Retinochoroidal Collateral Veins Protect Against Anterior Segment Neovascularization After Central Retinal Vein Occlusion

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Objective: To test the hypothesis that retinochoroidal collateral veins (RCVs), or alternatively, retinociliary or optociliary shunts/collaterals/veins or opticociliary anastomoses, act protectively against the development of anterior segment neovascularization (ASN) following central retinal vein occlusion (CRVO).

Design: Case-control retrospective medical record review of patients with CRVO.

Patients: We identified 107 patients with CRVO, of whom 34 had developed ASN, by reviewing their medical records. After applying exclusion criteria, a case group and an age-, sex-, and visual acuity–matched control group were selected. We analyzed these groups for the presence or absence of RCVs and noted the time course involved in their development.

Main Outcome Measures: Anterior segment neovascularization (including neovascularization of the iris and/or anterior chamber angle), neovascular glaucoma, and RCV development.

Results: Only 1 (5.4%) of 19 individuals who developed ASN did so in the presence of RCVs. In contrast, 11 (57.9%) of 19 individuals in the control group developed RCVs. Statistical analysis revealed that patients who developed ASN were roughly 25 times less likely to have had RCVs than individuals who never developed ASN (odds ratio = 24.74; \( P = .001 \)).

Conclusion: Retinochoroidal collateral veins are negatively associated with ASN post-CRVO and may function in a protective manner against such an outcome.

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Although not much is known concerning the physiologic significance of RCVs, investigators have postulated that they protect the eyes from poorer visual outcomes post-CRVO by acting as an alternative drainage route for retinal circulation. Others have contended this assertion (see “Comment” section). This study aims to delineate the possible prognostic significance of RCVs post-CRVO and analyze the possibility that they act protectively against the development of ASN.

METHODS

Patients diagnosed as having CRVO between January 1992 and January 2001 were identified, and their records were reviewed. Institutional review board approval was obtained prior to review of these patients' records. Patient age, sex, race, length of follow-up, and visual acuity at onset and at end point were recorded for these 107 individuals noting the presence or absence of ASN. Visual acuity was recorded using the Feinbloom and Snellen scales.

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Table 1. ASN Case Group

<table>
<thead>
<tr>
<th>Age, y/Race/Sex</th>
<th>Initial Visual Acuity</th>
<th>Final Visual Acuity</th>
<th>ASN</th>
<th>Time to ASN</th>
<th>RCVs (Time, mo)</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>83/White/M</td>
<td>20/650</td>
<td>NLP</td>
<td>INV/NVG</td>
<td>3 wk</td>
<td>Yes (6)</td>
<td>&gt;36</td>
</tr>
<tr>
<td>84/White/M</td>
<td>20/900</td>
<td>NLP</td>
<td>INV/NVG</td>
<td>1 mo</td>
<td>No</td>
<td>&gt;36</td>
</tr>
<tr>
<td>61/White/F</td>
<td>20/2300</td>
<td>HM</td>
<td>INV/NVG</td>
<td>15 mo</td>
<td>No</td>
<td>&gt;36</td>
</tr>
<tr>
<td>82/White/F</td>
<td>CF</td>
<td>HM</td>
<td>INV/NVG</td>
<td>&gt;18 mo</td>
<td>No</td>
<td>30</td>
</tr>
<tr>
<td>75/White/F</td>
<td>HM</td>
<td>NLP</td>
<td>INV/NVG</td>
<td>3 wk</td>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td>79/White/M</td>
<td>20/60</td>
<td>LP</td>
<td>INV/NVG</td>
<td>2 mo</td>
<td>No</td>
<td>&gt;36</td>
</tr>
<tr>
<td>80/White/F</td>
<td>20/1400</td>
<td>CF</td>
<td>INV/NVG</td>
<td>3 mo</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>71/White/M</td>
<td>20/700</td>
<td>20/2300</td>
<td>INV/NVG</td>
<td>1 mo</td>
<td>Yes (2)</td>
<td>4</td>
</tr>
<tr>
<td>72/White/F</td>
<td>NLP</td>
<td>NLP</td>
<td>NVG</td>
<td>&gt;2 mo</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>82/White/F</td>
<td>LP</td>
<td>LP</td>
<td>NVG</td>
<td>1 mo</td>
<td>No</td>
<td>13</td>
</tr>
<tr>
<td>83/White/F</td>
<td>HM</td>
<td>HM</td>
<td>NVA</td>
<td>3 mo</td>
<td>Yes (2)</td>
<td>16</td>
</tr>
<tr>
<td>72/White/M</td>
<td>20/1300</td>
<td>20/400</td>
<td>INV/NVA</td>
<td>4 mo</td>
<td>No</td>
<td>20</td>
</tr>
<tr>
<td>49/White/M</td>
<td>20/50</td>
<td>20/400</td>
<td>INV</td>
<td>1 mo</td>
<td>Yes (5)</td>
<td>&gt;36</td>
</tr>
<tr>
<td>67/White/M</td>
<td>20/200</td>
<td>20/200</td>
<td>INV</td>
<td>2 mo</td>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>64/White/F</td>
<td>20/400</td>
<td>20/1100</td>
<td>INV</td>
<td>3 mo</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>72/White/M</td>
<td>20/400</td>
<td>20/80</td>
<td>INV</td>
<td>6 mo</td>
<td>No</td>
<td>&gt;36</td>
</tr>
<tr>
<td>71/White/F</td>
<td>20/200</td>
<td>HM</td>
<td>NVA</td>
<td>9 mo</td>
<td>Yes (25)</td>
<td>&gt;36</td>
</tr>
<tr>
<td>79/White/M</td>
<td>20/200</td>
<td>20/400</td>
<td>NVA</td>
<td>8 mo</td>
<td>No</td>
<td>&gt;36</td>
</tr>
<tr>
<td>81/White/F</td>
<td>20/500</td>
<td>20/700</td>
<td>NVA</td>
<td>5 mo</td>
<td>No</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: ASN, anterior segment neovascularization; CF, counting fingers; HM, hand motions; INV, iris neovascularization; LP, light perception; NLP, no light perception; NVA, neovascularization of the angle; NVG, neovascular glaucoma; RCV, retinochoroidal collateral vein.

