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Relationship Between Nerve Fiber Layer Hemorrhages and Outcomes in Central Retinal Vein Occlusion

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Purpose. To evaluate the depth and pattern of retinal hemorrhage in acute central retinal vein occlusion (CRVO) and to correlate these with visual and anatomic outcomes.

Methods. Retinal hemorrhages were evaluated with color fundus photography and fluorescein angiography at baseline and follow-up. Snellen visual acuity (VA), central foveal thickness (CFT), extent of retinal ischemia, and development of neovascularization were analyzed.

Results. 108 eyes from 108 patients were evaluated. Mean age was 63.6 ± 16.1 years with a predilection for the right eye (73.1%). Average follow-up was 17.2 ± 19.2 months. Mean VA at baseline was 20/126 and 20/80 at final follow-up. Baseline (P = 0.005) and final VA (P = 0.02) in eyes with perivascular nerve fiber layer (NFL) hemorrhages were significantly worse than in eyes with deep hemorrhages alone. Baseline CFT was greater in the group with perivascular hemorrhages (826 ± 394 μm) compared to the group with deep hemorrhages alone (455 ± 273 μm, P < 0.001). The 10 disc areas of retinal ischemia was more common in patients with perivascular (80.0%) and peripapillary (31.3%) versus deep hemorrhages alone (16.1%, P < 0.001). Neovascularization of the iris was more common, although this difference was not significant, in the groups with peripapillary (14.3%) and perivascular (2.0%) NFL versus deep hemorrhages alone (0.0%).
Conclusions. NFL retinal hemorrhages at baseline correlate with more severe forms of CRVO, with greater macular edema, poorer visual outcomes, and greater risk of ischemia and neovascularization. This may be related to the organization of the retinal capillary plexus. The depth and pattern of distribution of retinal hemorrhages in CRVO may provide an easily identifiable early biomarker of CRVO prognosis.

Keywords: central retinal vein occlusion, nerve fiber layer hemorrhages, ischemia, neovascularization

Decades of research have been devoted to the identification of prognostic biomarkers that can predict central retinal vein occlusion (CRVO) visual outcomes and secondary complications. Initial studies identified poor baseline visual acuity, visual field, relative afferent papillary defects, cotton wool spots and density of retinal hemorrhage as factors that portended a worse visual prognosis in eyes with CRVO. The Central Vein Occlusion Study (CVOS) and other studies confirmed that baseline vision and confluent retinal hemorrhage, in addition to other factors such as afferent papillary defect, correlated with worse outcomes including a greater risk of neovascular glaucoma. The best way to assess CRVO outcomes may be to quantify the area of ischemia or non-perfusion with fluorescein angiography but interpretation was originally defined in the pre-widefield imaging era, can be limited by the presence of blood, and requires invasive dye injection.

Advanced retinal imaging has provided greater insight into the evaluation of retinal vascular disease. Mild forms of CRVO may present with only middle retinal ischemia, not detectable with dye-based angiography, and identified as bands of hyperreflectivity in the inner nuclear layer referred to as paracentral acute middle maculopathy (PAMM). These PAMM lesions may follow a perivenular distribution, best detected with en face optical coherence tomography (OCT), which may represent the mildest form of ischemic injury in CRVO and the initial manifestation of the process recently referred to as the ischemic cascade.

The progression of ischemic damage from the middle to the inner retinal layers in CRVO may share a parallel pathway with hemorrhage. Blood can be isolated in the Henle’s fiber layer (HFL) as a result of systemic or local etiologies of elevated venous pressure including retinal vein occlusion. Several studies have suggested that the intermediate and deep retinal capillary plexuses may represent the major level of venous outflow and it has therefore been proposed that ischemia and hemorrhage may first develop in the deeper layers of the retina. With more severe venous occlusion, inner retinal ischemia and inner retinal hemorrhage may occur more frequently.

We propose that the depth and pattern of distribution of retinal hemorrhages at presentation in eyes with CRVO may provide easily identifiable biomarkers that can predict visual and anatomical outcomes. Therefore, the purpose of this study was to correlate the level and location of retinal hemorrhage in eyes with CRVO with visual and anatomical parameters at baseline and follow-up.

