Acta Ophthalmologica

Acta Ophthalmologica 2019

Primary angle closure and primary angle closure glaucoma in retinal vein occlusion

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ABSTRACT.

Purpose: **To investigate the frequency of primary angle closure (PAC) and primary angle closure glaucoma (PACG) in patients with retinal vein occlusion (RVO) based on a hospital population.**

Methods: **A total of 375 consecutive cases newly diagnosed with RVO by fluorescein fundus angiography at a single eye centre in Peking were reviewed. Gonioscopy was performed in all patients. Glaucoma was diagnosed according to the criteria of the International Society of Geographical and Epidemiological Ophthalmology. Retinal vein occlusion was classified as central retinal vein occlusion (CRVO), hemicentral retinal vein occlusion (HRVO), or branch retinal vein occlusion (BRVO), and as arteriovenous crossing RVO (AV-RVO), optic cup RVO (OC-RVO), optic nerve RVO without optical nerve head swelling (NONHS-RVO), or RVO with optical nerve head swelling (ONHS-RVO) based on the site of venous occlusion. Percentage of PAC or PACG for each type of RVO were calculated.**

Results: **PACG had a frequency of 4.1% [95% confidence interval (CI) 2.2–6.9%] in 317 RVO patients [5.3% (95% CI 2.0–11.2%) in CRVO, 8.8% (95% CI 1.9–23.7%) in HRVO, and 1.9% (95% CI 0.4–5.4%) in BRVO]. Primary angle closure (PAC) had a frequency of 2.9% (95% CI 1.4–5.5%) in RVO. PAC/PACG had a frequency of 11.5% (95% CI 6.3–18.9%) in CRVO, 8.8% (95% CI 1.9–23.7%) in HRVO and 3.1% (95% CI 1.0–7.1%) in BRVO. PAC/PACG was significantly more prevalent in NONHS-RVO [18.9% (95% CI 9.4–32.0%)] than in ONHS-RVO [6.5% (95% CI 2.1–14.5%)], AV-RVO [3.1% (95% CI 0.9–7.8%)], and OC-RVO [2.3% (95% CI 0.1–12.3%)].**

Conclusion: **The overall frequency of PAC/PACG was much higher in patients with RVO (especially CRVO) than that in the general population. Eyes with PAC/PACG may undergo mechanical changes in the lamina cribrosa of the optic disc, resulting in RVO. Angle-closure conditions should be borne in mind when investigating Chinese patients with RVO.**

Key words: angle closure – glaucoma – retinal vein – retinal vein occlusion

Acta Ophthalmol. 2019: 97: e364–e372

doi: 10.1111/aos.13879

Introduction

An association between primary glaucoma and retinal vein occlusion (RVO) was first reported by Verhoeff (1913), who postulated that the critical factor responsible for these changes is increased intraocular pressure (IOP) compressing and collapsing the wall of the retinal vein, thereby leading to intimal proliferation in the vein. Since the report by Verhoeff, many studies have revealed a significantly higher prevalence of primary open angle glaucoma (POAG) in patients with central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) than in the general population (Larsson & Nord 1950; Becker & Post 1951; Duke-Elder 1936; Vannas & Tarkkanen 1960; Bertelsen 1961; Dryden 1965; Stokes 1966; Clement et al. 1968; Vannas & Raitta 1970; Soni & Woodhouse 1971; Blankenship & Okun 1973; Eye Disease Case-control Study Group 1993; Hayreh et al. 2004).

Few studies, however, have examined the relationship between PACG and RVO (Posner 1958; Vannas & Tarkkanen 1960; Vannas 1961; Michaelides & Foster 2010; Azar et al. 2013; Mohammadi et al. 2015; Wu et al. 2016). In the 1950s and 1960s, the prevalence of primary angle closure glaucoma (PACG) in patients with RVO was reported in only a small number of Caucasian cases (Posner 1958; Vannas & Tarkkanen 1960; Vannas 1961). The diagnostic criteria and methods used in the previous studies, however, were not clearly described and did not seem to conform to current international standards. Because PACG is very common in the Chinese population, we performed this hospital-based, consecutive enrolment study to evaluate the frequency of primary angle closure (PAC) and PACG in patients with RVO in Beijing in northern China. We applied the criteria of the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) for a uniform definition of glaucoma (Foster et al. 2002).

Gonioscopy was performed for each subject.

Materials and Methods

Study population

This study was a hospital-based, consecutively enrolled subjects study. From October 2011 to May 2013, subjects were consecutively enrolled from the Retina Service in the Department of Ophthalmology, Peking University Third Hospital. Inclusion criteria included: (1) patients with at least one eye was diagnosed with RVO by fluorescein fundus angiography (FFA); (2) their onset period did not exceed 1 year. Exclusion criteria included conditions that may affect a glaucoma diagnosis, such as uveitis, eye trauma, retinal detachment and proliferative diabetic retinopathy. The protocol followed the tenets of the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of Peking University Third Hospital. Written informed consent was obtained from each subject before undergoing any examinations.

