Retrobulbar Blood Flow in Glaucoma Patients With Nocturnal Over-Dipping in Systemic Blood Pressure

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• PURPOSE: **To evaluate the relationship between the circadian blood pressure rhythm and the retrobulbar blood flow in glaucoma patients.**
• DESIGN: **Cross-sectional study.**
• METHODS: **Circadian blood pressure measurements and color Doppler imaging (CDI) in the ophthalmic artery as well as the central retinal artery of one randomly selected eye were obtained in 193 primary open-angle glaucoma patients. CDI parameters were compared by means of analysis of covariance between patients with a nocturnal decrease in mean systemic blood pressure (MBP) below 20% of the average daytime MBP (over-dippers), patients with a decrease between 10% to 20% (dippers), and patients with a decrease of less than 10% (nondippers), using age, intraocular pressure (IOP), and MBP during color Doppler measurement as covariates.**
• RESULTS: **An analysis of covariance disclosed, after correcting for age, IOP, and MBP during color Doppler imaging, a significantly lower EDV ($P = .0096$) and a significantly higher RI ($P = .033$) in the central artery of over-dipping glaucoma patients compared with nondippers or dippers. This effect seemed independent of the use of vasoactive drugs.**
• CONCLUSIONS: **Glaucoma patients with a marked drop in nocturnal systemic blood pressure seem to have altered retrobulbar blood flow parameters, suggesting that an abnormal systemic blood pressure profile may be the manifestation of some kind of systemic vascular dysregulation relevant for the ocular circulation. (Am J Ophthalmol 2001;132:641–647. © 2001 by Elsevier Science Inc. All rights reserved.)**

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THE SUBSTANTIAL NUMBER OF CASES WITH OPEN-angle glaucoma continuing to progress in damage despite therapeutically lowered intraocular pressure (IOP) as well as the existence of patients developing glaucoma with normal IOP has stimulated the search for risk factors other then increased IOP. In addition to neurotoxicity, reduced ocular blood flow,[1–5] ocular vascular dysregulation,[6–8] and systemic blood pressure alterations[9–15] have been advocated as possible contributing factors in the etiology of glaucoma. An exaggerated nocturnal blood pressure "dip" has been the most frequently reported peculiarity in systemic blood pressure in glaucoma patients.[9,11,15]

Ambulatory monitoring studies have documented a reproducible circadian rhythm for blood pressure, characterized by a nocturnal fall.[16] This nocturnal fall in systemic blood pressure does not change with age.[17] Patients with the typical nocturnal decrease in blood pressure are termed dippers, whereas patients in whom the nocturnal decrease in blood pressure is absent or blunted are termed nondippers.[18] Left ventricular hypertrophy and stroke tend to be more frequent in patients with essential hypertension whose circadian blood pressure profile is flattened (nondippers), possibly because these patients suffer a longer duration of exposure to high blood pressure levels over the 24 hours.[18] Furthermore, the early morning surge in blood pressure is thought to represent a moment of increased risk for acute myocardial infarction, sudden cardiac death, and stroke.[19,20] Finally, excessive lowering (over-dipping) of blood pressure at night (whether naturally or due to the use of antihypertensive medications) can result in cardiac ischemia,[21] silent cerebrovascular damage,[22] and anterior ischemic optic neuropathy.[23]

An increased prevalence of a low blood pressure level and of over-dipping has been described in glaucoma patients.[9–11,15] A vascular dysregulation has been advocated as a further possible contributing factor in the etiology of glaucoma.[8] Because patients with systemic vascular dysregulation often have a low systemic blood pressure,[7,8,24] it may be hypothesized that an abnormal

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circadian systemic blood pressure profile is the manifestation of some sort of vascular dysregulation, which, in turn, could influence retrobulbar blood flow. Consequently, we sought to analyze the relationship between nocturnal decrease in blood pressure and retrobulbar blood flow in glaucoma patients.

