

SCIENTIFIC REPORT

Effect of nimodipine on ocular blood flow and colour contrast sensitivity in patients with normal tension glaucoma

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Aim: To investigate the effects of oral nimodipine on ocular haemodynamic parameters and colour contrast sensitivity in patients with normal tension glaucoma (NTG).

Design: The study was performed in a randomised, placebo controlled, double masked, crossover design.

Participants: Nimodipine (60 mg) or placebo was administered to 14 consecutive NTG patients.

Methods: The effects of oral nimodipine or placebo on ocular and systemic haemodynamic parameters and colour contrast sensitivity along the tritan axis were studied two hours after administration. Optic nerve head blood flow (ONHBF) and choroidal blood flow (CHBF) were assessed with laser Doppler flowmetry. Ocular fundus pulsation amplitude (FPA) was measured with laser interferometry. Colour contrast sensitivity (CCS) was determined along the tritan colour axis.

Main outcome measures: ONHBF, CHBF, FPA, intraocular pressure and CCS were assessed in patients with NTG.

Results: Mean ocular FPA increased by 14% (SD 14%) ($p=0.0008$), ONHBF by 18% (SD 16%) ($p=0.0031$), and CHBF by 12% (SD 14%) ($p<0.001$) after administration of nimodipine. Nimodipine also decreased the threshold of colour contrast sensitivity along the tritan colour axis ($-14%$ (SD 12%); $p=0.048$). However, individual changes in FPA, ONHBF, or CHBF were not correlated with changes in threshold of CCS along the tritan colour axis.

Conclusions: The results indicate that nimodipine increases ONH and choroidal blood flow in NTG patients and improves CCS. The latter effect does not, however, seem to be a direct consequence of the blood flow improvement.

controlled trial in patients with NTG. For the assessment of optic nerve head and choroidal blood flow we used laser Doppler flowmetry (LDF). In addition, pulsatile choroidal blood flow was assessed with laser interferometric measurement of fundus pulsation amplitude (FPA).

PATIENTS AND METHODS

Subjects

After approval from the Ethics Committee of Vienna University School of Medicine and written informed consent obtained, 14 consecutive NTG glaucoma patients (mean age 57 (SD 13) years) were included in this study. Inclusion criteria were normal tension glaucoma defined as pathological optic disc appearance and pathological visual field as evidenced from automated perimetry (Humphrey Field analyser program 30–2) as assessed on the study day. Pathological visual field testing was defined according to the criteria of the Ocular Hypertension Treatment Study:¹⁸ glaucoma hemifield test outside normal and/or a CPSD with $p<0.05$. All patients were experienced in visual field testing having performed at least three tests in total and one test within the last 6 months before the start of the study. Visual field eligibility criteria were $<33%$ false positives, $<33%$ false negatives, and $<33%$ fixation losses. Vertical cup:disc ratio, horizontal cup:disc ratio, and optic disc area were 0.73 (SD 0.07), 0.76 (SD 0.08), and 2.62 (SD 0.40), respectively. Further inclusion criteria were visual acuity better than 20/30 and ametropia <3 diopters. None of the included patients had a history of IOP >21 mm Hg without antiglaucoma therapy. This was verified by at least one diurnal tension curve, which was recorded no more than one year before inclusion in the present study. A washout period of three weeks was scheduled for patients with antiglaucomatous therapy or with intake of magnesium or ginkgo biloba preparations. Patients were excluded if they had a history of glaucoma surgery or any sign of another relevant retinal eye disease. Patients with uncontrolled systemic hypertension of more than 150/90 mm Hg or medication with systemic calcium channel blockers were also excluded from the trial. All patients underwent a standardised cold-warm challenge test using infrared telethermography to quantify Raynaud's phenomenon.

Study design

The study followed a randomised, placebo controlled, double masked, crossover design. On the first study day the NTG patients were randomised (1:1) to receive either 60 mg nimodipine (Nimotop, 30 mg tablets, Bayer, Vienna, Austria, two tablets orally, single dose) or two placebo tablets in a double masked fashion. In order to ensure double masked

Abbreviations: CHBF, choroidal blood flow; DSPS, Doppler shift power spectrum; ET-1, endothelin-1; FPA, fundus pulsation amplitude; IOP, intraocular pressure; LDF, laser Doppler flowmetry; NTG, normal tension glaucoma; ONHBF, optic nerve head blood flow; RBCs, red blood cells

Calcium channel blockers have been proposed for the treatment of normal tension glaucoma (NTG) based on their beneficial short-term effects on visual fields and colour contrast sensitivity.^{1–7} Nevertheless, to date calcium channel blockers are not generally accepted as a therapeutic approach for the prevention of visual field loss in NTG patients, because there is a lack of long term clinical outcome data from randomised placebo controlled studies. In addition, the mechanisms underlying the effects of calcium channel blockers on visual fields and colour contrast sensitivity are unknown.