Screening examination

At the initial visit, a structured questionnaire was administered that included questions about systemic and eye disease; surgical, trauma and family histories and the duration of the decrease in visual acuity (VA). Experienced examiners and ophthalmologists performed the screening examinations. The refractive status was measured using an autorefractometer (Topcon KR-8800; Topcon Corp, Tokyo, Japan), and the best-corrected VA was measured by Snellen chart. Intraocular pressure was measured three times using a non-contact tonometer (NT-2000; Nidek, Gamagori, Japan), and the median value was recorded. And these IOP data were collected for the IOP analysis. During a slit-lamp examination, the peripheral anterior chamber depth was first assessed using Van Herick's method (Van Herick et al. 1969). Intraocular lens information was recorded. The diameter of the undilated pupil and iris atrophy was also evaluated. Gonioscopy examination was performed for all participants using a Goldmann-type one-mirror lens (Haag-Streit AG, Bern, Switzerland) at $\times$ 25 magnification with low ambient illumination by a single glaucoma expert and experienced observer (L-L.W.). A narrow 1-mm long vertical beam was offset vertically for the superior and inferior quadrants, and offset horizontally for the nasal and temporal quadrants. Care was taken to avoid light falling on the pupil. The Shields (1997) grading system was used to record the static gonioscopy examination results. The angle was defined as an occludable angle (OA) when the posterior trabecular meshwork was not visible for 270° or more during a static gonioscopy examination (Foster et al. 2004). Dynamic examination was performed after the static gonioscopy of the four quadrants was completed for eyes with a narrow angle. Information regarding peripheral anterior synechiae (PAS) and any other abnormal conditions, such as new vessels, was also recorded. When gonioscopy showed no contraindications, such as an OA, the pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride for ocular fundus examination by direct and indirect ophthalmoscopy. When gonioscopy revealed an OA, ocular fundus examination was carried out through an undilated pupil, although the pupil was dilated in the FFA examination prior. Fundus photography was performed with a digital retinal camera (CR-1 Mark II; Canon, Tokyo, Japan) and reviewed by both retina experts and glaucoma experts. The vertical cup-to-disc ratio (VCDR) was calculated manually and recorded (from 0.1 to 1.0 in 0.05 increments). Disc haemorrhage, notching, rim width and nerve fibre layer defect (NFLD) information were recorded. If the optic disc was unsatisfactorily observed due to haemorrhage or oedema in the RVO-involved eye, 'optic disc not seen' was recorded. If any change suggestive of glaucoma was observed in the fundus examination, fundus photograph, IOP measurement or gonioscopy, the subjects underwent a definitive examination. Other criteria for a definitive examination included best-corrected visual acuity (BCVA) in the RVO-uninvolved eye of worse than 20/30; IOP >21 mmHg; a VCDR $\geq$0.6; a difference in the VCDR of $\geq$0.2 between eyes; rim width from 5 to 7 o'clock or from 11 to 1 o'clock $\leq$0.2 in either eye; or OA, PAS formation, and a history or evidence of previous acute angle closure in either eye.

Definitive examinations

The definitive examinations included Goldmann applanation tonometry, a slit-lamp biomicroscopic examination, further careful optic nerve evaluation, visual field (VF) testing and optical coherence tomography [Cirrus HD OCT, Carl Zeiss Meditec, Optic nerve head and retinal nerve fibre layer (RNFL) thickness analysis program] examination. White-on-white automated perimetry (Humphrey 750; Carl Zeiss Meditec, Inc., Dublin, CA, 30-2 SITA standard program) was performed with refractive correction. The VF results of the RVO-uninvolved eye were studied. For subjects with RVO in both eyes, the VF results were considered unreliable and diagnosis was made according to categories 2 and 3 (described below). If the reliability of the VF test was not satisfactory or there was a defect compatible with glaucoma, the patients were invited for a second VF test on another day. A VF compatible with glaucoma was defined as a glaucoma hemifield test result outside normal limits combined with a cluster of four or more contiguous points on the pattern deviation plot ($p < 5\%$ occurring in age-matched normal subjects) not crossing the horizontal meridian (Mitchell et al. 1996; Foster et al. 2000). Participants with OA but without IOP > 21 mmHg, PAS, or a history or evidence of previous acute angle closure underwent a dark room provocative test (DRPT) and dark room ultrasound biomicroscopy examination. Dark room provocative test (DRPT) was performed with subjects sitting in a dark room for 1 hr and not allowed to fall asleep. Intraocular pressure (IOP) was measured by Goldmann tonometer before and after the DRPT. An IOP elevation of $\geq$8 mmHg was considered positive.

Glaucoma diagnosis

Glaucoma was diagnosed based on the results of gonioscopy and evaluation of the optic disc, RNFL, and the VF test. For most of the CRVO and hemiretinal vein occlusion (HRVO)-involved eyes, the optic disc was usually unsatisfactorily observed due to haemorrhage or oedema, and therefore, the

optic nerve evaluation was based on the other eye. For BRVO-involved eyes, VCDR, rim width and NFLD could usually be evaluated in the uninvolved hemiretina, although the location of the optic nerve where the vein was occluded could not be evaluated. For all subjects, the VF results of the RVO-involved eye were not evaluated. The optic disc, RNFL and VF results were independently evaluated by three glaucoma specialists. The diagnosis was based on the consensus of at least two specialists.

Diagnosis of primary angle closure suspect and primary angle closure

When a patient had an OA based on static gonioscopy, dynamic gonioscopy was performed. Peripheral anterior synechiae (PAS) position was recorded as clock hour. Based on OA, PACS was diagnosed if IOP never exceeded 21 mmHg, there was no PAS under gonioscopy, no history or evidence of an acute IOP elevation, negative DRPT result and no glaucomatous change of the optic nerve and VF.

Primary angle closure (PAC) was diagnosed based on OA and one or more of the following: IOP > 21 mmHg, PAS formation; history and evidence of an acute IOP elevation (including iris atrophy, distortion of radial muscle fibres, or 'glaukomfleken' lens opacities), and without glaucomatous change of the optic nerve and VF.