Methods

This retrospective observational study was approved by the Institutional Review Board at the University of California, Los Angeles and adhered to the Health Insurance Porta-
NFL Hemorrhages in CRVO

A total of 108 eyes with CRVO from 108 patients were included and analyzed. Contribution of cases by each institution is summarized in Supplementary Table S1. At baseline, 37 eyes displayed deep retinal hemorrhages only, 21 eyes displayed deep retinal hemorrhages plus peripapillary NFL (nerve fiber layer) hemorrhages, and 50 eyes displayed deep hemorrhages plus peripapillary and perivascular NFL hemorrhages. An example of a case of CRVO with deep hemorrhages alone (Fig. 1), peripapillary NFL hemorrhages (Fig. 2), and perivascular NFL hemorrhages (Fig. 3) are shown. None of the patients presented with peripapillary or perivascular hemorrhages alone. Cohen’s $\kappa$ for inter-grader reliability was 0.76 (0.63–0.88) between graders for distribution of hemorrhage groups.

Average patient age in the total cohort was 63.6 ± 16.1 years of age and predominantly male (66/108 or 61.1%) with a predilection for the right eye 79/108 (73.1%) (Table 1). Average follow-up period was 17.2 ± 19.2 months (range 2.8 to 105.3 months). In total, 87.0% (94/108) of the patients received at least one anti-VEGF injection (mean 8.5 ± 9.3 injections, range 1–50), 3.7% (4/108) received intravitreal steroids, and 6.5% (7/108) received PRP laser therapy. No patients received intravitreal steroids as first line therapy. Of the four patients with intravitreal steroids, one received three Ozurdex injections, one received five Ozurdex injections, and the other two received one Ozurdex and one Kenalog injection during follow-up. Eyes with only deep retinal hemorrhages (26/37, 70.3%) were significantly less likely to have received anti-VEGF injections compared to eyes with peripapillary (21/21, 100.0%, $P = 0.006$) and perivascular NFL hemorrhages (47/50, 94.0%, $P = 0.003$). No difference in anti-VEGF frequency existed between the perivascular and peripapillary hemorrhage groups ($P = 0.25$). When comparing the rate of anti-VEGF injection over the entire follow-up, patients with only deep hemorrhages underwent $0.5 \pm 0.3$ injections per month, patients with deep retinal hemorrhages plus peripapillary NFL hemorhages received $0.9 \pm 0.9$ injections per month, and patients with deep retinal hemorrhages plus peripapillary and perivascular NFL hemorrhages underwent $0.8 \pm 0.9$ injections per month ($P = 0.20$).

Correlation Between Baseline NFL Hemorrhage Pattern and Baseline and Final Visual Acuity

Visual outcomes were compared in eyes with hemorrhages involving the NFL versus eyes without hemorrhage in the NFL at baseline presentation (Table 2). Baseline visual acuity in the group with deep retinal hemorrhages alone was 20/100, and in the group with peripapillary NFL hemorrhages it was 20/63, and in the group with perivascular NFL hemorrhages it was 20/200 ($P < 0.003$). Post-hoc Tukey’s HSD analysis showed that the significant difference in baseline visual acuity was between the peripapillary and perivascular ($P = 0.002$) groups and the deep and perivascular groups ($P = 0.005$) but not between the deep and peripapillary hemorrhage group ($P = 0.78$). However, at final follow-up there was a graded effect in average visual acuity. Eyes with deep hemorrhages alone improved to 20/40, eyes with peripapillary NFL hemorrhages stabilized at 20/80, and eyes...
**FIGURE 1. Case 1. Acute CRVO with deep retinal hemorrhages only.** Baseline color fundus photograph (A) and fluorescein angiogram (B) show deep retinal hemorrhages in the macula (arrowheads) and no evidence of NFL hemorrhages and no fluid with OCT (C). Follow-up at 3 months demonstrates progressive deep retinal hemorrhages (arrowheads) on color fundus photograph (D) and fluorescein angiogram (E), but still no evidence of NFL hemorrhages. One hemorrhage located in the macula can be identified as deep on OCT (F, arrow). Mild cystic changes were noted on the OCT (F) but no anti-VEGF injection was given. Vision was 20/40 at baseline and last follow-up.

**FIGURE 2. Case 2. Acute CRVO with deep retinal hemorrhages plus peripapillary NFL hemorrhages.** Baseline vision was 20/50. Baseline fundus photograph (A) shows superficial NFL hemorrhages in the peripapillary region (arrows) and deep retinal hemorrhages in the macula, which are confirmed on fluorescein angiography (B). At 9 months, follow-up widefield fundus photograph shows persistent deep hemorrhages (C) and follow-up widefield fluorescein angiography illustrates >10 disc areas of nonperfusion, most notably in the temporal retina (D). Baseline SD-OCT (E) shows cystoid macular edema and shallow central subretinal fluid. Follow-up SD-OCT (F) shows persistent CME and SRF despite six bevacizumab injections. Vision worsened to 20/125.

with perivascular NFL hemorrhages demonstrated the lowest VA at 20/100 ($P = 0.03$). Statistical significance occurred between the deep and perivascular hemorrhage group ($P = 0.02$); differences between the peripapillary versus perivascular ($P = 0.49$) and deep versus peripapillary ($P = 0.52$) groups were not significant.

