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The Effect of Central Retinal Venous Pressure in Patients with Central Retinal Vein Occlusion and a High Mean Area of Nonperfusion

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Ian L. McAllister, MBBS,[1] *Mei H. Tan, MBBS, PhD,*[1] *Lynne A. Smithies, BSc, PhD,*[1] *Wan L. Wong, MBioStat*[2]

Purpose: To evaluate the effect of central venous pressure (CVP) on visual outcomes and retinal ischemic consequences in patients with central retinal vein occlusion (CRVO).

Design: Prospective, single-center cohort study.

Participants: Eighty-eight patients with CRVO and a high overall mean area (21.6 disc areas) of capillary nonperfusion (CNP) who were followed for 18 months before the availability of intravitreal therapy and who were offered standard care of the time.

Methods: Patients were evaluated at baseline and at 3, 8, and 18 months. At each study visit, measurements of CVP, best-corrected visual acuity (BCVA), area of CNP, retinal fluorescein transit time (FTT), and an evaluation for rubeosis iridis were performed.

Main Outcome Measures: Evaluation of the effect of different levels of CVP on BCVA, retinal blood flow, and the development of retinal ischemia and rubeosis iridis.

Results: Mean BCVA was significantly higher in patients with lower CVP at all time points ($P<0.0001$). The area of CNP increased significantly with higher levels of CVP and progressed with time. The development of rubeosis iridis was significantly associated with CVP at all time points and was present in 5.6%, 27.9%, and 88.9% of those with low, moderate, and high CVP levels, respectively ($P<0.0001$), at the 18-month conclusion. Retinal blood flow as measured by FTT was reduced with higher levels of CVP. Spontaneous lowering of CVP had beneficial effects on BCVA, although this diminished with time.

Conclusions: Eyes with increased CVP after more severe CRVO demonstrate significantly reduced vision, reduced retinal blood flow, a higher incidence of rubeosis iridis, and larger areas of CNP that correlate with the degree of CVP elevation. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

Treatment options for central retinal vein occlusion (CRVO) have evolved significantly over the last decade with improvements in visual outcomes now being achievable for the first time since this condition was originally identified and described by Richard Liebreich in 1855.[1]

The major cause of visual reduction in the early stages of retinal vein occlusion is macular edema. The pathogenesis of this is probably multifactorial with increased venous hydrostatic pressure, upregulation of various cytokines, and inflammatory components all potentially playing a role. Of the various cytokines involved, vascular endothelial growth factor (VEGF) A seems to be the most predominant and is known to be upregulated in CRVO and to increase vascular permeability.[2,3] This has resulted in a number of agents that have the potential to modify this upregulation being investigated as therapeutic agents in phase 3 trials. These include steroids such as triamcinolone and dexamethasone implants, and anti-VEGF agents such as pegaptanib, ranibizumab, and aflibercept.[4–10] These agents have all shown varying degrees of effectiveness in resolving the macular edema with commensurate improvements in visual acuity, but all suffer from recurrence of the edema once the effect of the agent has worn off, requiring repeated injections for an as of yet undetermined period of time.

Although the pathogenesis of CRVO is still incompletely understood and controversial, there is little argument that the clinical picture seen in this condition is the end result of an obstruction to venous outflow.[11–13] This outflow obstruction can result in a significant elevation of the intravenous hydrostatic pressure, with ophthalmodynamometric assessments indicating that the venous pressure in this condition can be up to 24 times of that found in an unobstructed central retinal vein (CRV).[14] This article presents the effect of central venous pressure (CVP) in a group of patients with overall more severe CRVO who were followed over an 18-month period before the availability of intravitreal therapeutic agents. The effects of different levels of CVP over this period are correlated with the final visual outcomes, retinal blood flow, and development of retinal ischemia and anterior segment neovascularization.

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Methods

The patients in this study represent a single cohort with CRVO seen prospectively at the Lions Eye Institute in Perth, Australia, over a 3-year period. The patients were those seen while recruiting for the Central Vein Bypass Study (CVBS).[15,16] This was a prospective, randomized, controlled, multicenter clinical trial conducted in 3 centers in Australia between April 2000 and July 2003. Entry criteria for the CVBS included a nonischemic CRVO (<10 disc areas [DAs] of capillary nonperfusion [CNP] of 3 to 12 months duration), best-corrected visual acuity (BCVA) ≤20/50 Snellen equivalent measured using a logarithm of the maximum angle of resolution chart, using the protocol developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) read at 4 m, and an adequate view of the fundus. All patients were followed up for 18 months.

The patients in this article represent those in the control group of the CVBS recruited at the Lions Eye Institute who completed the 18-month follow-up (33 patients) together with all other patients seen with CRVO during the 3 years of recruitment at this center who did not meet the eligibility criteria for inclusion in the CVBS trial (66 patients) and therefore together represent a prospective cohort of patients seen with CRVO at one center over this period. Those not eligible for the CVBS trial were followed with a similar protocol to the study and offered the standard of care at that time as needed.