Diagnosis of primary angle closure glaucoma suspect and primary angle closure glaucoma

Primary angle closure glaucoma (PACG) was defined according to the ISGEO criteria (Foster et al. 2002; Iwase et al. 2004; He et al. 2006; Sawaguchi et al. 2012). Based on PACS or PAC, criteria for a category 1 diagnosis included a VCDR $\geq$ 0.7, or a difference in the VCDR $\geq$ 0.2 between eyes, or a neuroretinal rim width $\leq$0.1 VCDR (between 11 and 1 o'clock or 5 and 7 o'clock), or NFLD, in addition to a VF defect consistent with the optic disc appearance or NFLD. For category 2, based on PACS or PAC, when the VF results were unreliable or unavailable, diagnosis was based on a VCDR $\geq$ 0.8, or a difference in the VCDR $\geq$ 0.3 between eyes, or a neuroretinal rim width $\leq$0.05 VCDR (between 11 and 1 o'clock or 5 and 7 o'clock). For category 3, based on PACS or PAC, when VF examination could not be completed or the optic disc was not visible, diagnosis was based on a visual acuity <20/400 (not including the RVO-involved eye) combined with either an IOP > 99.5th percentile for Chinese subjects (i.e., $\geq$24 mmHg) (He et al. 2006), or definite glaucoma medical history, such as filtering surgery history.

Based on PACS or PAC, PACGS was diagnosed according to a VCDR $\geq$ 0.7 and <0.8, the rim width at the superior or inferior portion $\leq$0.1 but >0.05 VCDR, difference in the VCDR $\geq$ 0.2 but <0.3 between eyes, or NFLD, and the VF results were unreliable, unavailable or not consistent with the optic disc appearance or NFLD.

When each eye was given a different diagnosis, the subject was diagnosed with the more severe diagnosis. For example, if one eye had PAC and the other PACG, the subject was diagnosed with PACG.

RVO classification

Retinal vein occlusion (RVO) was diagnosed by retinal specialists based on the combined results of the fundus photography and FFA. In addition to the traditional classifications of CRVO, HRVO and BRVO, the cases were classified into four groups according to the site of venous occlusion as reported by Beaumont & Kang (2002a,b), as follows (Fig. 1): (1) arteriovenous crossing RVO (AV-RVO), occluded at the arteriovenous crossing; (2) optic cup RVO (OC-RVO), the occlusion was identified by an abrupt change in the calibre of the obstructed vein near the rim of the optic cup and the occlusion occurred before the lamina cribrosa; (3) optic nerve RVO without optical nerve head swelling (NONHS), the occlusion was at the lamina cribrosa within the optic nerve and was identified by the occluded vein entering the lamina cribrosa as a dilated vein without optical nerve head swelling. In some cases, it was difficult to distinguish OC-RVO from NONHS-RVO due to haemorrhage, oedema, blood vessels or an undermined optic cup rim obscuring the exact site of occlusion. In these cases, the appearance of the papillary vein as it crossed the floor of the optic cup was valuable in making the diagnosis. A narrowed papillary vein indicates occlusion in the optic cup, while a dilated papillary vein

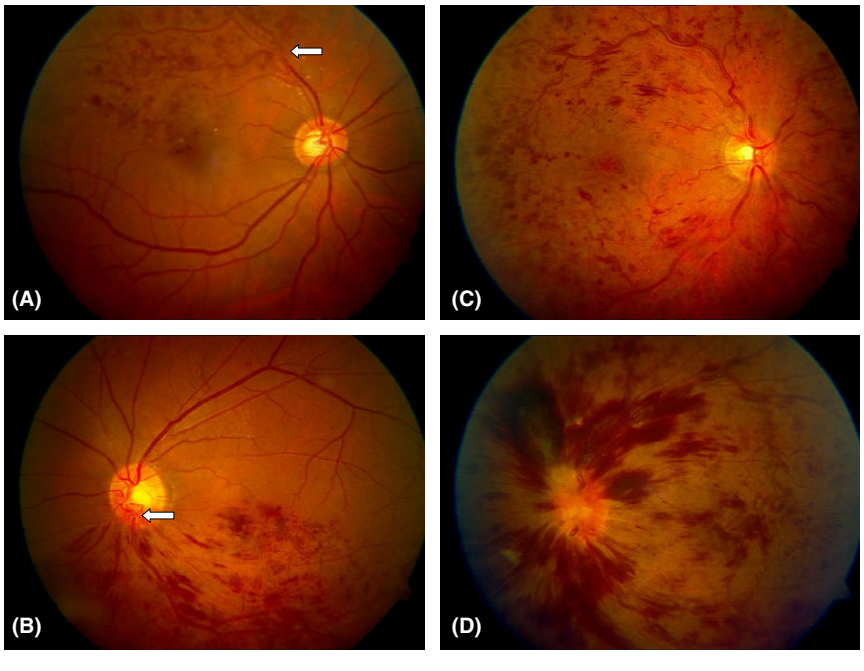

Fig. 1. RVO classified according to the site of venous occlusion. (A) AV-RVO, (B) OC-RVO, (C) NONHS-RVO, (D) ONHS-RVO. AV-RVO = arteriovenous crossing RVO, NONHS-RVO = optic nerve RVO without optical nerve head swelling, OC-RVO = optic cup RVO, ONHS-RVO = optic nerve RVO with optical nerve head swelling. The arrow in (A) and (B) shows the occlusion site.

