

Retinal Vessel Diameters Change Within 1 Hour of Intracranial Pressure Lowering

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Purpose: We tested the hypotheses that retinal venule diameter (Dv) is associated with baseline intracranial pressure (ICP) level and that Dv is reduced shortly after ICP lowering.

Methods: Dv and arteriole diameter (Da) were extracted from scanning laser ophthalmoscopic images in 40 eyes of 20 adult human subjects (10 with and 10 without papilledema) immediately before and after measurement of ICP (range, 10–55 cm H₂O) and ICP lowering by cerebrospinal fluid (CSF) drainage via lumbar puncture (LP). Generalized estimating equations (GEE) modeled the relationship between baseline ICP, Da and Dv before LP. Additional GEE modeled the relationship between initial ICP and change in Da and Dv (post-LP – pre-LP) following ICP lowering.

Results: Test–retest variability of diameter measurements ranged from 0.1 to 2.9 μm (0.1%–2.72%). Neither Da nor Dv pre-LP was associated with baseline ICP level ($P = 0.140$ Dv, $P = 0.914$ Da, GEE). Da and Dv change after ICP lowering was associated with baseline ICP, with vessel diameters increasing with lower baseline ICP and decreasing with elevated initial ICP ($P = 0.030$ baseline ICP vs. Dv change, $P = 0.012$ baseline ICP vs. Da change, GEE models).

Conclusions: Retina arteriole and venule diameters change immediately following ICP lowering. The direction of change is dependent on the initial ICP; both increased in subjects with high ICP and both decreased in subjects with normal ICP.

Translational Relevance: The relationship between initial ICP and direction of retinal vessel size change following ICP lowering suggests a potential effect of ICP on cerebral and ocular hemodynamics that is relevant when considering the use of retinal vessel measurements as a clinical marker of ICP change.

Introduction

Idiopathic intracranial hypertension (IIH) affects 1:100 000 individuals with a 20-fold higher prevalence in young, otherwise healthy women.¹ The overall incidence is rising in association with increasing prevalence of obesity.² In this condition, elevated intracranial pressure (ICP) causes morbidity through headaches, double vision from cranial nerve VI palsies and vision loss, sometimes to the extent of irreversible blindness. A presumably related condition, the visual impairment and intracranial pressure (VIIP) syndrome, which consists of optic nerve swelling and

ocular globe flattening, has been observed in astronauts following long duration space flight.³ A clinical challenge in IIH, VIIP, and other states with secondarily elevated ICP, such as brain tumors and venous sinus thrombosis, is monitoring ICP, which is the target of treatment. Accurate methodologies, such as spinal taps and ICP monitors, can provide this information, but are limited in their use due to their invasive nature and associated morbidity. Beyond traditional clinical observations of papilledema appearance and visual function, a number of ophthalmic characteristics, including retinal vessel features, are under development as markers of ICP. These are clinically attractive because they can be visualized

noninvasively through the pupil using imaging technologies with high spatial and temporal resolution.

There is theoretical support for retinal vessel diameter changes in association with ICP changes. Guidoboni et al.⁴ modeled retinal arteriole and venule pressures (directly related to diameter) based on inputs of intraocular pressure (IOP), optic nerve tissue pressure, and feeding arterial and draining venous pressures.⁴ ICP influences these feeding and draining blood pressures due to its action on the intracranial vasculature. ICP affects optic nerve tissue pressure through compression of the optic nerve by the pressure of cerebrospinal fluid (CSF) in the optic nerve sheath. Swelling of the optic nerve head (papilledema) caused by this retrobulbar compression further compresses the feeding and draining blood vessels.

There is experimental support for retinal vessel changes in association with ICP states. Firsching⁵ demonstrated retinal venous outflow pressure to be correlated with ICP. Furthermore, the idiopathic intracranial hypertension treatment trial (IIHTT) reported reduced arteriole:venule (A:V) diameter ratio to be associated with the degree of optic disc swelling.⁶ Acute ICP elevation in animal models is associated with retinal venule dilation.^{7,8} In humans, retinal venule widening has been observed with baseline high ICP states⁹ and retinal venule constriction has been observed following long-term ICP lowering.¹⁰ However, to our knowledge retinal vessel diameter changes in response to acute ICP reduction have not been reported in humans.

We tested the hypotheses that retinal venule caliber is associated positively with baseline ICP level and that retinal venule diameter is reduced shortly after ICP lowering.