**Baseline Hemorrhage Level Correlation with Central Foveal Thickness (CFT) and Fluid Status**

Baseline CFT was significantly less in the group with deep hemorrhages alone (455 μm ± 273 μm, $P < 0.001$) and in the group with peripapillary hemorrhages (534 ± 270 μm, $P = 0.001$).
FIGURE 3. **Case 3. Acute CRVO with deep retinal hemorrhages plus peripapillary NFL and perivascular NFL hemorrhages.** Widefield fundus photograph at baseline presentation (A) shows flame-shaped NFL hemorrhages in the peripapillary and perivascular regions (arrows) that nearly resolve at the 5-month follow-up visit (D). Widefield fluorescein angiography at baseline (B) demonstrates that the hemorrhages are superficial in a peripapillary and perivascular NFL distribution. Vision at presentation was 20/800. At the 5-month follow-up visit, vision improved to 20/200 but significant (greater than 10 disc areas) diffuse retinal ischemia was noted (E). SD-OCT shows significant central cystoid macular edema at baseline presentation (C) that was much improved at the 5-month follow-up visit (F) after six aflibercept injections.

### Table 1. Demographics and Treatment History of Study Population

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<tr>
<td>Age (yr, average ± SD)</td>
<td>63.6 ± 16.1</td>
<td>61.5 ± 18.3</td>
<td>68.0 ± 13.3</td>
<td>63.4 ± 15.4</td>
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<td>Male, n (%)</td>
<td>66 (61.1)</td>
<td>18 (48.6)</td>
<td>15 (71.4)</td>
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<td>Female, n (%)</td>
<td>42 (38.9)</td>
<td>19 (51.4)</td>
<td>6 (28.6)</td>
<td>17 (34.0)</td>
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<td>Eye</td>
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<td>OD, n (%)</td>
<td>79 (73.1)</td>
<td>31 (83.8)</td>
<td>15 (71.4)</td>
<td>33 (66.0)</td>
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<tr>
<td>OS, n (%)</td>
<td>29 (26.9)</td>
<td>6 (16.2)</td>
<td>6 (28.6)</td>
<td>17 (34.0)</td>
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<tr>
<td>Follow-up (mo, average ± SD)</td>
<td>17.2 ± 19.2</td>
<td>20.4 ± 23.7</td>
<td>20.0 ± 20.0</td>
<td>13.6 ± 14.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Received anti-VEGF treatment, n (%)</td>
<td>94 (87.0)</td>
<td>26 (70.3)</td>
<td>21 (100.0)</td>
<td>47 (94.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injections/total follow-up (injections/mo, average ± SD)</td>
<td>0.7 ± 0.8</td>
<td>0.5 ± 0.3</td>
<td>0.9 ± 0.9</td>
<td>0.8 ± 0.9</td>
<td>0.20</td>
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<tr>
<td>Intravitreal steroids, n (%)</td>
<td>4 (3.7)</td>
<td>0 (0.0)</td>
<td>2 (9.5)</td>
<td>2 (4.0)</td>
<td>0.21</td>
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<td>Panretinal photocoagulation, n (%)</td>
<td>7 (6.5)</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
<td>5 (10.0)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

NFL, nerve fiber layer; SD, standard deviation; VEGF, vascular endothelial growth factor.

$P = 0.002$ compared to the group with perivascular NFL hemorrhages (826 ± 394 μm). No difference was noted between the groups with deep versus peripapillary hemorrhages ($P = 0.72$) (Table 2). Illustrations of the correlation of CME and CFT are shown in Figures 1C (absent CME in a CRVO case with only deep hemorrhages), 2E (baseline CFT of 774 in a CRVO case with peripapillary NFL hemorrhage) and 3C (baseline CFT of 912 in a CRVO case with perivascular NFL hemorrhages). There was a correlation between baseline CFT and baseline visual acuity ($r = 0.45$, $P < 0.001$) and final visual acuity ($r = 0.24$, $p = 0.01$) across all groups.