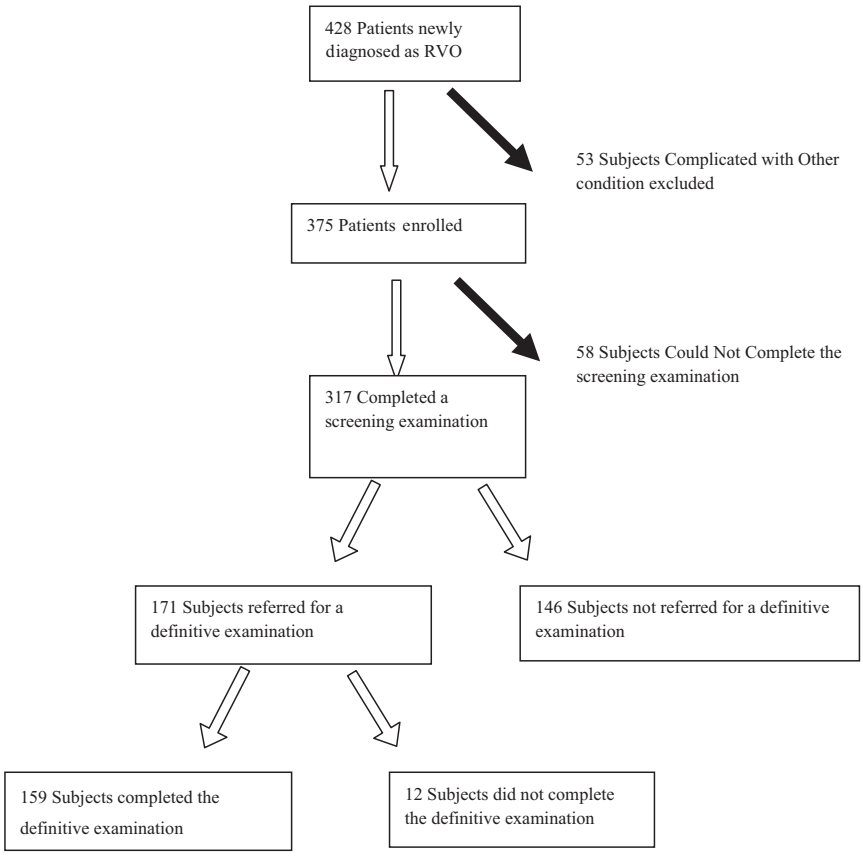

Fig. 2. Flowchart showing the case selection process for the study.

suggests that the occlusion is within the optic nerve (Beaumont & Kang 2002a); (4) optic nerve RVO with optical nerve head swelling (ONHS), the occlusion was behind the lamina cribrosa within the optic nerve. Optic nerve head swelling in RVO indicates that the venous occlusion caused sufficient ischaemia immediately behind the lamina cribrosa to block axoplasmic transport. The site of occlusion was identified by the occluded vein entering the lamina cribrosa as a dilated vein with optical nerve head swelling (Beaumont & Kang 2002a,b); (5) no site RVO (NS-RVO), the occlusion was not associated with any of the above anatomic landmarks.

Data analysis

Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA). χ^2 tests were used to compare proportions. One-way variance analysis was used to compare IOP in different types of glaucoma. All p values were two-sided, and p values < 0.05 were considered statistically significant.

Results

Study population and subjects selected

There were a total of 428 patients with newly diagnosed RVO. Figure 2 shows an overview of the subject selection process for the study. After excluding subjects complicated by other conditions that may affect a glaucoma diagnosis, 375 patients were enrolled. Of the 375 patients, 317 completed the screening examination and 58 did not due to inconvenience (e.g. long distance to reach the family hospital, poor general health). Of the 317 participants, 171 were referred for a definitive examination. Of the 171 participants, 159 completed the definitive examination, but 12 did not. These 12 subjects were diagnosed based on the screening examination as follows: two were diagnosed with PACGS, 2 with PACS, 1 with PACG category 2 and OA; seven did not have PACS/PAC/PACGS/PACG.

The mean age of the 317 subjects with RVO was 59 years [range, 13–91 years; 160 males (50.5%) and 157 females (49.5%)]. Retinal vein occlusion (RVO) occurred in the right eye in 144 (45.4%) subjects, left eye in 164 (51.7%), and both eyes in 9 (2.9%). In the 308 subjects with only one eye involved, 161 had BRVO, 34 had HRVO and 113 had CRVO (Table 1). There was a 13-year-old patient with CRVO without any particular causes. Among the 308 subjects, 128 had AV-RVO, 43 had OC-RVO, 53 had NONHS-RVO, 77 had ONHS-RVO and 7 had NS-RVO.

For the 317 subjects who completed a screening examination, the mean duration of vision loss was 90 ± 86 days. Sixteen had undergone previous cataract surgery. Among these 16 subjects, two had a definite history of POAG and 1 of PACG, three were diagnosed with POAG after definitive examination, and the other 10 subjects had a wide chamber angle and no glaucoma findings or VF deficits. When calculating the frequency of PAC or PACS, these 10 subjects were excluded from the analysis.

PAC, PACS, PACG, PACGS in different types of RVO

Of the 317 subjects, 13 were diagnosed with PACG, resulting in a frequency of

4.1% [95% confidence interval (CI) 2.2–6.9%] in RVO [1.9% (95% CI 0.4–5.4%) in BRVO, 8.8% (95% CI 1.9–23.7%) in HRVO, and 5.3% (95% CI 2.0–11.2%) in CRVO]. One subject had RVO in both eyes; one eye was diagnosed with PACG category 2 and the other eye with PACG category 3. For the 12 subjects with 1 eye affected by RVO, the diagnostic details of PACG were as follows: (1) eight had PACG diagnosed based on the RVO-uninvolved eye (5 with category 1, 3 with category 2). All the RVO-involved eyes had PAC/PACS according to gonioscopy findings; (2) three were diagnosed with the same category in both eyes (2 with category 2, one with category 3); (3) one was diagnosed with PACG category 2 in the RVO-involved eye and PAC in the RVO-uninvolved eye. One of the 317 subjects was diagnosed with PACGS, resulting in a frequency of 0.3% (95% CI 0–1.7%) in RVO.