All sites received approval from their respective institutional review boards before study initiation, and all participants provided written, informed consent before eligibility screening. The trial adhered to the tenets of the declaration of Helsinki but was not registered because all participants completed the trial before 2006.

Preoperative examinations are detailed in our initial publication[15] and included BCVA measured on an ETDRS chart at 4 m, slit-lamp examination, assessment of intraocular pressure, and standardized color photography and fluorescein angiography. An assessment of the CVP was made at each study visit. This was performed at the slit-lamp by applying increasing digital pressure on the eye while observing the optic disc with a handheld indirect lens with all measurements performed by a single examiner (I.L.M.). The pressure that the CRV collapsed in relation to the central retinal artery (CRA) diastolic and systolic pressures was recorded on a scale of 1 to 7; 1 was equivalent to normal CVP (i.e., spontaneous venous pulsations present or seen on minimal applied pressure), 2 was below CRA diastolic, 3 was equivalent to CRA diastolic (first sign of pulsations in CRA), 4 was between CRA diastolic and systolic, 5 was equivalent to CRA systolic (collapse of CRA), 6 was unable to compress the CRV, and 7 was unable to assess. Patients in this study were graded as having low CVP (levels 1−2) if their CRV collapsed before pulsations were seen in the CRA, medium CVP (levels 3−4) if their CRV collapsed at the same time or after pulsations in the CRA occurred, and high CVP (levels 5−6) if the CRV closed at the same time as the CRA or not at all. All patients had a formal estimation of both CRA and CRV pressures at baseline with an ophthalmodynamometer (Luneau Technology, Prunay le Gillon, France) to exclude any patient with an abnormally low CRA pressure (<60 mmHg systolic).

Fluorescein transit time (FTT) was calculated from the angiograms taken at each visit. After injection of 10 ml of 5% sodium fluorescein into an antecubital vein, frames were taken at 1-second intervals from first appearance of the dye into the choroid or arterial circulation until beyond full venous filling. The transit time was calculated from first appearance of dye into the retinal arterial circulation until full venous filling was achieved. This was performed for all patients with the same photographer and injecting physician to improve reproducibility.

The area of CNP was calculated from the 5 standard, 60-degree Canon (Tokyo, Japan) frames (as per the central vein occlusion study[17,18]) taken during mid-phase of the angiogram. The CNP was measured manually using a DA template and correlated with corresponding color photographs. Areas with overlying hemorrhage were considered to be CNP only if surrounded by confirmed areas of ischemia on the corresponding angiogram.

The data presented in this study consist of patients from the control group of the CVBS trial (33) and the parallel observation group that completed the study (55 of the original 66), who were recruited at a single study center (Lions Eye Institute). Fluorescein angiographic data could be retrieved from only 77 of the total of 88 patients because of misplacement or loss of the original photographic strips in the archiving system. The angiograms for some of the patients in the high CVP group at the later follow-up time points could not be read because of poor quality resulting from neovascular glaucoma and lack of media clarity. The data presented are that which can be measured from a clinical examination on all 88 patients plus that from the available angiograms.

Follow-up

The BCVA and a full ocular examination including gonioscopy and assessment of the CVP together with color photography and fluorescein angiography were performed on all patients both in the CVBS trial and in the parallel observational trial at baseline and at 3, 8, and 18 months. Patients in the CVBS trial were observed at intermediate time intervals between these time points in addition. All observations and measurements in this series were performed by one investigator (I.L.M.).

Statistical Analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago, IL). Descriptive statistics were used to summarize patient demographics and baseline ocular characteristics. A two-tailed Fisher exact test was used for comparison of categoric variables, and analysis of variance was used for the comparison of continuous variables between groups. Continuous variables are presented as mean values ± standard error. All confidence intervals presented are 95%, and the level of statistical significance was set at $P<0.05$. For patients who had missed follow-up visits, the measurements for BCVA, findings of rubeosis, and development of collateral vessels were expressed using last observation carried forward analyses.

Results

Over the duration of the recruitment period for this study (April 2000 to July 2003), a total of 99 patients with a CRVO of varying degrees of severity were followed with standard of care at the Lions Eye Institute. These included 33 from the control group of the CVBS trial and an original total of 66 in the parallel observational group. Over the course of the study, 7 patients from the parallel observational group were lost to follow-up. An additional 4 patients in this group were excluded at baseline because they had extensive hemorrhagic retinopathy also involving the optic disc, preventing an assessment of the CVP (CVP group 7) and the degree of CNP at baseline. No patients were excluded because of low CRA perfusion pressures. The following results include data from a total of 88 patients (33 from the CVBS control group and 55 from the parallel observation group) who completed study visits from baseline up to 18 months.

The CVP measurements were divided into 3 groups, low (CVP 1−2), medium (CVP 3−4), and high (CVP 5−6), and the results were analyzed according to the following variables.