PATIENTS AND METHODS

WE EVALUATED 193 CONSECUTIVE PATIENTS (115 WOMEN and 78 men) with primary open-angle glaucoma (mean ±SD age: 67.34 ± 14.54 years) in a cross-sectional study during the period between 1996 to 1999. All procedures conformed to the Declaration of Helsinki. Patients with closed iridocorneal angles, evidence of secondary glaucoma, pseudoexfoliation, pigmentary dispersion, a history of intraocular surgery, any form of retinal or neuroophthalmologic disease that could result in visual field defects, or with a history of chronic systemic disease, especially diabetes mellitus, systemic hypertension, or occlusive vascular disorders, were not included in this study. All patients had typical glaucomatous disk and visual field damage. After approval by the ethical committee, informed consent for the use of their clinical data in a scientific publication was obtained from each patient. The glaucoma patients underwent a diurnal IOP curve (6.00 AM, before arising from bed, 8.00 AM, 11.00 AM, 4.00 PM, and 10.00 PM), showing no readings above 21 mm Hg among the selected patients. Visual field examinations were performed with the program G1[25] on the Octopus Visual Field Analyzer (Interzeag, Schlieren, Switzerland). The criteria for glaucomatous visual field defects were a cluster of three points (except rim points) in at least one hemifield reduced by 5 dB or greater, and including at least one point reduced by 10 dB or greater; a cluster of two points reduced by 10 dB or greater; or three adjacent points on the nasal horizontal meridian that differed by 5 dB or greater from their mirror points on the opposite side of the meridian. Patients with poor visual field reliability (false-positive or false-negative errors exceeding 25%) were not enrolled. Enrolled patients had 3 mm or larger pupil diameters when their fields were plotted.

All patients had a 24-hour blood pressure monitoring with an automated portable blood pressure measuring device (Mobil-O-Graph, I.E.M. GmbH, Stolberg, Germany). This device measures the blood pressure automatically, on the same principle as the conventional mercury sphygmomanometer, with a cuff and a microphone. The interval between the measurements can be preselected, and BP readings are recorded on a data processor. We divided the 24 hours into 2 phases: in phase I (from 8.00 AM to 10.00 PM) as well as in phase II (from 10.00 PM to 8.00 AM) the measurement intervals were 30 minutes. If a reading is considered faulty by the device, it is programmed to reinflate a second time, which helps to avoid missing data points. A printout of the 24-hour record was later recovered from the recording chip. Recordings were performed in the hospital, so that the patients were all under comparable conditions during the 24-hour blood pressure measurement period. The mean systolic (SBP), and diastolic blood pressure (DBP) for daytime (phase I), and nighttime (phase II) were computed for each patient. From these readings, the daytime and nighttime mean blood pressure (MBP) levels were calculated according to the formula: $MBP = 2/3 \times DBP + 1/3 \times SBP$. The blood pressure dip, representing the fall in blood pressure during night-time expressed as a percentage of the average daytime reading level, was determined for MBP in each patient.

A measurement outlier rejection method, based on pulse pressure determination (calculated as: SBP–DBP) was applied.[15] A pulse pressure of less than 10 mm Hg when the SBP was below 100 mm Hg and of less than 10% of the systolic reading when the SBP was larger than 100 mm Hg were considered nonphysiologic and rejected. Diastolic blood pressure values greater than 160 mm Hg were also excluded. Furthermore, at least 80% of the programmed recordings were requested for a diurnal curve to be considered in the present analysis.

Patients were divided into three groups termed "nondippers," "dippers," and "over-dippers," based on the criteria that the daytime MBP fell by less than 10%, between 10% and 20%, and more than 20% respectively, during the night.[21] According to this classification, our pool of primary open-angle glaucoma patients comprised 69 nondippers, 76 dippers, and 48 over-dippers.