A variety of studies have shown that calcium channel blockers may improve ocular blood flow in healthy volunteers and patients with glaucoma.^{8–15} Hence, one may hypothesise that improvement in visual function may be closely related to the effects of calcium channel blockers on visual fields. Evidence for this hypothesis has been found in some,^{6, 11} but not in all studies.^{7, 16, 17} We set out to investigate the relation between nimodipine induced changes in colour contrast sensitivity and ocular blood flow in a randomised placebo

conditions, placebo tablets were identical in appearance and taste to the nimodipine tablets. On the second study day, each patient received the study medication (nimodipine or placebo) that was not administered on the first study day. The washout period between study days was at least five days.

All patients were asked to abstain from beverages containing xanthine derivatives for at least 12 hours before the study days. On the study days a resting period of at least 20 minutes was scheduled to ensure stable haemodynamic conditions, which was verified by repeated blood pressure measurements. Thereafter baseline measurements of fundus pulsations, LDF, colour contrast sensitivity, intraocular pressure, and systemic haemodynamics were performed. After completion of these measurements subjects received either nimodipine or placebo. Two hours later all measurements were performed again. This time schedule was based on the pharmacokinetics of nimodipine.¹⁹

Methods

Systemic haemodynamics

Systolic, diastolic, and mean blood pressures (SBP, DBP, MAP) were measured on the upper arm by an automated oscillometric device. Pulse rate (PR) was automatically recorded from a finger pulse oxymetric device (HP-CMS patient monitor, Hewlett Packard, Palo Alto, CA, USA).

Laser Doppler flowmetry

Choroidal and ONHBF were assessed with LDF according to Riva *et al* (Oculix 4000, Oculix Sarl, Arbaz, Switzerland).^{20, 21} The principles of LDF have been described in detail by Bonner and Nossal.²² Briefly, the vascularised tissue is illuminated by coherent laser light. Scattering on moving red blood cells (RBCs) leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency but lead to randomisation of light directions impinging on RBCs. This light diffusing in vascularised tissue leads to a broadening of the spectrum of scattered light (Doppler shift power spectrum, DSPS). From this DSPS the mean RBC velocity, the blood volume, and the blood flow can be calculated in relative units. In the present study the laser beam was directed to the fovea to assess blood flow in the submacular choroid (CHBF).²¹ Blood flow in the ONH was measured at the temporal neuroretinal rim (ONHBF).²⁰ Care was taken that the measurement location did not include any visible larger vessels.

Fundus pulsation technique

Ocular fundus pulsation was assessed by laser interferometry as described by Schmetterer *et al*.²³ Briefly, the eye is illuminated by the beam of a single mode laser diode ($\lambda = 783$ nm) along the optical axis. The light is reflected at both the front surface of the cornea and the retina. The two re-emitted waves produce interference fringes from which the distance changes between cornea and retina during a cardiac cycle can be calculated. These distance changes are caused by the pulsatile inflow of blood through the arteries and by the non-pulsatile outflow through the veins. The maximum change in corneo-retinal distance is called fundus pulsation amplitude (FPA). The method has been shown to estimate the pulsatile blood flow in the choroidal vasculature.²⁴ In the present study measurements were performed in the fovea.

Measurement of intraocular pressure

A Goldmann applanation tonometer was used to measure intraocular pressure (IOP).

Peripheral colour contrast sensitivity (threshold along tritan axis)

Peripheral colour contrast sensitivity was measured with a computer graphics device.²⁵ A program calculates the relative voltages required to produce any colour in terms of colour space. A high definition colour monitor driven by a personal computer with a graphics interface card displays an annulus subtending 25° at the eye. The program produces images without spatial luminance variations to test colour contrast. The colour contrast between the annulus and the background can be varied. Forty five degrees of the annulus is randomly removed in one of four quadrants. Patients are asked to identify the position of the gap while fixating a central spot. The minimum colour contrast between annulus and background at which the identification is possible is between 13–16% for the protan, deutan, and tritan axis in normal subjects. This threshold value changes little with age, refractive error, or pupillary aperture, and test-retest variability is low. Testing one eye takes only 1–2 minutes. Modulation is done along colour confusion lines for trichromatic vision (protan, deutan, tritan).²⁵ Contrast sensitivity was determined in 20° off axis²⁶ along the tritan colour axis²⁵ based on the results of previous studies.