1. Mean visual acuity according to CVP groups at the different study time points.
2. The CVP variation with time during the course of the study.
3. Percentage of patients with rubeosis iridis according to CVP and at the different follow-up time points.
4. Percentage of patients with medium to high CVP (3–6) at baseline who experienced CVP lowering at the various study time points.
5. Change in BVCA in patients with CVP lowering at the various study time points.
6. Correlation of retinal blood flow as determined by FTT with CVP.
7. Effect of CVP on the incidence and speed of collateral vasculature formation.

Baseline and Demographic Characteristics

The baseline characteristics of the 88 patients are shown in Table 1. There was a male preponderance of 61.4% (54), and 38.6% (34) were female. The mean duration of CRVO before enrollment into the study was 12.8 weeks. Most patients had a relatively short duration of symptoms before entry in the study, with 72% being less than 3 months. Mean BCVA at entry was low at 19.9 letters (Snellen equivalent of 20/400), and the mean CVP was 3.7, which is above CRA diastolic. This was also confirmed on formal ophthalmodynamometer measurements whereby the mean CVP measured was 69.9 mmHg compared with mean CRA systolic of 104.6 mmHg and mean CRA diastolic of 60.2 mmHg. The median area of CNP was 0; however, the mean was 21.6 DAs. The majority of patients (79.2%) had less than 10 DAs of nonperfusion at the start of the study; however, the mean was skewed because 10 patients had >100 DAs of CNP. Most of the patients in our sample were hypertensive with mean blood pressures of 157.1 mmHg systolic and 94.8 mmHg diastolic.

Table 1. Patient Demographics and Baseline Ocular Characteristics (n = 88)

Parameters	Baseline
Age, yrs ± SD (95% CI)	70.4±12.7 (67.2–72.5)
Gender, n (%)	
Male	54 (61.4)
Female	34 (38.6)
Study eye characteristics	
Time (wks) from diagnosis to inclusion Mean ± SD (95% CI)	12.8±16.3 (9.3–16.2)
Distribution, n (%)	
≤3 mos	63 (71.6)
3–6 mos	21 (23.9)
6–12 mos	3 (3.4)
>12 mos	1 (1.1)
BCVA, ETDRS letters ± SD (95% CI)	19.9±19.6 (15.7–24.1)
Mean CVP ± SD (95% CI)*	3.7±1.2 (3.5–4.0)
Median area of CNP on FFA, DA ± SD (95% CI)	0.0±50.6 (10.1–33.1)
Distribution of area of CNP, n (%)	
<10 DA	61 of 77 (79.2)
≥10 DA	16 of 77 (20.8)
CRA systolic, mmHg ± SD (95% CI)†	104.6±14.4 (101.4–107.7)
CRA diastolic, mmHg ± SD (95% CI)†	60.2±11.6 (57.7–62.8)
CVP, mmHg ± SD (95% CI)†	69.9±23 (64.9–75.0)
IOP, mmHg ± SD (95% CI)	19.4±8.7 (17.6–21.3)
Mean systolic blood pressure, mmHg ± SD (95% CI)	157.1±82.7 (139.6–174.7)
Mean diastolic blood pressure, mmHg ± SD (95% CI)	94.8±86.3 (76.5–113.1)

BCVA = best-corrected visual acuity; CI = confidence intervals; CNP = capillary nonperfusion; CRA = central retinal artery; CVP = central venous pressure; DA = disc area; ETDRS = Early Treatment Diabetic Retinopathy Study; FFA = fundus fluorescein angiography; IOP = intraocular pressure; SD = standard deviation.
Data are count, proportions, or means and SD.
*The CVP was measured digitally and graded on a scale of 1 to 6.
†The CRA systolic and diastolic and CVP measurements were taken with a Luneau Technology (Prunay le Gillon, France) ophthalmodynamometer and corrected for intraocular pressure.

Correlation between Mean Best-Corrected Visual Acuity with Central Venous Pressure

Mean BCVA was significantly higher in patients with lower CVP at all time points for the duration of this study (Table 2). At the 18-month conclusion, the mean BCVA was 34.0, 8.7, and 0 ETDRS letters for the low, moderate, and high CVP groups, respectively ($P<0.0001$). Mean BCVA for the low CVP group improved from 34 letters at baseline to 41 to 42 letters at the 3- and 8-month time points before decreasing to 34 letters at the final visit at 18 months. In contrast, the moderate and high CVP groups both showed a progressive decrease in BCVA at all time points with the moderate group decreasing from a mean entry BCVA of 19.5 to 8.7 letters at 18 months and the high CVP group decreasing from 3.3 to 0.0 letters.

Multiple linear regression analysis, with robust standard errors to account for within-patient correlations, showed that CVP is significantly correlated with BCVA after adjusting for macular leakage and study time points. Each unit increase in CVP was associated with a 9.69-unit decrease in BCVA ($P<0.001$). The presence of macular leakage seen on the fluorescein angiograms did not correlate significantly with BCVA ($P = 0.14$); however, this study was not designed to quantify the amount of macular edema in these patients.

