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Peripheral vasospasm and nocturnal blood pressure dipping - two distinct risk factors for glaucomatous damage?

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PURPOSE. *To evaluate the relationship between peripheral vasospasm and circadian blood pressure rhythm in patients with primary open angle glaucoma (POAG).*
METHODS. *Nail-fold capillaroscopy, combined with a cold provocation test, and 24-hour blood pressure monitoring was carried out in 130 patients with POAG (M:F 58:72; mean age 60 ± 14 years), 99 with high-tension glaucoma (HTG) and 31 with normal-tension glaucoma (NTG). Peripheral blood flow parameters were compared for patients with a nocturnal fall in mean systemic blood pressure (MBP) of less than 10% (non-dippers), patients with a nighttime MBP fall of 10-20% (dippers), and patients with a nighttime MBP fall of more than 20% (over-dippers).*
RESULTS. *Patients with POAG showed a significantly lower blood flow velocity both at baseline ($p < 0.01$) and after cold provocation ($p < 0.02$) and a significantly higher percentage of cold-induced blood-flow standstill ($p < 0.0001$) in the nail-fold capillaroscopy than normal controls. The numbers of non-dippers (50), dippers (66) and over-dippers (14) did not differ between the HTG and NTG group. There were no significant differences between non-dippers, dippers, and over-dippers in peripheral blood flow parameters.*
CONCLUSIONS. *Our findings indicate that vasospasm and low blood pressure may be distinct risk factors for glaucomatous damage. It also appears that screening for vascular dysregulation and systemic hypotension should not be restricted to NTG patients alone. (Eur J Ophthalmol 2003; 13: 260-5)*

KEY WORDS. *Glaucoma, Vasospasm, Peripheral blood flow, Blood pressure, Hypotension*

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INTRODUCTION

Besides elevated intraocular pressure (IOP), an additional risk factor for glaucomatous optic neuropathy may be hemodynamic insufficiency, which is mainly due to vascular dysregulation and systemic hypotension (1-5). Both risk factors can lead to low perfusion in the eye and therefore predispose the optic nerve head to ischemia and reperfusion damage (1, 6-9).

In previous studies we reported a relationship between peripheral and ocular circulation (10, 11), and reduced capillary blood-cell velocity in the nail-fold capillaries after cold provocation in glaucoma patients (12). In the latter study, vascular dysregulations appeared to play a greater role in patients with normal-tension glaucoma (NTG) than in patients with high-tension glaucoma (HTG). A similar observation was made by O'Brien et al, who measured finger blood flow velocity in glaucoma patients by laser Doppler technique and found a significantly altered cold response in patients with NTG compared to HTG patients and normals (4).

Low systemic blood pressure (BP) as a risk factor in glaucoma has been described by various groups.

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It has been proposed that glaucoma patients with progression despite well controlled IOP, as well as NTG patients, have markedly lower systolic BP (SBP) during both day and night (7). Graham et al indicated that patients with large nocturnal falls in BP (dippers) were more commonly found among those whose visual field loss progressed despite normalized IOP (2, 3). Glaucoma patients with a marked drop in nocturnal systemic BP also seem to have altered retrobulbar blood flow parameters, suggesting that an abnormal systemic BP profile may be a manifestation of some kind of systemic vascular dysregulation relevant to the ocular circulation (13).

As a statistical relationship between systemic hypotension and the incidence of vasospastic disorders has been reported (14), a relationship between both risk factors would be possible, from a theoretical point of view (7). Hypothetically, peripheral vasospasm may reflect an exaggerated local counterregulation to systemic hypotension. However, in a preliminary pilot study in a small population, we could not detect a correlation between the two risk factors (15). We therefore analyzed the results of nail-fold capillaroscopy and 24-h BP monitoring of 130 patients with primary open angle glaucoma (POAG), 99 with HTG and 31 with NTG, who were referred to our clinic for vascular evaluation in the years 1996-2001.

MATERIAL AND METHODS

Patients

We enrolled in this study 130 patients with POAG (M:F 58:72; mean age 60 ± 14 years) who presented to the University Eye Clinic in Basel between 1996 and 2001. They were divided into a high-tension glaucoma (HTG) group and a normal-tension glaucoma (NTG) group, defining HTG as follows: 1) glaucomatous optic disc change with corresponding visual field abnormalities; 2) maximum IOP ≥ 22 mmHg; and 3) normal open angle. The diagnostic criteria for NTG were: 1) glaucomatous optic disc change and visual field defects as in POAG; 2) maximum IOP ≤ 21 mmHg with or without glaucoma treatment; 3) normal open angle; 4) no other underlying intra-cranial or sinus disease; 5) no history of excessive bleeding or shock.

