Circadian Variation in Arterial Blood Pressure and Glaucomatous Optic Neuropathy—A Systematic Review and Meta-Analysis

Andrea Bowe, Michael Grünig, Jens Schubert, Münevver Demir, Vera Hoffmann, Fabian Kütting, Agnes Pelc, and Hans-Michael Steffen

BACKGROUND
Epidemiological studies have led to equivocal results concerning the role of arterial blood pressure as a risk factor for the development of glaucomatous damage and progressive visual field loss in glaucoma. It has been attributed to low nighttime blood pressure, especially when oral antihypertensives have been combined with beta-blocking eyedrops. In order to answer the question whether nocturnal blood pressure or blood pressure dip during ambulatory blood pressure monitoring are associated with progressive visual field loss we performed a systematic review and meta-analysis of studies in patients with primary open-angle glaucoma and normal tension glaucoma.

METHODS
After searching MEDLINE, the Cochrane Library, and EMBASE, only 5 studies could be found reporting information on the method of ambulatory blood pressure measurements, separate data for daytime and nighttime blood pressure, definition of nocturnal blood pressure dip, and assessment of visual fields over a period of at least 2 years.

RESULTS
There was no difference in mean systolic or diastolic diurnal and nocturnal blood pressure between patients with or without progressive visual field loss. The odds ratio for deteriorating visual fields over 2 years with nocturnal dips >10% in systolic or diastolic blood pressure was 3.32 (1.84–6.00) and 2.09 (1.20–3.64), respectively. Data allowing a separate analysis of over-dipping were not available.

CONCLUSIONS
Nocturnal blood pressure fall is a risk factor for progressive visual field loss in glaucoma. However, prospective studies are needed to define a tolerable degree of dipping. Antihypertensive therapy in glaucomatous patients should be controlled with ambulatory blood pressure monitoring.

Keywords: ambulatory blood pressure monitoring; blood pressure; glaucoma; hypertension; nocturnal dip; progressive visual field defects.

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Glaucoma is the second leading cause of blindness globally, and ocular hypertension is a major risk factor for the disease. However, since von Graefe’s report on patients with glaucomatous optic nerve atrophy without intraocular pressure elevation in 1857, it has been hypothesized that other factors would affect onset and progression of glaucoma, especially in patients with normal tension glaucoma (NTG). Abnormalities in the systemic hemodynamics and vascular dysregulation (e.g., impaired autoregulation) have been recognized as 2 equally important pathophysiological mechanisms. In addition to these main factors, age, a positive family history, ethnicity, slimness of the central cornea, myopia, and diabetes have been identified as risk factors for the disease and its progression. The complex interplay between systemic blood pressure and intraocular pressure determines the ocular perfusion pressure, which in turn regulates blood flow to the optic nerve. However, the relation of arterial blood pressure and glaucoma remains equivocal and one can find studies supporting the role of arterial hypertension as well as studies linking glaucoma with arterial hypotension.

A nocturnal fall in systemic blood pressure was discovered in the end of the 19th century and with the advent of ambulatory blood pressure monitoring, a physiological fall in systolic and diastolic blood pressure during sleep has been confirmed in both normotension, as well as primary hypertension. According to the latest recommendation of the European Society of Hypertension Working Group on Blood Pressure Monitoring nocturnal blood pressure dipping has been defined as a fall of >10% for systolic or diastolic blood pressure compared to the daytime values, respectively. While increased nighttime blood pressure or a nondipping profile are associated with cardiovascular organ damage, circadian fluctuation in mean ocular perfusion pressure, a predictor of advanced glaucomatous damage in NTG, has been noted in patients with a nocturnal dip >10% in mean arterial blood pressure. In addition, nocturnal hypotension was associated with progressive visual field deterioration, especially in patients on oral antihypertensive therapy combined with beta-blocking eyedrops.

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Hence, in order to answer the question whether nocturnal systolic and diastolic blood pressure or blood pressure dips are associated with progressive glaucomatous optic neuropathy we performed a systematic review and meta-analysis of studies in patients with primary open-angle glaucoma and normal intraocular pressure with or without arterial hypertension.

