Effect of Laser Photocoagulation on the Retinal Vessel Diameter in Branch and Macular Vein Occlusion

Noémi Maár, MD; Alexandra Luksch, MD; Alice Graebe, MD; Erdem Ergun, MD; Barbara Wimpissinger, MD; Michael Tittl, MD; Pia Vecsei, MD; Michael Stur, MD; Leopold Schmetterer, PhD

Objective: To investigate the response of retinal vessel diameters to photocoagulation treatment and their role for the success of laser treatment in patients with retinal vein occlusion.

Methods: The study included 14 patients with branch vein occlusion or macular vein occlusion. The ophthalmologic examination included best-corrected visual acuity, biomicroscopy, fundus photography, and fluorescein angiography. Retinal vessel diameters were quantified before and after laser photocoagulation using a retinal vessel analyzer.

Main Outcome Measure: Retinal vessel diameters.

Results: In cases manifesting macular vein occlusions, no significant change of the vessel diameter in any vessel was observed during the follow-up period. In the group with branch vein occlusion, all vessels tended to constrict after the laser photocoagulation. The effect of laser treatment on retinal vessel diameters was significant for superotemporal (P = .045, analysis of variance [ANOVA]) and inferotemporal branch veins (P = .03, ANOVA). Vasoconstriction was more pronounced in the occluded branch veins (P = .009, ANOVA) compared with the nonaffected veins (P = .12; ANOVA). The change of visual acuity after 3 months was correlated with the change of vessel diameter 3 months after laser treatment for occluded venular branches (r = 0.78, P = .02, linear regression). There was no correlation between the number of laser burns and the change of vessel diameters in the affected veins in this period (r = 0.12, P = .75, linear regression).

Conclusions: Our results show that retinal photocoagulation in patients with branch vein occlusion has a vasoconstrictive effect on occluded veins. The correlation between the change in visual acuity and the change in vessel diameter indicates that branch vein constriction after photocoagulation may be an early indicator of the success of laser treatment.

Arch Ophthalmol. 2004;122:987-991

Retinal vein occlusion is the second most frequently occurring disease of retinal vessels. A histopathologically detectable thrombus in the occluded retinal vein1,2 or the pressure of an artery with arteriosclerotic alterations at an arteriovenous crossing3,4 causes increased intravascular hydrostatic pressure and results in secondary macular edema that, in turn, is associated with severe vision loss. If the obstruction persists and macular edema cannot resolve spontaneously, chronic macular edema may develop.5 In some eyes, severe ischemia may follow retinal vein occlusion that leads to neovascularization.

In previous studies, sectorial or grid laser photocoagulation in ischemic or edematous areas was reported to have beneficial effects in stabilizing visual acuity (VA).6,8 The effect underlying the efficacy of laser therapy is not exactly known. Several theories for the mechanism underlying photocoagulation have been postulated: on the one hand, an effect on the retinal pigment epithelium with increased production of the pigment epithelium-derived factor (PEDF)9 and a suppression of vascular endothelial growth factor (VEGF)-induced migration growth has been proposed.10 On the other hand, a direct effect on retinal oxygen tension may occur. This may induce regulatory vasoconstriction and indirectly reduce retinal blood flow, as shown for panretinal photocoagulation applied in proliferative diabetic retinopathy.11,12 According to Starling’s law, reduced intravascular pressure in the capillary network due to reduced vascular caliber should then reduce retinal edema formation. The aim of this study was to investigate the response of retinal vessel diameters to laser photocoagulation in patients with branch vein occlusion or macular vein occlusion.

From the Departments of Ophthalmology (Drs Maár, Luksch, Graebe, Ergun, Tittl, Vecsei, and Stur), Clinical Pharmacology (Drs Luksch, Wimpissinger, and Schmetterer), and Medical Physics (Dr Schmetterer), University of Vienna, Vienna, Austria. The authors have no relevant financial interest in this article.
coagulation treatment in patients with retinal vein occlusion.