Visual field examinations were done using the program G1 (16) on the Octopus Visual Field Analyzer (Interzeag, Schlieren, Switzerland). Glaucomatous visual field defects were assumed if a cluster of three points (except rim points) in at least one hemifield was reduced by 5 dB or more, including at least one point reduced by 10 dB or more; a cluster of two points were reduced by 10 dB or more; or three adjacent points on the nasal horizontal meridian differed by 5 dB or more from their mirror points on the opposite side of the meridian. Patients with poor reliability (false-positive or false-negative errors >25%) were excluded from the study.

Patients with a history of systemic diseases (e.g. diabetes mellitus, systemic arterial hypertension), ocular diseases other than POAG, previous ocular surgery, and patients who were taking systemic medication were carefully excluded from the study. All participants gave informed consent for the use of their clinical data in a scientific publication. The protocol was approved by the local Ethical Committee and followed the tenets of the Declaration of Helsinki.

Nail-fold capillaroscopy - local cold exposure test

Nail-fold capillaries were studied using an incident-light microscope attached to a television monitor. Technical details have been described elsewhere (17). For each subject one finger was randomly chosen for evaluation. The examination was done in a room with a constant temperature of 23°C and the subjects were acclimatized in the room for 30 minutes before investigation. After measuring baseline blood-cell velocity, cold CO_2 (temperature approximately –15°C) was directed to the fingertip for 60 s. Immediately afterwards, the second measurement was taken. In case of a cold-induced flow stop the duration of blood stand-still was measured by a video timer by averaging stand-still time in seconds of all the capillaries visible in the given microscopic field. In accordance with previous protocols (12, 18), persons with a blood-flow stand-still of at least 12 s in one or more capillaries were defined as vasospastic.

24-hour blood pressure monitoring

We used a Mobil-O-Graph (I.E.M. GmbH, Stolberg, Germany) for 24-h blood pressure monitoring. The de-

vice measures BP automatically, on the same principle as the conventional mercury sphygmomanometer, with a cuff and a microphone. Measurement intervals can be preselected, and BP is recorded on a data processor. The 24 hours were divided into two phases: phase I (from 8.00 a.m. to 10.00 p.m.) and phase II (from 10.00 p.m. to 8.00 a.m.), both with 30-min measurement intervals. If the device considers a reading faulty, it is programmed to reinflate a second time, thus avoiding missing data points. A print-out of the 24-h record was later recovered from the recording chip.

All readings were taken in the Basel University Eye Clinic, so patients were under comparable conditions during the measurement period. For each patient, the mean systolic (SBP) and diastolic blood pressure (DBP) for day-time (phase I) and night-time (phase II) were computed. From these readings, the day-time and night-time mean BP were recorded according to the formula: MBP = 2/3 x DBP + 1/3 x SBP. The nocturnal BP dip, i.e. the fall in BP during night-time expressed as a percentage of the average day-time reading, was determined for MBP in each patient. A measurement outlier rejection method, based on pulse pressure determination (SBP - DBP) was applied (2). A pulse pressure of <10 mmHg when SBP was <100 mmHg and less than 10% of the systolic reading when SBP was >100 mmHg were considered non-physiological and rejected. Diastolic BPs >160 mmHg were excluded. At least 80% of the programmed recordings were required for a diurnal curve to be considered in the study.

Patients were distributed in the following categories: 1) “non-dippers”: patients with a nighttime MBP fall less than 10%; 2) “dippers”: patients with a nighttime MBP fall between 10% and <20% ; and 3) “over-dippers”: patients with a nighttime MBP fall of >20%(19).

Statistical analysis

The statistical package StatView 4.5 (Abacus Concepts, Berkley, CA) was used. The significance of differences between the study groups was determined by analysis of variance (ANOVA). The chi-square statistic (2x2 and 2x3 tables, contingency tables) was used for frequency comparisons of nominal categorized variables. In the case of 2x2 contingency tables, significances were calculated using Fisher’s exact test. Correlation analysis was done using Spearman rank correlation. P values of less than 0.05 were considered statistically significant. Values are means ± standard deviation (SD).