Nine of the 307 subjects were diagnosed with PAC, after excluding the 10 pseudophakic subjects from the analysis, the frequency was 2.9% (95% CI 1.4–5.5%) in RVO [1.3% (95% CI 0.2–4.6%) in BRVO, 0% (95% CI 0–10.3%) in HRVO and 6.4% (95% CI 2.6–12.7%) in CRVO]. Their diagnoses were based on OA plus PAS formation (5 subjects), IOP > 21 mmHg (1 subject), DRPT-positive result (1 subject), PAS formation and IOP > 21 mmHg (1 subject), or PAS formation and history and evidence of an acute IOP elevation (1 subject). Among the nine subjects with PAC, four had PAC in the RVO-involved eye and PACS in the other RVO-uninvolved eye, three had PAC in both the RVO-involved and the other RVO-uninvolved eye, and two had PACS in the RVO-involved eye and PAC in the other RVO-uninvolved eye.

Therefore, there were total 21 monocular RVO-involved subjects with PAC/PACG. Among them, 13 subjects had PAC/PACG in their both eyes; four subjects had PAC/PACG only in their RVO-uninvolved eyes; and four subjects had PAC/PACG only in their RVO-involved eyes. Seventeen of the 307 subjects were diagnosed with PACS, resulting in a frequency of 5.5% (95% CI 3.3–8.7%) in RVO.

Table 2 shows the frequency of PACG, PACGS, PAC and PACS for each RVO type. Comparing the prevalence of PAC/PACG with that reported by He et al. (2006) in the Liwan District, Guangzhou, southern China 50+ year-old population, and also with that reported by Wang et al. (2010) in the 40+ year-old population in the Beijing Eye Study, northern China, a higher frequency of PAC/PACG was detected in patients with CRVO (11.5%) and HRVO (8.8%) than in the general population (3.9%). The frequency of PAC/

Table 1. Characteristics of different RVO types.

RVO type	Case number	Involved eye Right eye (%)	Sex Male (%)	Age Mean (standard deviation)	Age Range
Monocular BRVO	161	81 (50.3)	77 (47.8)	60.9 (12.1)	33–91
Monocular HRVO	34	11 (32.4)	18 (52.9)	56.2 (14.5)	24–84
Monocular CRVO	113	52 (46.0)	58 (51.3)	56.4 (17.3)	13–85
Binocular RVO	9	–	7 (77.8)	67.2 (9.5)	50–82
All RVO	317	144 (45.4)	160 (50.5)	58.9 (14.5)	13–91

BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, HRVO = hemiretinal vein occlusion, RVO = retinal vein occlusion.

Table 2. Comparison of the frequency of primary angle closure suspect, primary angle closure, primary angle closure glaucoma, primary angle closure/primary angle closure glaucoma and primary angle closure glaucoma suspect and in different types of retinal vein occlusion with prevalence reported in published studies in the Chinese population.

	Published study		Monocular RVO RVO type				
	Liwan, Guangzhou eye study (He et al. 2006)	Beijing eye study (Wang et al. 2010)	Total RVO	BRVO	HRVO	CRVO	HRVO/CRVO
PACS			17/307	10/154	1/34	6/110	7/144
	6.3%	–	5.5%	6.5%	2.9%	5.5%	4.9%
95% CI	–		3.3–8.7%	3.2–11.6%	0.1–15.3%	2.0–11.5%	2.0–9.8%
PAC			9/307	2/154	0/34	7/110	7/144
	2.4%	–	2.9%	1.3%	0%	6.4%	4.9%
95% CI	(1.6–3.1%)		1.4–5.5%	0.2–4.6%	0–10.3%	2.6–12.7%	2.0–9.8%
PACG			13/317	3/161	3/34	6/113	9/147
	1.5%	1.0%	4.1%	1.9%	8.8%	5.3%	6.1%
95% CI	(0.8–2.1%)	(0.7–1.3%)	2.2–6.9%	0.4–5.4%	1.9–23.7%	2.0–11.2%	2.8–11.3%
PAC/PACG			22/317	5/161	3/34	13/113	16/147
	3.9%	–	6.9%	3.1%	8.8%	11.5%	10.9%
95% CI	–		4.4–10.3%	1.0–7.1%	1.9–23.7%	6.3–18.9%	6.4–17.1%
PACGS			1/317	1/161	0/34	0/113	0/147
	–	–	0.3%	0.6%	0%	0%	0%
95% CI			0–1.7%	0–3.4%	0–10.3%	0–3.2%	0–2.5%

BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, HRVO = hemiretinal vein occlusion, PAC = primary angle closure, PACG = primary angle closure glaucoma, PACGS = primary angle closure glaucoma suspect, PACS = primary angle closure suspect, RVO = retinal vein occlusion.

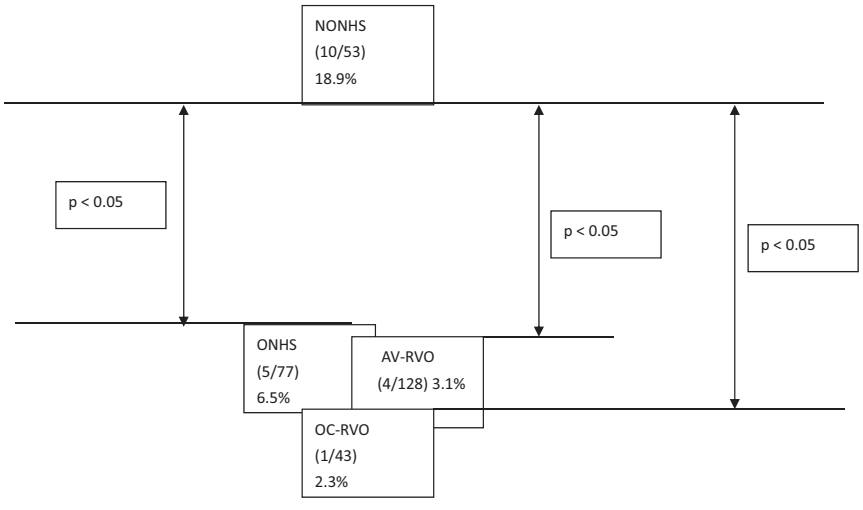

Fig. 3. Comparison of frequency of primary angle closure/primary angle closure glaucoma among the four subgroups of RVO classified according to the occlusion site (NS-RVO excluded). Overlapping rectangles indicate that the differences are not statistically significant (χ^2 tests). AV-RVO = arteriovenous crossing RVO, NONHS-RVO = optic nerve RVO without optical nerve head swelling, OC-RVO = optic cup RVO, ONHS-RVO = optic nerve RVO with optical nerve head swelling.