All the glaucoma patients underwent blood flow velocity assessment of their ophthalmic artery (OA) and their central retinal artery (CRA) by means of color Doppler imaging (CDI). Color Doppler imaging is an ultrasound technique that combines b-scan gray-scale imaging of tissue structure with colored representation of blood movement toward or away from the sensor based on Doppler shifted frequencies and pulsed-Doppler measurement of blood flow velocities. All retrobulbar CDI examinations were performed by the same experienced sonographer, who was unaware of the patients' clinical status. Blood-flow velocity was measured by means of a color Doppler imaging device (Siemens Albis AG, Zülrich, Switzerland) using a 7.5-MHz linear phase-array transducer. Samples of pulsed-Doppler signal from within a 0.2×0.2 mm sample volume were analyzed to calculate blood flow velocities. The transducer was applied gently to the closed eyelid using a coupling gel, and care was taken to avoid applying any pressure to the eye. During the examination, patients were in the supine position, with the upper body tilted upward at about a 30-degree angle. The various vessels were examined following a standard protocol, as described previously.[26,27] In each vessel, peak-systolic velocity (PSV), defined as the highest velocity of blood flow during the systolic phase of the cardiac cycle, the end-diastolic

TABLE 1. Characteristics (Mean ± SD) of the Study Groups

	Nondippers (69 patients)	Dippers (76 patients)	Over-dippers (48 patients)	*P Value
Age	67.00 ± 14.02	63.46 ± 15.65	68.77 ± 11.13	0.099
MD	8.27 ± 6.56	8.86 ± 6.62	10.46 ± 6.66	0.279
Average diurnal IOP	16.95 ± 3.33	17.45 ± 3.64	17.08 ± 3.51	0.700
SBP during CDI	124.24 ± 16.41	126.42 ± 18.01	133.77 ± 19.45	0.016
DBP during CDI	78.62 ± 9.56	82.11 ± 9.29	83.23 ± 10.42	0.023
MBP during CDI	93.83 ± 10.82	96.88 ± 10.10	100.08 ± 12.26	0.013
Day-time SBP	124.24 ± 15.54	126.01 ± 18.33	133.23 ± 18.50	0.019
Day-time DBP	79.16 ± 9.97	82.59 ± 10.17	83.75 ± 11.73	0.043
Day-time MBP	94.19 ± 10.67	97.06 ± 11.45	100.24 ± 12.45	0.020
Night-time SBP	116.75 ± 14.80	110.08 ± 16.92	99.03 ± 13.58	<0.001**
Night-time DBP	75.36 ± 10.21	69.97 ± 9.01	59.91 ± 8.17	<0.001**
Night-time MBP	89.16 ± 10.73	83.34 ± 10.28	72.95 ± 8.48	<0.001**
% Dip in MBP	5.35 ± 3.12	14.16 ± 2.56	26.91 ± 5.88	<0.001**

MD = mean defect in automated visual field testing; IOP = intraocular pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; CDI = color Doppler imaging; % dip in mean blood pressure = nocturnal fall in systemic blood pressure in percent of average day-time readings.

*P values prior to correction for multiple comparisons.

**P values significant after correction for multiple comparisons.

velocity (EDV), defined as the velocity of blood flow at the end of the diastolic phase of the cardiac cycle, and the resistivity index (RI) (RI = [PSV–EDV]/PSV) were computed in every glaucoma patient. The proximal and distal portions of the vessels were imaged as well as possible to determine the Doppler flow angle. The OA was traced approximately 10 to 15 mm behind the globe, nasal to the optic nerve after their crossing. The CRA was depicted within the anterior part of the optic nerve shadow, approximately 2 to 3 mm behind the surface of the optic disk.

Throughout the entire experimental procedure, systemic blood pressure and heart rate were recorded at three-minute intervals by means of an automatic device (Mobil-O-Graph, I.E.M. GmbH, Stolberg, Germany). Patients with relevant variations in blood pressure during the examination were excluded. SBP and DBP were measured and MBP was calculated according to the formula described above.