Methods

Subjects

Adult patients scheduled to undergo lumbar puncture (LP) for a clinical indication were recruited from the University of Illinois at Chicago Ophthalmology and Neurology clinics. Exclusion criteria were ophthalmic diseases other than possible papilledema. This research adhered to the tenets of the Declaration of Helsinki. Informed consents were obtained from all participants after explanations of the nature and possible consequences of the study. The study was approved by the University of Illinois at Chicago

institutional review board. Age, sex, ethnicity, and reason for LP were recorded from the medical record.

Experimental Design

Within 1 hour before LP, high resolution infrared scanning laser ophthalmoscopy (SLO) images (1536×1536 pixels covering a retinal area of $30^\circ \times 30^\circ$, centered on the optic nerve head) were obtained (Spectralis; Heidelberg Engineering, Heidelberg, Germany) in both eyes of each subject. In a single eye of four subjects, three images were obtained during the same imaging session to assess variability. IOP and blood pressure were recorded using Tono-Pen Avia (Reichert Technologies, Ametek, Inc., Buffalo, NY) and automated cuff (BP785, Omran Healthcare, Inc., Omran Corporation, Kyoto, Japan). Mean arterial pressure (MAP) was calculated based on systolic and diastolic values. Near visual acuity of each eye was measured using the subject's own glasses, pinhole occluder, and Rosenbaum pocket vision screener. LP position was recorded. During the LP, opening pressure was recorded as the maximum height of the CSF column above the spinal column (in cm) before collection of CSF. ICP lowering was accomplished by CSF removal during the LP. Within 1 hour after LP high resolution SLO images were obtained in the same manner as those obtained before LP.

Image Analysis

SLO images were analyzed using a validated methodology developed by the investigators using MATLAB (MathWorks, Natick, MA), which has been described in detail previously.^{9,11} All retinal vessels between 2.0 and 2.5 mm radius rings centered on the optic nerve head were segmented automatically after binarizing the image. Center lines were determined along each vessel segment. Intensity profiles of lines perpendicular to the center lines were analyzed to derive vessel diameter from the full width at half maximum of the intensity profiles. Basing the measurement on relative intensity profiles minimizes the effect of overall image brightness on vessel diameter measurements. Diameter measurements were obtained along each vessel segment and a mean diameter was calculated. Figure 1 shows an example of an SLO image with the vessel segment boundaries outlined. The four most prominent vessels, two arterioles and two venules in each eye (typically superior/inferior temporal relative to the optic disc), were selected based on manual review of the images as described previously.⁹ The diameters of these vessels

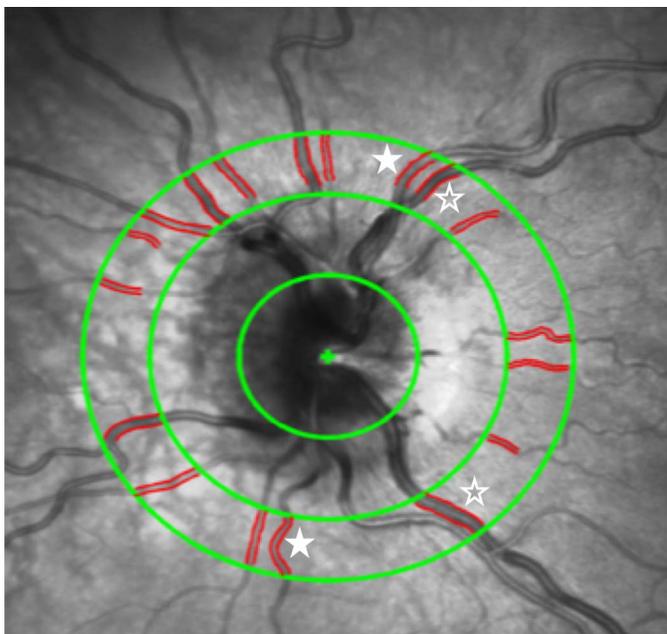


Figure 1. SLO image of swollen optic nerve with retinal vessels segmented. Outer two *green rings* are the boundaries of the region of interest. Automatic vessel segmentation shown in *red*. *Filled stars* denote selected arterioles. *Outlined stars* demonstrate selected venules.

were used in the comparative analyses. Paired images (pre-/post-LP) were reviewed to ensure the same vessels were selected on both images.

Statistical Analysis

Test–retest variability was assessed using the diameters of the four selected vessels on each of the three images taken during the same imaging session for four eyes. Variability was calculated as the percent and absolute differences between the largest and smallest measurements for each of the four vessels of interest in each eye. Pearson correlation analysis was applied to the largest and smallest vessel measurements for the four vessels of interest in each eye.