Infrared telethermography and assessment of Raynaud's phenomenon

Continuous temperature recordings of all 10 fingers were done during standardised provocation tests^{27, 28} using a previously described program.²⁹ For the experiments, mean room air temperature was kept at 22.0°C (SD 0.5°C). After adaptation to room air for at least 20 minutes basal finger tip skin temperature was measured. Thereafter a 1 minute warm challenge was induced by immersion of gloved hands in water at 39°C and recovery temperature was assessed 10 and 20 minutes thereafter. A second stimulation consisted of a 1 minute cold challenge by inducing immersion of gloved hands in water at 20°C. Again, temperatures were measured 10 and 20 minutes after this cold provocation test. Raynaud's phenomenon was diagnosed as having a positive test and a clear history of cold hands. None of the subjects showed symptoms of Raynaud's syndrome.

Data analysis

For data analysis the absolute values were chosen. The effects of nimodipine on haemodynamic variables and IOP were assessed with repeated measure analysis of variance (ANOVA) versus placebo. The percentage change over baseline in response to nimodipine and placebo was calculated. The association between percentage changes in ocular haemodynamic parameters and percentage changes in threshold were analysed with linear regression analysis. Data are presented as mean (standard deviation). A p value of less than 0.05 was considered the level of significance.

RESULTS

Baseline values of all outcome parameters are presented in table 1. No significant differences were found between the baseline values on the two study days.

Nimodipine did not affect blood pressure (fig 1) or pulse rate (data not shown). A small decrease in IOP was observed with oral nimodipine, but this effect was not significant versus placebo (fig 1). Nimodipine increased all ocular haemodynamic parameters. This effect was highly significant for all outcome parameters. Mean ocular FPA increased by 14% (SD 14%) ($p = 0.0008$), ONHBF by 18% (SD 16%) ($p = 0.0031$), and CHBF by 12% (SD 14%) ($p < 0.001$) after administration of nimodipine. Nimodipine also decreased the threshold of colour contrast sensitivity along the tritan colour axis ($-14%$ (SD 12%); $p = 0.048$). A non-significant tendency

Table 1 Baseline values (n = 14)

	Placebo day	Nimodipine day
Mean arterial pressure (mm Hg)	89 (8)	87 (9)
Pulse rate (beats/min)	69 (11)	70 (13)
Intraocular pressure (mm Hg)	14 (2)	14 (3)
Threshold (%)	19 (7)	21 (10)
Fundus pulsation amplitude (µm)	3.0 (0.8)	3.0 (0.7)
Optic nerve head blood flow (arbitrary units)	5.4 (1.8)	5.1 (1.8)
Choroidal blood flow (arbitrary units)	5.9 (1.4)	6.1 (1.2)

Data are presented as mean (SD).

towards a decrease in the threshold of colour contrast sensitivity was also observed during placebo infusion (-6% (SD 12%)), which may indicate a learning effect with this technique.

There was a wide variety of responses to nimodipine in all ocular haemodynamic parameters (fig 2). However, individual changes in FPA, ONHBF, or CHBF were not correlated with changes in threshold of colour contrast sensitivity along the tritan colour axis. By contrast, changes in ocular haemodynamic parameters in the ONH and the choroid were associated to some degree (table 2), indicating consistency between the employed methods.

Based on the results of infrared telethermography, five of the 14 patients showed signs of Raynaud's phenomenon. Changes in the threshold of colour contrast sensitivity and changes in ocular haemodynamic parameters in response to nimodipine are presented in table 3. No differences were observed between the two groups of patients.

DISCUSSION

In the present study we observed an increase in haemodynamic parameters in the ONH and the choroid after administration of nimodipine. There was a considerable interindividual variability in these responses to nimodipine. However, changes in individual glaucoma patients were consistently found with all employed techniques indicating that this interindividual variability is not caused by limited reproducibility of the techniques. In addition, we observed a significant improvement in colour contrast sensitivity along

