EARLY HISTOLOGIC AND FUNCTIONAL STUDY OF RADIAL OPTIC NEUROTOMY OUTCOMES IN NORMAL RAT EYES

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Background: Radial optic neurotomy (RON) has been proposed as a treatment for central retinal vein occlusion. However, it is still under debate whether RON would be an adequate treatment or a dangerous procedure, and persuasive animal studies are lacking. The aim of this study was to analyze the early histologic and functional outcomes of RON in normal rat eyes.

Methods: Radial optic neurotomy was performed by cutting into the optic nerve edge at the nasal hemisphere, while the contralateral eye underwent a sham procedure. The retinal function was assessed by scotopic electroretinography, and the visual pathway was assessed by flash visual evoked potentials. Intraocular pressure was assessed with a tonometer, the pupillary light reflex was measured after exposing eyes to a 30-second light flash, whereas the optic nerve head structure was examined by histologic analysis.

Results: In normal rat eyes, RON provoked minor histologic alterations at the optic nerve head level and a transient decrease in the electroretinography. No changes in visual evoked potentials, intraocular pressure, and pupillary light reflex were observed in rat eyes submitted to RON.

Conclusion: To our knowledge, this is the first study describing the early histopathologic and functional consequences of RON in normal rat eyes.

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Central retinal vein occlusion (CRVO) is the second most common retinal vascular disorder after diabetic retinopathy that often leads to visual disability, especially in patients experiencing ischemic type of CRVO.[1] Although the first description of CRVO was in 1878, the current therapeutic regimens are still disappointing.[2] In 2001, Opremcak et al[3] hypothesized that CRVO is a compartmentlike syndrome resulting from increased pressure on the central retinal vein (CRV) within the confined space of the scleral ring. To alleviate this neurovascular compression, the surgical dissection of the lamina cribrosa transvitreally via a radial incision on the nasal side of the optic nerve (ON) to improve venous outflow (i.e., radial optic neurotomy [RON]) was proposed as a new surgical treatment. In this pilot study,[3] the authors reported that 8 of 11 patients showed an average improvement in visual acuity of 5 lines after a mean follow-up of 9 months, whereas only 2 patients had worsened visual acuity. In 2006, the same group reported 117 cases treated with RON and 63 cases treated with RON and intravitreal triamcinolone injection. A gain of 2 and more lines was reported for 78% and 64% of patients, respectively.[4,5] Improvements in visual acuity by RON have been confirmed by other investigators.[6–10] However, soon after the proposal of RON as a potential treatment modality for CRVO, a debate arose regarding whether the incision of the scleral outlet is a reasonable or dangerous procedure.[11–14] The potential risk of nerve fiber defects resulting in visual field loss has especially been addressed by many authors.[11,12,15] Although the radial incision mode and site and the use of microvitreoretinal blades specially

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designed for RON should minimize vessel and nerve fiber injury, surgical complications cannot be ruled out completely. In fact, several surgical complications, such as laceration of the central retinal artery (CRA), further reductions in retinal blood flow, peripapillary retinal detachment from the RON site, ON fiber damage, visual field loss, and focal hemorrhagic pigment epithelium detachment, and chorioretinal neovascularization from the RON site, were described.[16–21]. While, as already mentioned, the original rationale of RON was the relief of increased tissue pressure within the ON that results from occlusion of the CRV, more recent experience suggests that any benefit from the procedure is more likely related to the production of a juxtapapillary chorioretinal anastomosis at the site of the optic neurotomy.[22]

Many variables, like the site of occlusion, cause and natural history of CRVO, and especially the adverse effects of RON on the ON function, can lead to confusion in data interpretation regarding the surgical outcome. The continuous and objective monitoring of visual functions and retinal and ON histology in easily accessible and reproducible animal models could contribute to shed light into RON side effects. In that sense, the use of animal models could help to get an insight into the histologic and functional outcomes of RON. Histologic effects of RON were previously studied in pig and cat eyes,[23–26] but no information about functional consequences of RON were provided in those reports. The use of rodents allows experimentation with sufficient number of animals and could provide a picture of both functional and morphologic effects of RON. Therefore, the aim of the present report was to analyze the early effect of RON in normal rat eyes.

