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Spontaneous Retinal Venous Pulsation and Disc Hemorrhage in Open-Angle Glaucoma

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PURPOSE. To investigate the relationship of spontaneous venous pulsation (SVP) with disc hemorrhage (DH) in open-angle glaucoma (OAG).

METHODS. Spontaneous venous pulsation was assessed and compared using a confocal scanning laser ophthalmoscope movie tool in 52 eyes of 52 patients with DH, and 111 eyes of 111 patients in without DH. Logistic regression analysis was used to determine the factors associated with the occurrence of DH.

RESULTS. The frequency of SVP was 60.7% in overall patients with OAG. The absence of SVP was associated with lower untreated IOP (OR 0.880; $P = 0.045$), longer axial length (OR 1.654; $P = 0.007$), and worse visual field mean deviation (OR 0.884; $P = 0.035$). The absence of SVP was not significantly associated with DH by logistic analysis (OR 0.844; $P = 0.626$). Better visual field mean deviation (OR 1.098; $P = 0.043$), lower untreated IOP (OR 0.886; $P = 0.021$), and the tendency to cold hands (OR 2.688; $P = 0.032$) were associated with DH.

CONCLUSIONS. In consecutive patients with OAG, the absence of SVP was not associated with DH.

Keywords: spontaneous retinal venous pulsation, disc hemorrhage, open-angle glaucoma

Disc hemorrhage (DH) is frequently observed in patients with glaucoma,^{1,2} and is now widely accepted as a risk factor for glaucoma progression.³⁻⁸ The pathogenesis of DH, however, is not yet fully understood.

It has been suggested that DH occurs from vessel damage arising with mechanical collapse of the lamina cribrosa⁹ or the disruption of the capillary network around the border of retinal nerve fiber layer (RNFL) defect during the process of RNFL defect enlargement.⁴ However, DH has been observed more frequently in patients with normal-tension glaucoma (NTG) than in patients with high-tension glaucoma,¹⁰⁻¹² and in early rather than in late stages of disease.^{2,13} Hemodynamic disturbances, including ischemic microinfarction in the optic nerve head,¹⁴ disorders of retinal circulation,¹⁵ decrease in capillary perfusion,¹⁶ and primary vascular dysregulation (PVD)¹⁷ also have been proposed as causes of DH; these support vascular factors having a significant role in the pathogenesis of DH.

Spontaneous retinal venous pulsation (SVP) is seen as a subtle variation in the caliber of the retinal vein of one or more vessel segments near or on the optic disc. The pulsations are caused by variation in the pressure gradient along the retinal vein as it traverses the lamina cribrosa.¹⁸ Recently, we reported that SVP is less frequent in glaucomatous eyes with lower untreated IOP.¹⁹ Because the absence of SVP likely is due to increased resistance of the retrolaminar central retinal vein (CRV),²⁰ it has been suggested that elevated resistance of CRV in NTG may be one of the contributing factors to the higher prevalence of DH in NTG.^{19,21}

The purpose of the present study was to investigate the relationship of SVP and DH in open-angle glaucoma (OAG) and, particularly, whether the absence of SVP is associated with DH in these eyes.

MATERIALS AND METHODS

This investigation was a retrospective analysis of serial optic disc photographs and fundus movie recording of consecutive OAG patients from a database of patients examined for glaucoma management between November 2010 and May 2012 at Seoul National University Bundang Hospital. This study was approved by the Bundang Seoul National University Hospital Institutional Review Board and followed the tenets of the Declaration of Helsinki.

Before the study, each patient underwent a complete ophthalmic examination, including visual acuity assessment, refraction tests, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, and dilated stereoscopic examination of the optic disc. They also underwent central corneal thickness (CCT) measurement (Orbscan II; Bausch & Lomb Surgical, Rochester, NY, USA), axial length measurement (IOL Master ver. 5; Carl Zeiss Meditec, Dublin, CA, USA), stereoscopic disc photography, red-free RNFL photography (EOS D60 digital camera; Canon, Utsunomiya, Tochigiken, Japan), standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec), and peripapillary RNFL thickness measurement by

spectral domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany).