Baseline CVP was low in 17%, moderate in 67%, and high in 16% of patients. Over the period of follow-up, there was a tendency for the overall CVP to decrease in all groups; the percentages at 18 months were 41%, 48.9%, and 10.2% for the low, moderate, and high groups, respectively (Fig 1).

Correlation between Area of Capillary Nonperfusion and Rubeosis with Central Venous Pressure

The area of CNP increased significantly with higher levels of CVP and progressed with time (Table 3). At baseline, mean CNP was 0, 16.5, and 74.8 DAs for the low, medium, and high CVP groups, respectively ($P = 0.0003$). The levels increased with time in all CVP groups, with the lowest increase seen in the group with low CVP. At the 8-month time point, the mean CNP had increased to 8.2, 57.3, and 146.3 DAs for the low, medium, and high CVP groups, respectively ($P = 0.001$). The 18-month CNP measurement for the high CVP group could not be accurately assessed in many of the patients in this group because of the poor quality of the fluorescein angiograms secondary to rubeosis iridis and high

Table 2. Mean Best-Corrected Visual Acuity in Early Treatment Diabetic Retinopathy Study Letter Score According to Central Venous Pressure Groups at Different Study Time Points (n = 88)

Parameter	CVP 1–2	CVP 3–4	CVP 5–6	*P* Value
Study time point				
Baseline				
Mean BCVA ± SE	34.2±4.6	19.5±2.5	3.3±2.3	<0.0001
95% CI for mean	25.1–43.3	15.0–24.1	0.0–12.7	
No. patients (%)	15 (17)	59 (67)	14 (16)	
3 mos				
Mean BCVA ± SE	42.2±3.1	15.4±2.6	0.3±0.3	<0.0001
95% CI for mean	35.2–49.3	10.8–20.0	0.0–10.5	
No. patients (%)	23 (26.1)	54 (61.4)	11 (12.5)	
8 mos				
Mean BCVA ± SE	40.7±3.8	12.5±2.5	0.0±0.0	<0.0001
95% CI for mean	33.7–47.6	7.7–17.2	-	
No. patients (%)	25 (28.4)	54 (61.4)	9 (10.2)	
18 mos				
Mean BCVA ± SE	34.0±3.8	8.7±2.1	0.0±0.0	<0.0001
95% CI for mean	28.2–39.9	3.4–14.1	-	
No. patients (%)	36 (41.0)	43 (48.8)	9 (10.2)	

BCVA = best-corrected visual acuity; CI = confidence interval; CVP = central venous pressure; SE = standard error.
P values from analysis of variance (ANOVA) tests for comparison of means between groups.

Table 3. Area of Capillary Nonperfusion According to Central Venous Pressure at Different Time Points

Parameter	CVP 1–2	CVP 3–4	CVP 5–6	*P* Value
Baseline				
Mean CNP ± SE	0.0±0.0	16.5±5.6	74.8±24.9	0.0003
95% CI	-	4.1–28.9	47.4–102.3	
n	12	54	11	
3 mos				
Mean CNP ± SE	1.4±1.2	50.3±11.2	128.3±33.8	<0.0001
95% CI	0.0–31.2	30.4–70.2	81.4–175.4	
n	20	45	8	
8 mos				
Mean CNP ± SE	8.2±5.3	57.3±12.6	146.3±58.4	0.001
95% CI	0.0–38.4	35.4–79.2	75.3–217.2	
n	22	42	4	
18 mos				
Mean CNP ± SE	21.2±8.9	68.0±16.2	128.3±44.9	0.01
95% CI	0.0–47.8	41.8–94.2	44.1–212.6	
	30	31	3	

CI = confidence interval; CNP = capillary nonperfusion; CVP = central venous pressure; SE = standard error.
P values from analysis of variance (ANOVA) tests for comparison of means between groups.

intraocular pressures leading to the 16.8% reduction in the number of patients with available data at this time point.

The development of rubeosis iridis was significantly associated with CVP at all time points (Fig 2). Low CVP appeared to be protective for the development of this condition. At baseline, rubeosis iridis was not seen in any patient with low CVP but was seen in 10.2% of those with moderate CVP levels and 35.7% of those with high CVP levels ($P = 0.011$). At the 18-month conclusion, rubeosis was present in 5.6%, 27.9%, and 88.9% of those with low, moderate, and high levels, respectively ($P<0.001$).

Lowering of Central Venous Pressure and the Effects on Best-Corrected Visual Acuity

Spontaneous lowering of the CVP at any time point in general had beneficial effects on BCVA (Table 4). In the group of patients with moderate and high CVP (CVP 3–6) at baseline (73 of the total 88), 10 patients (13.7%) had a lowering of their CVP at the 3-month time point, and of these 70% gained ≥5 letters and only 10% lost vision. Although the number of patients who had lowering of CVP increased as time passed, the extent of the improvement in BCVA with CVP lowering diminished. At the 8-month time point, 14 patients (19.2%) with moderate or high CVP had a lowering of their CVP, and of these 64.3% gained ≥5 letters and 21.4% lost vision. At 18 months, CVP lowering was seen in 24 patients (32.9%), and among these only 50.0% gained ≥5 letters and 20.9% lost vision.