The BP monitoring, the diurnal IOP curve, and the CDI measurements were obtained during the same 24-hour interval for each patient. One eye/patient was randomly selected for statistical analysis.

Sample size calculations were based on an earlier study where, compared with normals, a 27.5% lower EDV was found in the CRA of progressive glaucoma patients.[8] Based on the average standard deviations found in the latter study for each of the six retrobulbar blood flow parameters analyzed in the present investigation, 43 individuals needed to be included into each group to obtain a difference of 25% between two groups in any of the analyzed parameters, with a power of 90%, and a probability of an alpha error of 5%. Differences between the three study groups in age, average diurnal IOP, blood pressure during CDI measurements, and 24-hour blood pressure were determined by means of analysis of variance (ANOVA). Differences between the three study groups in retrobulbar hemodynamics (PSV, EDV, and RI measured in the retrobulbar vessels) were determined by means of analysis of covariance (ANCOVA), with age, average diurnal IOP, and MBP during CDI measurements as covariates. The differences in number of patients taking systemic and topical medication were assessed by means of a two-tailed χ^2 test in 2×3 contingency table calculations. The influence of topical betablockers, dorzolamide, prostaglandin analogs, systemic acetazolamide, or systemic calcium channel-blockers on retrobulbar hemodynamics (PSV, EDV, and RI measured in the retrobulbar vessels) was determined by means of analysis of covariance models with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates.

RESULTS

THE CHARACTERISTICS OF THE STUDY PATIENTS AND *P*-values before correction for multiple comparison are given in Table 1 (the latter *p*-values are provided here for the sake of completeness). There were no statistically significant differences between groups in age, visual field defect, and average diurnal IOP (Table 1). Although significant differences were observed in systemic blood pressure (Table 1), blood pressure during the CDI procedure, or average day-time blood pressure levels, did not differ between groups after correcting for multiple comparisons. Percent-

TABLE 2. Retrobulbar Hemodynamic Parameters in the Three Study Groups (Mean ± SD)

	Nondippers	Dippers	Over-dippers	*F* Value	**P* Value
OA PSV	36.84 ± 12.07	35.39 ± 8.18	36.94 ± 8.80	0.78	0.46
OA EDV	7.22 ± 2.73	7.57 ± 2.51	7.76 ± 2.63	0.53	0.59
OA RI	0.80 ± 0.05	0.78 ± 0.06	0.78 ± 0.07	0.78	0.46
CRA PSV	9.47 ± 2.86	9.01 ± 2.29	8.67 ± 2.60	2.11	0.12
CRA EDV	2.32 ± 0.79	2.16 ± 0.71	1.88 ± 0.58	7.49	0.0008**
CRA RI	0.75 ± 0.06	0.76 ± 0.05	0.79 ± 0.05	6.02	0.003**

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

**P* values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates.

***P* values significant after correction for multiple comparisons.

age dip in MBP was different by definition ($P < .001$); and, consequently, because average daytime blood pressure levels did not differ between groups, nighttime SBP, DBP, and MBP were statistically significantly different between the three study groups ($P < .001$ for all three parameters).

The retrobulbar hemodynamic parameters (mean ± SD) are outlined in Table 2. The ANCOVA, with age, average diurnal IOP, and MBP during CDI measurements as covariates, showed differences between the three groups for EDV and RI measured in the CRA (Table 2). After applying Holm's correction for multiple comparisons, the same differences were still statistically significant. Post-hoc comparisons (Scheffé test) disclosed a significant difference between over-dippers and nondippers ($P = .002$) and a borderline significant difference between over-dippers and dippers ($P = .055$) for EDV measured in the CRA and between over-dippers and nondippers ($P = .003$) and between over-dippers and dippers ($P = .037$) for RI measured in the CRA (Figure 1).

The number and percentage of patients receiving systemic and topical medication during the test period are outlined in Table 3. There were no statistically significant differences between the three study groups with regard to the use of topical or systemic drugs.