Materials and Methods

Animals

Male Wistar rats (average weight, 300 ± 50 g) were housed in a standard animal room with food and water ad libitum under controlled conditions of humidity and temperature (21 ± 2°C), and under a 12-hour light and 12-hour dark lighting schedule (lights on at 07.00 hours). All animal-use procedures were in strict accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

Radial Optic Neurotomy

Rats were anesthetized with ketamine hydrochloride (150 mg/kg) and xylazine hydrochloride (2 mg/kg) administered intraperitoneally. A drop of proparacaine (0.5%) was administered in each eye for local anesthesia. Animals were subjected to RON in one eye, whereas the contralateral eye was subjected to a sham procedure. Radial optic neurotomy was performed as follows: eyes were focused under a binocular Colden surgical microscope with coaxial light for fundus visualization and illumination. Using a 30-gauge dental cartridge needle, a scleral puncture was made at 1 mm of the corneoscleral limbus. A single incision at the nasal hemisphere of the optic disk was performed in the edge of the neuroretinal ring, cutting an equal part of ON and parapapillary retina, avoiding damage to the central retinal vessels. Care was taken to make the stab radial to the optic disk and parallel to the nerve fiber pattern. The sham-operated eyes were subjected to a similar procedure (a scleral puncture was made at 1 mm of the corneoscleral limbus), but without any incision.

Histologic Evaluation

One, 3, or 7 days after surgery, rats were killed, and their eyes were immediately enucleated including not less than 3 mm of ON attached. Eyes were immersed for 24 hours in a fixative containing 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2) and embedded in paraffin. Eyes were cut into sections through the equatorial meridian. The posterior calotte including the optic disk and nerve was serially sectioned every 5 μm from the interior surface of the optic disk to the retrobulbar segment of the ON. Microscopic images were digitally captured with a Nikon Eclipse E400 microscope (illumination 6-V halogen lamp, 20 W, equipped with a stabilized light source) via a Nikon Coolpix s10 camera. Sections were stained with hematoxylin–eosin and analyzed by masked observers. Microscopic examination of hematoxylin-eosin–stained slides was used to assess for scleral canal incision and to determine whether damage to ON vasculature occurred.

Electroretinography

Electroretinographic activity was assessed before and 1, 3, or 7 days after surgery (sham operation or RON), as previously described.[27] Briefly, after 6 hours of dark adaptation, rats were anesthetized under dim red illumination. Phenylephrine hydrochloride and tropicamide were used to dilate the pupils, and the cornea was intermittently irrigated with balanced salt solution to maintain the baseline recording and to prevent keratopathy. Rats were placed facing the stimulus at a distance of 20 cm. All recordings were completed within 20 minutes, and animals were kept warm during and after the procedure. A reference electrode was placed through the ear, a grounding

electrode was attached to the tail, and a gold electrode was placed in contact with the central cornea. A 15-W red light was used to enable accurate electrode placement. This maneuver did not significantly affect dark adaptation and was switched off during the electrophysiologic recordings. Electroretinograms (ERGs) were recorded from both eyes simultaneously, and 10 responses to flashes of unattenuated white light (5 milliseconds, 0.2 Hz) from a photic stimulator (light-emitting diodes) set at maximum brightness (6 cd/m^2 without filter) were amplified, filtered (1.5-Hz low-pass filter, 1,000 Hz high-pass filter, notch activated), and averaged (Akonic BIO-PC; Akonic, Buenos Aires, Argentina). The a-wave was measured as the difference in amplitude between the recording at onset and the trough of the negative deflection, and the b-wave amplitude was measured from the trough of the a-wave to the peak of the b-wave. Runs were repeated 3 times with 5-minute intervals to confirm consistency. Mean values from each eye were averaged, and the resultant mean value was used to compute the group mean a- and b-wave amplitudes ± standard error. The mean peak latencies and peak-to-peak amplitudes of the responses from each group of rats were compared. Baseline (before surgery) recordings were taken at least 3 days before surgery.