RESULTS

Population characteristics

Out of the 130 patients with POAG, 99 presented with HTG and 31 with NTG. As regards age and sex, there were no significant differences between the HTG group (M:F 47:52; mean age 62 ± 14 years) and the NTG group (M:F 11:20; mean age 54 ± 13 years). Mean defect in automatic visual field testing (MD) was 6.1 ± 4.9, but differed significantly between the HTG (6.9 ± 5.0) and the NTG group (3.8 ± 4.0; p = 0.003). By definition, no patient was under any systemic medication; 57 patients (44%) were under treatment with topical beta-blockers, 22 (17%) local carbonic anhydrase inhibitors (CAI), 23 (18%) prostaglandin analogs, and 8 (6%) alpha-1 agonists.

Nail-fold capillaroscopy - local cold exposure test

Patients with POAG had a significantly lower blood flow velocity both at baseline (p<0.01) and after cold provocation (p<0.02) compared to our own normal values (12). There was also a significantly higher percentage of cold-induced blood-flow standstill in glaucoma patients (69%) than among the healthy controls (13%; χ^2 = 82.6; df = 1; p <0.0001). Interestingly, the HTG and NTG groups showed no significant differences in baseline flow, flow after cold provocation, and percentage of cold-induced blood-flow standstill. Likewise, there were no differences between males and females (Tab. I).

There was a tendency towards lower flow at baseline and after cold provocation and to a higher percentage of blood-flow standstill after cold provocation in patients using topical anti-glaucomatous medication, but this finding did not reach statistical significance.

24-hour blood pressure monitoring

Of the 130 patients, 50 were classified as non-dippers, 66 as dippers, and 14 as over-dippers. The per-

centage dip in MBP was significantly different between groups (p<0.001), by definition. Day-time SBP, DBP, and MBP did not differ in the three groups. Consequently, night-time SBP, DBP, and MBP were significantly different (p<0.004; see Tab. II).

The number of non-dippers, dippers and over-dippers did not differ for HTG and NTG. Also, there were no significant differences between the HTG and NTG group in diurnal SBP (123 ± 15 vs 122 ± 14 mmHg), DBP (79 ± 8 vs 80 ± 8 mmHg), and MBP (94 ± 9 vs 94 ± 8 mmHg) or nocturnal SBP (109 ± 15 vs 108 ± 15 mmHg), DBP (69 ± 8 vs 70 ± 8 mmHg), and MBP (82 ± 9 vs 82 ± 9 mmHg). Likewise, there were no real differences in capillary blood flow at baseline (0.51 ± 0.5 vs 0.53 ± 0.4 vs 0.49 ± 0.3 mm/s for the three subgroups) and after cold provocation (0.18 ± 0.3 vs 0.15 ± 0.2 vs 0.13 ± 0.1 mm/s) or in the percentage of cold-induced blood-flow standstill (68 vs 67 vs 77%).

No correlations were found between blood-flow parameters and diurnal and nocturnal SBP, DBP, and MBP. The three groups did not differ significantly in age and sex (Tab. II) or in their topical medication (Tab. III). In addition, the topical medications had no significant influence on diurnal and nocturnal SBP, DBP, and MBP.

TABLE I - NAIL-FOLD CAPILLAROSCOPY RESULTS AND MAIN CHARACTERISTICS OF PATIENTS WITH NORMAL-TENSION GLAUCOMA (NTG), HIGH-TENSION GLAUCOMA (HTG) AND NORMAL CONTROLS

	NTG	HTG	Controls (12)
Age (years)	54 ± 13	62 ± 14	59 ± 13
Females (%)	65	47	60
Baseline blood-flow velocity (mm/s)	0.56 ± 0.5	0.51 ± 0.4	0.71 ± 0.3
Blood-flow velocity after cooling (mm/s)	0.14 ± 0.2	0.17 ± 0.3	0.22 ± 0.1
Cold-induced blood-flow standstill (%)	68	69	13

DISCUSSION

We analyzed nail-fold capillaroscopy data and circadian BP measurements of 130 patients with POAG referred to our clinic for vascular evaluation in the years 1996-2001. Nail-fold capillaroscopy showed a reduced peripheral blood flow with an increase in reactivity to cold provocation in glaucoma patients. Nail-fold capillaroscopy showed capillary blood flow was reduced both at baseline and after local cooling, compared to our own normal values (12). In addition, a pathological cold-induced blood standstill was seen in 68% of the patients.