The influence of topical beta-blockers, dorzolamide, prostaglandin analogs, systemic acetazolamide, or systemic calcium channel-blockers on retrobulbar hemodynamics are outlined in the Tables 4–8. None of the drugs had a significant effect on the latter parameters after correcting for multiple comparisons.

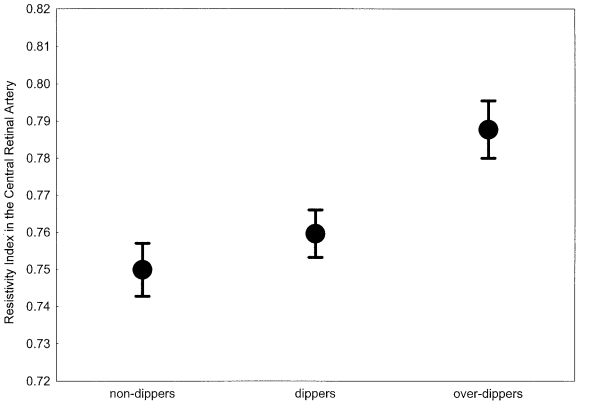

FIGURE 1. After correcting for age, average diurnal intraocular pressure, and mean blood pressure during color Doppler measurements, resistivity index in the central retinal artery (mean ± SEM) was significantly different ($P = .015$ after correction for multiple comparisons) between nondippers (69 patients), normal dippers (76 patients), and over-dippers (48 patients), as assessed by means of color Doppler imaging. Post hoc comparisons (Scheffé test) disclosed a significantly higher resistivity index in over-dippers, compared with nondippers ($P = .003$) or to dippers ($P = .037$).

DISCUSSION

CIRCADIAN BLOOD PRESSURE MEASUREMENTS AND COLOR Doppler imaging in the ophthalmic artery and the central retinal artery of one randomly selected eye were obtained in 193 primary open-angle glaucoma patients. After correcting for age, intraocular pressure, and mean blood pressure during retrobulbar blood flow measurements, a lower end diastolic velocity and a higher resistivity index were found in the central retinal artery of glaucoma patients showing a decrease in mean blood pressure during the night of more than 20% from the average daytime mean blood pressure (over-dippers), when compared with glaucoma patients with a decrease not exceeding 20% (dippers and nondippers). This effect seemed independent of the use of vasoactive drugs. These results suggest that patients with a marked nocturnal drop in systemic blood pressure may harbor some kind of vascular dysregulation leading to alterations in the retinal circulation.

Besides a flattened circadian rhythm of blood pressure and the early morning surge in blood pressure, both

TABLE 3. Patients (Number and %) Receiving Systemic and/or Topical Medication

	Nondippers	Dippers	Over-dippers	*p Value
Topical beta-blockers	34 (49.27%)	37 (48.68%)	29 (60.42%)	0.387
Dorzolamide	13 (18.84%)	18 (23.68%)	11 (21.92%)	0.760
Prostaglandin	7 (10.15%)	6 (7.89%)	8 (16.67%)	0.302
Acetazolamide	6 (8.69%)	2 (2.63%)	4 (8.33%)	0.250
Calcium channel-blockers	6 (8.69%)	5 (6.58%)	3 (6.25%)	0.845

*P values were assessed by means of a two-tailed chi-square test in 2 × 3 contingency table calculations and no correction for multiple comparisons was applied.

TABLE 4. Influence of Beta-blockers on Retrobulbar Hemodynamic Parameters (Mean ± SD)

	Not Treated With Beta-blockers (93 patients)	Treated With Beta-blockers (100 patients)	*p Value
OA PSV	35.97 ± 9.20	36.53 ± 10.77	0.80
OA EDV	7.57 ± 2.64	7.40 ± 2.69	0.63
OA RI	0.78 ± 0.06	0.79 ± 0.07	0.39
CRA PSV	8.88 ± 2.44	9.32 ± 2.77	0.53
CRA EDV	2.21 ± 0.76	2.10 ± 0.72	0.22
CRA RI	0.75 ± 0.06	0.77 ± 0.06	0.037

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

*P values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates (none of the models was significant after correcting for multiple comparisons).