Flash visual evoked potentials

For scotopic flash visual evoked potentials recording, 2 stainless steel electrodes were surgically placed 4 mm lateral to the interhemispheric fissure and 5.6 mm behind bregma (active electrode), as previously described.[27] Reference electrodes were placed 2 mm lateral to the midline and 2 mm before bregma. A ground electrode was placed in the animal tail. Both electrodes were isolated and fixed with dental acrylic, and the skin was sutured with nylon 5/0. Visual evoked potentials were assessed 7 days after surgery as follows: after 6 hours of dark adaptation, rats were anaesthetized, pupils were dilated, and the cornea was intermittently irrigated as previously described, under dim red illumination. All recordings were completed within 20 minutes of the induction of anesthesia, and animals were kept warm during and after the procedure. Each eye was registered individually, occluding the contralateral eye, and a 70-stimuli average was registered. Eyes were stimulated with unattenuated white light (1 Hz) from a photic stimulator (light-emitting diodes) set at maximum brightness, were amplified, filtered (0.5-Hz low-pass filter, 100-Hz high-pass filter, notch activated), and averaged (Akonic BIO-PC; Akonic). The amplitude between the N2 deflection and the P2 peak was assessed, and the N2 latency was measured from the onset to the second negative peak.

Assessment of the Pupillary Light Reflex

For the assessment of the pupillary light reflex, one eye was submitted to RON or a sham operation, whereas the contralateral eye remained intact. All animals were dark adapted for 1 hour before pupillary light reflex (PLR) assessment. While 1 eye received light stimulation from a white light source (1,200 lux), the other eye was video monitored under infrared light with a digital camcorder (Sony DCR-SR60; Sony, Tokyo, Japan). Pupil diameter before (dark adapted) and after a light pulse (30 seconds) was measured. Sampling rate was 30 images per second. The digital video recording was deconstructed to individual frames using OSS Video Decompiler Software (One Stop Soft, New England). The percent pupil constriction was calculated as the percent of pupil area at 30 seconds after the initiation of the stimulus (steady state) relative to the dilated pupil size. In one experiment, eyes submitted to sham operation or RON were stimulated by light, and the pupillary light reflex was assessed in the contralateral intact eyes, whereas in a second experiment, light stimulated the intact eyes and the pupillary light reflex was assessed in sham- or RON-operated eyes.

Intraocular Pressure Assessment

A tonometer (TonoPen XL; Mentor, Norwell, MA) was used to assess intraocular pressure (IOP) in conscious, unsedated rats, as previously described.[28] All IOP determinations were assessed by operators who were masked with respect to the treatment applied to each eye. Animals were wrapped in a small towel and held gently, with one operator holding the animal and another making the readings. Five IOP readings were obtained from each eye by using firm contact with the cornea and omitting readings obtained as the instrument was removed from the eye. Differences among reading were $<10\%$ (standard error). The mean of these readings was recorded as the IOP for this eye. Mean values from each rat were averaged, and the resultant mean value was used to compute the group mean IOP ± standard error. Intraocular pressure measurements were performed at the same time each day or week (between 11.00 and 12.00 hours) to correct for diurnal variations in IOP.[28]

Results

Figure 1 shows serial photomicrographs of the ON head (ONH) from eyes submitted to RON at 1, 3, or 7 days

