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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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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;121:2228-2236 © 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.