Cystoid macular edema was present in 64.9% (24/37) of CRVO eyes with deep retinal hemorrhages alone, 81.0% (17/21) of eyes with deep retinal hemorrhages and peripapillary NFL hemorrhages, and 86.0% (43/50) of eyes with deep
retinal hemorrhages and peripapillary and perivascular NFL hemorrhages ($P = 0.03$, Table 3). Post-hoc \( \chi^2 \) tests demonstrated that these differences were primarily between the groups with deep and perivascular NFL hemorrhages that did not reach significance with the conservative Bonferroni correction ($P = 0.02$). Subretinal fluid was present in 29.7% (11/37) of eyes with deep retinal hemorrhages alone, 52.4% (11/21) of eyes with peripapillary NFL hemorrhages, and 40.0% (20/50) of eyes with perivascular NFL hemorrhages ($P = 0.23$) (Table 3).

### Baseline Hemorrhage Level Correlation with Ischemic Outcomes

In total, 26 of the 108 eyes were excluded only as pertains to the ischemic evaluation due to lack of widefield imaging or blockage from hemorrhage. Specifically this occurred in 6 eyes in the deep (n=31), 5 eyes in the peripapillary (n=16), and 15 eyes in the perivascular (n=35) groups. In total, 38 (46.3%) eyes displayed >10 disc areas of ischemia (i.e., ischemic CRVO), whereas 44 (53.7%) eyes were considered nonischemic CRVO. Ischemic CRVO was identified in 16.1% (5/31) of eyes with deep hemorrhages alone, 31.3% (5/16) of eyes with peripapillary NFL hemorrhages, and 80.0% (28/35) of eyes with perivascular NFL hemorrhages ($P < 0.001$) (Table 3). Please see Figures 2D, 3B, and 3E for case examples. Post-hoc \( \chi^2 \) tests illustrated continued statistical significance between the peripapillary versus perivascular ($P = 0.001$) and deep versus perivascular ($P < 0.001$) groups but not between the deep versus peripapillary groups ($P = 0.23$). In the 39 eyes with less than 6-month follow-up, 0/13 (0.0%) in the deep hemorrhage alone group, 1/5 (20.0%) in the peripapillary group, and 14/21 (66.7%) in the perivascular group illustrated evidence of ischemic CRVO.

### Discussion

This study evaluated the depth and pattern of distribution of retinal hemorrhages at presentation as a potential biomarker for visual and anatomic outcomes in patients with acute CRVO. Eyes with baseline retinal hemorrhages in a perivascular NFL distribution i.e. radial extension of the hemorrhages along the temporal vascular arcades exhibited significantly worse baseline and final visual acuities, a greater prevalence and severity of cystoid macular edema, a greater frequency of ischemic CRVO (versus nonischemic CRVO), and a greater rate of anti-VEGF injection therapy.

Other known biomarkers of ischemic CRVO have been described and include baseline visual acuity, relative afferent pupillary defect, cotton wool spots and extent of retinal hemorrhages.\(^1,2,4\) From the CVOS, nonperfusion of greater than 10 disc areas with FA was a key risk factor for neovascularization.\(^4,22\) In fact, Nicholson et al.\(^5\) demonstrated that
ischemia or nonperfusion area of 75 to 150 disc areas was associated with an 80% rate of neovascularization. Tsui et al.\textsuperscript{23} confirmed that eyes with a nonperfused area or ischemic index of 45% of the total retina area were at a significantly greater risk of neovascularization. Hayreh et al.\textsuperscript{2} evaluated the pattern of retinal hemorrhages in acute CRVO and found that 92% of patients with ischemic CRVO displayed peripapillary hemorrhages versus 71% of eyes with nonischemic CRVO at baseline. In more severe cases, ischemia and hemorrhage may track superficially into the inner retina, and as suggested by this study, extend into the radial peripapillary capillary plexi (RPC) within the NFL. This is mainly in an area radiating away from the disc where the NFL is thickest and the RPC is present; more peripheral, the RPC is absent and only deep retinal hemorrhages are seen.\textsuperscript{20,27}