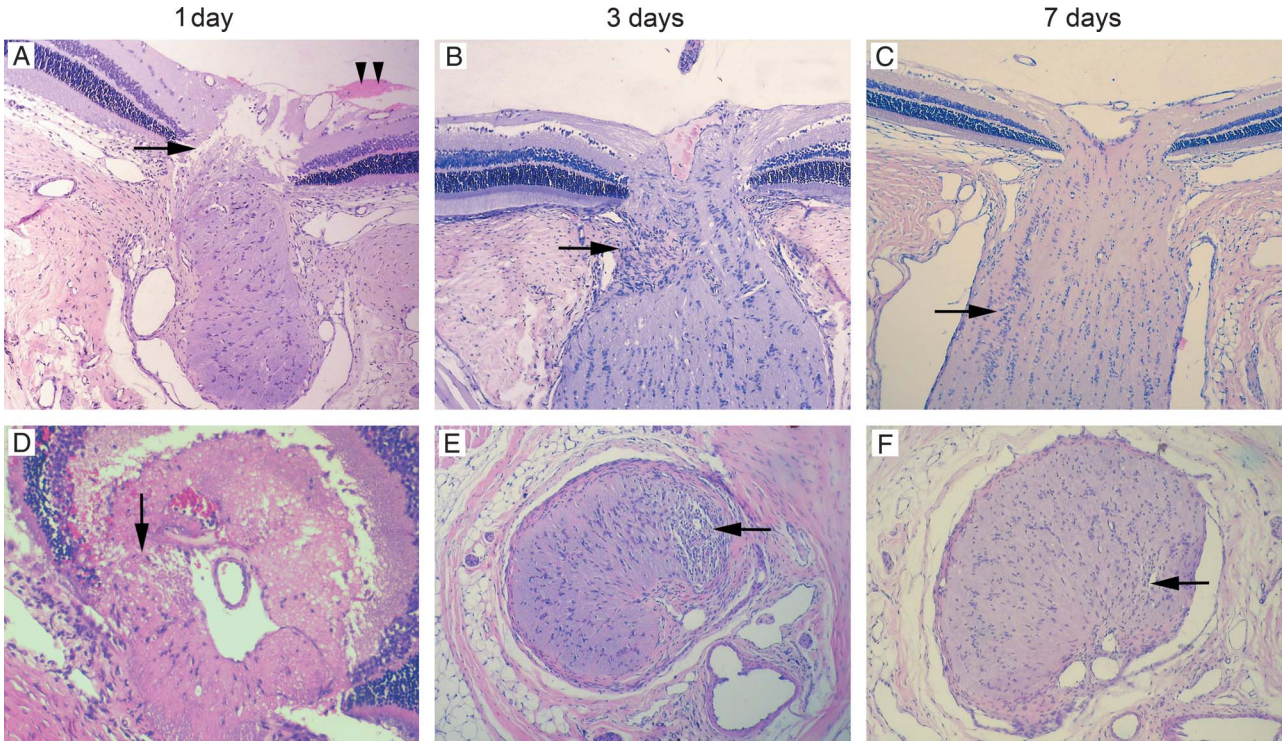

Fig. 1. Longitudinal and cross-sectional histologic images of the ON at 1 (**A** and **D**), 3 (**B** and **E**), and 7 (**C** and **F**) days after radial incisional neurotomy (hematoxylin–eosin stain). **A.** Incision from RON (arrow) and focal hemorrhages at the edge of the optic disk (arrowheads). **B.** Wedge-shaped cellular scar at the site of ON incision (arrow). **C.** Mild irregularity of nerve fiber bundles and gliosis of the ON (arrow). **D.** Optic nerve edema and extravasated erythrocytes in the adjacent retina (arrow). **E.** Circumscribed area of gliosis within the ON. **F.** No major abnormalities were observed at Day 7 after the procedure. Narrow nerve fiber bundles and increased cell density in the interaxonal tissue (arrow).

postsurgery. At 24 hours postsurgery, a discrete tissue defect and edema (Figure 1, A and D) were noted at the ONH that reached the cribriform plate, without involving the adjacent sclera or the retinal vessels. The CRV and CRA remained undisturbed, whereas the nerve fiber layer was minimally disrupted. The globe was not ruptured in any eye, and a few extravasated erythrocytes within the retina were observed. At Day 3 postsurgery, the gaping wound was replaced and enlarged by a cellular scar (Figure 1, B and E). No neovascularization was observed, and there was no damage to adjacent vessel wall. Serial sections of the ON from Day 7 after the procedure show minimal tissue changes. On the side of the neurotomy incision, there was increased cellularity of the glial columns and irregularity of the nerve fiber bundles (Figure 1, C and F).

To assess the effect of RON on retinal function, ERGs were registered at different time points after surgery. Figure 2 shows scotopic ERGs assessed at 1, 3, or 7 days after RON or sham procedure. One day after surgery, a significant decrease in the ERG a- and b-wave amplitude was observed, whereas no differences in these parameters between sham-operated eyes and eyes submitted to RON were evident at 3 or 7 days after surgery. The sham operation did not affect the ERG as compared with intact eyes (data not shown). No changes in the a- and b-wave latencies were observed among groups at any time point.

