

# The effect of nifedipine on retinal venous pressure of glaucoma patients with the Flammer-Syndrome

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## Abstract

**Purpose** The purpose was to measure the retinal venous pressure (RVP) in both eyes of primary open-angle glaucoma (POAG) patients before and 3 weeks after treatment with low-dosed Nifedipine.

**Methods** This retrospective study included 20 POAG patients who were treated with Nifedipine (5 mg daily) and 20 untreated control POAG patients. In both the treated and untreated control group, a distinction was made between those patients who had the Flammer-Syndrome (FS) and those who did not. The RVP was measured in all patients bilaterally at baseline and 3 weeks later by means of contact lens ophthalmodynamometry and the RVP measurements of the treated POAG patients were compared to the RVPs of the untreated POAG controls. Ophthalmodynamometry is done by applying an increasing force on the eye via a contact lens. The minimum force required to induce a venous pulsation is called the ophthalmodynamometric force (ODF). The RVP is defined and calculated as the sum of ODF and intraocular pressure (IOP) [ $RVP=ODF+IOP$ ].

**Results** The RVP decreased significantly after 3 weeks in both eyes of patients treated with low-dosed Nifedipine compared to the untreated group (mean decrease of 12.5 mmHg (SD 12.5),  $P<0.001$ ). A larger response to therapy was found in patients with the FS compared to patients lacking the FS (mean decrease of 16.07 vs. 7.28 mmHg, confidence Interval (CI): 5.2 to 9.3 vs. 12.3 to 19.7;  $P<0.001$ ). No significant differences were accounted for in the IOP's of the patients after treatment. In the untreated control group, no significant differences were accounted for either in the RVP or the IOP after 3 weeks.

**Conclusions** Treatment with low-dosed Nifedipine decreases RVP in both eyes of glaucoma patients, particularly in those with the Flammer-Syndrome. This effect may be due to the partial inhibition of Endothelin-1 (ET-1) by Nifedipine.

**Keywords** Retinal venous pressure · Flammer-Syndrome · Nifedipine

## Introduction

Calcium channel blockers (CCBs) such as Nifedipine are a chemically and pharmacologically diverse group of drugs that reduce the calcium conduction of calcium channels. The selectivity of CCBs for the heart and smooth muscle cells varies [1, 2]. Nifedipine belongs chemically to the group of dihydropyridines, which in contrast to other CCBs, have a greater selectivity for vascular smooth muscle [3] than for myocardium because they block smooth muscle calcium channels at concentrations below those required for significant cardiac effects. In smooth muscle cells, intracellular calcium concentration is partly regulated by ET-1 [4].

Under physiological conditions, the majority of ET-1 is produced by the vascular endothelial cells. The ET-1 is secreted predominantly abluminally, but a small portion is secreted intraluminally, thereby leading to a certain concentration of ET-1 in the blood [5, 6]. Increased levels of ET-1 have been reported in glaucoma patients, particularly in those with a primary vascular dysregulation [7–11]. The ET-1 plays a role in the pathogenesis of glaucomatous damage by constricting extraocular vessels [12, 13], reducing optic nerve head blood flow [14], impairing anterograde and retrograde axoplasmic transport [15, 16] and activating astrocytes [17]. Being a vasoconstrictor, it may also play an important role in constricting the retinal veins locally [18] thereby leading to an increased retinal venous pressure (RVP) as observed in glaucoma patients [19–23].

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Since ET-1 is involved in the pathogenesis of glaucomatous damage, the therapeutic use of ET-1 blockers are of interest. Although ET-1 blockers are used for experimental work, they are not yet clinically available for use in glaucoma. We know, however, that CCBs, such as Nifedipine, inhibit contractions to ET-1 in the porcine ciliary arteries, while endothelium-dependent relaxation to bradykinin as well as endothelium-independent relaxation to Na<sup>+</sup>nitroprusside remains unaffected [24]. By acting on vascular smooth muscle, Nifedipine can lead to vasodilation or relief from vasospasm [25, 26], and can partially block the effect of ET-1 [27]. Recently, it was shown that glaucoma patients, particularly those with the Flammer-Syndrome (FS) [28], had significantly higher RVPs [29]. To see whether treatment with Nifedipine affects ocular hemodynamics we retrospectively analysed RVPs of eyes of glaucoma patients (with and without FS) who were treated with Nifedipine and compared results to an untreated control group (with and without FS).

## Methods

### Patients

We retrospectively analysed values of RVP and IOP of 40 POAG patients, 20 of which were treated systemically only with Nifedipine (5 mg daily) and 20 of which who had no systemic treatment. No ethical approval was required to measure RVP in glaucoma patients as RVP measurements are always taken in all glaucoma patients at the Department of Ophthalmology of the University of Basel. All patients had glaucomatous visual fields or glaucomatous optic nerve cupping and the absence of alternative causes of optic neuropathy.

