Graefe's Arch Clin Exp Ophthalmol (1989) 227:408–412

Graefe's Archive
for Clinical and Experimental
Ophthalmology



# The effect of $Ca^{2+}$-antagonist on visual field in low-tension glaucoma

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**Abstract.** A prospective study was conducted to evaluate the effects of $Ca^{2+}$-antagonist on the visual field in low-tension glaucoma (LTG). Twenty-five consecutive patients (50 eyes) with LTG received nifedipine at 30 mg/day per os for 6 months. Visual field was tested with an Octopus 201 (program G1) prior to and each month during the period of nifedipine administration. In addition to tonometry and the measurements of systemic blood pressure and pulse rate, the reactivity of peripheral vessels was estimated by determining the response of skin temperature of a finger to cold water (4° C). Twelve eyes (six patients) showed a constant improvement of visual field as expressed by an increase in mean sensitivity (MS). Canonical discriminant analysis demonstrated that the visual field is likely to improve with systemic nifedipine in patients who are young, have a higher initial MS and lower intraocular pressure, and have less decrease in diastolic blood pressure with the nifedipine administration and better cold recovery of skin temperature after their hand is soaked in cold water.

## Introduction

The mechanism of damage to the optic nerve in low-tension glaucoma and primary open-angle glaucoma remains unknown. There is now much evidence that ischemia of the optic nerve head might be responsible for the damage. However, whether ischemia is mechanically induced by intraocular pressure (IOP) or is due to a primarily vascular pathology is not clear.

In 1985, Phelps and Corbett reported on the high incidence of migraine in low-tension glaucoma patients and suggested for the first time that vasospastic events might play a role in the optic nerve changes in low-tension glaucoma [7]. In 1986, Gasser and associates described an ocular vasospastic syndrome in which patients with glaucomatous field defects but without elevated IOP had abnormal capillaroscopic responses to cold in the nail fold of the finger [6]. They noted that visual-field defects became aggravated by the immersion of a hand in cold water and that the scotomata often improved after they received a calcium channel blocker. Recently, Drance and associates measured blood flow in the finger of normal subjects and in subjects with low-tension glaucoma using a Doppler flow meter [1]. They found that the mean baseline flow and the flow after exposure to cold was significantly lower in the patients with low-tension glaucoma than in the normal subjects.

We conducted a prospective study in an attempt to evaluate the effect of $Ca^{2+}$-antagonist on visual field in low-tension glaucoma.

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## Patients and methods

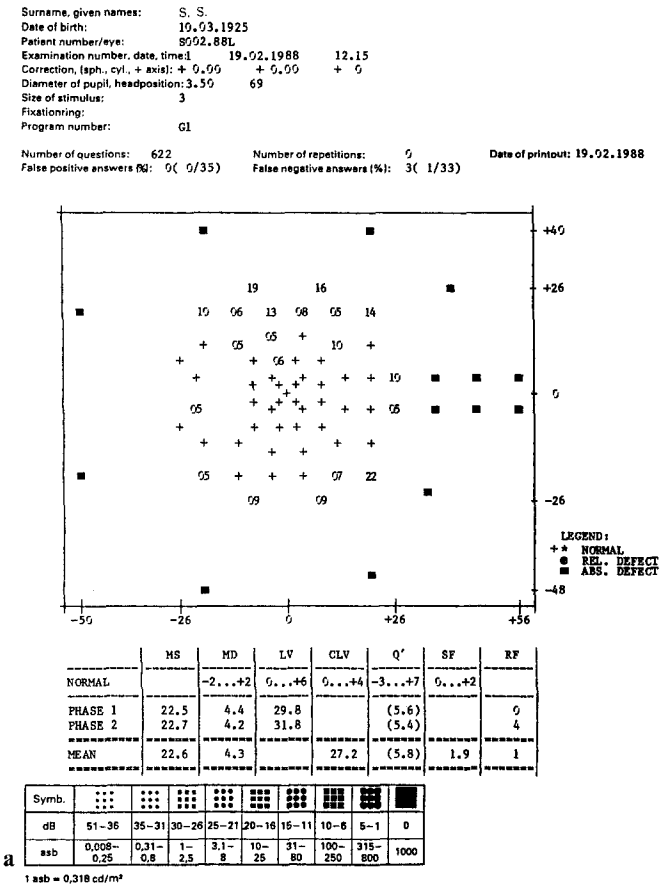
Twenty-five patients with low-tension glaucoma (50 eyes) were randomly selected for the study. Their demographic data and clinical background are listed in Table 1. Low-tension glaucoma was defined as a characteristic optic disk change with classic visual-field defects of the nerve fiber bundle type. IOP, including diurnal measurements, was no greater than 21 mm Hg.