For the assessment of the effect of RON on the visual pathway, visual evoked potentials were recorded in eyes submitted to RON or the sham procedure at 7 days after surgery. No changes in visual evoked potentials were observed between sham- and RON-operated eyes, as shown in Figure 3. The pupillary light reflex was assessed 7 days after surgery (Figure 4). No significant differences in this parameter were observed when the sham-operated or RON-treated eyes were stimulated by light, and the pupil contraction was assessed in the contralateral (intact) eyes. A similar result was obtained when intact eyes were stimulated by light and the PLR was assessed in eyes submitted to a sham operation or RON. As shown in Figure 5, no changes in IOP were observed between sham- and RON-operated eyes at 7 days postsurgery.

Discussion

Radial optic neurotomy is one of many attempts to surgically treat CRVO. Despite that the results from

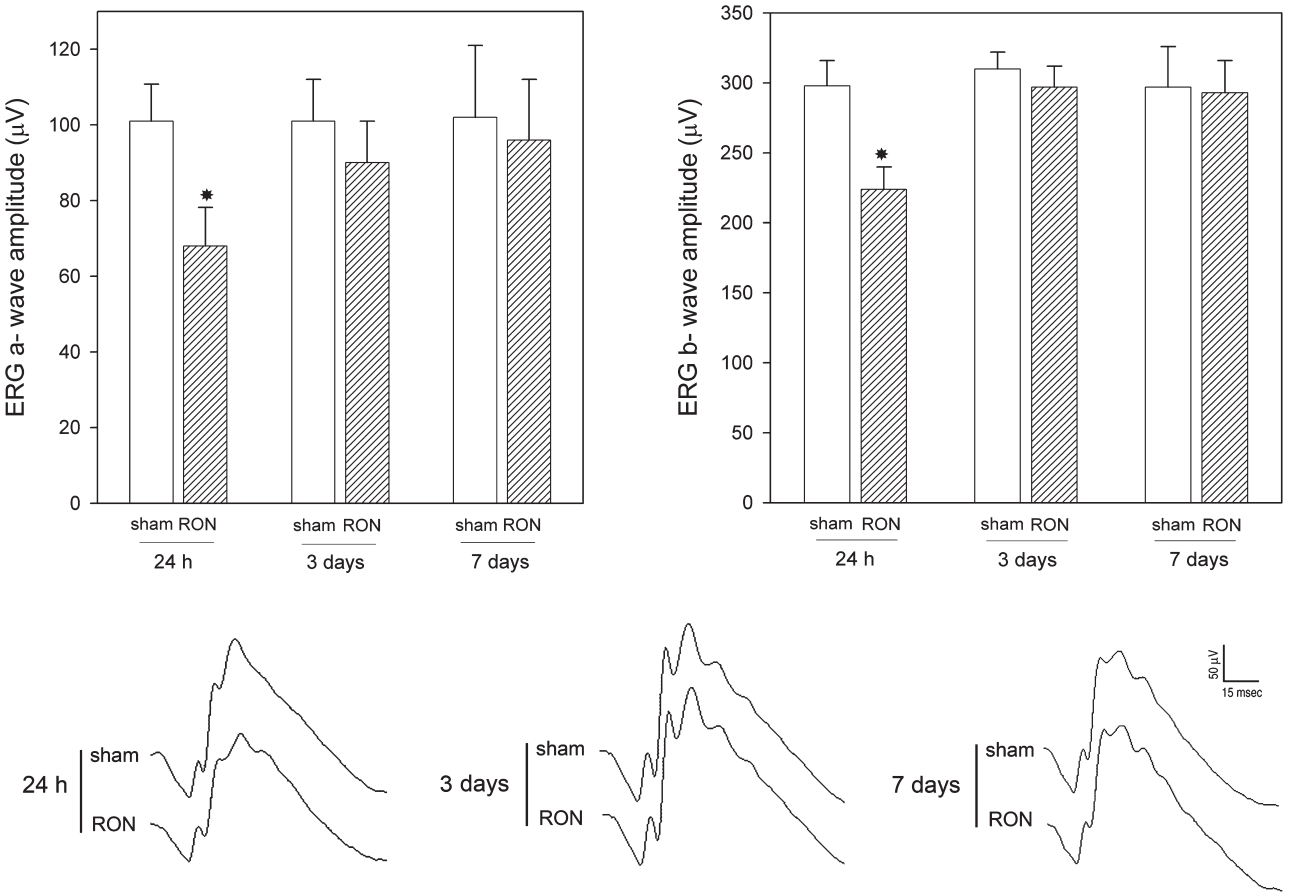

Fig. 2. Scotopic ERGs in eyes submitted to RON or sham procedure at several time points after surgery. The upper panel shows average amplitudes of scotopic ERG a and b waves, and in the lower panel, representative scotopic ERG traces are shown. A significant reduction in the scotopic ERG a- and b-wave amplitude was observed in eyes submitted to RON at 24 hours after surgery, whereas no differences in these parameters were observed at 3 days or 7 days postsurgery. Data are mean ± standard error of the mean (n = 10 eyes per group), $*P < 0.05$, by Student *t*-test.

the initial case series were encouraging, this procedure remains unproven, both mechanistically and clinically, and animal studies are still necessary to test it. Although this report was not aimed at determining the effectiveness of RON for CRVO treatment, it was our goal to better understand the early functional and histologic consequences of the procedure in normal rat eyes (without CRVO), because several side effects of RON were described by different authors.