### The Flammer-Syndrome

A distinction was made between those patients who had the FS and those who did not. The FS was defined as being present if it was detected in the patient history and confirmed by the dynamic retinal vessel analyser (DVA). Cases in which the patient history and DVA results were contradictory were excluded from the study.

Evaluation of patient history for FS: FS is defined as present (FS+) in the patient history if the subjects answer five of the following six questions with “Yes”, and it is defined as absent (FS-) if the subjects answer less than five questions with “Yes”: 1) Do you suffer from cold hands or feet even in summer [30]?; 2) Do you have trouble falling asleep, especially when you are cold [31]?; 3) Are you seldom thirsty, and do you have to remind yourself to drink enough [32]?; 4) Do you suffer from migraine attacks [33]?; 5) Do you have low blood pressure [34]?; and 6) Do you identify smells better than others [35]?

Evaluation of DVA results for FS was that the results of DVA were considered positive for FS (pathological) if the reaction of the vessels in both eyes was reduced in response to flickering light.

### Application of nifedipine

Nifedipine was applied orally in the form of liquid drops (Nifedipine Ratiopharm Drops, 1 drop=1 mg Nifedipine) mixed in 1 l of water and the patients were told to drink the 1 l of liquid slowly throughout the day. The reason for this particular application was due to the fact that Nifedipine has a short half-life (approximately 15 min) and its systemic effect can be increased when taken in this manner.

### Measurement of RVP

For all patients RVP was measured in both eyes by ophthalmodynamometry (IMEDOS Jena Germany) at baseline and 3 weeks later. This device consists of a conventional Goldmann contact lens fitted with a pressure sensor at its outer margin where the Goldmann contact lens is usually held during an ophthalmoscopic examination. The contact lens is fitted to an outer ring by strain gauges, which give an electrical signal. This signal is linearly related to the force by which the contact lens is attached to the eye. It is given to the input of a central unit by a thin flexible cable. This central unit has the size of a pocket calculator. It shows the increase of the IOP induced by the force applied on a LCD display. The conversion from force to pressure is based on a biophysical calibration [36, 37].

Ophthalmodynamometry was conducted by applying increasing force to the eye via the contact lens. This applied pressure can be read as a pressure increase on the attached

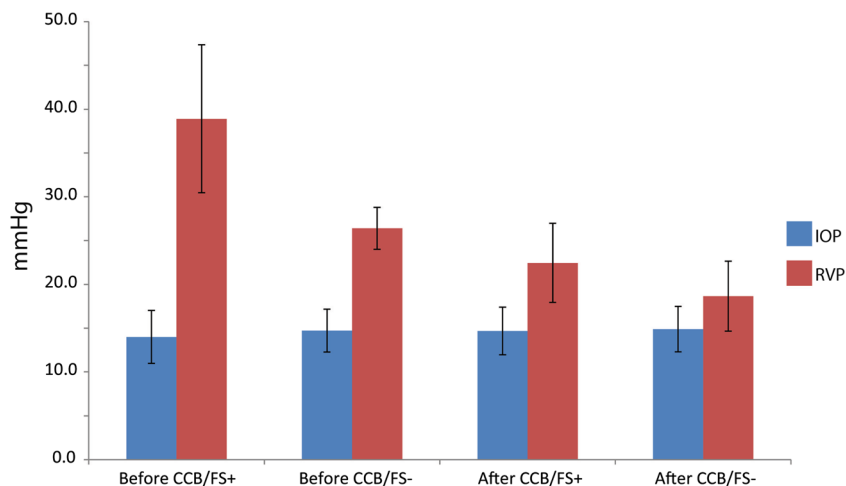
**Table 1** Demographic and baseline characteristics of the two groups of patients

	POAG Treated with Nifedipine	Control POAG	P-Value
N (FS+/FS-)	20 (11/9)	20 (7/13)	
Gender (F/M)	(10/10)	(12/10)	n.s
Age Mean (SD)	56.7 (14.9)	60.6 (16.3)	n.s

FS+ patients with the Flammer-Syndrome

FS - patients who did not have the Flammer-Syndrome

**Fig. 1** Intraocular pressure (IOP) and retinal venous pressure (RVP) in the group of patients treated with Nifedipine. Measurements were taken at baseline and after 3 weeks