The patients received nifedipine hydrochloride 30 mg/day per os for 6 months. Prior to, during, and after the oral administration of nifedipine, the following clinical factors were determined: IOP, visual field, resting systemic blood pressure and pulse rate, and the reactivity of peripheral vessels. IOP was measured with a Goldmann applanation tonometer. Visual field was tested with an Octopus 201 (program G1) at least three times prior to the administration of nifedipine, and the last perimetric data were used as the baseline. The reactivity of peripheral vessels was estimated as follows: a Thermistor (Shibaura Electrics, Inc., Model MG II) was attached to the skin of the middle finger [8]. A baseline skin temperature was recorded until a steady baseline reading was achieved. The hand was then immersed in ice-cold water (4° C) for 10 s, and the temperature was

**Table 1.** Demographic data and clinical background of patients

| | |
|---|---|
| Number of patients | 25 |
| Number of eyes | 25 |
| Sex (male/female) | 12/13 |
| Age (years) | 53.9±11.5 |
| IOP (mm Hg) | 13.1±3.2 |
| Visual-field changes (Aulhorn's classification) | |
| I–II | 13 |
| III–IV | 12 |
| Disk hemorrhage (no. of eyes)[a] | 2 |
| Migraine headache (no. of cases) | 0 |
| Cold hands (no. of cases) | 1 |

[a] Including all hemorrhagic episodes in the past and during the present study
IOP, Intraocular pressure

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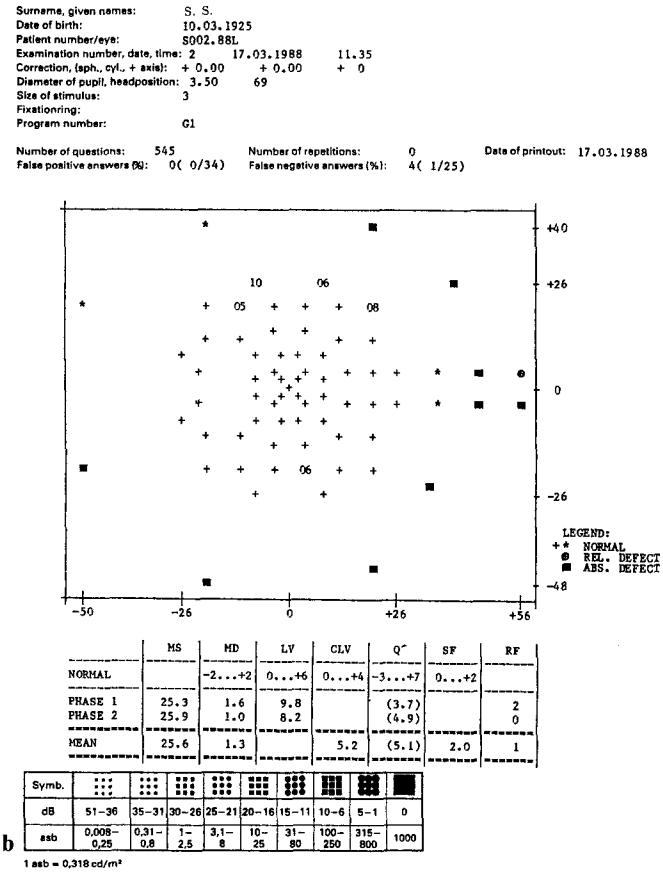