TABLE 5. Influence of Dorzolamide on Retrobulbar Hemodynamic Parameters (Mean ± SD)

	Not Treated With Dorzolamide (151 patients)	Treated With Dorzolamide (42 patients)	*p Value
OA PSV	35.99 ± 7.80	36.06 ± 5.86	0.54
OA EDV	7.51 ± 2.29	7.90 ± 2.18	0.41
OA RI	0.79 ± 0.06	0.78 ± 0.06	0.85
CRA PSV	9.06 ± 2.60	8.12 ± 1.77	0.18
CRA EDV	2.13 ± 0.72	1.99 ± 0.45	0.28
CRA RI	0.77 ± 0.05	0.75 ± 0.05	0.46

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

*P values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates.

associated with pernicious consequences such as cerebrovascular damage and cardiovascular events,[18–20,28] evidence suggests that a marked nocturnal fall of blood pressure (extreme dipping) may lead to silent cerebrovascular damage,[22,29] or myocardial infarction.[30] The pathogenic significance of extreme dipping might be a reduction in blood pressure at night beyond the lower limit of blood flow autoregulation. It is further possible that a greater blood pressure variability in extreme dippers may be the manifestation of some sort of vascular dysregulation leading to extreme variability in local blood flow, a hallmark of altered autoregulation, which, in turn, might hasten ischemic tissue damage. Although the role of systemic blood pressure in glaucomatous damage remains undefined, with systemic hypertension and hypotension being implicated in different studies,[24] it has been reported that not only the physiologic nocturnal blood pressure dip may be exaggerated in some glaucoma patients, but that the long-term outcome of the glaucomatous disease might be worse among glaucoma patients with lower nocturnal blood pressure variables, suggesting that the exaggerated nocturnal reduction in blood pressure may be a risk factor in glaucoma.[31]

The present study did neither evaluate the preponderance of excessive nocturnal blood pressure decrease in glaucoma patients, nor did it indicate a lowering of local blood flow during episodes of low blood pressure. It simply demonstrated that, in the presence of a circadian blood pressure profile with an excessive nocturnal blood pressure reduction, retrobulbar blood flow parameters may be altered, the latter situation being reportedly related to progressive glaucomatous damage.[2,32,33] This study should not be interpreted as a demonstration of a reduction in blood flow at nighttime beyond the lower limit of blood flow autoregulation, but rather as an indication that nocturnal blood pressure over-dipping may be the manifestation of a vascular dysregulation, which has already been suggested to represent a risk factor in glaucoma.[8] This contention is supported, at least partly, by the observation that therapeutic increase in systemic blood pressure may partly improve systemic vascular dysregulation.[34]

TABLE 6. Influence of Prostaglandin Analogs on Retrobulbar Hemodynamic Parameters (Mean ± SD)

	Not Treated With Prostaglandin Analogs (172 patients)	Treated With Prostaglandin Analogs (21 patients)	*P Value
OA PSV	36.67 ± 7.06	32.35 ± 7.32	0.073
OA EDV	7.73 ± 2.30	7.04 ± 1.95	0.33
OA RI	0.79 ± 0.06	0.77 ± 0.05	0.35
CRA PSV	9.02 ± 2.39	7.46 ± 2.09	0.036
CRA EDV	2.12 ± 0.65	1.92 ± 0.61	0.41
CRA RI	0.77 ± 0.05	0.74 ± 0.04	0.070

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

*P values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates (none of the models was significant after correcting for multiple comparisons).

SD = standard deviation.