Based on sample size estimates, a target enrollment of 10 subjects with high ICP and 10 with normal ICP was chosen. This had 0.8 power to detect retinal vein diameter differences between subjects with high and normal baseline ICP states based on our prior data (effect size 1.34, 2-tailed *t*-test for independent samples, $\alpha = 0.05$).¹² This had over 0.9 power to detect retinal vein diameter decrease within subjects based on prior data (effect size 1.7–1.84, paired *t*-test, $\alpha = 0.05$).¹² These power estimates are conservative, since we used generalized estimating equation models

that used measurements in both eyes of subjects and accounted for intrasubject correlation.

To assess the relationship between baseline ICP and retinal vessel diameter, generalized estimating equation (GEE) models accounting for within-subject correlations of individual vessel size on pre-LP images (continuous variable) as a function of ICP (LP opening pressure) (continuous variable) using a linear link function were constructed (SPSS v24; IBM, Inc., Armonk, NY). Statistical hypothesis testing was based on evaluating for a slope different from zero with $P = 0.05$ as the threshold. Arterioles and venules were studied separately. Arteriole:venule ratio also was studied. Age, IOP, and MAP were included in the models as covariates.

To assess the relationship between change in vessel size following acute ICP lowering, GEE intercept–only models of change in individual vessel size (difference between pre- and post-diameter) were constructed. Statistical hypothesis testing was based on evaluation for an intercept different from zero with $P = 0.05$ as the threshold. Arterioles and venules were studied separately. Arteriole:venule ratio change also was studied. Absolute and percent change in vessel size were modeled. Age, IOP, MAP, and initial ICP were included in the models as covariates. A subgroup analysis was performed limited to subjects ($n = 9$) meeting diagnostic criteria for IIH (i.e. papilledema and opening pressure greater than or equal to 25cm).

Results

Of 34 subjects enrolled, 14 did not complete the LP. Therefore 20 subjects (15 [75%] female; age, 23–86 years) with 40 eyes were included in the analysis. LPs were performed for workup of neuro-inflammation/multiple sclerosis ($n = 3$), dementia ($n = 4$), and possible IIH ($n = 13$). LP was performed in the lateral decubitus position in 19 patients and in the prone position in one. Baseline ICP (opening pressure) range was 10 to 55 cm H₂O. Seven subjects had normal ICP (≤ 20 cm H₂O), three had borderline ICP ($20 < \text{ICP} < 25$ cm H₂O), and 10 had elevated ICP (≥ 25 cm H₂O). Papilledema was seen in one subject with borderline and nine with elevated ICP. MAP was 110.1 ± 12.1 and IOP was 17.3 ± 3.6 mmHg (Table).

Test–retest variability of diameter measurements ranged from 0.1 to 2.9 μm (0.1%–2.72%) and was similar for arterioles (0.1–2.9 μm [0.1%–2.72%]) and venules (0.3–2.7 μm [0.3–1.79%]). Pearson correlation coefficient (*r*) for the 16 vessels was 0.999 and was similar for arterioles only ($r = 0.998$) and venules only

Table. Subject Characteristics

Age	Median 36, range 23–86 y
Sex	15 (75%) female
Reason for LP	Neuro-inflammation/MS: 3 (15%) Dementia: 4 (20%) Possible IIH: 13 (65%)
Baseline ICP	Normal: 7 (35%) Borderline: 3 (15%) Elevated: 10 (50%)
Blood pressure (MAP)	110.1 ± 12.1 mm Hg
IOP	17.3 ± 3.6 mm Hg

MS, multiple sclerosis.

($r = 0.998$). The differences in vessel measurements between eyes within subjects were $12.0 \pm 10.0 \mu\text{m}$ (venules) and $12.0 \pm 11.0 \mu\text{m}$ (arterioles). Vessel diameter correlations between eyes were 0.48 ($P = 0.03$ venule) and 0.40 ($P = 0.08$ arteriole).

Neither venule diameter, arteriole diameter, nor A:V diameter ratio pre-LP was associated with baseline ICP level ($P = 0.140$ venule, $P = 0.914$ arteriole, $P = 0.331$ A:V ratio GEE models; Fig. 2). Pre-LP venule diameters decreased with increasing age ($P < 0.0005$, GEE models), but were not associated with MAP or IOP. Pre-LP arteriole diameters decreased with increased MAP ($P = 0.043$, GEE models), but were not associated with age or IOP. There remained no statistically significant association between arteriole or venule diameter and baseline ICP in multivariate models that included these covariates.