**METHODS**

The study was performed in adherence to the guidelines of the Declaration of Helsinki and the Good Clinical Practice guidelines, after written informed consent was obtained. The study protocol was approved by the Ethics Committee of the School of Medicine, University of Vienna, Vienna, Austria.

The patient group was prospectively recruited from our outpatient clinic that specializes in retinal vascular and macular diseases. It consisted of 7 men and 7 women who had ophthalmoscopic evidence of recent retinal vein occlusion, that is, a history of 3 to 9 months. The patients had to have 1 of the following criteria on the study eye for inclusion: (1) a capillary nonperfusion area of 5 disc diameters, as demonstrated by fluorescein angiography, or (2) the presence of neovascularization or evidence of macular edema and reduced VA due to vein occlusion.

Only patients with ocular media clear enough to permit safe laser photoocoagulation were included. Exclusion criteria were history of retinal photoocoagulation treatment, presence of other intraocular pathologic conditions, evidence of metabolic diseases such as diabetes mellitus, systemic hypertension higher than 180/100 mm Hg, ametropia of 6 diopters (D) or more, and smoking more than 20 cigarettes daily.

The ophthalmologic examination included the best-corrected VA (Snellen), intraocular pressure measured with applanation tonometry, slitlamp examination, biomicroscopy with a +90 D Volk lens, stereo fundus photography, and fluorescein angiography of the involved area using a fundus camera set to a 40° angle (model CF60UV; Canon Co, Tokyo, Japan). Systolic, diastolic, and mean blood pressures were measured on the arm by an automated oscillometric device (HP-CMS patient monitor; Hewlett-Packard, Palo Alto, Calif). Pulse rate was automatically recorded from a finger pulse-oxymetric device (HP-CMS patient monitor; Hewlett-Packard). Retinal vessel diameters were quantified using the retinal vessel analyzer (Carl Zeiss, Jena, Germany).13,14

The retinal vessel analyzer is a commercially available system that comprises a fundus camera (model FF 450; Carl Zeiss), a video camera, a real-time monitor, and a personal computer with an analyzing software for the accurate determination of retinal arterial and venous diameters.13 Every second a maximum of 25 readings of vessel diameter can be obtained. For this purpose the fundus is imaged onto the charged-coupling device chip of the video camera. The consecutive fundus images are digitized using a frame grabber. In addition, the fundus image can be inspected on the real-time monitor and, if necessary, stored on a video recorder. Evaluation of the retinal vessel diameters can either be done online or offline from the recorded videotapes. Owing to the absorbing properties of hemoglobin, each blood vessel has a specific transmittance profile. Measurement of retinal vessel diameters is based on adaptive algorithms using these specific profiles. Whenever a vessel profile is recognized in the region of interest, the retinal vessel analyzer can follow this vessel as long as it appears within the measurement window.

Measurements were done at the main superior and inferior temporal or nasal vein and artery, 1 to 2 disc diameters (DD) from the optic disc. The same segment of the vessel was selected at all visits. A sectorial scatter photoocoagulation combined with grid laser treatment in case of macular edema in branch vein occlusion (BrVO) or grid laser treatment only in macular vein occlusion was performed with blue-green argon laser according to the recommendation of the Branch Vein Occlusion Study Group5,6 and Miller.7

The presence of macular edema was established by biomicroscopy. The fundus photographs and the angiograms were graded by an experienced ophthalmologist (N.M.). For the grading of the fundus photographs, a transparent overlay with a circle with a 1-DD radius was fixed over the image. By using a Donaldson ×5 stereoscopic viewer, the degree of macular edema was determined using the modified Airlie House Classification.15 As morphologic variables the following lesions were graded as follows: degree of macular edema (0, no evidence; 1, questionable involvement; and 2, definitely present), size of macular retinal thickening less than 1 DD from the center (0, no evidence; 1, questionable involvement; 2, size of thickening less than one half of the disc area; 3, size of thickening <1 disc area; 4, size of thickening <2 disc areas; and 5, size of thickening ≥2 disc areas), and maximal retinal thickness at the center (0, no evidence; 1, questionable involvement; 2, thickness <1× reference; 3, thickness ≥1× reference but <2× reference; 4, thickness ≥2× reference but <1/2 DD; and 5, thickness ≥1/2 DD). After 3 months, macular edema was graded as reduced if the size of retinal thickening and/or the maximal retinal thickness decreased, and graded as worsened if these scores increased.