TABLE 7. Influence of Acetazolamide on Retrobulbar Hemodynamic Parameters (Mean ± SD)

	Not Treated With Acetazolamide (181 patients)	Treated With Acetazolamide (12 patients)	*P Value
OA PSV	36.30 ± 10.10	35.96 ± 10.08	0.77
OA EDV	7.52 ± 2.68	6.88 ± 2.43	0.24
OA RI	0.79 ± 0.06	0.80 ± 0.06	0.32
CRA PSV	9.10 ± 2.53	9.48 ± 3.92	0.69
CRA EDV	2.17 ± 0.74	1.86 ± 0.68	0.14
CRA RI	0.76 ± 0.06	0.79 ± 0.08	0.10

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

*P values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates.

SD = standard deviation.

TABLE 8. Influence of Systemic Calcium Channel-blockers on Retrobulbar Hemodynamic Parameters (Mean ± SD)

	Not Treated With Calcium Channel Blockers (179 patients)	Treated With Calcium Channel Blockers (14 patients)	*P Value
OA PSV	36.36 ± 10.12	35.26 ± 9.78	0.79
OA EDV	7.47 ± 2.59	7.55 ± 3.51	0.96
OA RI	0.79 ± 0.06	0.79 ± 0.06	0.67
CRA PSV	9.23 ± 2.61	7.88 ± 2.62	0.09
CRA EDV	2.17 ± 0.74	1.91 ± 0.71	0.14
CRA RI	0.76 ± 0.06	0.77 ± 0.05	0.64

OA = ophthalmic artery; CRA = central retinal artery; PVS = peak systolic velocity; EDV = end diastolic velocity; RI = resistivity index.

*P values (prior to correction for multiple comparisons) were calculated by means of an analysis of covariance with age, intraocular pressure, and mean blood pressure measured during color Doppler imaging as covariates.

SD = standard deviation.

It is not clear how much the present findings may be imputed to the use of vasoactive drugs. The statistical analysis applied suggests that the drugs used by some patients in the current study may not have influenced the presented findings. None of the drugs had a significant effect on retrobulbar blood flow parameters, and the three study groups did not differ with regard to the use of the same drugs. A drug effect however, cannot be entirely ruled out based on such an analysis. Larger studies with untreated glaucoma patients may provide an answer to the question whether the observed alteration in retrobulbar blood flow in patients with an exaggerated nocturnal reduction in systemic blood pressure is somehow related to the treatment of glaucoma itself, or whether it is a genuine condition in these patients. Finally, intraocular pressure was not assessed just before color Doppler imaging and, depending on the variability in intraocular pressure in individual patients, correcting for the average diurnal intraocular pressure during statistical analysis might not have been sufficient. However, because none of the patients had intraocular pressure readings above 21 mm Hg, the inaccuracy introduced by this omission may, supposedly, be minimal.

The clinical relevance of the present study and how the observed relative decrease in local blood flow may be related to the glaucomatous damage is not clear. Retrobulbar blood flow parameters were evaluated by means of color Doppler imaging. Color Doppler imaging, however, provides only an average estimate of blood flow velocity. In a situation where blood flow is only reduced to a distinct region of the evaluated vascular bed, as has been advocated to occur in vascular dysregulation,[6] only a relative blood flow alteration will be authenticated with relatively crude methods such as color Doppler imaging. Consequently, although only a moderate decrease in blood flow was measured, it must be expected that in a tissue with moderate ischemia, microinhomogenities in flow may exist, leading to preferential perfusion of some microvessels to the exclusion of others, possibly hastening very local damage.[35] The existence of such mechanisms influencing the injury process in glaucoma remains to be clarified.

In conclusion, the present study suggests that, independently of age, average diurnal intraocular pressure, and mean blood pressure during retrobulbar blood flow measurements, glaucoma patients with an exaggerated nocturnal reduction in systemic blood pressure have an altered retrobulbar blood flow outside the period of blood pressure reduction, possibly related to a general vascular dysregulation.

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