Ophthalmic Artery and Superior Ophthalmic Vein Blood Flow Dynamics in Glaucoma Investigated by Phase Contrast Magnetic Resonance Imaging

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Precis: Ophthalmic artery (OA) and superior ophthalmic vein (SOV) blood flow were quantified by phase contrast magnetic resonance imaging (PC MRI) and seemed lower in glaucoma. Venous flow dynamics was different in glaucoma patients with a significantly decreased pulsatility.

Introduction: Studies using color Doppler imaging and optical coherence tomography flowmetry strongly suggested that vascular changes are involved in the pathophysiology of glaucoma, but the venous outflow has been little studied beyond the episcleral veins. This study measured the OA and the SOV flow by PC MRI in glaucoma patients compared with controls.

Methods: Eleven primary open-angle glaucoma patients, with a mean ± SD visual field deficit of 2.3 ± 2.7 dB and retinal nerve fiber layer thickness of 92 ± 13 μm, and 10 controls of similar age, were examined by PC MRI. The mean, maximal and minimal flow over cardiac cycle were measured. The variation of flow (ΔQ) was calculated.

Results: The OA mean ± SD mean flow was 13.21 ± 6.79 mL/min in patients and 15.09 ± 7.62 mL/min in controls (P = 0.35) and the OA maximal flow was 25.70 ± 12.08 mL/min in patients, and 28.45 ± 10.64 mL/min in controls (P = 0.22). In the SOV the mean ± SD mean flow was 6.46 ± 5.50 mL/min in patients and 7.21 ± 6.04 mL/min in controls (P = 0.47) and the maximal flow was 9.06 ± 6.67 in patients versus 11.96 ± 9.29 mL/min in controls (P = 0.47). The ΔQ in the SOV was significantly lower in patients (5.45 ± 2.54 mL/min) than in controls (9.09 ± 5.74 mL/min) (P = 0.04).

Discussion: Although no significant difference was found, the mean and maximal flow in the OA and SOV seemed lower in glaucoma patients than in controls. The SOV flow waveform might be affected in glaucoma, corroborating the hypothesis of an impairment of venous outflow in those patients.

Key Words: glaucoma, ocular blood flow, venous outflow, phase contrast MRI

Glaucoma is a disease characterized by progressive optic neuropathy that can lead to blindness. Although elevated intraocular pressure (IOP) is strongly associated with the onset and progression of optic nerve damage, it cannot alone account for the broad spectrum of patients with primary open-angle glaucoma (POAG). First, a large proportion of these patients display typical glaucomatous optic neuropathy in the absence of elevated IOP (a condition known as normal-tension glaucoma). Second, some patients show signs of disease progression even after an effective, treatment-induced reduction in their IOP. Approximately 1 in 6 treated POAG patients will become blind in both eyes at some point in their life.1 Ocular hypertension is the main risk factor for glaucoma but is not the direct cause. The disease mechanism underlying glaucoma remains unclear. Extensive research has been performed on the condition’s etiology, methods for early diagnosis and factors that might be predictive of disease progression. The search for risk factors other than elevated IOP has led to the recognition that patients with systemic hypotension2 or sleep-apnea syndrome3 are at greater risk of developing glaucoma; this suggests the involvement of vascular factors in the onset and progression of glaucoma.

Several studies have reported on various aspects of orbital hemodynamics in glaucoma. Many researchers have used color Doppler imaging to assess orbital blood flow in various cohorts of glaucoma patients and healthy controls. Evidence of abnormally low peak systolic velocity (PSV) and end diastolic velocity (EDV) values, and abnormally high resistive index [RI, defined as (PSV-EDV)/PSV, a marker of vascular resistance] in the ophthalmic, central retinal, and posterior ciliary arteries were found in POAG groups, in both untreated and IOP-controlled groups, compared with controls4,5 or to patients with elevated IOP but no glaucoma.6 It has been suggested that changes in ocular blood flow may precede damage to the optic nerve6 and may increase the risk of developing glaucoma in “glaucoma suspects.”7 Moreover, a high RI in the ophthalmic artery (OA) was found to be a strong risk factor for glaucoma progression.8,9 Those findings led to the hypothesis that impaired regulation of ocular blood flow results in periods of relative ischemia and repeated reperfusion injury to the optic nerve.