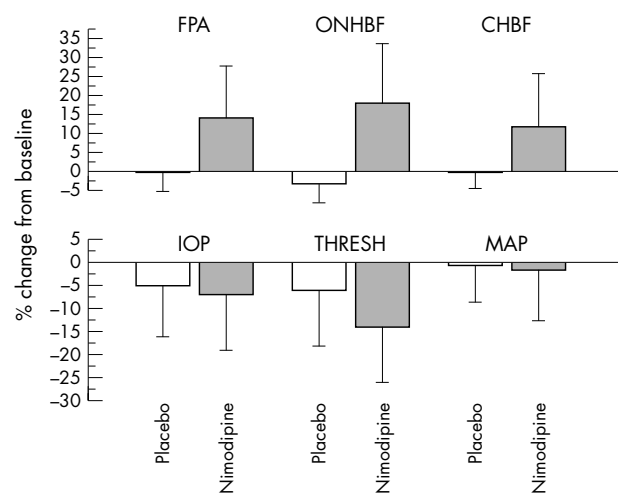


Figure 1 Effects of oral nimodipine or placebo on haemodynamic parameters and intraocular pressure (IOP) two hours after administration. Data are presented as means (SD). FPA, fundus pulsation amplitude; ONHBF, optic nerve head blood flow; CHBF, choroidal blood flow; THRESH, threshold of colour contrast; MAP, mean arterial pressure.

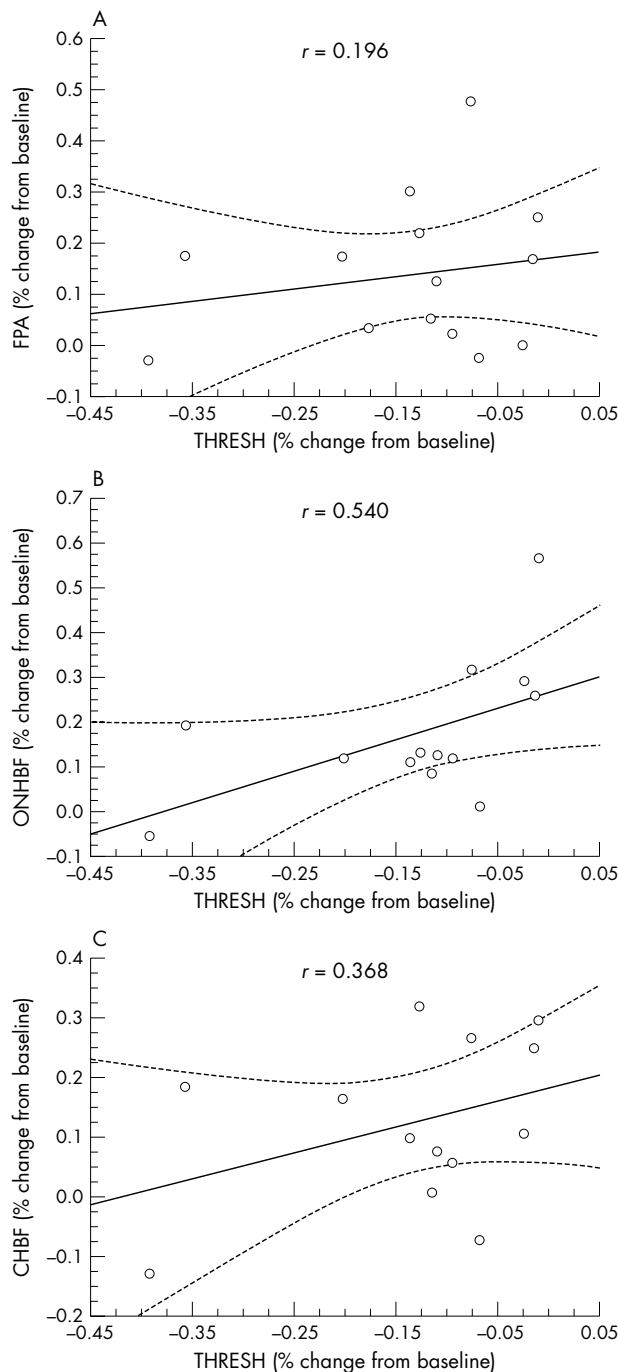


Figure 2 Correlation coefficients between individual ocular haemodynamic changes (% change from baseline) and changes in the threshold of colour contrast sensitivity (THRESH) induced by oral nimodipine. FPA, fundus pulsation amplitude; ONHBF, optic nerve head blood flow; CHBF, choroidal blood flow.

Table 2 Correlation coefficients between individual haemodynamic changes (% change from baseline) induced by oral nimodipine

	FPA	ONHBF	CHBF
FPA	-	0.52 (p=0.069)	0.74 (p=0.004)
ONHBF		-	0.74 (p=0.004)

FPA, fundus pulsation amplitude; ONHBF, optic nerve head blood flow; CHBF, choroidal blood flow.