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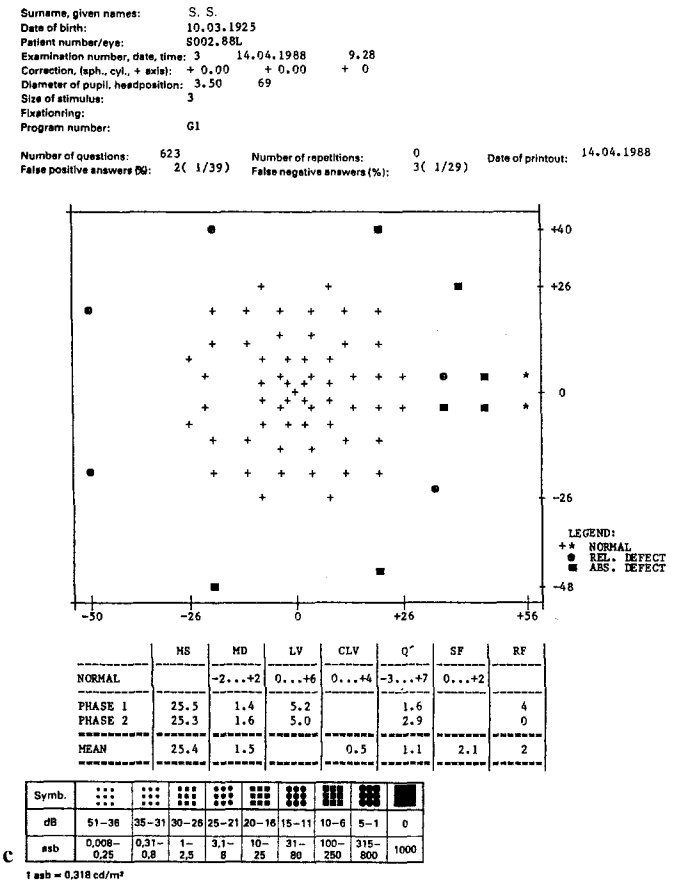


c

**Fig. 1a–c.** Three visual fields of a patient: **a** before nifedipine treatment, **b** at 4 weeks of nifedipine treatment, **c** at 8 weeks of nifedipine treatment

monitored every minute for the next 10 min. The change in skin temperature after the immersion in cold water was expressed as the percentage recovery from the lowest to the baseline temperature at each measurement. None of the patients had typical migraine headache. One patient admitted that she had cold hands even in spring and summer. In no case were any antiglaucoma drugs used for at least 3 months prior to and during the period of nifedipine administration. Univariate analyses of variance and of covariance and discriminant analyses were performed, the latter to separate the patients who showed improvement of the visual field with systemic administration of nifedipine from those who failed to improve.

## Results

Twelve eyes (six patients) showed an increase in mean sensitivity (MS) at each perimetric examination throughout the 6-month follow-up and were judged to have improved [2, 3]. An example of three visual fields of a patient is illustrated in Fig. 1. In the remaining 38 eyes (19 patients) MS failed to show a constant improvement as compared with the baseline value and the cases were classified as unimproved; in no case did MS show a constant decrease during the follow-up period. One eye of each individual patient was randomly selected for the analyses. Thus, six eyes of the improved and 19 eyes of the unimproved were subjected to the analyses. The demographic and clinical data of the

**Table 2.** Comparison of demographic and clinical data for the improved and the unimproved group

| | Improved | Unimproved |
|---|---|---|
| Number of patients | 6 | 19 |
| Number of eyes | 6 | 19 |
| Sex (male/female) | 3/3 | 9/10 |
| IOP (mm Hg) | 12.8±3.8 | 13.2±2.9 |
| Before nifedipine administration | | |
| Visual-field changes (Aulhorn's classification) | | |
| I–II | 4 | 9 |
| III–IV | 2 | 10 |
| Disk hemorrhage (no. of eyes)[a] | 0 | 2 |
| Cold recovery rate at 4 min (%) | | |
| – Before nifedipine administration | | |
| 80.5±7.0 | | 75.9±7.3 |
| – During nifedipine administration | $P<0.05$ | |
| 87.2±7.5 | | 79.0±7.5 |
| | $P<0.01$ | |