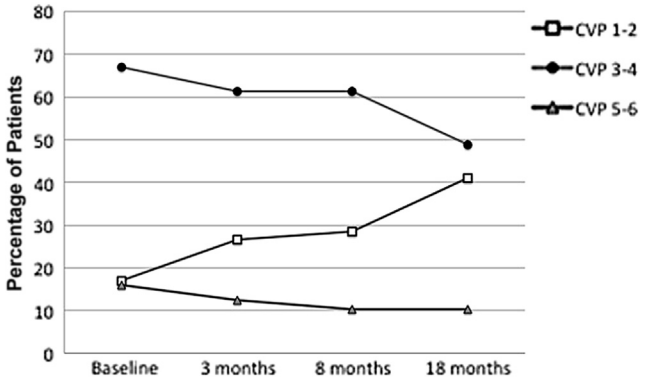

Figure 1. Percentage of patients in the 3 central venous pressure (CVP) groups over the 18 months of follow-up.

Correlation between Retinal Blood Flow and Collateral Development with Central Venous Pressure

Retinal blood flow as estimated by FTT was found to be significantly associated with CVP levels. At baseline, the mean FTT for the group with low CVP was fairly normal at 14.2 seconds; however, this increased to 18.2 and 26.2 seconds for the moderate and high CVP groups, respectively ($P<0.0001$). For each CVP group, the FTTs remained fairly constant at the subsequent follow-up time points, and at the 18-month conclusion the mean times remained significantly different between the CVP groups at 14.3, 19.7, and 23.4 seconds for the low, moderate, and high CVP groups, respectively ($P = 0.0035$) (Table 5).

The development of collateral circulation on the optic disc in the form of optociliary or vein-to-vein shunt vessels also appears to be related to CVP. In general, collateral vasculature appeared to develop earlier and more frequently in the 2 groups with higher CVP (CVP 3–6) compared with the patients in the low CVP group (CVP 1–2) (Table 6).

Discussion

The results from this study indicate that CVP has a significant effect on visual acuity and the ischemic and

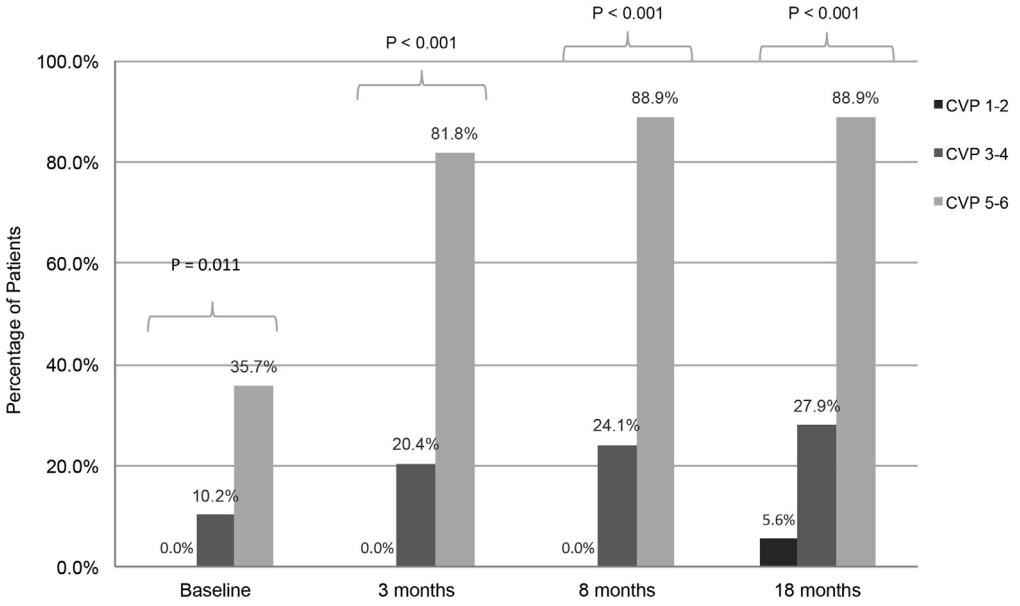

Figure 2. Percentage of patients with rubeosis iridis in the 3 central venous pressure (CVP) groups at the follow-up time points. The total patients at each of the 4 time points is 88. *P* value from Fisher exact test.

neovascular complications that can occur in those with more severe degrees of CRVO. Patients with persistently higher CVP had worse final visual acuities and were more likely to develop progressive CNP and have rubeosis iridis. There was a progressive increase in the mean CNP in all CVP groups over the 18 months of the study, with the largest increase seen in the groups in which the CVP was at or above CRA diastolic (CVP 3–6) (Table 3). In these groups, there is likely to be some degree of reduction in retinal capillary flow due to the venous backpressure with increasing hypoxic damage, which may account for the increase in mean CNP seen over time. In contrast, those who had a spontaneous lowering of their CVP, especially when this occurred in the first 3 months, were more likely to have an improved visual outcome. This improvement is most likely due to resolution of the macular edema. However, because this study was commenced before the widespread introduction of optical coherence tomography machines into clinical practice, this cannot be directly shown.