Measurement of retinal vessel diameter was repeated 1 and 4 weeks as well as 3 months after laser photoocoagulation. At the visit 3 months after laser treatment best-corrected VA (Snellen), slitlamp examination, biomicroscopy with a +90 D Volk lens, stereo fundus photography, and fluorescein angiography were additionally repeated.

Statistical analyses were done using the Statistica software package (Release 4.5; StatSoft Inc, Tulsa, OK). Data are presented as mean (SD). For subgroup analysis patients were divided into 2 groups: patients with macular vein occlusion and patients with BrVO. In the second group the effect of laser photoocoagulation on the affected arteries and veins was also studied. Visual acuity before laser therapy was compared with VA 3 months after photoocoagulation by t test for dependent samples. The number of laser burns was correlated to the change in vessel diameter by using linear regression analysis. The change of the retinal vessel diameters at the follow-up visits was analyzed using analysis of variance (ANOVA). Probability values smaller than .05 were considered statistically significant.

**RESULTS**

The mean (SD) age of the 14 patients was 66.3 (8.6) years (age range, 51-80 years), and the mean (SD) duration of symptoms (decrease in VA) when they visited in our outpatient department was 6.4 (2.1) months (range, 3-9 months). Five and 6 eyes were initially seen with temporal inferior BrVO and temporal superior BrVO, respectively, whereas in 3 eyes macular vein occlusion was detected. At the initial ophthalmologic examination all eyes manifested macular edema. Three months after laser treatment the macular edema disappeared in 3 cases only but was reduced in all eyes. The number of burns used for photoocoagulation ranged between 4 and 821 (mean [SD], 245 [222]; range, 4-140 in the macular vein occlusion group and 101-821 in the BrVO group), usually with a 0.1-mm spot size, 0.05- to 0.1-second exposure, and the minimal energy to create a light gray burn (range, 90-400 mW; mean [SD], 139 [96] mW).

In the macular vein occlusion group, VA was not significantly changed after 3 months (P = .23, t test; mean [SD] VA before therapy, 0.37 [0.45], and 3 months later, 0.47 [0.35]). The VA in patients with BrVO increased significantly (P = .02, t test) at the 3-month follow-up visit.
The results of the measurements of retinal vessel diameters are summarized in the Table. In the macular vein occlusion group, no significant change of the vessel diameter in any vessel was observed during the follow-up period. In the BrVO group, all vessels under study tended to constrict after laser photocoagulation. This tendency was more pronounced in the veins than in the arteries. The effect of laser treatment on retinal vessel diameters was significant for superior temporal (P = .045, ANOVA) and inferior temporal branch veins (P = .03, ANOVA). Vasocostriction was more pronounced in the occluded branch veins (P = .009, ANOVA) compared with the nonaffected veins (P = .12, ANOVA) (Figure). In the retinal arteries, none of the effects reached the level of significance although a tendency was seen in almost all vessels under study, particularly in the affected arteries. The change of VA after 3 months correlated with the change of vessel diameter 3 months after laser treatment for occluded venular branches (r = 0.78, P = .02, linear regression). There was no correlation between the number of laser burns and the change of vessel diameters in the affected veins in this period (r = 0.12, P = .75, linear regression).