More recently, retinal and optic nerve head microcirculation have also been extensively studied, thanks to the
developments of optical coherence tomography (OCT). The optic nerve head blood flow measured by laser speckle flowgraphy increased during the earliest stage of glaucoma, followed by a linear decline that was strongly correlated with thickness reduction of the retinal nerve fiber layer (RNFL). In studies using OCT angiography, the peripapillary vessel density was reduced in glaucomatous eyes compared to controls, and the area of decreased vessels density corresponding to areas of RNFL thinning and visual field defects. However, it remains unknown whether those changes in the microvasculature of the optic nerve head and peripapillary retina are the cause or the consequence of the disease.

Phase contrast magnetic resonance imaging (PC MRI) provides new perspectives in the field of blood flow imaging. Cerebral blood and cerebrospinal (CSF) flows have been quantified both in healthy subjects and in pathologic situations (eg, intracranial hypertension and cerebral venous thrombosis). PC MRI has also been used to quantify blood flow in the OA and in the superior ophthalmic vein (SOV). The OA provides the blood supply of the globe through the central retinal artery and the posterior ciliary arteries. The venous outflow is mainly assured by the SOV. The aqueous humor drains through the trabecular meshwork and the uveo-scleral pathway to the episcleral veins, so the venous flow in the orbit is closely related to the regulation of IOP. Yet it has been little studied in the setting of glaucoma. PC MRI may be a way of assessing the possible impairment of the blood flow of the OA and of the SOV in glaucoma. The purpose of this study was to quantify the blood flow and the wave flow patterns during cardiac cycle, in the OA and in the SOV in glaucoma patients compared with controls.

**METHODS**

**Patients**

This study was conducted in accordance with the Declaration of Helsinki, was approved by Ethical Institutional Review Board (Comité de Protection des Personnes Nord-Ouest, Amiens, France). All participants gave their informed, written consent. The study included 11 patients (22 eyes) diagnosed with POAG. As the standard of care, the patients received complete examination including gonioscopy, and regularly repeated automated visual field and RNFL thickness measurement with spectral-domain OCT. Primary open-angle glaucoma was defined as asymptomatic, progressive, optic nerve head changes (disc cupping and/or RNFL thinning), with or without elevated IOP, and detectable visual field defects corresponding to the localization of RNFL thinning, an open angle with no angle dysgenesis on gonioscopy, in the absence of ocular disease or congenital anomaly. The course of treatment was at the discretion of the ophthalmologist and was not part of the study. In the uncertainty of an effect on flow patterns, patients treated with beta-blockers, systemic or topical, were not included. Also, patients were not included if they presented with a contraindication to MRI, cardiovasculor or neurovascular comorbidity (eg, stroke, carotid stenosis, cardiac failure, uncontrolled systemic hypertension), other form of glaucoma (eg, angle closure, traumatic, pseudoexfoliation, pigmentary, neovascular, inflammatory, congenital glaucomas) or history of significant ocular disease, recent intraocular or intraorbital surgery.

Ten healthy volunteers (20 eyes) with no known past ocular history, no known neurological or vascular disease, no family history of glaucoma and normal eye examination were included as controls. Before inclusion, the control subjects underwent screening by one of the investigators (V.P.) including visual acuity, IOP, slit-lamp examination and nondilated fundus examination.