To be included, subjects were required to have diagnosed OAG and to have best-corrected visual acuity of 20/40 or greater and clear media. Open-angle glaucoma was defined as the presence of glaucomatous optic nerve damage and associated visual field defect without ocular disease or conditions that may elevate the IOP. Glaucomatous visual field defect was defined as outside normal limit on glaucoma hemifield test; or three abnormal points with P less than 5% probability of being normal, one with P less than 1% by pattern deviation; or pattern standard deviation of 5%, confirmed on two consecutive tests. A visual field measurement was considered as reliable when false-positive/negative results were less than 25% and fixation losses were less than 20%.

Eyes that had a history of ocular surgery other than uncomplicated cataract surgery, history of ocular trauma and uveitis, or other coexisting retinal or neurologic diseases that could have affected the visual field were excluded from analysis. Eyes with poor quality of movie recording (media opacity and severe eye movement) were also excluded. Further, patients with previously unknown untreated IOP (average of at least two measurements before applying IOP-lowering medications) were excluded. Only reliable visual field tests were included in the analysis. In cases in which both eyes of a subject were eligible for the study, a randomly selected eye was included.

Eyes were classified into DH group and control group. The DH group was defined as OAG patients in whose eyes DH was present on the stereoscopic disc photography taken on the day of movie clip recording. The control group was selected from OAG patients who were followed for more than 4 years. Patients in whose eyes DH has never been observed were included in the control group. We compared sex, age, diagnosis, associated systemic abnormalities (diabetes mellitus, systemic hypertension, migraine, tendency to cold hands) obtained through history taking²² between the DH group and the control group.

Assessment of the Spontaneous Retinal Venous Pulsation

The SVP was assessed by a confocal scanning laser ophthalmoscope (Spectralis HRA; Heidelberg Engineering) movie tool, as previously described.¹⁹ In brief, the real-time fundus movies centered on the optic nerve head were recorded for 20 seconds after pupil dilation. The recorded movie clip was reviewed after adjustment of image movement by an “eye movement correction tool” installed in the device by two glaucoma specialists (MK, T-WK), who independently evaluated the presence of SVP. The presence of SVP was defined when at least partial vein wall collapse indicated by inward movement was observed on the optic disc or near the disc margin. Agreement on the presence of SVP was evaluated between the two observers. All disagreements were resolved by a third adjudicator (EJL).

Data Analysis

Interobserver reproducibility for determining the presence of SVP was assessed using kappa statistics. Strength of agreement was categorized according to the method proposed by Landis and Koch²³: 0 = poor, 0 to 0.20 = slight, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial, and 0.81 to 1.00 = almost perfect. Statistical analyses were performed with Statistical Package for the Social Sciences (version 18.0; SPSS, Inc., Chicago, IL, USA). Two groups of subjects were compared using the independent t -test and the χ^2 test, and a P value less

FIGURE. The untreated IOP of a 59-year-old woman was 14 mm Hg, and the IOP at the time of recording was 10.5 mm Hg with ocular hypotensive medication. Disc hemorrhage (arrows) was observed at the inferotemporal sector (left) and then again 6 months later (right).

than 0.05 was accepted as significant. Logistic regression analysis was used to determine the factors associated with DH and the absence of SVP. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Variables found to be significant in the univariate analysis were included in the multivariate analysis.

RESULTS

A total of 508 OAG patients who underwent fundus movie clip recording and stereoscopic disc photography on the same day were initially selected from the patient database. Based on the stereoscopic disc photography, 60 individuals had DH in at least one eye. Of these, eight patients were excluded because of unknown untreated IOP ($n = 4$) or history of intraocular surgery ($n = 4$). For the 448 patients who had no DH on the day of recording, previous fundus photographs and medical records were reviewed. Through this process, 122 patients who had no history of DH for at least 4 years were identified. Of these, 11 were excluded because of unknown untreated IOP ($n = 3$) or history of intraocular surgery ($n = 8$), leaving a final 111 control subjects without DH. Total follow-up period for control subjects was 75.6 ± 17.7 months, and the number of examinations was 25.7 ± 7.8 times with mean follow-up interval of 3.1 ± 0.9 months. Disc photographs were taken every 11.2 ± 3.2 months for the control subjects. A representative patient is shown in the Figure and Supplementary Video.

