. Significances are marked with asterisks.

been shown that low ocular perfusion pressures represent a risk factor for the incidence and prevalence of glaucoma. Furthermore, recent studies emphasized (Leske 2007; Sung et al. 2009; De Moraes et al. 2012; Choi et al. 2013) the importance of low ocular perfusion pressures for the progression of glaucoma. The lower limits of ocular perfusion pressures vary considerably between these studies. This is probably due to the fact that these studies did not differentiate between normotensive or hypertensive individuals in their cohorts and that mostly daytime BPs were analysed.

One major disadvantage of the current study as well as of all epidemiological studies is the cross-sectional design. Blood pressure was only measured during one day and night, while visual field defects or glaucoma in general develop over time and are also influenced by other factors. Nevertheless, it is generally accepted that reduced ocular perfusion pressures have an important role in the prevalence and progression of glaucoma. Ocular perfusion pressure depends primarily on BP (Wang et al. 2015) especially if IOP is controlled like it was in this study population. In a number of patients with glaucoma, visual field defects progress despite well-controlled IOP. In these patients, other risk factors besides IOP have to be taken into account. One of them might be the nocturnal BP and perfusion pressure range. As there seems to be an optimal ('safe') BP range while asleep, the aim was to find the range of mean arterial BPs (MAP) with the highest number of patients with early visual field defects (>−6 dB). This 'Dresden safety range' for the nocturnal MAP was found to be between 65 and 90 mmHg. Patients within this safety range are expected not to progress or to have a slower progression compared with patients outside this range as long as IOP is controlled. The J-curve phenomenon, already described in the internistic literature (Bechetoille & Bresson-Dumont 1994; Hedner et al. 2009; Filippone & Foy 2012; Panjrath et al. 2012; Angeli et al. 2013; Ivanovic & Tadic 2014), shows that there is a greater end organ damage at both extremes of the BP range (Memarzadeh et al. 2010). This is also in agreement with the results of a recent metaanalysis (Zhao et al. 2014) on the association of BP and POAG which showed an increased risk for POAG with low and high BPs. Low ocular perfusion can occur due to low BP, high IOP or reduced blood flow secondary to arteriosclerotic changes (Costa et al. 2014). As the patients with glaucoma in this study were IOP-controlled with the average IOP on the diurnal IOP curve less than 15 mmHg and fluctuations less than 5 mmHg, we could estimate an optimal nocturnal mean arterial perfusion pressure range from 50 to 75 mmHg (supine: OPP = MAP − IOP).

Daytime BPs did not show any correlation with the severity of visual field damage in our sample, the same has already been shown in other studies (Graham et al. 1995; Leske et al. 1995). Obviously, there are factors that accelerate glaucomatous damage more while asleep than while awake. This stresses the importance of measuring night-time BP and night-time IOP in patients with glaucoma (Agnifili et al. 2015). There is a possibility that vascular autoregulation is more vulnerable during the night and/or in a supine position.

Sixty-four per cent of the patients with glaucoma in this study suffered from systemic hypertension, and 36% (treated hypertensive patients included) were normotensive. Unfortunately, we do not have an age-matched control group. Hermida et al. (2013) demonstrated in a population of 3344 individuals with a mean age of 52.6 ± 14.5 years a 40% prevalence of systemic hypertension and a 60% prevalence of normotension (treated hypertensive patients included). Thirty-six per cent of the normotensives were non-dippers, which is comparable to the 37% of non-dippers in the normotensive group of this study. Fifty-seven per cent of the hypertensives were non-dippers which is much higher than in our study (28%). Hermida's study did not differentiate between physiological dippers and over-dippers. Therefore, there are no data available to be compared to our results in patients with glaucoma. Furthermore, it is important to notice that there is quite an age difference between the individuals in the mentioned study and our cohort.

Until now, nocturnal BP analysis in ophthalmology has mainly focused on identifying over-dippers among patients with NPG. Little attention was given to the BP dynamics of patients with HPG. In this study, we could not find differences in the distribution of systemic normotension and hypertension between HPG and NPG

Table 3. Visual field parameters (MD and PSD) in systemic normotensives and hypertensives for the whole group and HPG and NPG patients according to MAP-dipper status.

	Non-dippers	Physiological dippers	Over-dippers	p Value
Normotensives				
MD (dB)	−4.19 (−5.93 to −2.81)	−4.73 (−6.59 to −3.68)	−10.76 (−15.32 to −6.59)	0.015
PSD (dB)	4.49 (3.52–5.74)	4.97 (4.01–6.14)	7.93 (5.32–11.62)	0.022
Hypertensives				
MD (dB)	−6.59 (−8.09 to −5.30)	−6.59 (−7.31 to −5.30)	−4.19 (−5.30 to −2.81)	0.011
PSD (dB)	5.41 (4.37–6.67)	5.94 (5.06–6.95)	4.08 (3.25–5.06)	0.028
HPG Normotensives				
MD (dB)	−5.07 (−2.89 to −8.01)	−7.09 (−4.67 to −10.37)	−11.89 (−6.59 to −19.97)	0.034
PSD (dB)	5.19 (3.61–7.36)	5.41 (3.91–7.36)	7.19 (5.10–13.79)	0.251
HPG Hypertensives				
MD (dB)	−7.69 (−5.13 to −11.16)	−6.39 (−4.73 to −8.41)	−3.94 (−2.49 to −5.86)	0.043
PSD (dB)	5.99 (4.34–8.19)	5.74 (4.57–7.19)	4.15 (3.11–5.51)	0.138
NPG Normotensives				
MD (dB)	−5.93 (−3.84 to −2.93)	−2.22 (−1.74 to −4.40)	−8.49 (−3.89 to −16.12)	0.025
PSD (dB)	4.19 (2.87–5.99)	4.1 (3.02–5.51)	6.95 (3.55–13.06)	0.341
NPG Hypertensives				
MD (dB)	−5.55 (−3.89 to −7.62)	−5.99 (−4.51 to −7.77)	−3.89 (−2.30 to −6.06)	0.045
PSD (dB)	5.15 (3.91–6.73)	6.30 (5.06–7.86)	3.74 (2.59–5.37)	0.051

MD = mean deviation, PSD = pattern standard deviation, adjusted mean values and 95% confidence intervals, MAP = mean arterial blood pressure, HPG = high-pressure glaucoma, NPG = normal pressure glaucoma.

patients (p = 0.916). Therefore, ambulatory monitoring of systemic BP is at least as important in patients with HPG.

The main findings of this study show that it seems important to evaluate the nocturnal dipping pattern of an individual patient with glaucoma in relation to the diurnal BP. As BP, especially while asleep, is a modifiable risk factor, 24-hr BP monitoring might be important to be included into glaucoma care.

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