Radial optic neurotomy in the human cadaver eye reproducibly results in lysis of the scleral canal at the ONH.[29] In rat eyes, RON provoked minor histopathologic changes. We were able to create a defect in the lamina cribrosa and surrounding scleral ring of the ON, which did not significantly affect ocular functions. At all time points, no injury of the CRV and CRA were observed, and no significant vitreous hemorrhage was found. Moreover, no other serious complications, such as globe perforation and retinal detachment, were observed. The wound healing response after RON in this rat model evolved more rapidly than those observed in the eyes of pig.[23] However, later histopathologic findings in both rats and pigs showed similar appearance of the scar with loss of axons distal to the neurotomy site represented by irregular fiber bundles and increased cellularity of the interaxonal glial tissue.

To our knowledge, no study in the literature describes the early functional effects of RON in an animal eye. To assess retinal function, scotopic flash ERGs were performed in sham- or RON-operated eyes because the rat has a predominantly rod retina. It should be noted that before RON or the sham procedure, we had ascertained that flash ERGs in the two eyes of the rats were very similar. Thus, the different records between treated and control eyes would be valid indicators of the effects RON. Only a slight (but significant) decrease in the ERG a- and b-wave amplitude was observed in eyes submitted to RON as compared with sham-operated eyes at 24 hours postsurgery, whereas at 3 or 7 days postsurgery, no differences between groups were evident. Transient changes in the ERG correlated with