Table 3. Frequency of primary angle closure/primary angle closure glaucoma in different retinal vein occlusion sites and in different types of retinal vein occlusion.

PAC/PACG	BRVO	HRVO	CRVO
In retinal vein occlusion sites	155	33	113
PAC/PACG/AV-RVO (%)	4/128 (3.1%)	0/0 (0%)	0/0 (0%)
PAC/PACG/OC-RVO (%)	1/27 (3.7%)	0/16 (0%)	0/0 (0%)
PAC/PACG/NONHS-RVO (%)	0/0 (0%)	1/3 (33.3%)	9/50 (18%)
PAC/PACG/ONHS-RVO (%)	0/0 (0%)	1/14 (7.1%)	4/63 (6.3%)

AV-RVO = arteriovenous crossing RVO, BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, HRVO = hemiretinal vein occlusion, NONHS-RVO = optic nerve VO without optical nerve head swelling, OC-RVO = optic cup RVO, ONHS-RVO = optic nerve RVO with optical nerve head swelling, PAC = primary angle closure, PACG = primary angle closure glaucoma, RVO = retinal vein occlusion.

PACG in BRVO (3.1%) was similar to that of the general population. Difference of the frequency of PAC/PACG among CRVO/HRVO/BRVO was statistically significant ($\chi^2 = 7.614$, $p = 0.022$). The frequency of PAC/PACG was significantly higher in CRVO than that in BRVO ($\chi^2 = 7.631$, $p = 0.006$). PAC/PACG frequency was not significantly different between CRVO and HRVO ($\chi^2 = 0.016$, $p = 0.900$) and between HRVO and BRVO ($\chi^2 = 1.106$, $p = 0.293$). Difference of the frequency of PACG among CRVO/HRVO/BRVO was not statistically significant ($\chi^2 = 4.585$, $p = 0.101$).

Among the 13 subjects with PACG, nine were newly diagnosed with glaucoma; one was previously diagnosed with PACG (both eyes with category 3); two were previously diagnosed with PACG before and one had a history of IOP elevation (these three subjects were diagnosed with category 1 or 2 in the examination). Among the nine subjects with PAC, eight were newly diagnosed, none of them had ever experienced any symptoms of IOP elevation, and one had a history of acute IOP elevation.

PAC/PACG in RVO classified by occlusion site

Figure 3 shows the frequency of PAC/PACG for different RVO and PAC/PACG was significantly more prevalent in NONHS-RVO [18.9% (95% CI 9.4–32.0%)] than in ONHS-RVO [6.5% (95% CI 2.1–14.5%)], AV-RVO [3.1% (95% CI 0.9–7.8%)] and OC-RVO [2.3% (95% CI 0.1–12.3%)].

Proportion of NONHS-RVO was 44.2% (50/113) in CRVO, 9.1% (3/33) in HRVO, and 0% (0/155) in BRVO. Table 3 shows the relationship between the vein occlusion site and type.

IOP in involved and uninvolved eye of RVO in PACS, PAC, PACG and no-angle-closure

There was no statistically significant difference in IOP between the involved and uninvolved eye of monocular RVO (paired *t*-test, $p = 0.089$). In the RVO-uninvolved eye group, IOP of the group of no-angle-closure, PACS, PAC and PACG were 15.2 ± 2.7, 15.1 ± 1.7, 18.0 ± 5.3, and 18.8 ± 9.2 mmHg, respectively (one-way variance analysis, $p = 0.000$). In the RVO-involved eye group, IOP of the group of no-angle-closure, PACS, PAC and PACG were 14.6 ± 2.7, 14.6 ± 1.7, 18.2 ± 5.6, and 24.3 ± 15.0 mmHg, respectively (one-way variance analysis, $p = 0.000$). The result of comparing IOP in the 4 types of glaucoma in involved and uninvolved eyes of RVO was showed in Fig. 4. Among 21 monocular RVO subjects with PAC/PACG, there were nine subjects whose IOP exceeded 21 mmHg.

Discussion

The present study demonstrated that the frequency of PACG was 4.1% (95% CI 2.2–6.9%) and PAC/PACG was 6.9% (95% CI 4.4–10.3%) in RVO, a higher frequency than that in the general Chinese population (PACG: 1.0–1.5%, PAC/PACG: 3.9%) (He et al. 2006; Wang et al. 2010), based on the same ISGEO criteria. To the best of our knowledge, this is the first study reporting the frequency of PAC and PACG in RVO among Chinese according to the ISGEO definition. Gonioscopy was performed for each subject in this study, making the results more accurate and reliable.