**Imaging Procedure**

All included participants filled out a screening form to rule out any contraindication immediately before the realization of the MRI. The MRI used was a 3 Tesla scanner (Philips Achieva) with a 32-channel head coil. First, morphologic axial T2-weighed sequences with and without fat saturation were acquired, in order to track the course of the SOV and the OA. The spatial resolution of these morphologic T2-weighed sequences was 0.5×0.5×1 mm³. Using those images, the acquisition planes for the phase contrast sequences were positioned perpendicularly to the axis of the studied vessel by an investigator. Cardiac synchronization was set using peripheral gating. Accordingly, the sequences’ acquisition time depended on the subject’s heart rate. One phase contrast sequence was acquired for each OA and one for each SOV. The parameters of those sequences were as follow: repetition time 13 ms, echo time 8 ms, flip angle 30 degrees, a field of view of 120×120 mm, a pixel size of 0.5×0.5 mm, and a slice thickness of 3 mm. The encoding velocity was set at 40 cm/s for the OA and 20 cm/s for the SOV. The encoding velocity parameter is set by the investigator, according to the expected blood velocity in the studied vessel. A first visualization of the acquired sequence, without quantitative analysis, was possible at the time of acquisition, allowing to repeat the sequence with a different acquisition plane or encoding velocity if the first acquisition was not satisfying. However, to maintain a reasonable duration of MR exam for the patient, no more than 1 additional acquisition per vessel was performed.

**Data Analysis**

The acquired PC MRI image series were transferred to a computer and analyzed using a Flow Analysis software (Amiens University Medical Center, Amiens, France). Each series consisted in 40 images (corresponding to 20 phases of the cardiac cycle): 20 amplitude images providing morphologic information and 20 phase images providing velocity measurements. The software automatically extracts the pulsatile components of the signal, and the region of interest (ie, the blood vessel’s cross-section) is then manually segmented. For each vessel of interest, the change in blood flow over the cardiac cycle can then be displayed and exported as a standard text file format.

For right and left OA and SOV, the following parameters (in mL/min) were analyzed: the mean flow ($Q_m$), the maximum flow ($Q_{max}$), the minimum flow ($Q_{min}$), the amplitude of the flow variation ($\Delta Q = Q_{max} - Q_{min}$), the maximum velocity ($V_{max}$, in cm/s), the mean cross-sectional area of the segmented vessel (in mm²) over the cardiac cycle. In order to compare the flow curves of each studied vessel, parameters such as skewness, kurtosis, and area under the curve were computed for each subject using Matlab 2020a (The Mathworks, Natick, MA).

**Statistics**

Statistical analysis was performed using R version 3.5.1 (R Core Team (2017). R: A language and environment for numerical analysis).
statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Results of \( Q_{m}, Q_{\text{max}}, Q_{\text{min}}, \Delta Q, V_{\text{max}}, \) and CSA for all included eyes were compared between patients and controls using a test of Mann-Whitney and a bootstrap hypothesis testing with 10,000 replications. This test, implemented in R (MKinfer package) and corresponding to the method proposed by Efron and Tibshirani,\(^{23}\) was used to control the dependence between the 2 eyes. For each analysis, \( P \)-values were reported for the result of the Mann-Whitney test (\( P \)) and after verification with the bootstrap analysis (\( P_{B} \)). The curve shape parameters were compared between the groups using a test of Mann-Whitney. For each group of subjects, correlations between the hemodynamic parameters (\( Q_{m} \) vs. \( V_{\text{max}} \) and \( Q_{m} \) vs. CSA) measured in the OA and SOV were studied with a Spearman correlation test. Statistical significance threshold was set to 5%.

RESULTS

The study included 42 eyes of 21 subjects: 11 patients of a mean [range] age of 62.36 [31 to 76] years and 10 controls of mean [range] age of 57.60 [42 to 78] years (\( P = 0.52 \)). The clinical characteristics of the included patients and control subjects are detailed in Table 1. Three patients were diagnosed with glaucoma in our department shortly before their inclusion in the study, the other patients had been referred to our clinic by other centers. Within the 12 months following the inclusion, none of the patients underwent glaucoma surgery, 1 underwent bilateral selective laser trabeculoplasty, none of the patients changed their medication. On follow-up examination between 6 and 12 months after the inclusion, 1 eye showed a progression of the MD of \( -1 \) dB on visual field and 2 other eyes showed a mild decrease in the RNFL thickness (of 8 and 11 \( \mu \)m). Eleven series with no detectable flow or too much artifacts could not be reliably processed: the final analysis included 21 OA and 15 SOV in patients and 18 OA and 19 SOV in controls (Fig. 1).