Table 4. Change in Best-Corrected Visual Acuity in Patients with Central Venous Pressure Lowering Compared with Baseline (N = 88)

Parameter	n (%)
No. of patients with moderate-high CVP (3–6) at baseline	73
No. of patients with lowered CVP at 3 mos	10 (13.7)
BCVA change at 3 mos in patients with CVP lowering	
Gain of >10 letters	4 (40.0)
Gain of 5–9 letters	3 (30.0)
No change, ±4 letters	2 (20.0)
Loss of 5–9 letters	0 (0.0)
Loss of >10 letters	1 (10.0)
No. of patients with lowered CVP at 8 mos	14 (19.2)
Gain of >10 letters	5 (35.7)
Gain of 5–9 letters	4 (28.6)
No change, ±4 letters	2 (14.3)
Loss of 5–9 letters	1 (7.1)
Loss of >10 letters	2 (14.3)
No. of patients with lowered CVP at 18 mos	24 (32.9)
Gain of >10 letters	8 (33.3)
Gain of 5–9 letters	4 (16.7)
No change, ±4 letters	7 (29.2)
Loss of 5–9 letters	1 (4.2)
Loss of >10 letters	4 (16.7)

BCVA = best-corrected visual acuity; CVP = central venous pressure.

The management of CRVO has changed significantly since the first randomized phase 3 studies on the treatment of this condition were published in 1995.[17,18] These showed that for CRVO-associated macular edema, grid laser photocoagulation had no beneficial effect on visual acuity outcomes.[17] Subsequently, VEGF has been identified as the major cytokine released within the eye in response to venous outflow obstruction, and its role in the blood–retina barrier breakdown, which contributes to the development and maintenance of macular edema, has been confirmed.[2,3,19] This has led to the development of several intravitreal therapeutic agents that block the effects of VEGF within the eye to varying degrees of effectiveness.[4–10] Although these agents can be effective in ameliorating the VEGF-mediated vascular leakage within the eye for a short period of time, once the agent has dissipated, the macular edema returns with subsequent deterioration in vision, thus requiring repeated injections for an as of yet undetermined period of time.

The effectiveness of these agents confirms that in the short-term, macular edema is the major cause of the

Table 5. Fluorescein Transit Time in Seconds According to Central Venous Pressure at Different Time Points

Parameter	CVP 1–2	CVP 3–4	CVP 5–6	P Value
Baseline				
Mean FTT ± SE	14.2±1.6	18.2±0.6	26.2±2.6	<0.0001
95% CI	11.0–17.4	16.7–19.7	22.6–29.6	
n	12	54	11	
3 mos				
Mean FTT ± SE	12.7±0.8	19.5±1.0	26.2±4.1	<0.0001
95% CI	9.6–15.8	17.4–21.6	21.4–31.0	
n	20	42	8	
8 mos				
Mean FTT ± SE	12.7±1.1	19.8±1.1	27.2±3.4	<0.0001
95% CI	9.8–15.5	17.8–21.9	21.4–32.9	
n	20	40	5	
18 mos				
Mean FTT ± SE	14.3±1.0	19.7±1.4	23.4±5.8	0.0035
95% CI	11.9–16.6	17.3–22.2	15.9–30.4	
	28	27	3	

CI = confidence interval; CVP = central venous pressure; FTT = fluorescein transit time; SE = standard error.
P values from ANOVA tests for comparison of means between groups.

reduction of vision in acute CRVO. The cause of macular edema is multifactorial, with one cause being the elevated VEGF levels within the eye. Another cause is the elevation of the intravascular pressure within the retinal circulation in response to an outflow obstruction within the only exit for retinal blood flow in the CRV. To treat a CRVO completely and to provide a stable and long-lasting improvement in visual function will require that both of these components are addressed.

Table 6. Development of Collaterals in Patients According to Central Venous Pressure at Different Time Points

Parameter	CVP 1–2	CVP 3–4	CVP 5–6	P Value*
Baseline				
Collaterals present, n (%)	0 (0.0)	4 (7.4)	1 (9.1)	0.808
Optociliary shunts, n	0	2	0	
Vein-vein shunts, n	0	2	1	
Total patients	12	54	11	
3 mos				
Collaterals present, n (%)	1 (5.0)	11 (23.4)	1 (10.0)	0.197
Optociliary shunts, n	1	9	0	
Vein-vein shunts, n	0	2	1	
Total patients	20	47	10	
8 mos				
Collaterals present, n (%)	1 (4.5)	21 (44.7)	2 (25.0)	0.001
Optociliary shunts, n	1	19	1	
Vein-vein shunts, n	0	2	1	
Total patients	22	47	8	
18 mos				
Collaterals present, n (%)	7 (22.6)	19 (54.3)	2 (18.0)	0.013
Optociliary shunts, n	7	17	1	
Vein-vein shunts, n	0	2	1	
Total patients	31	35	11	

CVP = central venous pressure.
**P* from 2-sided Fisher exact test.