Although some studies had showed the relationship between PACG and RVO (Posner 1958; Vannas & Tarkkanen 1960; Vannas 1961; Michaelides & Foster 2010; Azar et al. 2013; Mohammadi et al. 2015; Wu et al. 2016), the association between POAG and RVO is better recognized (Vannas & Tarkkanen 1960; Bertelsen 1961; Linnër 1961; Dryden 1965; Soni & Woodhouse 1971; Hitchings & Spaeth 1976; Appiah & Trempe 1989a,b; Rath et al. 1992; Eye Disease Case-control Study Group 1993, 1996; Lindblom 1998; Sperduto et al. 1998; Beaumont & Kang 2002a, b; Hayreh et al. 2004; Kim et al. 2011). Most of these reports suggest that pre-existing glaucoma predisposes an eye

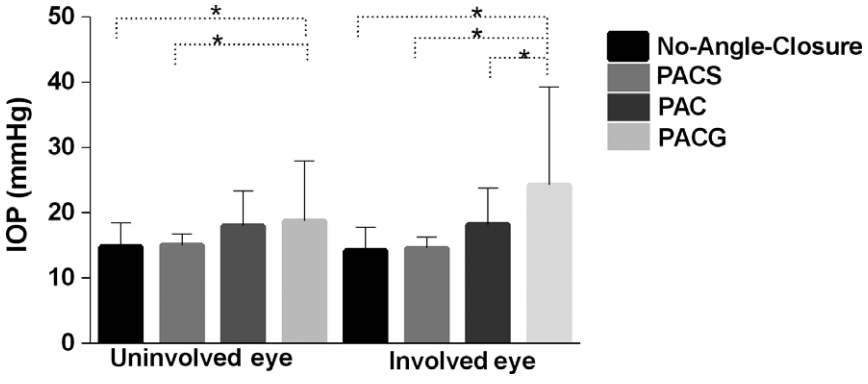

Fig. 4. In involved and uninvolved eye of monocular RVO group, comparison of IOP in no-angle-closure/primary angle closure suspect/primary angle closure/primary angle closure glaucoma. *Indicate that the differences are statistically significant, $p < 0.05$ (one-way ANOVA, Bonferroni). PAC = primary angle closure, PACG = primary angle closure glaucoma, PACS = primary angle closure suspect.

to RVO (Vannas & Tarkkanen 1960; Bertelsen 1961; Linnër 1961; Dryden 1965; Soni & Woodhouse 1971; Hitchings & Spaeth 1976; Appiah & Trempe 1989a,b; Rath et al. 1992 Eye Disease Case-control Study Group 1993, 1996; Lindblom 1998; Sperduto et al. 1998; Beaumont & Kang 2002a,b; Hayreh et al. 2004; Kim et al. 2011). There are several potential reasons for it. First, optic cupping may cause mechanical displacement of the main venous trunk, leading to stretching and weakening of the vein wall, which facilitates transmission of an increased IOP through the vein wall into the lumen (Moore 1924; Dobree 1957). Second, increased IOP leads to compression and collapse of the vein and induces venous stasis, potentially obstructing the vein (Duke-Elder & Dobree 1967).

It is plausible that the PAC/PACG induces RVO through a similar mechanism as suggested for POAG (Hitchings & Spaeth 1976; Hayreh et al. 2004; Hayreh 2005; Mohammadi et al. 2015). Furthermore, among the 21 subjects with PAC/PACG and monocular RVO, 17 subjects had PAC/PACG in the RVO-uninvolved eye. This finding supports the notion that PAC/PACG induces RVO, rather than the reverse association, although it has been proposed that in some cases of CRVO, vascular engorgement and oedema of the posterior segment results in anterior rotation of the cilio-lenticular diaphragm, thereby closing a previously narrow but open drainage angle (Grant 1973; Mendelsohn et al. 1985; Wu et al. 2016). In 2010, a retrospective study reported 19 patients with sustained RVO and PAC (Michaelides & Foster 2010), which also supported the association between angle-closure and RVO. And in 2015, a study using anterior segment optical coherence tomography (AS-OCT) showed CRVO patients had shallower anterior chamber depth in both eyes (Mohammadi et al. 2015). These suggest that PAC leads to RVO, rather than the reverse RVO leading to PAC.

The frequency of PACG in CRVO (5.3%) was higher than that in BRVO (1.9%), although the difference was not statistically significant. It may be due to the small number of subjects in each group. It was quite similar to some previous findings in Caucasian cases during 1958–1961 of a prevalence of PACG in CRVO of 5.6–8% and in BRVO of 1.72% (Posner 1958; Vannas & Tarkkanen 1960; Vannas 1961). The definition of PACG in the present study, however, was quite different from that in the previous studies. If subjects with PACG are combined with those having PAC according to the old PACG definition, the frequency of assumed 'PACG' in Chinese would be 11.5% in CRVO and 3.1% in BRVO, which is much higher than the previous findings in Caucasians.

The reason for the higher frequency of PACG in CRVO than in BRVO is likely associated with local anatomic factors. This study demonstrated that for eyes with PAC/PACG-CRVO/HRVO, all occlusion sites were within the optic nerve, and for eyes with PAC/PACG-BRVO, no occlusion sites were in the optic nerve. The possible reasons for this are: (1) optic cupping causes mechanical displacement of the main venous trunk, leading to stretching and thus weakening of the vein wall, and the lack of protection by optic nerve glial tissue due to the loss of glial cells. These two factors allow IOP to be transmitted directly into the interior of the vein where the increased IOP compresses and collapses the vein and then induces venous stasis (Moore 1924; Dobree 1957; Duke-Elder & Dobree 1967). (2) Elevated IOP causing retrodisplacement of the lamina cribrosa and thereby exerts an adverse local hemodynamic influence (Beaumont & Kang 2002b). Because the lamina cribrosa is located in the optic disc, this mechanism could easily cause CRVO. The occlusion site of most BRVO was arteriovenous, and therefore, BRVO is less related to these local anatomic factors. As a risk factor, CRVO is more closely related to POAG than BRVO (Appiah & Trempe 1989a,b; Sperduto et al. 1998). The prevalence of POAG was higher in CRVO (6–69%) (Duke-Elder 1936; Becker & Post 1951; Vannas & Tarkkanen 1960; Dryden 1965; Vannas & Raitta 1970; Hayreh et al. 2004; Soni & Woodhouse 1971) than in BRVO (6.6–15%) (Larsson & Nord 1950; Becker & Post 1951; Vannas & Tarkkanen 1960; Bertelsen 1961; Stokes 1966; Clement et al. 1968; Blankenship & Okun 1973; Eye Disease Case-control Study Group 1993).