TABLE 1. Characteristics of Patients and Control Subjects

| Characteristic                      | Patients (21 eyes) | Controls (15 eyes) |
|-------------------------------------|--------------------|--------------------|
| Age (mean ± SD) (year)              | 62 ± 12 [31-76]    | 57.60 [42-78]      |
| Sex                                 | M/6 F              | M/4 F              |
| Ethnicity                           | 10 Caucasian       | 9 Caucasian        |
| 1 African                           | 0                  | 1 African          |
| Family history of 1st glaucoma      | 0/10               |                    |
| Systemic hypertension               | 3/11               |                    |
| Glaucoma therapy                    | No treatment 2/11  |                    |
| Prostaglandin analog 6/11           |                    |                    |
| Carbbic anhydrase inhibitor 1/11    |                    |                    |
| Prostaglandin + Alpha2 adrenergic   |                    |                    |
| agonist 2/11                        |                    |                    |
| IOP (mean ± SD) (mm Hg)             | 8.9 ± 6            | 14.2 ± 2           |
| Mean cup-to-disc ratio              | 0.4 ± 0.2          |                    |
| Mean visual field deficit MD (dB)   | -2.3 ± 2.7         |                    |
| Mean ± SD global RNFL thickness (\( \mu \)m) | 92 ± 13           |                    |

The mean ± SD \( Q_{m} \) in the OA was 13.21 ± 6.79 mL/min in glaucoma patients and 15.09 ± 7.62 mL/min in controls (\( P = 0.35 \), \( P_{B} = 0.44 \)). The mean flow (\( Q_{m} \)) in the OA was moderately correlated with the IOP (Spearman correlation: \( r_{s} = 0.4996 \), \( P = 0.03 \)) but not correlated to functional damage by MD (\( r_{s} = 0.1149 \), \( P = 0.68 \)) or RNFL thickness (\( r_{s} = -0.1799 \), \( P = 0.49 \)). The mean ± SD \( Q_{\text{max}} \) in the OA was 25.70 ± 12.08 mL/min and 28.45 ± 10.64 mL/min in the glaucoma group and in the controls, respectively (\( P = 0.22 \), \( P_{B} = 0.49 \)). The mean ± SD ΔQ in the OA was 21.57 ± 10.18 mL/min in the glaucoma patients versus 21.73 ± 6.75 mL/min in the controls, \( P = 0.54 \), \( P_{B} = 0.95 \) (Fig. 2). There was no significative difference in the \( Q_{\text{max}} \), the \( V_{\text{max}} \) and the mean cross-sectional area between the 2 groups (Table 2). The correlation between \( Q_{m} \) OA and \( Q_{\text{max}} \) OA was \( r_{s} = 0.3085 \) (\( P = 0.17 \)) in patients and 0.6450 (\( P = 0.004 \)) in controls; the correlation between \( Q_{m} \) OA and the cross-sectional area was \( r_{s} = 0.6012 \) (\( P = 0.004 \)) in patients and \( r_{s} = 0.4753 \) (\( P = 0.046 \)) in controls.

In the SOV, the mean ± SD \( Q_{m} \) was 6.46 ± 5.50 mL/min in patients and 7.21 ± 6.04 mL/min in controls (\( P = 0.81 \), \( P_{B} = 0.72 \)), while the mean ± SD \( Q_{\text{max}} \) was 9.06 ± 6.67 mL/min in patients and 11.96 ± 9.29 mL/min in controls (\( P = 0.47 \), \( P_{B} = 0.29 \)). The mean ± SD ΔQ was 5.45 ± 2.54 mL/min and 9.09 ± 5.74 mL/min in patients and controls, respectively (\( P = 0.04 \), \( P_{B} = 0.008 \)). The ΔQ was moderately correlated with IOP (\( r_{s} = 0.6169 \), \( P = 0.02 \)) but not with the level of visual field damage MD or RNFL thickness. The mean ± SD \( Q_{\text{min}} \) in the SOV was 3.61 ± 5.14 mL/min in patients and 2.87 ± 4.75 mL/min in controls.