METHODS

Our meta-analysis was conducted according to the Quorum statement. Using the terms "open-angle glaucoma," "normal tension glaucoma," "circadian blood pressure," "blood pressure variation," and "ambulatory blood pressure" we searched the databases of MEDLINE, EMBASE, and the Cochrane Library as well as the reference lists of the retrieved studies in adult glaucoma patients with no language constraints. Inclusion criteria were defined as follows: (i) description of the method of ambulatory blood pressure measurements (ABPM), (ii) separate data for daytime and nighttime blood pressure reported, (iii) a definition of nocturnal blood pressure dip is mentioned or can be derived, and (iv) assessment of visual fields over a study period of at least 2 years of follow-up. Study quality was assessed independently by 2 investigators (H.-M.S., J.S.) using the STROBE Statement checklist establish from von Elm et al.24 for cohort studies excluding the final item concerning the financing of studies. Disagreement was resolved by discussion. The primary outcome we evaluated was visual field defects on at least 2 occasions, 2 years apart, assessed with the same technique. The effect of diurnal and nocturnal systolic and diastolic blood pressure, as well as systolic and diastolic blood pressure dip on the defined outcome was calculated from the extracted quantitative data and analyzed with the Cochrane Review Manager (RevMan 5.2). In Figures 2 and 3 blood pressure values are considered as continuous data and the inverse variance method was used to estimate the relative blood pressure effect and its SE. Each study estimate of the relative blood pressure effect is given a weight that is equal to the inverse of the variance of the effect estimate (i.e., one divided by the SE squared). We assume that every study in our analysis has the same effect so we used the fixed effect model ("Fixed") to combine the “mean difference” of every single study. In Figure 4 blood pressure dip is considered as a dichotomous variable so we used the Mantel–Haenszel method to combine the odds ratio, using the fixed effect model. Statistical heterogeneity between studies was evaluated by Cochran chi²-test and was considered to exist when \( P < 0.05 \). Mean differences in systolic and diastolic daytime and nighttime blood pressure, as well as odds ratios for nocturnal systolic and diastolic blood pressure dip with 95% confidence intervals were determined for patients with and without progressive visual field loss.

RESULTS

Our bibliographic searches yielded 230 candidate publications prior to the deadline 31 March 2014. Only 66 publications were left after exclusion of studies that according to their title or abstract dealt with cross-sectional studies or acute pharmacologic interventions. However, after thorough full-text analysis of these trials, only 5 studies met the defined inclusion criteria (Figure 1). The reasons for excluding articles (number excluded in brackets): no data on deterioration of visual field (56), no ambulatory blood pressure

![Flowchart showing the process of study selection](https://academic.oup.com/ajh/article-abstract/28/9/1077/175748)

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>First author/reference citation</th>
<th>Study population</th>
<th>Patients (n)</th>
<th>ABPM method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashiwagi et al.8</td>
<td>Patients with NTG</td>
<td>Total: 27 Male: 12</td>
<td>“A&amp;D; Toshimaku, Tokyo” every 30 minutes</td>
</tr>
<tr>
<td>Graham et al.13</td>
<td>Patients with POAG/NTG</td>
<td>Total: 70 Male: n.a.</td>
<td>“CH Druck monitor”a every 30 minutes</td>
</tr>
<tr>
<td>Collignon et al.12</td>
<td>Patients with POAG/NTG</td>
<td>Total: 70 Male: 35</td>
<td>“Space Labs Holter” 6-220 every 20 minutes</td>
</tr>
<tr>
<td>Bresson-Dumont et al.19</td>
<td>Patients with POAG/NTG</td>
<td>Total: 83 Male: 35</td>
<td>“Space Labs Holter” 6-220 every 30 minutes</td>
</tr>
<tr>
<td>Detry et al.25</td>
<td>Patients with POAG</td>
<td>Total: 36 Male: 19</td>
<td>“Space Labs Holter” 6-220 every 20 minutes</td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure measurement; n.a., not available; NTG, normal tension glaucoma; POAG, primary open-angle glaucoma.

aDisetronic Medical Systems, Burgdorf, Switzerland.
Table 2. ABPM results in patients with progressive or stable visual field defects