Table 3 Haemodynamic changes (% change from baseline) induced by oral nimodipine in the group of patients with Raynaud's phenomenon (n=5) and the group of patients without the disease (n=9)

	Raynaud's phenomenon	No Raynaud's phenomenon
Threshold	-14 (11)	-13 (13)
FPA	+14 (11)	+14 (20)
ONHBF	+17 (18)	+18 (13)
CHBF	+14 (15)	+10 (14)

FPA, fundus pulsation amplitude; ONHBF, optic nerve head blood flow; CHBF, choroidal blood flow.

the tritan axis after administration of nimodipine. However, nimodipine induced changes in the threshold of colour contrast sensitivity and ocular haemodynamic parameters were not associated indicating that the improvement in colour vision is not a consequence of improved ocular blood flow. Hence, improved colour contrast sensitivity after nimodipine administration could be caused by the central nervous system.

In previous studies in glaucoma patients several calcium channel blockers including nifedipine,^{1 3 6 9 16 30 31} brovincamine,³ flunarizine,¹¹ nilvadipine,^{12 14 15} and nimodipine^{4 7} were used. Among these drugs nimodipine has a potential advantage, because it is able to cross the blood-brain barrier,³² due to its high lipid solubility. Calcium antagonists induce vasodilatation at smooth muscle cells and are neuroprotective through their intracellular decrease of K⁺. Several clinical trials have unequivocally shown that nimodipine is capable of preventing neurological deficits secondary to aneurysmal subarachnoid haemorrhage. Based on these results prophylactic nimodipine therapy is now routinely used in subarachnoid haemorrhage. On the other hand the results of the recent VENUS (Very Early Nimodipine Use in Stroke) study do not support the concept that early nimodipine exerts a beneficial effect in stroke patients.³³ As with other calcium channel blockers, clinical outcome data from randomised placebo controlled studies in glaucoma patients are lacking. This is a general limitation in estimating potential effects of calcium channel blockers in glaucoma patients, because very few of the above mentioned studies followed a randomised, placebo controlled, double masked design.^{2 4 5 7}

How could increased ocular blood flow after nimodipine exert beneficial effects in glaucoma patients? Based on our current understanding of the role of ischaemia in the pathophysiology of glaucomatous optic neuropathy^{34 35} improving blood supply to the eye may exert long term rather than short term effects in glaucoma patients. On the one hand ONH ischaemia may play a role in optic disc cupping due to malnutrition of ONH astrocytes,³⁵ which play a major role in the remodelling of the ONH in glaucoma.³⁶ On the other hand retinal ischaemia may lead to release of glutamate, resulting in retinal ganglion cell death in glaucoma due to activation of ionotropic glutamate receptors. The hypothesis that ischaemia may lead to optic disc cupping and results in retinal ganglion cell death was recently supported by several animal experiments. In a rabbit model of chronic ischaemia of the optic nerve head, induced by continuous application of endothelin-1 (ET-1) into the retrobulbar optic nerve via osmotically driven mini-pumps, optic nerve head cupping and optic nerve head tissue loss were seen without any increase in IOP.³⁷ Excavation and enlargement of the optic disc was also observed in another rabbit model in which ET-1 was injected into the posterior vitreous twice a week for 4 weeks.³⁸ This is particularly

important, because it has been suggested that ET-1 may contribute to ONH ischaemia in glaucoma patients.^{39 40} Moreover, there is a functional antagonism between the ocular haemodynamic effects of ET-1 and calcium channel blockers.^{41 42} Based on these previous results, one may hypothesise that in the present study nimodipine exerted vasodilator effect in ocular vessels in those patients with extensively elevated local ET-1 production. Whether this hypothesis holds true, however, remains to be shown, especially when considering that the results of the present study refer to short term effects only and cannot necessarily be extrapolated to long term results.

Interestingly, the responses in colour contrast sensitivity and ocular blood flow parameters were not different in patients showing signs of Raynaud's phenomenon. In addition to causing IOP, vasospastic episodes have been implicated in the pathogenesis of glaucoma and a variety of other eye diseases.⁴⁰ This is compatible with the results of the present study, because we observed a high incidence of Raynaud's phenomenon in our study population of more than 30%. Interpreting the results of this subgroup analysis one needs, however, to consider that the power of this study was small, because only five patients had evidence of Raynaud's phenomenon. Future long term clinical trials are required to clarify whether nimodipine treatment is indeed more effective in vasospastic subjects than in other glaucoma patients.

In conclusion, the results of the present study indicate that nimodipine increases ONH and choroidal blood flow in NTG patients and improves colour contrast sensitivity.

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