FIGURE 1. Flow chart.

FIGURE 2. Variation of flow in the ophthalmic artery (OA) during the cardiac cycle in glaucoma patients and in control subjects.
TABLE 2. Results of Flow Measurements in the Ophthalmic Artery and in the Superior Ophthalmic Vein in Glaucoma Patients and in Controls.

|                      | Ophthalmic Artery | Superior Ophthalmic Vein |     |
|----------------------|------------------|--------------------------|-----|
|                      | (n = 21)         | (n = 18)                 | P   |
|                      |                  |                          | P   |
|                      |                  |                          |     |
| Q (mL/min)           | 13.21 ± 6.79     | 15.09 ± 7.62             | 0.35 |
| Qmax (mL/min)        | 25.70 ± 12.08    | 28.45 ± 10.64            | 0.22 |
| Qmin (mL/min)        | 4.13 ± 5.95      | 6.72 ± 6.04              | 0.21 |
| ΔQ = Qmax − Qmin     | 21.57 ± 10.18    | 21.73 ± 6.75             | 0.54 |
| (mL/min)             |                  |                          |     |
| R1 = (Qmax − Qmin)/Qmax | 0.86 ± 0.2     | 0.80 ± 0.15              | 0.34 |
| Vmax (cm/s)          | 35.45 ± 11.15    | 35.71 ± 13.47            | 0.92 |
| CSA (mm²)            | 2.36 ± 0.75      | 2.44 ± 0.71              | 0.67 |
|                      |                  |                          |     |
|                      |                  |                          |     |
|                      |                  |                          |     |

Bold P value indicates statistical significance.

The P-values reported are the results of a Mann-Whitney test (P) and verification by bootstrap technique to control the dependence between the 2 eyes (Pstr).

Mean ± SD of the Mean Flow Qm, the Maximal Flow (Qmax), the Minimal Flow (Qmin) during the cardiac cycle, the variation of flow during the cardiac cycle ΔQ = Qmax − Qmin, the maximal velocity vmax, and cross-sectional area CSA (mm²).

DISCUSSION

The disease mechanism underlying glaucoma is still the subject of intense investigation. In addition to the IOP, the most recent pathophysiological models of glaucoma notably include the role of ocular perfusion pressure,22 translamina cribrosa pressure,23 intracranial cerebrospinal (CSF) pressure and optic nerve CSF pressure.24 Glaucoma is a disease of pressure, and the easily distensible wall of the veins makes them sensitive to pressure changes. Our study with flow PC MRI showed different characteristics of the hemodynamics of the SOV in patients compared with controls.

The phase contrast imaging requires an encoding velocity to be chosen a priori based on the maximal velocity usually expected in the vessel. In vessels with a high variability of flow between subjects, this chosen encoding velocity may be too low, yielding artifacts, or too high, making the flow undetectable on phase contrast images. Despite repeated acquisition, some of the acquired datasets had to be excluded from final analysis because of these artifacts. This was especially seen in the SOV of patients, in which group 7 of 22 acquired series were excluded. Measuring the orbital venous blood flow by PC MRI is more difficult than in arteries17 because of its low pulsatility and its high variability of course and size. It is possible that the number of excluded series in the SOV of patients interfered with the results, but it may also suggest that the blood velocities in this group might be more likely to be outside the expected range. While the artifacts inherently associated with phase contrast imaging may be one limitation of its possible applications, to the best of our knowledge it is the only imaging modality that is able to provide actual blood flow values and flow waveform data in the orbital vessels. The other limitations of our study include the only one measurement per vessel and absence of interoperator repeatability assessment. The small number of participants, their relatively young age and the low level of glaucoma damage of the patients, were mostly related to the exclusion of patients with any systemic or topical beta-blocker medication, with known past ocular history or with neurovascular or cardiovascular disease.

Although glaucoma patients showed lower flow values (mean flow, maximal, and minimal flow over the cardiac cycle) in the OA and the SOV, we were not able to demonstrate a significant difference with control subjects, and the flow curves were not different between glaucoma and controls. It is now well demonstrated with color Doppler imaging25 that glaucoma is associated with low blood flow velocities and high RI in the ophthalmic, central retinal, and short posterior ciliary arteries. Using Color Doppler imaging...

