Laser Treatment and the Mechanism of Edema Reduction in Branch Retinal Vein Occlusion

Ársæll Arnarsson and Einar Stefánsson

PURPOSE. To test a hypothesis on the physiological mechanism of the disappearance of macular edema after laser treatment. The hypothesis is based on the effect grid laser treatment has on retinal oxygenation and hemodynamics. It predicts that laser-induced reduction of macular edema is associated with shortening and narrowing of retinal vessels in patients with branch retinal vein occlusion (BRVO).

METHODS. The study included 12 subjects, treated with argon laser photocoagulation for BRVO and macular edema. Fundus photographs taken at the time of diagnosis and again after laser treatment, were digitized, and diameter and segment length of retinal vessels was measured using NIH-Image program.

RESULTS. Macular edema disappeared or was dramatically reduced in all cases after laser treatment. The diameter of occluded venules constricted to 0.81 ± 0.02 (mean ± SD, P = 0.019) of the prelaser diameter and adjacent arterioles constricted to 0.78 ± 0.01 (P = 0.008). The laser treatment also led to shortening of the affected vessels. The final segment length of the occluded venules was 0.95 ± 0.17 (P = 0.005) of the length before treatment. The corresponding value for the adjacent arterioles is 0.95 ± 0.14 (P = 0.008). Control arterioles and venules in the same fundus did not change in either length or width.

CONCLUSIONS. These results do not reject the authors’ hypothesis that the disappearance of macular edema in BRVO can be explained by the effect the laser photocoagulation has on retinal oxygenation. Increased oxygenation causes vessel constriction and shortening and lower intravascular pressure, which reduces edema formation according to Starling’s law. (Invest Ophthalmol Vis Sci. 2000;41:877–879)

It has been demonstrated in many species¹–⁵ including humans,⁴ that retinal grid laser treatment improves oxygenation of the inner retina. The photocoagulation of the photoreceptors reduces the oxygen consumption of the outer retina and allows oxygen to diffuse from the chorioid to the inner retina, where it raises the oxygen tension and relieves hypoxia.²–⁴ Increasing oxygen tension in the inner retina results in autoregulatory vasoconstriction and more resistance in the arterioles, leading to reduced hydrostatic pressure in the capillaries and venules.¹–² According to Starling’s law, this will decrease the fluid flux from the intravascular compartment into the tissue and reduce tissue edema, assuming that the oncotic pressures are constant (Fig. 1). The decrease in hydrostatic pressure will at the same time cause the venules to constrict and shorten according to the law of Laplace and the study of Kylstra et al.⁵

This hypothesis has previously been tested in diabetic macular edema and its disappearance after grid laser treatment of the macula.⁶–⁷ In this study we test the hypothesis in macular edema resulting from branch retinal vein occlusion (BRVO).

METHODS

We evaluated fundus photographs from 24 consecutive patients with BRVO and macular edema examined at the University eye clinic in Reykjavik and treated with laser between 1990 and 1994. Twelve subjects, 2 women and 10 men, had fundus photographs before and after laser treatment that could be used for measurement of retinal blood vessels. Twelve patients were excluded from this study because their fundus photographs were of insufficient quality or because of blood masking the vessels so that vessel measurements could not be performed. The age of the patients at the time of diagnosis ranged from 48 to 80 years, with the mean age of 64 years. The right eye was involved in five cases, and the left in seven. The temporal veins were involved in all cases, the superotemporal in five subjects, and the inferotemporal in seven (Table 1). None of the patients had more than one occluded vessel, and none had BRVO in the other eye.

The recorded biomicroscopic findings, color stereo pairs of fundus photographs, and fluorescein angiography were used to assess edema. All of the 12 subjects had macular edema indicated by thickening of the retinal tissue in the macula. Four eyes were thought to have cystoid macular edema. In all cases the edema disappeared or was markedly reduced after the laser treatment. A few hard exudates were seen in the fundus of four patients, and soft exudates in six. Drusen were seen in one case. Five were diagnosed having hypertensive changes in the vessels, mostly arteriovenous nicking. Shunts were seen in five cases. Two patients had mild retinal neovascularization that

From the Department of Ophthalmology, University of Iceland, Reykjavik, Iceland.
Supported by Research Funds of the University of Iceland.
Submitted for publication January 5, 1999; revised August 18, 1999; accepted September 23, 1999.

Commercial relationships policy: N.
Corresponding author: Einar Stefánsson, University of Iceland, Landspítili, IS-101 Reykjavik, Iceland. einarste@rsp.is
Fundus photographs were taken with a Canon 60° fundus camera using a 100 ASA Kodak Ektachrome film (Eastman Kodak, Rochester, NY). The slides were digitized into a Power Macintosh 7600/132 (Apple Inc., CA) via a flatbed scanner (UMAX PowerLook 2000; UMAX Data Systems Inc.). The image was transferred via Photoshop software (Adobe Systems Inc.) with a UMAX MagicScan DA v.3.0 program and saved on a TIFF format. The geometric resolution was 1200 dpi. Analysis was performed using the public domain NIH Image program (developed at the US National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/).

After digitizing the fundus photographs, a cursor was used to measure the diameter of the optic disc. These measurements were then used to correct for the difference in magnification between photographs of the same patient, by dividing it into measurements of vessel segment length and vessel diameter. The intraobserver variability of this method, calculated from the diameter measurements of one investigator of each optic disc five times, was 0.6%. The interobserver variability between two investigators was 1.4%. The diameter of the occluded venule and its adjacent arteriole was measured distal to the occlusion. The intraobserver variability of these measurements was 0.5%, and the interobserver variability 0.8%. The length of the occluded branched venule and the adjacent arteriole was measured by using a cursor and tracing from the bifurcation closest to the occlusion to another bifurcation more distal. The intraobserver variability of these measurements was 0.2%, but the interobserver variability was 2.1%. For control, measurements were taken the same way from the other temporal arcade.