[a] Including all hemorrhagic episodes in the past and during the present study

improved and the unimproved group are listed in Table 2. Except for the mean age the factors, were not significantly different between the improved and the unimproved group. The mean age of the improved patients was 45.8±8.3 years ($n=6$), whereas the unimproved patients had a mean age of 56.6±11.2 years ($n=19$). This difference was statistically significant ($P<0.05$).

*Visual field*

The Global Indices before, during, and after nifedipine administration are summarized in Table 3. As expected from the criteria for improved visual field, MS and mean defect (MD) significantly differed between the pretreatment and the treatment with nifedipine ($P<0.05$, Wilcoxon rank-sum test). At 4 weeks after the withdrawal of nifedipine MS and MD were numerically deteriorated but the difference was not of statistical significance ($P<0.10$). Among the Global Indices, only corrected loss variance (CLV) was significantly smaller in the improved group than in the unimproved group throughout the study ($P<0.01$).

*Systemic blood pressure and pulse rate*

There was no significant difference in blood pressure and pulse rate between the improved and the unimproved group throughout the period of observation. Within the unimproved group systolic, diastolic, and mean blood pressures were decreased during nifedipine administration as compared with the pretreatment value ($P<0.05$, $P<0.01$, and $P<0.01$ respectively; Table 4). The diastolic blood pressure was significantly lower, not only during nifedipine administration but after cessation of administration, than in the pretreatment period ($P<0.01$ and $P<0.05$ respectively). In the improved group, no significant change in blood pressures was noted throughout the study period. Resting pulse rate failed to show any significant change in either group or between the two groups throughout the observation period.

*Cold recovery rate*

Prior to nifedipine administration, the cold recovery rate was not significantly different between the improved and the unimproved group. With the administration of nifedipine, the improved group showed a significantly better cold recovery rate as compared with the pretreatment value at 4, 5, 6, 7, 8, 9, and 10 min ($P<0.05$ at 4 min, $P<0.01$ from 5 to 10 min, respectively; Fig. 2), while in the unimproved group cold recovery rate failed to improve with the administration of nifedipine (Fig. 3). During the period of nifedipine administration, the cold recovery rate was significantly better in the improved group than in the unimproved group at 3, 4, 5, 6, and 7 min ($P<0.01$, $P<0.01$, $P<0.01$, $P<0.05$, and $P<0.05$ respectively).

*Other factors*

IOP was not significantly different throughout the observation period within each group or between the two groups. None of the six improved eyes had disk hemorrhages, while two eyes developed disk hemorrhages among the 19 unimproved eyes (10.5%). This difference was not of statistical significance.

*Correlation between the change in visual field during nifedipine administration and clinical factors*

The relation between the visual field changes, as represented by MS, during the administration of nifedipine and the

**Table 3.** Global Indices (dB) during the study

| Patient group | Nifedipine | MS | MD | CLV | SF |
|---|---|---|---|---|---|
| Improved | Before | 19.3±6.9 | 9.2±9.2 | 48.7±14.9 | 1.9±0.3 |
| | During | 21.2±7.7 * | 7.2±9.8 * | 44.2±15.0 | 1.8±0.4 |
| | After | 19.5±8.4 | 8.0±9.6 | 46.1±14.8 ** | 1.8±0.4 |
| Unimproved | Before | 17.1±8.3 | 10.4±8.0 | 82.3±12.9 ** | 2.4±1.4 |
| | During | 16.9±7.7 | 10.5±8.2 | 83.3±13.7 | 2.5±1.5 |
| | After | 16.4±8.4 | 10.9±8.7 | 89.0±13.9 | 2.4±1.4 |

dB, decibel; MS, mean sensitivity; MD, mean defect; CLV, corrected loss variance; SF, short term fluctuation;
* $P<0.05$; ** $P<0.01$