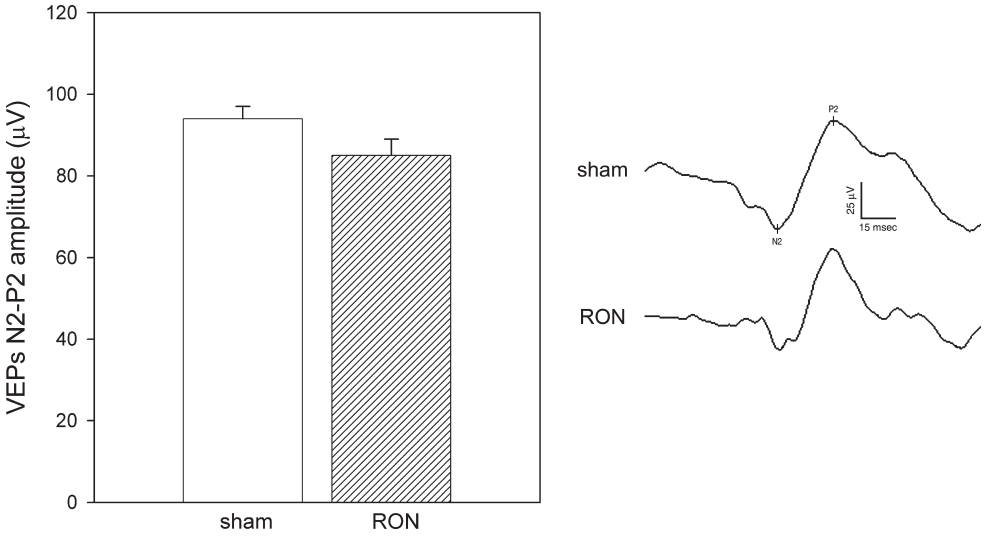

Fig. 3. Flash visual evoked potentials in rat eyes submitted to RON or sham procedure. Left panel shows average amplitudes of visual evoked potential N2-P2 component amplitude and right panel shows representative visual evoked potential traces. No changes in flash visual evoked potential N2-P2 component were observed between groups. Data are mean ± standard error of the mean (n = 10 eyes per group).

the histopathologic findings and were evident only after a short period postsurgery (i.e., 24 hours).

Assessment of visual evoked potentials enables the study of the integrity and function of the intracranial visual pathways.[30–32] To our knowledge, the effect of RON on ERG and visual evoked potentials has not been previously reported in other animal models. The present results indicated that RON did not affect the visual pathway function, supporting that RON in rats did not provoke ON fiber damage, as described in some reports for RON in humans.[33] Moreover, no changes in afferent or efferent defects in the PLR or IOP were observed in RON-treated eyes.

A major issue of the present results relies on the differences between the rat and human eye. Although results from some authors[34] support that the lamina cribrosa in the rat eye is thin and poorly developed, the rat eye was shown to be a good model for ophthalmologic studies because its anatomy is similar to that of the human eye. In fact, it was shown that the rat ONH possesses an identifiable lamina cribrosa with structural proteins nearly identical to that of the primate.[35,36] In contrast, the rabbit, chicken, and quail seem to be less adequate models to study the lamina cribrosa, the major problem being the myelinization of the axons penetrating through the sparsely developed lamina cribrosa into the nerve fiber layer of the retina, changing profoundly the situation of cell composition and mechanical reactivity in the ONH region. In addition, the retina from these species is avascular,

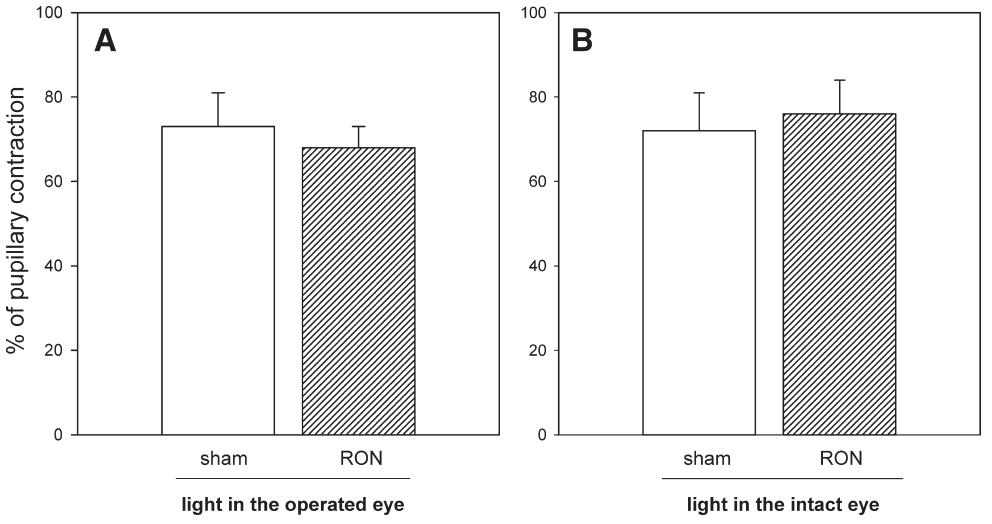

Fig. 4. Assessment of the consensual PLR in animals in which one eye was submitted to RON or a sham operation. The pupil diameter relative to the limbus diameter was measured before and after a photic stimulus, and the percentage of pupil constriction was calculated as the fraction of the pupil area of the maximum contraction over the pupil area at the maximal dilation (i.e., 2 seconds before light stimulus). **A.** The light pulse was applied to the eye subjected to RON or sham operation, and the recordings were made in the contralateral intact eye. The maximal contraction of the pupil did not differ between groups. **B.** The stimulus was applied to the intact eye, and the recordings were made in the contralateral operated eye. No significant differences were observed between groups. Data are means ± standard error of the means (n = 6 eyes for group).