The characteristics of the patients with DH ($n = 52$) and without DH ($n = 111$) are presented in Table 1. Patients with DH had lower untreated IOP, better mean deviation (MD) of visual field, and more commonly reported cold hands than individuals without DH. There were no significant differences between the two groups regarding age, sex, history of diabetes mellitus or systemic hypertension, history of migraine, spherical equivalent, IOP at the time of Spectralis HRA, CCT, axial length, and presence/absence of SVP (all $P > 0.05$).

The frequency of SVP in overall OAG patients of the study was 60.7%. The interobserver agreement was almost perfect for the presence/absence of SVP (kappa value = 0.857, $P < 0.001$). Disagreements between the two observers occurred in 11 patients (6.75%), and were resolved by a third adjudicator. The frequency of SVP was 59.5% in patients without DH, and 63.5% in patients with DH ($P = 0.731$). There was 80% power to detect a difference in the frequency of SVP of 23% between the DH group and control group at a significance of 5%. Of the DH group, DH was found only once on the day of movie clip recording in 31 eyes (59.6%, single DH group), and 21 eyes (40.4%) had additional DH either before or after the movie clip

TABLE 1. Demographic and Descriptive Statistics of OAG Patients With and Without DH

Variables	Patients With DH, 52 Eyes of 52 Patients	Patients Without DH, 111 Eyes of 111 Patients	P Value
Age, y*	59.83 ± 12.61	62.15 ± 12.22	0.269
Female, %†	31 (59.6)	52 (46.7)	0.135
Laterality, right eye %†	23 (44.2)	56 (50.5)	0.614
Diabetes mellitus†	7 (13.5)	20 (18.0)	0.508
Systemic hypertension†	11 (21.2)	38 (34.2)	0.102
Migraine†	5 (9.6)	7 (6.3)	0.523
Tendency to cold hands†	14 (26.9)	13 (11.7)	0.023
Refractive errors, diopters*	−0.98 ± 2.88	−1.55 ± 2.87	0.239
Untreated IOP, mm Hg*	15.74 ± 2.94	17.86 ± 4.81	0.001
IOP at imaging, mm Hg*	13.22 ± 2.87	13.52 ± 2.68	0.514
CCT, μm*	563.63 ± 31.09	565.33 ± 33.82	0.772
Axial length, mm*	24.14 ± 1.22	24.33 ± 1.36	0.497
MD, dB*	−3.27 ± 4.07	−5.40 ± 5.71	0.007
Absence of SVP†	19 (36.5)	45 (40.5)	0.731
Follow-up period, mo*	47.5 ± 33.0	75.6 ± 17.7	<0.001

Statistically significant values are in bold.

* Mean ± SD, comparison performed using independent-samples *t*-test.

† *n* (%), comparison performed using χ^2 test.

recording (recurrent DH group). There was no significant difference in the frequency of SVP between the single DH group and recurrent DH group (58.1% vs. 71.4%, respectively, $P = 0.389$, χ^2 test).

In univariate analysis, statistically significant differences between patients with and without DH were observed in the untreated IOP, visual field MD, and the tendency to cold hands (Table 2). Spontaneous venous pulsation status was not significantly associated with DH (OR 0.844; 95% CI 0.412–1.913; $P = 0.626$). In multivariate logistic regression analysis using variables with P values of less than 0.1 in univariate analysis, the lower untreated IOP (OR 0.886; 95% CI 0.799–0.982; $P = 0.021$), better visual field MD (OR 1.098; 95% CI 1.003–1.202; $P = 0.043$), and tendency to cold hands (OR 2.688; 95% CI 1.087–6.650; $P = 0.032$) were significantly associated with DH.

The characteristics of the patients with SVP ($n = 99$) and without SVP ($n = 64$) are presented in Table 3. Patients without SVP had lower untreated IOP, worse MD of visual field, and longer axial length/greater myopic refractive error. Logistic regression analysis showed that lower untreated IOP ($P = 0.045$), worse visual field MD ($P = 0.035$), and longer axial length ($P = 0.007$) were associated with the absence of SVP in patients with OAG on multivariate analysis (Table 4).

DISCUSSION

The frequency of SVP in overall OAG patients of the study was 60.7%. Disc hemorrhage was not associated with either the presence or absence of SVP. To our knowledge, this is the first study on the relationship between DH and SVP in OAG.