**Table 4.** Systemic blood pressure (mm Hg) during the study

| Patient group | Nifedipine | | | |
|---|---|---|---|---|
| | Administration | Systolic | Diastolic | Mean |
| Improved | Before | 120.3±14.8 | 78.7±5.9 | 92.0±9.5 |
| | During | 117.2±14.9 | 75.2±7.1 | 88.8±10.0 |
| | After | 119.7±15.3 | 74.3±11.2 | 85.7±14.7 |
| Unimproved | Before | 125.0±19.2 | 78.3±10.2 | 93.7±12.1 |
| | During | 114.3±12.7 | 69.6±8.8 | 84.6±9.4 |
| | After | 115.9±18.5 | 74.6±10.9 | 88.4±12.7 |

* $P<0.05$; ** $P<0.01$

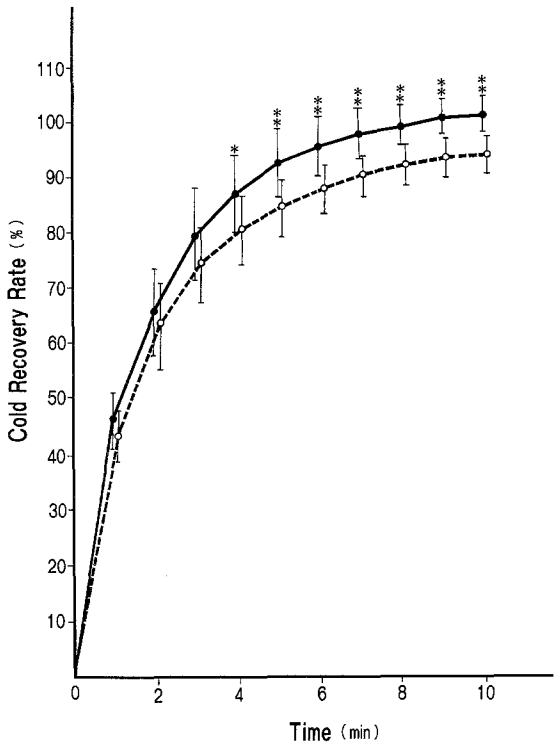


**Fig. 2.** Cold recovery rate in improved patients. *Broken line* indicates rate prior to oral nifedipine, *solid line* denotes rate during oral nifedipine treatment. Each *vertical bar* indicates SEM ($n=6$). Note that difference between the values with and without treatment is statistically significant at each measurement from 4 to 10 min after the immersion of a hand in cold water

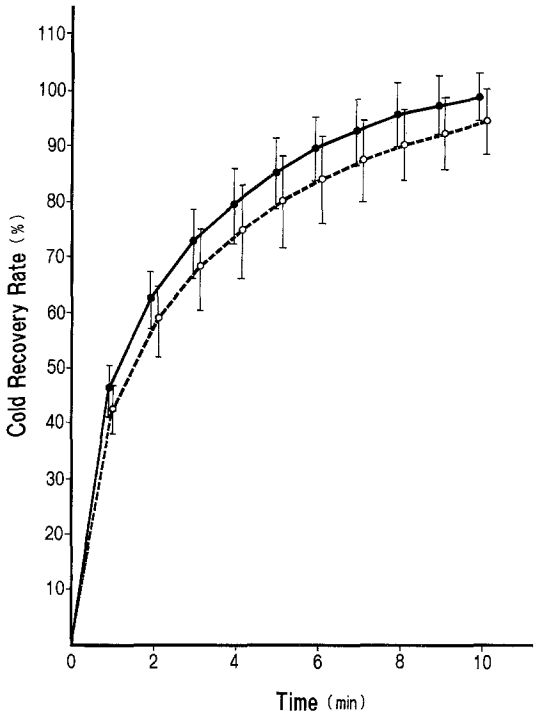


**Fig. 3.** Cold recovery rate in unimproved patients. *Broken line* indicates the rate prior to oral nifedipine, *solid line* denotes the rate during oral nifedipine therapy. Each *vertical bar* indicates SEM ($n=19$). Note no significant difference in the cold recovery rate between the values with and without treatment