Overall, neither arteriole diameter, venule diameter, nor A:V diameter ratio change (pre-LP – post-LP) was associated with acute lowering of ICP ($P = 0.098$ venule, $P = 0.91$ arteriole, $P = 0.144$ A:V ratio, GEE intercept only models). However, there was an association between baseline ICP and vessel diameter change following ICP lowering ($P = 0.027$ venule, $P = 0.013$ arteriole, GEE models of absolute change; $P = 0.030$ venule, $P = 0.012$ arteriole, GEE models of relative change; Fig. 3). The relationship was such that arterioles and venules increased in size after ICP lowering when initial ICP was normal, whereas arteriole and venule diameter decreased after ICP lowering when initial ICP was elevated. There was no association between ICP and A:V ratio change ($P = 0.297$ absolute change, $P = 0.282$ relative change, GEE models) Neither venule nor arteriole diameter change was associated with age, MAP, or IOP. When

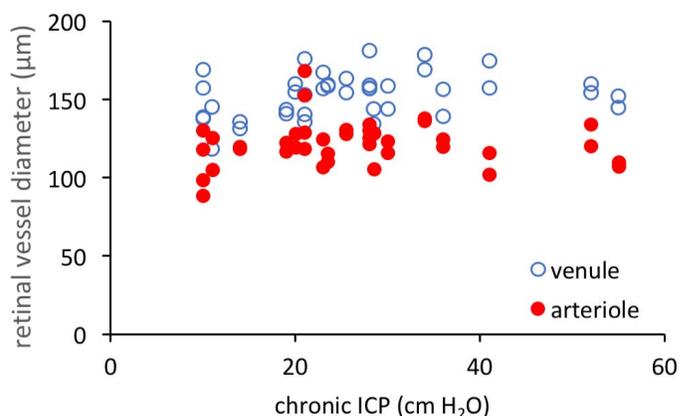


Figure 2. Relationship between baseline ICP and diameter of retinal vessels. Each marker represents average of arteriole (filled marker) or venule (unfilled marker) diameters within an eye.

considering only patients with untreated IIH ($n = 9$), venule diameter decreased following LP, but this did not meet statistical significance ($P = 0.074$, GEE intercept only model) and the arteriole diameter did not change significantly ($P = 0.207$, GEE intercept only model).

Discussion

We investigated retinal arteriole and venule diameters as markers of ICP by analyzing SLO images of human retinas obtained within 1 hour before and after ICP lowering via CSF draining using LP. Unique features of this study included a prospective study of retinal vessels as a function of baseline ICP, assessment of short-term retinal vessel diameter changes following ICP lowering, and inclusion of subjects with a large range of ICP levels (i.e., not restricted to subjects with high ICP). We did not find support for the hypotheses that retinal venule diameters are associated positively with baseline ICP level. We found support for the hypothesis that retinal venule diameters are reduced following ICP lowering among subjects with high initial ICP. Our results contribute to the evolving literature on retinal changes associated with high ICP and the broader field of retinal vessel size as a marker of neurological diseases.^{13,14}

Neither retinal arteriole nor venule diameter was associated with baseline ICP levels in the cross-sectional component of this study. The arteriole results matched those from our prior retrospective study.⁹ However, the venule results were different from our prior study, in which venule diameter was

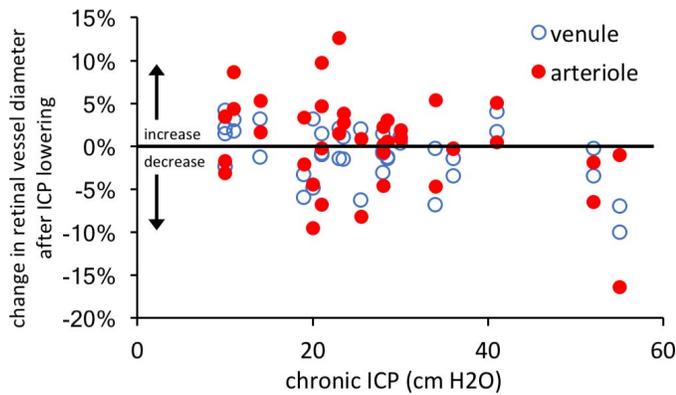


Figure 3. Relationship between baseline ICP and change in diameter of retinal vessels immediately following ICP lowering via CSF drainage by LP. Each marker represents average change of arteriole (filled marker) or venule (unfilled marker) diameters within an eye. Markers above the black line represent diameter increase. Markers below the black line indicate diameter decrease.

larger in subjects with high compared to normal ICP. The prior study was similar to the current study in terms of analysis of SLO images obtained before LP, but it differed from the current study by smaller sample size, longer interval between imaging and LP (prior study, mean 12.5 days; range, 0–53 days vs. within 1 hour in the current study), inclusion of neurologically normal subjects in the normal ICP group, and categorical versus continuous statistical analysis. Another factor that can account for the discrepancy in observations is covariates, such as age, MAP, and IOP, which confounded the relationship between ICP and vessel diameter and were not included in the prior study. While the current study considered age, IOP, and MAP, a larger study is necessary to accommodate consideration of other covariates, including medications and comorbidities. Taken together, the two studies suggest that although venule diameter may be enlarged in some subjects with high ICP, it is not a promising marker for baseline ICP levels between subjects.