FIGURE 3. Variation of flow in the superior ophthalmic vein (SOV) in patients and in controls.
The glaucoma patients in this study demonstrated a significantly lower variation of flow over cardiac cycle in the SOV, meaning that the difference between maximal and minimal flow during a cardiac cycle was lower. They were treated with topical IOP-lowering drugs that increase the uveo-scleral flow, when this pathway accounts for only ~20% of the outflow in normal subjects. Could the increased proportion of uveo-scleral pathway be responsible for some change in the venous pulsatility? As per the European Glaucoma Society treatment guidelines,27 most of our patients had started a treatment at the ocular hypertension or glaucoma suspect stage and only 2 patients with untreated glaucoma could be included. In the same way, the outflow might be distributed in the ophthalmic veins (not only superior but also medial and inferior ophthalmic veins) in different proportions in glaucoma patients. Finally, a decrease in the venous pulsatility might be the consequence of an increase in the resistance to the outflow, either from a change in the capillaries (vascular dysfunction) or from a change in the orbital and intracranial environment. Investigating retinal venous pulsation, researchers found that spontaneous venous pulsation was observed less frequently in glaucoma patients than in glaucoma suspects or controls, and that the force required to induce venous pulsation was strongly related to the amount of visual field damage,28 RNFL thickness,29 disc excavation,30 and disc hemorrhages.31 Interestingly, it seemed that a reduction of IOP was strongly associated with a reduction of venous pulsation pressure.32 Studies using ophthalmodynamometry showed that the retinal venous pulsation greatly depended on CSF pulse,33,34 and suggested that retinal venous pulsation was related to the transmural pressure gradient experienced by the central retinal vein resulting, in glaucoma, in increased retinal vein shear.33

In our patients, we did not find the expected correlation between flow and velocity in the SOV, while it was present in controls. The lack of correlation between the mean flow and the mean maximum velocity may reflect a change in the structure of the vessel or in the hydrodynamics state of the flow. In patients, the relation between the mean flow and the section seemed also different: for a same increase in flow, the patients demonstrated a bigger increase in section (Fig. 4). The change of section can be considered as a hemodynamic response to the change of pressure (ie, the change of flow, as pressure and velocities are interrelated) meaning that in patients, there could be an increase in the downstream resistance to the flow. Previous studies showed that the lumbar CSF pressure was lower in glaucoma patients than controls35 and the amount of glaucomatous damage to the optic nerve was more strongly correlated with the transmalar pressure difference than with the IOP or CSF pressure alone.23,36 As intracranial blood flow and CSF flow dynamics are strongly interrelated,15,20 the pressure in the cavernous sinus might also be changed. The orbital venous outflow drains directly from the SOV to the cavernous sinus, so any change of environment in the cavernous sinus would be likely to yield a change in the flow waveform of the SOV. Our study demonstrated (i) a lower pulsatility, (ii) a loss of correlation between flow and velocity, (iii) a different relationship between flow and section, in the SOV in the patients, suggesting a change of the venous hemodynamics state in glaucoma. In the future, the developments of constantly improving imaging techniques such as 4D flow MRI17 may be key in the understanding of the relationship between the blood flow impairment, the venous flow changes and the CSF pressure state in glaucoma.

In conclusion, if glaucoma patients showed lower mean flow in the OA and in the SOV, this study was not able to demonstrate a significant difference with control subjects. However, the patients had a lower variation of flow in the SOV during cardiac cycle than controls, as well as different hemodynamic responses to the variation of flow, suggesting an increased resistance to outflow, either from a change in the capillaries and vascular dysfunction, or from a change in the orbital or intracranial pressure environment.

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FIGURE 4. Correlation between A) Maximal Velocity during the cardiac cycle ($V_{\text{max}}$), and B) Cross sectional area, with the mean flow over cardiac cycle (Qm) in the superior ophthalmic vein in glaucoma patients and in controls.
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