clinical factors was tested with nonparametric measures of correlation (Spearman rank correlation). The MS during the administration of nifedipine was significantly related to age ($P=0.023$), cold recovery rate at 4 min prior to and during the administration of nifedipine ($P=0.014$ and $P=0.018$ respectively), diastolic blood pressure during nifedipine administration ($P=0.03$), and the MS prior to nifedipine therapy ($P=0.048$; Table 5).

Canonical discriminant analysis revealed that the discriminant function containing five variables (age, cold recovery rate prior to nifedipine administration, maximum diurnal IOP, mean diastolic blood pressure during nifedipine therapy, and degree of visual-field defects) gives the best separation between the improved and the unimproved group (sensitivity: 80.0%, specificity: 83.3%, discriminant efficacy: 80.8%; Table 6).

## Discussion

Our observations indicate that the visual field can improve with oral administration of nifedipine, a $Ca^{2+}$-antagonist, in some cases of low-tension glaucoma. The patients who responded favorably to $Ca^{2+}$-antagonist were found to share certain clinical features. They were younger than those who failed to respond with an improvement of MS. It is of particular interest to note that the patients whose visual field improved with nifedipine had significantly lower CLV prior to nifedipine therapy, although MS was not significantly different between those who improved with nifedipine and those who failed to do so. This finding seems to indicate the possibility that patients with localized, marked depression, reflecting a selective loss of nerve fiber bundle, are less likely to respond to oral administration

**Table 5.** Correlation between the change of mean sensitivity during nifedipine administration and clinical factors

| Factor | Spearman rank | |
|---|---|---|
| | Correlation Coefficient | *P*-value |
| Age | −0.39601 | 0.0232 |
| Cold recovery rate | | |
| – Prior to nifedipine | 0.33465 | 0.0179 |
| – During nifedipine | 0.4391 | 0.0140 |
| Mean diastolic blood pressure during nifedipine | 0.36434 | 0.0310 |
| Mean sensitivity prior to nifedipine | 0.2930 | 0.0477 |

**Table 6.** Standardized canonical discriminant function coefficients

| Variable | Coefficient |
|---|---|
| Age | −0.84700 |
| Cold recovery rate prior to nifedipine | 0.60262 |
| Maximum diurnal IOP | −0.24484 |
| Mean diastolic blood pressure during nifedipine | 0.78796 |
| Severity of visual-field defects | 0.30403 |

of $Ca^{2+}$-antagonist with the improvement of visual-field changes.

Another clinical feature that seems to deserve attention is that the responsive patients had a significant improvement of the cold provocation test when they were kept on nifedipine, while the nonresponsive patients failed to show a significant change of cold recovery rate with the administration of nifedipine. Since the cold recovery rate is the measure of the rate of recovery from the vasospasm induced by the exposure to cold, those who showed an improvement of the visual field may have retained the reactivity of peripheral vessels to $Ca^{2+}$-antagonist, with vasodilatation resulting in an increased blood supply to the optic nerve. The analytical result that the cold recovery rate before nifedipine administration is a reliable indicator of its effect lends further support to this possibility, but it neither proves or disproves the notion that the vasospastic events are not responsible for fields defects in the patients who fail to show improvement with nifedipine.

Our results appear to support what has been reported by Flammer and associates [4, 5, 6]: in some cases of low-tension glaucoma vasospasm plays a significant role in the development of visual-field defects, and a $Ca^{2+}$-antagonist may be effective in improving the visual field by reversing the vasospastic events.

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Received August 2, 1988 / Accepted January 27, 1989