<table>
<thead>
<tr>
<th>First author/reference</th>
<th>Patients (n)</th>
<th>Mean systolic BP (day) (mm Hg)</th>
<th>Mean diastolic BP (day) (mm Hg)</th>
<th>Systolic dipper</th>
<th>Diastolic nondipper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashiwagi et al. 8</td>
<td>Total:16 p</td>
<td>128.6</td>
<td>68.7</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>Total:11 p</td>
<td>107.8</td>
<td>65.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Graham et al. 13</td>
<td>Total:48 p</td>
<td>122.9</td>
<td>70.6</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Total:13 p</td>
<td>119.5</td>
<td>75.4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Collignon et al. 12</td>
<td>Total:47 p</td>
<td>128.7</td>
<td>69.2</td>
<td>28</td>
<td>31</td>
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<tr>
<td></td>
<td>Total:13 p</td>
<td>120.9</td>
<td>79.8</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Bresson-Dumont et al. 19</td>
<td>Total:34 p</td>
<td>124.5</td>
<td>68.4</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Total:12 p</td>
<td>n.a.</td>
<td>n.a.</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Detry et al. 25</td>
<td>Total:43 p</td>
<td>117.0</td>
<td>71.4</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Total:24 p</td>
<td>n.a.</td>
<td>n.a.</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total:12 p</td>
<td>n.a.</td>
<td>n.a.</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure, n.a., not available; p, progressive visual field defects; s, stable visual field defects.

Data (4), and reference not related to study objective (1). The included studies were all retrospective cohort studies of no more than moderate quality. Two studies 8,13 used exclusively a Humphrey field analyzer (program 30–2) where deterioration of visual fields was defined as a significant difference in mean deviation or corrected pattern SD, one study used either the Humphrey system or a Goldmann perimeter with newly developed or extended scotoma as definition of progressive field loss. 19 An Octopus G1 perimeter with an increase of at least 3 dB of the mean defect as indication of field loss progression was used together with a Goldmann perimeter 13 and in another study visual fields were analyzed by all 3 systems. 25 The types of ABPM monitor, as well as the definition of daytime and nighttime differed between studies and was 6 AM to 10 PM and 10 PM to 6 AM, respectively. 12,13,19 and 8 AM to 10 PM and 10 PM to 8 AM, respectively. 25 Daily activity was recorded in one study 19 in order to define waking and sleeping periods. (Table 1) The age of included patients ranged from 28 to 85 years, the proportion of patients with accompanying arterial hypertension varied between 0% and 44%. From the study of Kashiwagi et al. 8 only mean values for systolic and diastolic blood pressure as well as nocturnal dips could be retrieved, while Detry et al. 25 published only the distribution of blood pressure dips for patients with and without progressive visual field defects. (Table 2) A 10% fall in systolic or diastolic blood pressure during the night as criterion for the definition of dipping was available for 4 studies. 12,13,19,25

There was no difference in mean systolic or diastolic diurnal and nocturnal blood pressure between patients with or without progressive visual field loss. (Figures 2 and 3) However, the odds ratio for deteriorating visual fields with nocturnal dips >10% in systolic or diastolic blood pressure was 3.32 (1.84–6.00) and 2.09 (1.20–3.64), respectively. (Figure 4) Data allowing a separate analysis of nondipping or over-dipping were not available.

**DISCUSSION**

In a significant number of patients with glaucoma, the progression of visual field defects occurs despite adequate control of intraocular pressure. One of the factors suspected to be most important is a vascular dysfunction with disturbed autoregulation, leading to reduced perfusion toward the capillary network of the optic nerve. It is in this context that aggressive antihypertensive therapy may worsen visual field defects. In our systematic review, we were able to include only 5 studies 8,12,13,19,25 investigating 24-hour ambulatory blood pressure and progression of glaucomatous neuropathy with an observation period of at least 2 years. While a nocturnal dip of more than 10% in systolic or diastolic blood pressure conferred a significant risk for progressive visual field loss, we were unable to demonstrate a similar effect for the absolute diurnal and nocturnal systolic or diastolic blood pressure values. The adaptive mechanisms obviously cannot compensate for the nocturnal drop in arterial blood pressure 26 and the subsequent reduction in perfusion pressure at the optic nerve head. Unfortunately, the definition of blood pressure dips and the small number of included patients in
the available studies precludes further analyses with respect to different unphysiological dipping patterns, e.g., nondipping or over-dipping. We are left with the fact, that even a normal dipping pattern may be dangerous for patients suffering from glaucoma.