In a previous study (12) we found a significant difference between unselected patients with HTG and NTG, whereas the present study with a selected group of patients brought to light no significant differences. The different outcome of these studies may be par-

TABLE II - BLOOD PRESSURE IN THE STUDY POPULATION

	Non-Dippers	Dippers	Over-Dippers	p-value
Age (years)	60 ± 13	59 ± 15	66 ± 12	n.s.
Females (%)	54	42	50	n.s.
Day-time SBP (mmHg)	122 ± 14	123 ±16	126 ± 12	n.s.
Day-time DBP (mmHg)	78 ± 9	79 ± 8	81 ± 7	n.s.
Day-time MBP (mmHg)	93 ± 9	94 ± 10	96 ± 7	n.s.
Night-time SBP (mmHg)	115 ± 15	107 ± 14	99 ± 10	0.0003
Night-time DBP (mmHg)	74 ± 7	67 ± 6	60 ± 6	< 0.0001
Night-time MBP (mmHg)	88 ± 8	80 ± 8	73 ± 6	< 0.0001
Dip in MBP (%)	5.5 ± 3.3	14.6 ± 2.5	23.9 ± 3.4	< 0.004

SBP= Systolic blood pressure; DBP= Diastolic blood pressure; MBP= Mean blood pressure

TABLE III - PATIENTS USING TOPICAL MEDICATION (number and percentage)

	Non-Dippers (n = 50)	Dippers (n = 66)	Over-Dippers (n = 14)	p-value
Topical beta-blockers	18 (36%)	34 (52%)	5 (36%)	0.227
Local CAI	8 (16%)	11 (17%)	3 (21%)	0.827
Prostaglandin analogs	9 (18%)	13 (26%)	1 (7%)	0.101
Alpha-1 agonists	1 (2%)	7 (11%)	0 (0%)	0.586

CAI= Carbonic anhydrase inhibitors

tially explained by different definitions of HTG and NTG. In 1991, when the earlier study was done, HTG was defined as "optic nerve head excavation and visual field defects with an untreated mean of IOP greater than 24 mmHg at repeated measurements" (12). NTG was defined as "typical optic nerve head excavation and visual field defects with an untreated mean IOP of less than 21 mmHg and a peak IOP of less than 25 mmHg based on several diurnal pressure curves" (12), leaving a gray area between 21 and 24 mmHg. Nowadays, patients who present any peak above 21 mmHg would no longer be considered NTG cases. Assuming there is no abrupt change in pathophysiology between NTG and HTG (5), the results of the present study are not that surprising. However, the high percentage of vascular dysregulation in our HTG patients may not be typical of the average HTG population. Patients included, with NTG or HTG, were referred by their ophthalmologists for investigation, including vascular examination. A selection bias is therefore likely.

Vasospasm is the result of a complex and only partly understood interaction of the endothelium, perivascular nerves and a variety of vasoactive substances. Theoretically, peripheral vasospasm may also reflect an exaggerated local counterregulation to systemic hypotension (7). However, in this study, we could not detect a direct relationship between peripheral blood flow and low BP. According to the 24-h BP readings, patients with a nighttime MBP fall of less than 10% were classified as non-dippers, those with a nighttime MBP fall between 10% and <20% as dippers, and those with a nighttime MBP fall of >20% as over-dippers. However, we found no real differences between these three classes either in capillary blood flow at baseline and after cold provocation or in the percentage of cold-induced blood-flow standstill. Moreover, the numbers of non-dippers, dippers and over-dippers did not differ in the HTG and NTG groups. These findings confirm and extend the results of our pilot study (15), indicating that vasospasm and low BP may be additive but distinct risk factors for glaucomatous damage.

However, our study has a further limitation that calls for comment. Even though patients under systemic medication were carefully excluded, most of our patients used topical anti-glaucomatous therapy. It cannot be excluded, for instance, that topical beta-blockers induce a systemic vasospastic response (20), and the alpha-1 agonist brimonidine has been reported to cause a slight reduction in SBP during recovery from exercise and 4 hours after instillation (21). Even though we found no difference between patients under different types of local therapy as regards peripheral blood-flow and BP, we cannot entirely rule out a drug effect.

Taken together, our findings indicate that vasospasm and low BP may damage the optic nerve head in a distinct fashion. Moreover, the results teach us that screening for peripheral vascular dysregulation should not be restricted to patients with NTG alone.

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