Longer-term studies have shown that the initial improvements with VEGF blockade are often not maintained after the first year despite receiving continued therapy. In the HORIZON study during the second year of treatment with ranibizumab for CRVO, between 4.1 and 5.2 letters of BCVA were lost with most patients still requiring intravitreal therapy.[20] A longer-term study of 20 patients treated with ranibizumab for up to 6 years showed resolution of edema with injections alone in 25% and failure of edema resolution in 40%, with the remaining 35% being indeterminate because they left the trial early without edema resolution.[21] The reason for the reduced effectiveness of long-term VEGF inhibition in CRVO is unresolved, with possible reasons being the intervals between intravitreal injections being too long, patient fatigue with the continued burden of treatment with subsequent nonattendance, and progressive damage to the capillary vasculature. The other possible reason is that, although these agents address the cytokine-mediated breakdown in the blood ocular barrier with regular administration, they fail to address the CVP elevation in CRVO.

The relationship of elevated CVP with CRVO and the association of higher degrees of CVP elevation with a worsening prognosis in this condition have been recognized for some time.[14,22–24] The method of estimating the magnitude of the CVP elevation has differed, with some using a simple digital method of applying pressure on the eye while observing the CRV on the optic disc to determine the collapse of the CRV in relationship to the CRA diastolic and systolic pressures.[22,23] Other investigators have used more sophisticated methods involving a modified contact lens that places continued pressure on the eye to determine CVP and CRA pressures and to ascribe a numeric value to them.[14,24] Ophthalmodynamometry allows an indirect measure of the CVP, which is elevated in CRVO because of increased outflow resistance. The CRV will pulsate when the sum of intraocular pressure plus an external pressure applied to the eye equals the diastolic of the CRV.[24,25] Central venous pressure elevation has been found to be significantly higher in ischemic CRVOs than nonischemic CRVOs, with the levels in the former usually being higher than CRA diastolic levels.[24]

In this study, CVP was estimated semiquantitatively by applying digital pressure while observing the CRV and dividing the results into 3 main groups. Low CVP (1–2) included those with normal or mild elevations of CVP that are below CRA diastolic; in this group, retinal blood flow may be slowed, but there is still likely to be an effective retinal circulation. Medium CVP (3–4) included those with a venous pressure elevated to the level of or above CRA diastolic; in this group, although there may be some blood flow during part of the blood pressure pulse cycle, there will be variable periods of retinal circulatory stagnation. High CVP (5–6) included those with a venous pressure at or above the level of arterial systolic, and with significant or complete stagnation of the retinal circulation. Although this technique does not give an exact estimation of CVP such as may be obtained with the more sophisticated contact lens

methods, it is simple and quickly done and gives information about the level of retinal perfusion, which has prognostic significance. The level of intraocular pressure and the diastolic and systolic blood pressure levels are relevant if exact numeric values are required for the ophthalmodynamometric estimations of both CRV and CRA pressures.[26] However, in the context of using the level of CVP as an estimation of the outflow resistance and thus the level of compromise to the retinal circulation in CRVO, the relationship of the CVP to the CRA diastolic and systolic levels is the relevant clinical sign. The exception to this would be in the situation of venous stasis retinopathy due to low CRA pressures in conditions such as carotid insufficiency.[26] In this study, patients were screened for low CRA pressures at baseline by a more formal estimation of CRA pressures by ophthalmodynamometry; however, no abnormal values were found. This was done by a spring-loaded plunger-type instrument (Luneau Technology) applied to the sclera with the pressure advanced while observing the CRA and CRV. The values were corrected for the intraocular pressure. This method is significantly more inaccurate than the more sophisticated instruments developed and used by other investigators[14,25–27] but is sufficient to exclude patients in this category.

Blood flow velocity in the retrobulbar CRV of patients with CRVO has been found by color Doppler imaging to be significantly reduced compared with normal controls or the unaffected fellow eye in most studies.[27] Low CRV flow rates were found to be associated with retinal ischemia, iris neovascularization, and longer retinal dye transit times.[28–30] In our study, FTTs were found to be significantly associated with the CVP level. Those in the group with low CVP had fairly normal transit times; however, the transit times increased with increasing CVP levels at all study time points, indicating that a measure of the CVP will provide useful information about retinal blood flow rates in patients with CRVO.