Although the mechanism of SVP is not fully understood, the increased resistance of the retrobulbar CRV is the most likely explanation for the absence of SVP.²⁴ In line with this concept, the absence of SVP was related to longer axial length/more myopic refractive error and worse MD in the current study. Myopic eyes and eyes with severe glaucoma may have increased CRV resistance due to the distortion in the deep optic nerve head. Our group has previously reported that the optic disc may change in childhood in myopic eyes.²⁵ As the eyeball elongates, the optic disc is pulled toward the temporal direction. In this process, the optic disc becomes tilted and the central retinal vessels come to run nasally oblique, which may potentially increase the resistance of CRV. In eyes with severe

glaucoma, the distortion of the lamina may be associated with a decrease in the overall aperture of the pores, resulting in an increased CRV resistance and decreased frequency of SVP.²⁶

Assuming that the absence of SVP is derived from the increased resistance of the retrobulbar CRV, we expected that the absence of SVP would be associated with DH. Contrary to our expectation, however, SVP status was not different between the patients with and without DH. This was not only for the single DH group but also for the recurrent DH group. This finding may suggest that DH is not derived from the increased resistance of venous drainage.

Our finding is in line with the results of a previous investigation by Balaratnasingam et al.,²⁷ who examined the influence of the ophthalmodynamometric force (ODF) to the future optic disc excavation. ODF was compared in patients with and without DH as a subgroup analysis and no significant difference between the DH group and non-DH group was found. However, only nine eyes were included in the DH group in this analysis. The present study, which included a much larger sample, further indicates the absence of a relationship between SVP status and DH.

The lack of the association between SVP and DH does not necessarily mean that DH is unrelated to vascular factors. As DHs are generally very small, it is possible that any hemodynamic disturbance related to DH has a role only in a very limited area. If this is the case, a relevant hemodynamic disturbance would not be detected by observing the pulsation of large vessels, such as CRV.²⁸ Furthermore, a single vascular parameter would be insufficient to represent the vascular dysregulation of the optic nerve, because optic nerve head circulation involves multiple vascular systems, including the ciliary circulation.

In the present study, cold extremities were associated with DH. This finding is consistent with previous studies.^{17,29} Disc hemorrhage has been hypothesized to be associated with PVD,¹⁷ which is characterized by inappropriate arterial constriction (vasospasm) and insufficient venous dilation.^{30,31} Increased level of circulating ET-1, a potent vasoconstrictor, has been demonstrated in PVD, and the link between PVD and DH has been explained by increased level of ET-1.¹⁷ Elevated ET-1 leads to weakening of the blood-retinal barrier,³² thereby potentially inducing DH. This hypothesis is considered as evidence supporting that hemodynamic disturbance may cause DHs.

TABLE 2. Logistic Regression Analysis of Factors on DH

Variables	Univariate		Multivariate	
	P Value	OR (95% CI)	P Value	OR (95% CI)
Age, y	0.268	0.985 (0.960–1.011)		
Female	0.130	1.675 (0.859–3.266)		
Untreated IOP, mm Hg	0.005	0.869 (0.788–0.958)	0.021	0.886 (0.799–0.982)
IOP at imaging, mm Hg	0.511	0.960 (0.849–1.085)		
CCT, μm	0.770	0.998 (0.988–1.009)		
Axial length, mm	0.493	0.891 (0.640–1.124)		
Refractive error, diopters	0.239	1.076 (0.952–1.216)		
MD, dB	0.021	1.101 (1.014–1.195)	0.043	1.098 (1.003–1.202)
Absence of SVP	0.626	0.844 (0.428–1.667)	0.762	0.888 (0.412–1.913)
Diabetes mellitus	0.467	0.708 (0.279–1.797)		
Systemic hypertension	0.093	0.515 (0.238–1.116)	0.183	0.573 (0.253–1.300)
Tendency to cold hands	0.018	2.777 (1.196–6.451)	0.032	2.688 (1.087–6.650)
Migraine	0.454	1.581 (0.477–5.238)		

Statistically significant values are in bold. Variables with *P* values of less than 0.1 in the univariate analysis and absence of SVP were included in the multivariate analysis.