Studies investigating blood pressure dips in glaucoma patients have reached heterogenous conclusions, most likely related to differences in the classification of dipping and different techniques of assessment of the progression of visual field defects. Studies that aimed to show hemodynamic...
differences related to the underlying glaucoma pathology found elevated blood pressure to be associated with primary open-angle glaucoma and NTG could not confirm the glaucoma phenotype as an independent risk factor, which highlights the importance of other aforementioned risk factors in the course of disease progression. In 1995 the Baltimore Eye Survey has shown an age-related association between blood pressure and glaucoma. Interestingly, there seems to be a protective effect of hypertension in younger patients, an effect that can probably be attributed to higher perfusion pressure, whereas in older patients, this positive effect is lost and leads to an increased glaucoma risk, most likely as a result of blood vessel alterations (atherosclerosis, increased resistance, rigidity, insufficient autoregulation) induced by arterial hypertension with disturbed oxygen and nutrition supply. These findings lead to the assumption of a U-shaped relationship between blood pressure and the progression of glaucoma.

The complex interaction of arterial blood pressure and intraocular pressure as determinants of ocular perfusion pressure could very well explain why some patients show a progress of visual field loss despite adequate control of intraocular pressure using locally applied therapies. Whereas a temporary increase in blood pressure could have a protective effect, this is most likely limited long term through the appearance of secondary chronic changes with impairment of vascular autoregulation and a loss of the ability to sustain a constant intensity of blood flow despite perfusion pressure alterations, e.g., by adapting vessel diameter. Interestingly, a compensatory proportional vasodilatation of the retinal blood vessels has been shown during intraocular pressure elevation in glaucoma patients. One can therefore easily imagine that the delicate balance of ocular perfusion pressure may be destabilized by arterial hypo- and hypertension especially in case of disturbed vascular autoregulation, reduced blood flow at the optic disc, and intraocular pressure-induced ischemic ganglion cell lesions as in patients with glaucoma. These complex interactions point to an important clinical dilemma, cardiovascular protection by controlling systemic hypertension vs. reducing the ocular perfusion pressure. Large prospective studies with particular focus on circadian systolic and diastolic blood pressure variation, dipping pattern, and the progression of glaucomatous optic neuropathy are required.

The methodological limitations of our meta-analysis warrant some discussion. None of the included studies was double-blinded and classification of stable or progressive visual field defects was carried out retrospectively in all patients. Although the assessment of visual fields within each study did not change during the study period, 2 different techniques (Goldmann perimeter and Humphrey 30–2) were employed. Three different 24-hour ABPM systems were used with differing measurement intervals of 20–30 minutes during the day and 30 minutes, respectively, during the night. Also, there was no uniform definition of daytime and nighttime with possible misinterpretation of the real nocturnal drop in arterial blood pressure. Nocturnal blood pressure dips have been shown to be sleep dependent rather than a function of the time of day or a circadian rhythm. The number of included patients and events is rather small precluding further analyses of unphysiological dipping patterns. Finally, since no reassessment of blood pressure measurements was performed, the conclusions are based on the observations of a single 24-hour period in the course of this chronic disease.

In summary, we found progressive visual field defects in patients with open-angle glaucoma or NTG to be associated with nocturnal blood pressure dips which in turn may lead to ocular perfusion pressure fluctuations with ischemic episodes at the optic nerve head. Thus, it is important to consider the fall in nocturnal blood pressure as a risk factor for progressive glaucomatous optic neuropathy despite adequate intraocular pressure control, especially in patients with concomitant cardiovascular risk factors or diseases and antihypertensive or vasoactive medication. The data published so far do not allow a differentiation between physiologic dipping and over-dipping as a risk factor for glaucomatous optic neuropathy. For the time being, as there are currently no large prospective studies to rely on, careful dose adjustment of blood pressure-lowering drugs together with repeated 24-hour ABPM seems reasonable in order to provide optimal cardiovascular as well as visual field protection.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