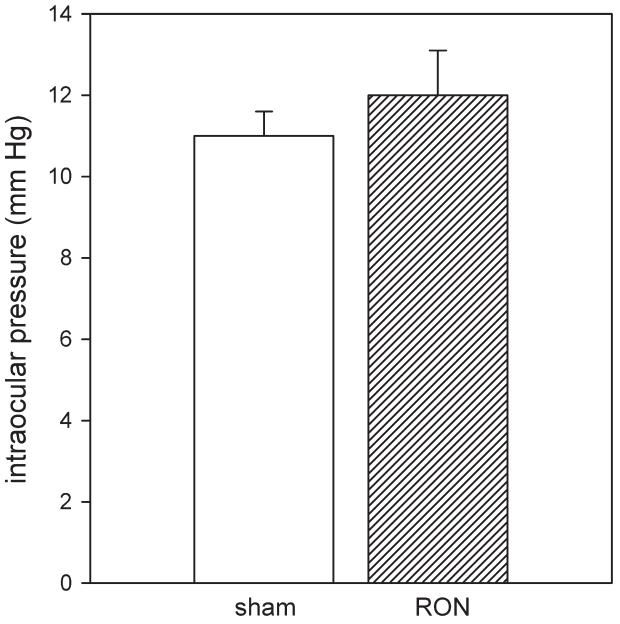

Fig. 5. Tonometer measurements of IOP in eyes submitted to RON or a sham procedure at 7 days after surgery. No differences in this parameter were observed between groups. Data are mean ± standard error of the mean (n = 10 eyes per group).

which probably has a major influence on the ONH blood supply too.[36]

In rats, the CRA is derived from a branch of the ophthalmic artery before its ramification into the posterior ciliary arteries. A v-shaped intraarterial cushion is regularly present in the ophthalmic artery just before the branching of the CRA that might influence the vascular flow in this specific region.[37–39] The CRA runs toward the sclera and enters the ON obliquely at the level of the sclera and choroid toward the center of the ONH, where it branches further forming the retinal arteries. The CRV runs closer to the ON than the artery and is connected with the pial venous system.[37,40,41] The central retinal vessels of the primate arise from one CRA and one CRV. The CRA branches from the ophthalmic artery and enters the ON posteriorly to the lamina cribrosa. The CRV runs parallel with the artery through the lamina cribrosa. Both vessels branch in the center of the ONH forming the main retinal vessels. Therefore, the vascular supply and the localization of the central retinal vessels in rats should be taken into account when comparing findings with the human situation.

Even with cautions, these inexpensive, readily available laboratory animals may prove appropriate models to understand the behavior of the lamina cribrosa. Essentially because of the small size of the rat eye, an intensive training was needed to optimize the surgical procedure. However, after this training, we were able to obtain reproducible results both at functional and histologic level.

Whether RON truly allows for decompression of the CRV through the creation of a perivascular space in the lamina cribrosa remains to be elucidated by physiologic studies of the procedure. Moreover, RON effects may differ in ischemic versus nonischemic eyes. Our data, however, provide early histologic and functional effects of RON, which support that minor and transient functional and histologic alterations were provoked by RON in normal rat eyes. Notwithstanding, it remains unclear whether RON can indeed relieve pressure on the central retinal vessels and, if so, how long this effect might last. Further histopathologic correlation studies are warranted to evaluate the safety and efficacy of RON, particularly for CRVO treatment.

Key words: electroretinogram, intraocular pressure, optic nerve, pupillary light reflex, radial optic neurotomy, rat, visual evoked potentials.

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