A:V diameter ratio was not associated with baseline ICP level in the cross-sectional component of this study. In comparison, a large interventional trial of subjects with high ICP and papilledema due to IIH, the IIHTT, reported an association between baseline papilledema grade and increased A:V ratio.⁶ Together, these studies highlight possible differences in two potential factors contributing to retinal vessel size and A:V ratio. The first is ICP acting on the intracranial circulation and optic nerve circulation to alter vessel resistances and pressures with resulting effects on retinal vessel pressures and diameters.

These effects have been well documented in short-term studies of ICP change within animals and humans, including in the current study.⁸ However, the current study did not find differences between individuals at baseline to suggest use of retinal vessel diameters as a clinical marker of baseline ICP. The second is direct tissue pressure exerted by swollen ganglion cell axons on the central retinal vessels to alter their resistance, with resulting effects on retinal vessel pressures and diameters. The IIHTT results support this mechanism as one that could allow distinction between individuals based on retinal vessel diameters, though clinical use is questionable since distinguishing papilledema severity is not a clinical challenge.

In the longitudinal component of this study the direction of change in retinal venule diameter following ICP lowering was different depending on the initial ICP level. Among subjects with elevated ICP, venule diameters decreased following ICP lowering. Though short-term venule diameter changes following ICP lowering in humans have not been reported previously to our knowledge, they are in agreement with previously reported retinal venule size decrease weeks to months following ICP lowering interventions in subjects with high ICP.^{9,10} The corollary to these observations is retinal venule diameter increasing following ICP increase from a normal to an elevated state, which have been reported in the short term in animal models.^{7,8} A possible explanation for these observations is that manipulation of ICP in an elevated range is associated with changes in cerebral venous resistance, with higher ICP being associated with increased resistance, decreased flow, and increased venous pressure in the brain with resulting increased retinal venule pressure and diameter in the eyes. Theoretical and in vivo studies support this notion of dependence of cerebral venous hemodynamics on ICP in high ICP states.^{15,16} Our results combine with prior results and theory to support retinal venule size as a marker of short-term ICP changes in subjects with high ICP. In contrast, in subjects with initial normal ICP, retinal venule diameter increased following ICP lowering. This unexpected result requires further investigation, since to our knowledge ICP manipulation in this population has not been studied previously. A possible explanation is that the effects of lowering ICP on cerebral hemodynamics are dependent on the initial ICP state.

In the longitudinal component of this study the direction of change in retinal arteriole diameter

following ICP lowering was different depending on the initial ICP level. Retinal arteriole changes following ICP lowering have not been observed in prior studies that reported venule diameter change.^{9,10} This might be attributable to one of the unique features of this study, which is the time scale with which observations were made following ICP intervention, allowing us to capture a transient change that does not persist in the long term and, therefore, was not detected in other studies. Future studies that assess vessel diameter measurements in the short, medium and long term following ICP lowering would provide insight into the dynamics of retinal arteriolar size and inform potential clinical application of such measurement on earth and in microgravity conditions with regards to the VIIP syndrome.

A limitation of this study is the sample size. The sample was of a broad population of age and disease with the goal of obtaining a broad sample of ICP and this limits subgroup analyses on the diseased population of interest with high ICP. It was not powered to study associations between age, blood pressure, IOP, and retinal vessel size. These parameters were included in models for the purposes of adjusting for them in the relationship between the variables of interest. The normal ICP subjects were not normal neurologically due to their clinical indication for LP.

In conclusion, we demonstrated that arteriole and venule diameters change immediately following ICP lowering and that the direction of change is dependent on the initial ICP. In subjects with normal ICP, venule and arteriolar diameters increased, which was unexpected. In subjects with high ICP, venule and arteriolar diameter decreased, as expected. The relationship between initial ICP and direction of retinal vessel size change following ICP lowering suggests a potential effect of ICP on cerebral and ocular hemodynamics. Further study with a larger sample size is necessary to determine the time course of retinal vessel size change following ICP lowering interventions to further their candidacy as a clinical marker in patients with high ICP.

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