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Title: The Effect Of Primary Vascular Dysregulation On Retinal Venous Pressure.

Authors:

Maneli Mozaffarieh MM (Maneli.Mozaffarieh@usb.ch)
Baertschi Michael MB (Michael.Baertschi@usb.ch)
Flammer Josef JF (Josef.Flammer@usb.ch)

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The Effect of Primary Vascular Dysregulation on Retinal Venous Pressure

Mozaffarieh M, Bärtschi M, Flammer J
University of Basel, Switzerland
Department of Ophthalmology

Correspondence
Josef Flammer, MD
University of Basel
Department of Ophthalmology
Mittlere Strasse 91
4031 Basel, Switzerland
Phone: ++41/61/2658651
Fax: ++41/61/2658652
Email: josef.flammer@usb.ch
Abstract

Purpose: The purpose of the study was to measure the retinal venous pressure (RVP) in the eyes of primary open-angle glaucoma (POAG) patients and healthy subjects with and without a primary vascular dysregulation (PVD).

Methods: RVP was measured in the following four groups of patients and age- and sex-matched healthy controls: (a) 15 patients with a POAG and a PVD (POAG/PVD+); (b) 15 patients with a POAG but without a PVD (POAG/PVD-); (c) 14 healthy subjects with a PVD (healthy/PVD+) and (d) 16 healthy subjects without a PVD (healthy/PVD-). RVP was measured in all participants bilaterally by means of contact lens ophthalmodynamometry. Ophthalmodynamometry is done by applying increasing pressure on the eye via a contact lens. The minimum force required to induce a venous pulsation is called ophthalmodynamometric force (ODF). The RVP is defined and calculated as the sum of ODF and intraocular pressure (IOP) \[ RVP = ODF + IOP \].

Results: The participants with a PVD (whether patients with POAG or healthy subjects), had a significantly higher RVP compared to subjects without a PVD (\( p = 0.0103 \)). Patients with a POAG and PVD (POAG/PVD+) had a significantly higher RVP compared to patients without a PVD (POAG/PVD−) (\( p = 0.0301 \)). There was a notable trend for a higher RVP in the healthy/PVD+ group compared to the healthy/PVD− group, which did not reach statistical significance (\( p = 0.0898 \)).

Conclusions: RVP is higher in subjects with a PVD, particularly in glaucoma patients. The causal relationship needs to be further evaluated.
Introduction

Disturbances of ocular blood flow are involved in many ophthalmic diseases and are therefore of utmost clinical relevance. [1–5] There are various causes for blood flow disturbances, such as diseased blood vessels [6] or mechanical compression of the vessel wall. [7] However, some organs are not well perfused, despite anatomically healthy blood vessels, when the regulation of blood flow is not adapted to the needs of the tissue. [8] Such a vascular dysregulation implies either inappropriate vasoconstrictions (vasospasms) or an insufficient vasodilation (more or less than is required). [9] Dysregulation can be secondary in nature, as in multiple sclerosis, [10] wherein the high level of Endothelin-1 reduces ocular blood flow OBF. Dysregulation can also be primary in nature (primary vascular dysregulation or PVD), [9] meaning that it can occur without any underlying disease and caused by an inborn tendency to respond differently to various stimuli, such as cold temperatures or mechanical or emotional stress.

The eye is one of the best-perfused organs in the body. One factor influencing this process is the ocular perfusion pressure (OPP) [11–14]. OPP is the difference between systemic blood pressure and the RVP. In the eye, arterial pressure is assumed to be 2/3 of the brachial arterial pressure. The RVP is assumed equal to the IOP. The latter assumption is not always true in glaucoma patients. [15–18]

As summarized in the literature reviews, glaucoma patients often concomitantly suffer from a PVD. [19, 20] One of the clinical observations that we made in patients with a PVD was that they often had dilated retinal veins, which is why we hypothesized that RVP may be higher in PVD than in non-PVD subjects. We therefore set out to measure RVP in glaucoma patients and healthy subjects with and without a PVD.