The organization of the retinal capillary plexus has been extensively studied but the exact arrangement, specifically the nature of the venous drainage, has not been clearly elucidated.\textsuperscript{20} Fouquet et al.\textsuperscript{28} have illustrated a serial arrangement of the retinal microvasculature in which the RPC drains directly into the DCP and subsequently empties into a post-capillary venule in pigs (Fig. 4). This has been confirmed in other mammals and in humans.\textsuperscript{20,29–32} More recent human ex vivo studies, however, contradict this pattern of venous drainage.\textsuperscript{33} Our findings suggest that in eyes with CRVO, the ICP and DCP (closest to the draining venules) may be at greatest risk of injury from increased hydrostatic pressure while the SCP and the RPC may be more resistant. Thus hemorrhage and ischemia will develop first in the region of the ICP and DCP and with more severe occlusion, hemorrhage and ischemia will be evident in the superficial capillary plexus and ultimately the RPC NFL.\textsuperscript{8–12,34} This pathway may explain the salient finding of this study, which identified RPC NFL hemorrhages, particularly along the radial perivascular extensions, as a biomarker of a more severe phenotype of CRVO with worse visual outcomes and increased retinal ischemia and cystoid macular edema.
This pathway may also explain why patients with more severe CRVO display more extensive retinal hemorrhages. The extent of hemorrhage is a commonly accepted biomarker for ischemic CRVO but its identification lacks the mechanistic understanding this paper provides. Further, it is important to note that in this study NHL hemorrhage correlated not only with that ischemia but also with worse visual outcomes, greater central macular thickness, and greater prevalence and severity of CME and increased rate of treatment with anti-VEGF. This would indicate that NHL hemorrhages correspond to outcomes beyond ischemia that strengthen its independence from extent of hemorrhages.

An unexpected finding of our study is the predilection of acute CRVO in the right eye across the entire cohort of patients. We speculate that this may be due to the unique anatomy of the right internal jugular vein which connects directly with the SVC or superior vena cava (the left internal jugular vein is separated from the SVC by the innominate vein) leading to greater venous pressures on the right side. As the right atrium fills during diastole against a closed tricuspid valve, the pressure increases due to increased blood volume. This pressure is likely exacerbated in patients with chronic hypertension who have hypertrophic myocardium, stiffened vessels, or sclerotic or incompetent tricuspid valve. As a result, this increases retrograde pressure that can be transmitted to the superior venous plexus, which is greater on the right side. As the right atrium fills during diastole against a closed tricuspid valve, the pressure increases due to increased blood volume. This pressure is likely exacerbated in patients with chronic hypertension who have hypertrophic myocardium, stiffened vessels, or sclerotic or incompetent tricuspid valve. As a result, this increases retrograde pressure that can be transmitted to the superior vena cava (the left internal jugular vein is separated from the SVC by the innominate vein) leading to greater venous pressures on the right side. As the right atrium fills during diastole against a closed tricuspid valve, the pressure increases due to increased blood volume. This pressure is likely exacerbated in patients with chronic hypertension who have hypertrophic myocardium, stiffened vessels, or sclerotic or incompetent tricuspid valve. As a result, this increases retrograde pressure that can be transmitted to the superior vena cava (the left internal jugular vein is separated from the SVC by the innominate vein) leading to greater venous pressures on the right side.

Limited by this study include the retrospective design, the nonstandardized imaging protocols, and the variable follow-up which prevented uniform analysis of all eyes. As ischemia was considered within and outside the standard seven fields, bias may have been introduced as areas of the peripheral retina may not have been appropriately captured in all cases. The heterogenous follow-up made it difficult to assess subtle changes in visual acuity and the relative impact of anti-VEGF therapy efficacy and its effect on macular edema and neovascularization. The development of neovascularization of the iris or neovascular glaucoma may have been masked by anti-VEGF therapy given for coexistent cystoid macular edema. Furthermore, the extent of ischemia can change over time and can be masked by blockage from hemorrhage on fluorescein angiography. Additional systemic factors (e.g. anticoagulation, blood pressure) may have influenced the extent and severity of hemorrhages and may have also confounded our findings. Last, the study was underpowered to statistically evaluate for trends that were not significant, such as the number of injections performed per month. Future prospective longitudinal studies with a standardized imaging protocol and a natural history control cohort will be necessary to formally validate the findings of this study. However, this investigation may serve as a pilot study to be further validated with larger prospective data sets that include uniform multimodal retinal imaging.

In conclusion, we provide evidence that in CRVO patients, eyes with retinal hemorrhages located in the RPC NFL specifically along the major vascular arcades, may represent more severe forms of CRVO with worse visual outcomes, increased cystoid macular edema, and greater risk of ischemic complications. As such, perivascular NFL hemorrhage radiating along the vascular arcades may provide an easily identifiable biomarker of ischemic CRVO at greater risk for iris and angle neovascularization and with more adverse visual and anatomic outcomes.

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References


NFL Hemorrhages in CRVO