The data were analyzed using a paired Student’s t-test and correlation, where a P value below 0.05 was considered significant.

The study adhered to the principles of the Helsinki Declaration.

**RESULTS**

The effect of the laser treatment on vessel diameter and segment length is shown in Table 2. The diameter of the occluded venule and the adjacent arteriole showed a significant constriction after the treatment (Table 2). The diameter of the occluded venules was reduced by 19% and the diameter of the adjacent arterioles by

**TABLE 1. Site of Occlusion and Changes in Visual Acuity**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before</th>
<th>After</th>
<th>Involved Branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/24</td>
<td>6/8</td>
<td>Superotemporal</td>
</tr>
<tr>
<td>2</td>
<td>6/6</td>
<td>6/5</td>
<td>Superotemporal</td>
</tr>
<tr>
<td>3</td>
<td>CF2m</td>
<td>6/60</td>
<td>Superotemporal</td>
</tr>
<tr>
<td>4</td>
<td>6/24</td>
<td>6/12</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>5</td>
<td>6/36</td>
<td>6/12</td>
<td>Superotemporal</td>
</tr>
<tr>
<td>6</td>
<td>2/60</td>
<td>4/60+2</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>7</td>
<td>6/24</td>
<td>6/12</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>8</td>
<td>1/60</td>
<td>6/9</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>9</td>
<td>6/36+1</td>
<td>6/9</td>
<td>Superotemporal</td>
</tr>
<tr>
<td>10</td>
<td>6/60</td>
<td>3/60</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>11</td>
<td>6/60+1</td>
<td>6/24</td>
<td>Inferotemporal</td>
</tr>
<tr>
<td>12</td>
<td>1/60</td>
<td>6/60</td>
<td>Inferotemporal</td>
</tr>
</tbody>
</table>

Measurements of visual acuity are before and after laser-treatment.
Changes were calculated by dividing the measurements taken at the end of the observation period by measurements taken at the time of diagnosis, before laser treatment was applied. Values are means ± SD, and P value by Student’s t-test are shown. NS, not significant.

22%. The control arterioles did not exhibit any change in diameter. There was no significant correlation between the number of laser burns and the change in vessel diameter in the occluded or nonoccluded venules and arterioles.

Laser treatment also resulted in a statistically significant reduction in the segment length of the occluded venules and adjacent arterioles (Table 2). The segments from the occluded venule and the adjacent arteriole were both 5% shorter after the laser treatment. No significant change was seen in the segment length of the control retinal venules and arterioles.

**DISCUSSION**

Laser treatment of macular edema in BRVO leads to shortening and constriction of the occluded venule and the adjacent arteriole. It does not affect the length and diameter of vessels on the opposite temporal arcade. These findings fail to disprove our hypothesis shown in Figure 1. The shortening and constriction of vessels would, according to the law of Laplace and the study of Kylstra et al., indicate lowering of intravascular hydrostatic pressure, and therefore, according to Starling’s law, a reduction in fluid flux to the surrounding tissue and decreasing edema (Fig. 1).

Starling’s law describes the equilibrium between the two types of force that move water in the body, i.e., hydrostatic and oncotic pressure gradients. All fluid flux between blood vessels and tissue and thereby the formation and disappearance of edema can be described as

\[ FP = (HP_e - HP_d) - (\pi_e - \pi_d), \]

where \( FP \) is the net filtration pressure, \( HP_e \) is the hydrostatic pressure in the capillary, and \( HP_d \) is the hydrostatic pressure of the interstitial fluid. Representing the oncotic pressure due to proteins in the capillary and interstitial fluid is \( \pi_e - \pi_d \). The law states that reduced intravascular pressure in the capillaries and venules will reduce the net filtration pressure and the fluid flux into the tissue and reduce edema.

Laplace’s law predicts that decreased hydrostatic pressure in capillaries and venules decreases their diameter: \( r = \sqrt{rP}, \) where \( r \) equals the radius of the vessel, \( t \) is the vessel wall tension, and \( P \) the transmural pressure. According to the study of Kylstra et al., increasing the pressure in a passive tube not only leads to an increase in its diameter, but also in length.

The present study shows that similar changes in retinal vessel diameter and length are seen after laser treatment for macular edema in BRVO and diabetes, both in human and animal studies. Vasoconstriction in the retina after panretinal laser treatment was first demonstrated by Wilson et al. in patients in the Diabetic Retinopathy Study. Gottfredsdottir et al. measured 12% to 20% constriction of macular arterial and venular branches after photocoagulation in diabetic macular edema. Kristinsson et al. using methods similar to ours, showed that 4% elongation and 6% to 19% dilatation of retinal vessels precedes the formation of diabetic macular edema and that grid photocoagulation causes constriction of these vessels, along with the disappearance of edema. In experimentally produced BRVO, the veins upstream from the occlusive site dilate (between 10% and 20%) and become more tortuous. In monkeys it has been demonstrated that retinal capillary area decreases around the site of laser photocoagulation, indicating vasoconstriction.

BRVO and macular edema are clinically associated with fluorescein leakage on angiographies, and it is tempting to attach a causative association between that leakage and the edema formation, as some authors have done for diabetic macular edema. However, the free flow of water through capillary wall fluxes is most likely controlled by hydrostatic and oncotic pressure gradients, and permeability is only important to the extent that it affects osmotically active molecules, such as albumin. The term edema denotes increased tissue water content, and we believe that its formation in BRVO patients is explained by the forces of Starling’s law. Starling’s law is the general principle describing water fluxes and edema in the body, and our data suggest that the retina is no exception.

**References**