*Initial and final visual acuity measurements refer to the affected eye.

All pertinent clinical findings (eg, ASN, RCVs, and type of CRVO) were obtained from the examination notes of 3 of us (R.M.F., J.O.M., and M.F.W.). In many instances, the ophthalmoscopic findings were correlated with other data (notably, data from fluorescein angiograms and fundus photographs) to help assure proper classification, especially in cases in which RCVs could not be differentiated from neovascularization of the disc. No attempt was made to “grade” the RCVs. End points for our data collection included the development of ASN and last follow-up visit.

Patients with ASN (n=34) were identified and separated from those who never developed this complication (n=73). Our interest focused on patients who developed ASN and whether or not they had RCVs prior to this development, so we excluded those who initially had a diagnosis of ASN and those with less than 3 months of follow-up. We also excluded individuals who developed ASN more than 24 months after their initial diagnosis of CRVO; this late-developing ASN was probably not related to the initial insult and more likely represented a separate thrombotic event (see “Comment” section).
Because ASN is a complication of nonperfused (ischemic) CRVO, we excluded patients from this group who had a diagnosis of perfused (nonischemic) CRVO. Nineteen of the 34 individuals met the aforementioned criteria. Subsequently, a matched control group was created with 19 subjects who did not develop ASN (see Table 1 and Table 2). These 2 groups of 19 individuals were analyzed for the presence or absence and time to development of RCVs.

### RESULTS

The ASN group had a mean age of 74.1 years (range, 49-84 years), had a median visual acuity of 20/500 in the affected eye, consisted of 8 men and 11 women, and had a mean follow-up time of 22 months. Similarly, the control group had a mean age of 75.5 years (range, 54-93 years), had a median visual acuity of 20/400 in the affected eye, was made up of 9 men and 10 women, and had a mean follow-up time of 13 months. Median visual acuity was used (instead of mean visual acuity) because of quantification difficulty with many recorded acuities (eg, counting fingers, hand motions, light perception, and no light perception). The mean time to develop ASN was 4.5 months (range, 3 weeks to 18 months) with a median time of 3 months. The mean time to develop RCVs among 12 individuals from both groups was 3.9 months (median, 4 months).

As shown in the Figure, only 1 individual (3.3%) from our ASN group exhibited RCVs before developing ASN. This is contrasted with 11 individuals (37.9%) from our control group who developed RCVs. These results were statistically significant ($P=.001$). An odds ratio of 24.75 (95% confidence interval, 2.72-25.62) was calculated signifying that an individual who develops ASN is nearly 25 times less likely to have RCVs than an individual who does not develop ASN.

We further analyzed our data by reviewing all 107 cases and calculating the frequency of RCVs in both the ASN and non-ASN groups. For this analysis, we extended the data collection time to the last visit for all patients (ie, we did not use ASN development as an end point). The results revealed that 49 (46%) of 107 patients with CRVO developed RCVs. Stratification revealed that 38 (52%) of 73 individuals without ASN developed RCVs compared with 11 (32%) of 34 in the ASN group (there was no attempt to distinguish perfused from nonperfused CRVO in either group). More strikingly, only 3 (8.8%) of the 34 individuals from the ASN group were found to have RCVs before their development of ASN (ie, 8 of the 11 developed RCVs after ASN). Of these 3 patients, 2 developed ASN 3 to 4 years after their initial CRVO diagnosis and likely represent a new occlusive event. However, even including these 2 individuals, statistical analysis revealed that those who develop ASN are 10 times less likely to have RCVs than individuals who do not develop ASN (odds ratio = 10.33; 95% confidence interval, 2.90-36.78; $P < .001$).

The mean time to develop RCVs among all 107 individuals was 6.7 months (excluding the 4 individuals who developed RCVs at 12 months or longer, the mean time to RCVs was 3.9 months). The mean time to develop ASN was 7.5 months (excluding the 3 individuals who developed ASN at 12 months or longer, the mean time to ASN was 3.1 months).