Development of collateral vasculature in response to the venous outflow obstruction also appears to be influenced by the CVP, with higher venous pressures associated with more rapid and more frequent shunt vessel development on the optic disc. Thought to arise from preexisting capillary networks, collateral vessels in the form of optociliary or retinochoroidal shunt vessels have been observed to develop and mature between 3 and 15 months after a CRVO.[31–33] The influence of these collateral vessels on final visual acuity appears to be minimal. Some have found a beneficial effect[34]; however, most have found the development of these vessels confers no benefit.[33,35,36] Our finding that the collateral vessels develop more frequently in those with higher CVP and thus in more severe forms of CRVO supports the findings of Hayreh et al.[33] They suggested that optociliary vessels may indicate a more severe disease; they found that eyes that developed collaterals in nonischemic CRVO had worse visual acuity at baseline and took twice as long for the resolution of macular edema, with a lower proportion of eyes having visual improvement.[33] This was also supported by the Standard Care vs. Corticosteroid for Retinal Vein Occlusion study, in which the investigators found the strongest predictor for development of collaterals in nonischemic CRVO was the area of CNP and hypothesized that a greater area of capillary nonperfusion was an indicator of greater hemodynamic stress and pressure gradient within the venous system.[32]

Most studies of ophthalmodynometry in CRVO have performed measurements at a single point and correlated the measured value with the clinical state of the vein occlusion at that particular point in time. Few studies have measured these values prospectively and correlated them with the progressive changes seen in the natural course of CRVO. Improvements in retinal venous outflow over time have been noted in patients with CRVO by both indirect and direct methods.[37,38] One study noted that at 3 months after presentation in patients with CRVO, although retinal blood flow in the veins had not changed, both the blood velocity had increased and the retinal venous diameter had decreased, implying that the intravascular venous pressure had decreased over the 3-month period.[38] Luckie et al[23] followed 50 patients with CRVO over a 6-month period and found that all had high CVP (equal or higher than arterial diastolic) at entry. By the 6-month end point, 52% had lowering of the CVP, and this was associated with improvements in visual acuity and reduced incidence of rubeosis iridis compared with those in whom the CVP remained high.[23] These results are similar to those of our study, but they do not represent a true natural history cohort because 25 of the patients in this group also underwent hemodilution.

This study has demonstrated that CVP remains a significant and largely unaddressed factor in our approach to the treatment of CRVO. The low baseline BCVA and high mean area of CNP suggest that patients in this study are skewed to those with more severe CRVOs, and although these results are significant in those with more severe disease, they may not be able to be generalized to entire populations of patients with CRVO. This is possible because our institution serves as a tertiary referral center attracting those with more severe disease, and some patients with nonischemic CRVOs were randomized into the treatment arm of the concurrent CVBS trial, as mentioned in the "Methods" section. The baseline mean CNP was similar to other studies of the natural history of CRVO,[39] and this should not alter the findings. Eyes with increased CVP after CRVO demonstrated significantly reduced vision, higher incidence of rubeosis, and larger areas of CNP that correlated with the degree of CVP elevation. We know from previous studies that visual acuity, at least in the early stages of CRVO, is directly related to the degree of macular edema,[7–10] and in this study, although it was not measured because of the nonavailability of optical coherence tomography at the time, the reduction in BCVA that was associated with increasing levels of CVP was most likely due to greater degrees of macular edema; however, this would need to be confirmed. Treatments that directly address the elevation in CVP as one of the factors in the cause and maintenance of CRVO-associated macular edema are required as part of an overall management approach. This study would suggest that any such treatment aimed at reducing the elevated CVP should be introduced early in the course of the disease at least in those with more significant CVP elevation to maximize visual recovery. We currently

have treatments that are effective at least in the short-term against the cytokine-induced breakdown in the blood–ocular barrier;[7–10] however, there is evidence appearing that their effectiveness in the longer-term is reduced.[20,21] A more comprehensive approach would be to use these cytokine antagonists against the blood–ocular barrier breakdown and another potential treatment to address the other component of the macular edema in this condition, the elevated CVP. The only treatment to date that has been proven to have the ability to do this is the laser-induced chorioretinal anastomosis.[15,16] There has been a limitation to the uptake of this as a potential treatment because of the nonavailability of a laser with sufficient power to create the anastomosis; however, this has been resolved recently.[40]

In conclusion, estimation of CVP provides useful information about retinal blood flow and the visual prognosis of each individual with a CRVO. Treatments can be potentially tailored to the level of venous obstruction as measured by CVP at each point in time. Those with low CVPs could be observed or treated with VEGF antagonists depending on the degree of macular edema. In the future, those with more elevated levels of CVP may benefit from a combination of treatments aimed at the elevated venous pressure, as well as the macular edema.

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[1] Centre for Ophthalmology and Visual Science, Lions Eye Institute, The University of Western Australia, Perth, Australia.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CNP** = capillary nonperfusion; **CRA** = central retinal artery; **CRV** = central retinal vein; **CRVO** = central retinal vein occlusion; **CVBS** = Central Vein Bypass Study; **CVP** = central venous pressure; **DA** = disc area; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FTT** = fluorescein transit time; **VEGF** = vascular endothelial growth factor.

Correspondence:
Ian L. McAllister, MBBS, Lions Eye Institute, 2 Verdun Street, Nedlands, WA 6009, Australia. E-mail: ianmcallister@lei.org.au.