Methods

Patients with POAG were recruited from the University Eye Clinic, Basel, between January 2011 and December 2012. Healthy volunteers, age- and sex-matched to the POAG patients, were recruited in our outpatient department. The control subjects did not have any relevant eye disease and attended our outpatient department for various reasons, including prescriptions for eyeglasses, dry eye symptoms and
regular ophthalmic check-up examinations. Ethical approval was obtained from the local medical ethics committee of Basel before commencing the study. For inclusion, the patients with POAG met the following criteria: (1) treated IOP less than 23 mmHg on multiple measurements, (2) glaucomatous visual fields or glaucomatous optic nerve cupping and (3) the absence of alternative causes of optic neuropathy.

PVD was defined as being present if it was detected in the patient history and confirmed by the pathological results of the dynamic retinal vessel analyser (DVA). PVD was defined as being absent if the patient history for PVD was negative and the results of DVA were normal. Cases in which the patient history and RVA results were contradictory were excluded from the study. The following groups of subjects were compared: (1) POAG patients with a PVD (POAG/PVD+); (2) POAG patients without a PVD (POAG/PVD−); (3) healthy controls with a PVD (healthy/PVD+) and (4) healthy controls without a PVD (healthy/PVD−). Demographic data of the different groups of subjects are presented in Table 1.

For all patients and controls, RVP was measured in both eyes by ophthalmodynamometry (Meditron GmbH, Völklingen, Germany). 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 device is connected to an LCD screen.

Ophthalmodynamometry is conducted by applying increasing pressure to the eye via the contact lens. This applied pressure can be read as an IOP increase on the attached LCD screen based on a calibration curve. The IOP increase that is required to induce a venous pulsation is called the ophthalmodynamometric force (ODF). If a spontaneous venous pulsation is present, ODF is said to be 0, if not present, increasing pressure is applied. The RVP is defined and calculated as the sum of the ODF and IOP \[ RVP = ODF + IOP \].

**Statistical Analysis**

RVP was analysed with a linear fixed effects model. The participant group (POAG/PVD+, POAG/PVD−, healthy/PVD+ and healthy/PVD−) was taken as 'fixed effect', and participants (patients and healthy controls) were taken as 'random effects' to account for repeated measures. Gender and age were included as covariates to
account for baseline differences. The RVP was log-transformed to meet the
assumption of normally distributed errors. Three a priori defined group comparisons
were made: PVD+ vs PVD−, POAG/PVD+ vs POAG/PVD− and Healthy/PVD+ vs
Healthy/PVD−.

Results

The mean values of the RVP in the four groups are presented in Table 2. Participants
with a PVD (whether patients with a POAG or healthy subjects), had a significantly
higher RVP compared to participants without a PVD (P = 0.0103). Patients with a
POAG and PVD had a statistically significant higher RVP compared to patients with a
POAG but without PVD (p = 0.0301, Fig 1).

There was a notable trend for a higher RVP in the healthy/PVD+ group compared to
the healthy/PVD− group, which did not reach statistical significance (p = 0.0898).
RVP of healthy subjects was on average 23% higher compared to healthy subjects
without PVD (Fig 1).

Discussion

The term vascular dysregulation in the context of glaucoma was first introduced by
Flammer. [9] Later, a distinction was made between primary and secondary vascular
dysregulation. [21] A systemic vascular dysregulation can be due to another disease.
A secondary vascular dysregulation occurs in the context of another disease, such as
rheumatoid arthritis. [22] A primary vascular dysregulation (PVD), [2] which is the
type of dysregulation examined in this research, is a term used to describe an inborn
disposition to respond differently to stimuli. This type of dysregulation can also occur
in otherwise healthy subjects. Since we made the clinical observation that glaucoma
patients with a PVD often had dilated retinal veins, we hypothesized that the RVP in
the subset of glaucoma patients with a PVD may be higher than in those glaucoma
patients without a PVD.