### COMMENT

Investigators have long noted the importance of being able to identify patients with CRVO who may be at an increased risk of developing ASN so that they might receive more aggressive follow-up and treatment. Because ASN is essentially a complication of nonperfused CRVO, much research has been aimed at proper differentiation of nonperfused from perfused CRVO (alternatively called ischemic and nonischemic types, respectively). Many studies have identified various possible prognostic factors including initial visual acuity, ophthalmoscopic findings,
evidence of nonperfusion by fluorescein angiography, visual field testing, relative afferent pupillary defect, electroretinography, and color Doppler imaging. Although these findings may provide useful information, especially when used in combination, they all have their limitations. The Central Vein Occlusion Study (CVOS) found that “ancillary studies [including digital venous pressure, relative afferent pupillary defect, and electroretinography] do not add notable prognostic information beyond that obtainable in routine clinical examination or alter clinical care recommendations.”17(p489) Additionally, many of these studies are burdensome on the patient and physician, increase the cost of care, and may not be generally available.

Visual acuity and ophthalmoscopy stand out as being the most widely available and regularly tracked findings. Visual acuity holds some predictive information for future ASN development,17-19 but its usefulness is limited; macular edema, which generally causes a severe reduction in visual acuity, is a common finding in perfused CRVO. Ophthalmoscopically, the number and distribution of retinal hemorrhages and cotton-wool spots are unreliable predictors of ASN development.20

In light of this information, there is a strong need for prognostic ophthalmoscopic findings or RCVs. Although some researchers believe that ophthalmoscopic findings are too subjective to provide information that may affect treatment, many of the previously mentioned tests are also affected by subjective interpretation. Notably, Welch and Augsburger21 showed that with fluorescein angiography, agreement levels may be as low as 68% between 2 assessments by the same observer. Furthermore, some studies have found that RCVs have a beneficial effect post-CRVO. The CVOS mentioned that patients with “venous collaterals were somewhat less likely” to develop ASN.17(p488) Two studies23,26 have found that RCVs lead to a better prognosis as far as visual acuity is concerned; others, however, contest these findings.14,27 Interestingly, Guillette et al27 noted that none of their 8 patients with NVG displayed RCVs as opposed to 34% of the patients without NVG.

Arguing against a protective effect of RCVs, one study stated that “development of disc collateral vessels [is] of no statistical prognostic value.”18(p739) This study included a small total number of eyes that progressed to ASN (12/59), provided no documentation of whether the time course to development of RCVs and ASN was followed, and made no comment on whether the RCVs occurred before or after ASN development. Similarly, most studies regarding RCVs post-CRVO have not made it clear if time courses for developing RCVs and/or ASN were followed. Because it is not infrequent for an eye with ASN to later develop RCVs (about a third of our ASN group eventually did), if the time course for each occurrence is not followed, investigators may not realize the association. Therefore, this study focuses on the possible temporal relationship between RCVs and ASN.

As alluded to earlier, we excluded individuals who developed ASN more than 24 months after their initial CRVO diagnosis from the control-partition of the study. Studies have shown that ASN most commonly develops within 6 months post-CRVO and that development after 12 months is extremely rare.17 In the rare cases of ASN developing after 12 months, some investigators have proposed that a more recent insult (ie, a new CRVO that was not compensated by the RCVs) was the cause of the subsequent ASN. This mechanism has been proposed as a likely means of progression from perfused CRVO to nonperfused CRVO.28,29 The CVOS found that approximately one third of all patients with perfused CRVO progress to nonperfused status within 3 years, with nearly half of the progressions occurring in the first 4 months.17

In light of this mechanism, it is interesting to reanalyze our data on all 107 cases; 2 of the 3 individuals who developed ASN in the presence of existing RCVs did so at 3 and 4 years post-CRVO. Assuming a recent insult that would negate any protective effects of existing RCVs, only 1 (2.9%) of the 34 individuals who developed ASN did so in the presence of functioning RCVs. Interestingly, this individual developed RCVs 2 months post-CRVO, developed neovascularization of the angle 1 month later, subsequently received panretinal photocoagulation, and did not progress to NVG or have a decrease in visual acuity during her 16 months of follow-up.

Both the case-control results and those from the full data set suggest a strong negative association between the presence of RCVs and the subsequent development of ASN. Even more dramatic is that none of the 107 individuals developed NVG within 2 years after the initial visualization of RCVs.

Currently, most researchers suggest treatment protocols for CRVO that focus on the prompt identification and treatment of patients with ASN.17,20 Although our results suggest less concern regarding the progression to ASN in patients with RCVs, we do not recommend less frequent follow-up for such individuals at this point. However, if these results are confirmed in other studies, the presence or absence of RCVs may one day influence the clinical guidelines for follow-up post-CRVO. Notably, there is a need for prospective studies as well as more medical record review with proper attention to the time course relationship between RCVs and ASN.

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REFERENCES


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