### Measurements of Retinal Vessel Diameters*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>1 wk</th>
<th>4 wk</th>
<th>3 mo</th>
<th>P Values (ANOVA)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Branch vein occlusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSV</td>
<td>150.6 (21.3)</td>
<td>149.7 (19.7)</td>
<td>146.8 (18.3)</td>
<td>147.7 (19.6)</td>
<td>.045</td>
</tr>
<tr>
<td>TIV</td>
<td>156.6 (25.8)</td>
<td>151.4 (22.0)</td>
<td>149.3 (19.3)</td>
<td>147.8 (19.1)</td>
<td>.03</td>
</tr>
<tr>
<td>NSV</td>
<td>129.8 (16.0)</td>
<td>119.3 (18.6)</td>
<td>116.7 (16.7)</td>
<td>117.6 (16.0)</td>
<td>.26</td>
</tr>
<tr>
<td>NIV</td>
<td>122.4 (17.6)</td>
<td>116.8 (19.0)</td>
<td>116.3 (20.1)</td>
<td>117.6 (18.5)</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Affected vein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSV</td>
<td>157.5 (25.0)</td>
<td>151.3 (23.3)</td>
<td>147.0 (20.6)</td>
<td>145.3 (20.7)</td>
<td>.009</td>
</tr>
<tr>
<td>TIV</td>
<td>124.1 (11.0)</td>
<td>123.2 (8.2)</td>
<td>122.0 (5.5)</td>
<td>119.2 (6.6)</td>
<td>.36</td>
</tr>
<tr>
<td>NSV</td>
<td>129.9 (21.4)</td>
<td>128.8 (16.1)</td>
<td>127.0 (15.0)</td>
<td>130.4 (20.2)</td>
<td>.50</td>
</tr>
<tr>
<td>TIV</td>
<td>105.2 (19.4)</td>
<td>109.1 (19.1)</td>
<td>105.4 (16.5)</td>
<td>104.3 (16.6)</td>
<td>.16</td>
</tr>
<tr>
<td>NIV</td>
<td>108.9 (13.6)</td>
<td>105.3 (11.8)</td>
<td>106.0 (13.2)</td>
<td>105.1 (10.0)</td>
<td>.59</td>
</tr>
<tr>
<td><strong>Affected artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSV</td>
<td>131.0 (15.1)</td>
<td>126.0 (13.2)</td>
<td>125.1 (10.2)</td>
<td>124.5 (11.5)</td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; NIA, nasal inferior artery; NIV, nasal inferior vein; NSA, nasal superior artery; NSV, nasal superior vein; TIA, temporal inferior artery; TIV, temporal inferior vein; TSA, temporal superior artery; TSV, temporal superior vein.

*Data are given as mean (SD).
†Boldfaced values indicate statistical significance P < .05.

(Received [SD] VA before laser therapy, 0.30 [0.22], and 3 months later, 0.45 [0.21]).

The results of the measurements of retinal vessel diameters are summarized in the Table. In the macular vein occlusion group, no significant change of the vessel diameter in any vessel was observed during the follow-up period. In the BrVO group, all vessels under study tended to constrict after laser photocoagulation. This tendency was more pronounced in the veins than in the arteries. The effect of laser treatment on retinal vessel diameters was significant for superior temporal (P = .045, ANOVA) and inferior temporal branch veins (P = .03, ANOVA). Vasocostriction was more pronounced in the occluded branch veins (P = .009, ANOVA) compared with the nonaffected veins (P = .12, ANOVA) (Figure). In the retinal arteries, none of the effects reached the level of significance although a tendency was seen in almost all vessels under study, particularly in the affected arteries. The change of VA after 3 months correlated with the change of vessel diameter 3 months after laser treatment for occluded venular branches (r = 0.78, P = .02, linear regression). There was no correlation between the number of laser burns and the change of vessel diameters in the affected veins in this period (r = 0.12, P = .75, linear regression).

### Comment

In the present study sectorial laser photocoagulation in BrVO resulted in a significant decrease of the temporal branch vein diameter and tended to decrease retinal arterial diameters. This is in keeping with the findings of previous studies,16,17 which detected retinal vascular changes after grid photocoagulation.