In the 21 cases with PAC/PACG and monocular RVO, RVO occurred in the optic disc in 76.2% (16/21) cases, especially at the lamina cribrosa (47.6% of NONHS-RVO, 10/21), and at the arteriovenous crossing in 19.0% (4/21) cases. Lindblom (1998) noted that in patients with open angle glaucoma, 89% of the RVO occurred on or at the margin of the optic disc, whereas in nonglaucomatous patients, 72% occurred at an arteriovenous crossing. Our finding was similar with this result about POAG in RVO.

Even though the number of PAC/PACG cases in subgroups was small, the preliminary trend showed that PAC/PACG was significantly more prevalent in the vein occlusion site of NONHS-RVO (18.9%) than in groups with occlusion occurring at other sites [ONHS-RVO (6.5%), AV-RVO (3.1%), and OC-RVO (2.3%)]. For POAG cases, *however, a previous study showed that* an RVO occlusion site is

significantly more prevalent in OC-RVO (39.1%) and NONHS-RVO (18.1%) than in other groups (ONHS-RVO, 8.8% and AV-RVO, 4.1%) (Beaumont & Kang 2002b). One reason for the difference in vein occlusion site between PAC/PACG study and POAG may be the decreased tolerance to increased IOP in the unhealthy optic nerve of POAG eyes in addition to the IOP compression. The weak optic disc in POAG eyes with glaucomatous optic neuropathy may be prone to induce OC-RVO (occlusion site in the disc cup). The subjects in our study included not only PACG patients, but also PAC patients with an almost normal optic disc. Even for eyes with PACG, unlike POAG, high IOP is almost the only factor that causes glaucomatous neuropathy. For NONHS-RVO, the site of occlusion is located at the lamina cribrosa that would be retro-displaced when IOP is elevated (Beaumont & Kang 2002b) (e.g. with the angle is closed). This may have an adverse local hemodynamic effect and become a main event contributing to venous occlusion in this group.

There is limited information for comparison of PACG prevalence between BRVO patients and the general population, although a higher prevalence of POAG is reported in BRVO than in the general population (Vannas & Tarkkanen 1960; Blankenship & Okun 1973). In the present study, however, the frequency of PAC/PACG in BRVO (3.1%) was similar to that of the general population (3.9%) (He et al. 2006).

Until now, there have been no reports on PACG in HRVO, and our study revealed that the frequency of PACG in HRVO was 8.8%, higher than that in CRVO (5.3%) and BRVO (1.9%). However, the differences in frequency of PACG among CRVO/HRVO/BRVO were not statistically significant ($p > 0.05$, χ^2 tests). If we combine the subjects with PAC, the frequency of PAC/PACG in CRVO was 11.5%, HRVO (8.8%) and BRVO (3.1%). For the proportion of the occlusion site, consistent with the above results, NONHS-RVO was 44.2% in CRVO, 9.1% in HRVO and 0% in BRVO.

A total of 22 subjects were diagnosed with PAC/PACG in the present study. Among them, 17 patients had never experienced any symptoms of IOP elevation or had any record of IOP elevation. This strengthened the importance of performing gonioscopy for all patients presenting with RVO, and angle-closure should be borne in mind when investigating Chinese patients with RVO, especially HRVO/CRVO.

Although this research emphasizes on the frequency of PAC/PACG in RVO, not the IOP measured among the different types of RVO, we found in either involved eyes or uninvolved eyes of RVO, IOP in eyes with PAC and/or with PACG was significantly higher than those with PACS or no-angle-closure. Among 21 monocular RVO subjects with PAC/PACG, the subjects whose detected IOP exceeded 21 mmHg were less than half, which also suggested that the diagnosis of PACG was not simply based on the IOP.

Like the previous reports (Larsson & Nord 1950; Becker & Post 1951; Duke-Elder 1936; Vannas & Tarkkanen 1960; Bertelsen 1961; Dryden 1965; Stokes 1966; Clement et al. 1968; Vannas & Raitta 1970; Soni & Woodhouse 1971; Blankenship & Okun 1973; Eye Disease Case-control Study Group 1993; Hayreh et al. 2004), our study also showed that the frequency of POAG (8.2%) in patients with RVO was much higher than that in the Chinese general population. It will be reported separately.

A major limitation of this study is that the RVO diagnosis was determined by FFA in the Retina Clinic at the Department of Ophthalmology. Some patients with vitreous haemorrhage caused by RVO could not be screened by FFA and would be lost from this study. This study was performed in a single hospital in the capital of China. Further clinical investigations from multiple centres with large numbers of cases are needed.

In conclusion, this hospital-based study using ISGEO criteria reported that the frequency of PAC/PACG in RVO was 6.9% (PACG 4.1%), 2 times higher than that in the general population. The frequency of PAC/PACG in CRVO was 11.5%, almost 3 times higher than that in the general population. Unlike POAG with the most frequent OC-RVO, PAC/PACG was significantly more prevalent in subjects with NONHS-RVO than in those with RVO at other sites, suggesting that PAC/PACG causes mechanical change in lamina cribrosa of the optic disc and results in RVO. Angle-closure condition should be borne in mind when investigating Chinese patients with RVO.

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Received on November 26th, 2017.
Accepted on June 13th, 2018.

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