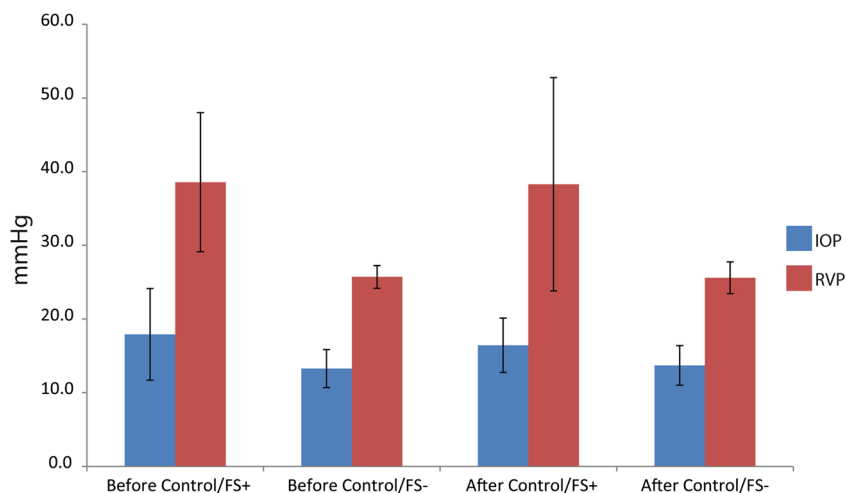
LCD screen based on a calibration curve. Any small pulsatile synchronous movement of the central retinal vein or its major branches inside the optic disc was noted as spontaneous pulsation. In short, after placing the contact lens on the eye, the ONH was brought into sight. If a spontaneous venous pulsation was present it was noted. If not, the compressive force was increased until the first venous pulsation was detected, and the measurement value was fixed and read. RVP was calculated as the sum of pressure increase induced by the instrument and IOP as measured by Goldman tonometry. Measurements by the ophthalmodynamometer are reproducible [29].

### Statistical analysis

Descriptive statistics are presented as mean (SD). Overall, p-values were calculated using ANOVA based on linear mixed effects models (with the exception of patient's age).

To compare the RVP change from baseline between the group with Nifedipine therapy and the control group, a linear

**Fig. 2** Intraocular pressure (IOP) and retinal venous pressure (RVP) in the control group (no treatment). Measurements were taken at baseline and after 3 weeks



mixed-effects model was performed. Mixed effects models are suitable tools to examine repeated measure data.

The dependent variable is the RVP change from baseline, the independent variables are “study group,” “FS” (Flammer-Syndrome), “age,” “baseline RVP,” and “eye-side.” Hence, results are adjusted for “age,” “baseline RVP,” and “eye-side.” Subjects are treated as random factor. A potential interaction between “FS” and “Group” is also included in the regression model.

Results are presented as differences of the means of the two groups, namely treated and untreated control, with corresponding 95 % confidence interval and p-value. A p-value <0.05 is considered significant. All analyses were conducted using the statistical software package R, version 3.1.1. Mixed effects models are performed using the package “nlme.”

### Results

Table 1 gives an overview of the demographic data of patients and controls. RVP decreased significantly after 3 weeks in

both eyes of patients treated with low-dosed Nifedipine compared to the untreated group (mean decrease of 12.5 mmHg (SD 12.5),  $P < 0.001$ ). A larger response to therapy was found in patients with the FS compared to patients lacking the FS (mean decrease of 16.07 mmHg vs. 7.28 mmHg, Confidence Interval (CI): 5.2 to 9.3 vs. 12.3 to 19.7;  $P < 0.001$ ). No significant differences were accounted for in the IOP's of the patients after treatment (Fig. 1). In the untreated control group, no significant differences were accounted for either in the RVP or the IOP after 3 weeks (Fig. 2).

## Discussion

An increased RVP in the eyes of glaucoma patients has previously been reported [19–23], and in a previous study we observed that this increase is higher in patients with the Flammer-Syndrome [38]. To the best of our knowledge, this is the first report showing the possibility of a therapeutic reduction of RVP by the low-dosed calcium channel blocker Nifedipine.

At present, the cause of this increased RVP and the fact that it can be therapeutically reduced by means of low-dosed Nifedipine is not known. At the moment we can only hypothesize that the increased RVP may possibly in part be due to a dysregulation of the veins [18]. This may explain why we can reduce it by means of the CCB, Nifedipine. Both retinal arteries and veins, like elsewhere in the body, are highly regulated. In general, however, the regulation of the arteries has attracted more attention. In patients with a dysregulation the arteries produce an increased amount of ET-1 [39]. This increases both the ET-1 concentration in the circulating blood [40] as well as the ET-1 concentration in the surrounding tissue of the artery causing nearby veins to react with a vasoconstriction [18].

Supportive of this hypothesis are the various studies showing the effect of CCB on ocular blood flow. Ex vivo studies show that CCBs reduce the vasoconstrictive effect of ET-1 [24, 41]. Various animal studies show that OBF, particularly ONH blood flow [42], is increased after application of CCBs, such as nifedipine [43, 44]. CCBs mitigate the OBF-reducing effect of an ET-1 infusion in healthy volunteers [27]. Studies on healthy subjects with PVD show that CCBs improve the regulation of blood flow [45]. Finally, studies on glaucoma patients also show an improvement in OBF [38, 46, 47].

This study has limitations, as it is retrospective and not randomized. Future randomized, controlled studies are warranted to clarify the effect of CCBs on the increased RVP of glaucoma patients with the Flammer-Syndrome.

**Conflict of Interest Statement** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in

speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, expert testimony, or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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