TABLE 3. Demographic and Descriptive Statistics of OAG Patients With and Without SVP

Variables	Patients With SVP, 99 Eyes of 99 Patients	Patients Without SVP, 64 Eyes of 64 Patients	P Value
Age, y*	62.48 $\pm$ 11.60	59.75 $\pm$ 13.70	0.173
Female, %†	52 (52.5)	31 (48.4)	0.633
Laterality, right eye %†	44 (44.4)	34 (53.1)	0.336
Diabetes mellitus†	20 (20.2)	7 (10.9)	0.136
Systemic hypertension†	29 (29.3)	20 (31.3)	0.862
Migraine†	7 (7.1)	5 (7.8)	0.544
Tendency to cold hands†	15 (15.2)	12 (18.8)	0.667
Refractive errors, diopters*	−0.88 $\pm$ 2.31	−2.24 $\pm$ 3.49	0.005
Untreated IOP, mm Hg*	17.85 $\pm$ 4.85	16.14 $\pm$ 3.40	0.009
IOP at imaging, mm Hg*	13.62 $\pm$ 2.84	13.13 $\pm$ 2.57	0.259
CCT, μm *	564.48 $\pm$ 34.71	565.29 $\pm$ 30.24	0.885
Axial length, mm*	23.97 $\pm$ 1.11	24.78 $\pm$ 1.48	0.006
MD, dB*	−3.54 $\pm$ 4.20	−6.56 $\pm$ 6.31	0.001
Follow-up period, mo*	66.5 $\pm$ 26.6	66.7 $\pm$ 27.7	0.969

Statistically significant values are in bold.

* Mean $\pm$ SD, comparison performed using independent-samples *t*-test.

† *n* (%), comparison performed using χ^2 test.

TABLE 4. Logistic Regression Analysis of Factors on the Absence of SVP

Variables	Univariate		Multivariate	
	P Value	OR (95% CI)	P Value	OR (95% CI)
Age, y	0.174	0.983 (0.958–1.008)		
Female	0.610	0.849 (0.453–1.593)		
Untreated IOP, mm Hg	0.017	0.903 (0.829–0.982)	0.045	0.880 (0.776–0.997)
IOP at imaging, mm Hg	0.258	0.934 (0.831–1.051)		
CCT, μm	0.884	1.001 (0.991–1.011)		
Axial length, mm	0.005	1.661 (1.166–2.368)	0.007	1.654 (1.145–2.390)
Refractive error, diopters	0.014	0.868 (0.775–0.971)		
MD, dB	0.001	0.893 (0.835–0.955)	0.035	0.884 (0.788–0.991)
Diabetes mellitus	0.126	0.485 (0.192–1.224)		
Systemic hypertension	0.790	1.098 (0.554–2.174)		
Tendency to cold hands	0.547	1.292 (0.561–2.976)		
Migraine	0.859	1.114 (0.338–3.673)		
Follow-up period, mo	1.000	0.969 (0.989–1.012)		

Statistically significant values are in bold. Variables with *P* values of less than 0.10 in the univariate analysis were included in the multivariate analysis. The variable of refractive error was excluded in the multivariate analysis to control for multicollinearity with other variables of axial length.

Our study has limitations. First, only Korean patients were included. Thus, it may not be directly applicable to other ethnic populations. Second, as the optic disc is observed for the detection of the venous pulsation, it is impossible to have the examiner completely masked to disc appearance. However, we believe that our results were not affected by the potential bias from unmasking because DH was not visible in the movie clip in most cases. This is probably because the movie clip was recorded using infrared light. Further, we expected that SVP was less frequent in eyes with DH. Third, there was a significant difference in the length of follow-up period between the DH group and control group (Table 1). One may consider the possibility that the longer follow-up period (thus, potentially having disease for a longer period) led to the tendency for the control group to have absent SVP. However, we think this is not the case because the follow-up period was not different between patients with and without SVP (Table 3). In addition, the follow-up period was not associated with the presence/absence of SVP in the logistic regression analysis (Table 4). Last, tendency to cold hands, history of diabetes mellitus or systemic hypertension, and history of migraine were elicited from patients, not from physical examination or microscopic study.

In conclusion, the absence of SVP was not associated with DH in patients with OAG. This may be relevant to understanding the mechanism of DH in glaucoma.

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