Interestingly, the change of VA at 3 months after laser treatment was correlated to the decrease of the diameter of occluded veins, but not to the number of laser burns. Based on this finding one may hypothesize that early vasoconstriction as assessed with the retinal vessel
analyzer may have predictive character for the success of laser treatment. This needs, however, to be confirmed in large-scale studies.

Following retinal vein occlusion, the inner blood-retinal barrier is damaged resulting in abnormal fluid homeostasis. Occlusion of a retinal branch vein leads to an increase of the intravascular pressure and a decrease of the oxygen concentration, resulting in abnormal permeability of the perifoveal retinal capillaries. If the volume exceeds a certain quantity, the retinal pigment epithelium as the outer blood-retinal barrier is not able to sufficiently transport the accumulated fluid from the retina to the choriocapillaris and intraretinal edema develops.

The mechanism underlying the beneficial effect of photocoagulation in BrVO is still unclear. The following hypotheses have been discussed:

1. After photocoagulation the oxygen flux increases from the choroid to the inner retina leading to constriction of retinal vessels. This hypothesis is supported by the evidence that photocoagulation results in an increase in the oxygen flux from the choroid to the inner retina. The oxygen tension plays a significant role in retinal autoregulation because arterioles dilate when oxygen tension decreases and constrict when it increases resulting in modulation of retinal blood flow. In our study, the observed vasoconstriction of the retinal branch vessels in response to photocoagulation may well result from the increase of retinal oxygen tension in the ischemic area. This, in turn, decreases intravascular tension in capillaries and veins associated with passive vasoconstriction of the veins according to Laplace’s law. At the same time, the decreased intravascular pressure leads to reduced edema formation.

2. The increased concentration of VEGF during hypoxia normalizes after photocoagulation. Previous studies show an up-regulation of VEGF during vasobliterative and hypoxic phases in retinal disease, which normalizes after photocoagulation. The photocoagulation-induced decrease in VEGF may well contribute to retinal branch vein constriction because VEGF is an important vasodilator in retinal vessel in healthy and diabetic rats. This occurs as a direct effect of the laser photocoagulation on the cells of the retina and the retinal pigment epithelium and/or develops as a consequence of improved oxygenization of retinal tissue.

3. The increased concentration of PEDF and reduced expression of VEGF after laser treatment lead to stabilization of the blood-retinal barrier. The high concentration of VEGF and the reduced concentration of PEDF can induce increased retinal vascular permeability leading to breakdown of the blood-retinal barrier. Retinal laser photocoagulation increases PEDF production. This factor exerts effects opposite to VEGF by suppressing the VEGF-induced retinal endothelial growth and migration. In addition, neuroprotective properties have been described. In this way increased concentration of PEDF and decreased concentration of VEGF after laser treatment can be indicative for inhibition of neovascularization and resorption of macular edema through stabilization of the blood-retinal barrier after laser treatment.

Which of these mechanisms underlying the therapeutic effect of laser photocoagulation in retinal vein occlusion is predominant remains to be established. The fact that the increase of VA correlates with the change of diameter of affected branch veins in BrVO is compatible with the idea that the first 2 mechanisms play an important role, but do not exclude the third possibility.

In macular vein occlusions we did not detect significant changes in vessel diameter or changes in VA after grid photocoagulation. In eyes with minimal laser treatment, where the areas of photocoagulation are small, it might well be that the effect of oxygen tension is localized thereby affecting capillary but not branch vein diameters.

Our results show that sectorial retinal photocoagulation of BrVO has a vasoconstrictive effect on occluded veins. The correlation between the change in VA and the change in vessel diameters suggests that branch vein constriction after photocoagulation may be an early indicator of the success of laser treatment. Whether this holds true remains, however, to be investigated in a large number of subjects.

Submitted for publication March 10, 2003; final revision received October 31, 2003; accepted December 12, 2003.

Correspondence: Leopold Schmetterer, PhD, Department of Medical Physics, Wahlinger Strasse 13, 1090 Vienna, Austria (Leopold.Schmetterer@univie.ac.at).

REFERENCES