Our results clearly indicate that glaucoma patients who suffer from a PVD have a
significantly higher RVP than non-PVD glaucoma patients. The vascular systems of
people with a PVD respond differently (e.g., reacting with vasoconstrictions to various stimuli such as cold or stress). [23, 24] Despite the anatomically normal appearance of their vessels, those people with a PVD have stiffer retinal vessels, as pulse waves in their retinal vessels propagate faster compared to those of subjects without a PVD. [25] The spatial irregularity of the vessels of people with a PVD is increased, [26] whereas neurovascular coupling is decreased, [27] and autoregulation of ocular blood flow is disturbed. [24]

A reduced and unstable OPP has been reported to be risk factor for glaucoma progression; [11, 13, 28–30] therefore, a better estimate of OPP obtained by considering RVP may reveal an even stronger relationship. At present, the cause of this increased RVP is not known. Theoretically, it could be due to structural changes in the optic nerve head or to a local dysregulation at the outflow level of the retinal vein, as already postulated for the mechanism of a retinal vein occlusion. [31] Such dysregulation is most likely a consequence of the local increase of vasoactive molecules, such as Endothelin-1, which are diffused from the circulating blood or are produced in the neural tissue of the retina. [32] Endothelin-1 values are higher in glaucoma patients, particularly normal-tension glaucoma patients who commonly suffer from a PVD, compared to healthy controls. [33-35]

In summary, PVD is associated with an increased RVP in glaucoma patients. By virtue of the growing body of evidence supporting the role of ocular hemodynamics in glaucoma, it is desirable to establish future glaucoma drugs that specifically lower the RVP.

### Competing Interests
The authors declare that they have no competing interests. Baertschi M and Flammer J are the co-owners of the patent for the ophthalmodynamometer.

### Authors’ Contributions
MM drafted the manuscript and made substantial contributions to the acquisition of data. MB carried out RVP measurements. JF designed and coordinated the study
and helped draft and revise the manuscript for intellectual content. All authors read and approved the final manuscript.

Acknowledgments
We would like to thank Dr Deborah Vogt from the Clinical Trial Unit, University Hospital, Basel, for performing the statistical analysis of the data.
Figure Legends

Table 1: Demographic and baseline characteristics of the four groups of participants

Patients with POAG and PVD: POAG/PVD+
Patients with POAG but without PVD: POAG/PVD−
Healthy subjects with PVD: Healthy/PVD+
Healthy subjects without PVD: Healthy/PVD−

Table 2: Mean values of retinal venous pressure (RVP) in the four groups of participants

Figure 1: Intraocular pressure (IOP) and retinal venous pressure (RVP) in the four groups of participants: for IOP mean ± 1 standard deviation of base line measurements are shown; for RVP mean ± 1 standard error are shown
### Table 1

<table>
<thead>
<tr>
<th></th>
<th>POAG/PVD+</th>
<th>POAG/PVD−</th>
<th>Healthy/PVD+</th>
<th>Healthy/PVD−</th>
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<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>16</td>
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<td>Gender (F/M)</td>
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<td>7/8</td>
<td>7/7</td>
<td>10/6</td>
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<td>67.0 (8.7)</td>
<td>62.8 (8.7)</td>
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<td>IOP Mean (SD)</td>
<td>10.6 (1.5)</td>
<td>13.33 (2.55)</td>
<td>11.71 (1.33)</td>
<td>13.12 (3.3)</td>
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### Table 2

**RVP: Mean Values and Standard Deviation (SD)**

<table>
<thead>
<tr>
<th></th>
<th>Right Eye (mmHg)</th>
<th>Left Eye (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>POAG/PVD+</td>
<td>34.67 (± 8.92)</td>
<td>36.47 (± 9.15)</td>
</tr>
<tr>
<td>POAG/PVD−</td>
<td>28.20 (± 8.20)</td>
<td>28.47 (± 7.66)</td>
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<tr>
<td>Healthy/PVD+</td>
<td>23.29 (± 4.16)</td>
<td>22.50 (± 4.11)</td>
</tr>
<tr>
<td>Healthy/PVD−</td>
<td>18.81 (± 5.61)</td>
<td>19.49 (± 6.05)</td>
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14. Gherghel D, Orgul S, Gugleta K, Gekkieva M, Flammer J. Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with...


hypertension and its association with the level of glaucomatous damage.


