The Role of Inflammation in CW Nd:YAG Contact Transscleral Photocoagulation and Cryopexy

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Cyclodestructive modalities in humans have been shown to be effective when applied 3.5 mm or more posterior to the limbus. Therefore, CW Nd:YAG contact transscleral laser and cryopexy were applied 6 mm posterior to the limbus of pigmented rabbits. The intraocular pressure (IOP), flare, iritis, cells and conjunctival hyperemia were monitored clinically up to 3 weeks. The pressure lowering effect was \(-7.5 \pm 7.7\) mm Hg for laser retinopexy and \(-14.2 \pm 6.0\) mm Hg for retinocryopexy at 3 weeks and was comparable to application of the same modalities directly over the ciliary body. Similarly, induction of intraocular inflammation by injecting 10 \(\mu\)g of endotoxin intravitreally lowered IOP significantly. These findings suggest that hypotension may not be directly due to cyclodestruction but may be related to the ocular irritative response and extent of neuroepithelial defect, irrespective of its distance from the limbus. Invest Ophthalmol Vis Sci 30:543–549, 1989

Recent interest in the transscleral effects of the contact CW Nd:YAG laser\(^1,2\) led us to a comparison with the effects of conventional cryopexy in the rabbit.\(^3\) In this previous study,\(^3\) both laser and cryopexy were applied just posterior to the limbus and ciliary body lesions were verified histologically. From these findings as well as from numerous histological studies on cycloablation,\(^4-19\) it was tempting to conclude that the reduction in intraocular pressure (IOP) was critically related to destruction of the ciliary processes. Other studies, however, revealed highly variable aiming and focus of the cyclodestructive modality, raising doubts as to what exactly the target tissue was and whether it was at all important to selectively destroy some tissues and not others.\(^20-23\) The pressure had been lowered in most cases reported, at least transiently. While cryopexy and ultrasound might be more forgiving because of spread of the lesion, diathermy and transscleral noncontact laser might need to be placed more precisely due to the smaller size of the thermal burn. As is apparent from larger clinical studies, noncontact laser has been focused 3.5 mm posterior to the limbus\(^21-23\) and nonpenetrating diathermy has been applied as far as 6–8 mm posterior to the limbus with good pressure-lowering success.\(^24-26\) It was therefore of interest to place laser and cryopexy identical in amount to a previous study,\(^3\) 6–7 mm posterior to the limbus, and observe IOP and inflammatory effects. Parallel and comparable to this, IOP and inflammation related to intravitreal endotoxin were studied. These three models of ocular inflammation did not directly injure the ciliary body yet they all lowered pressure, suggesting that for the period of observation IOP may be mediated by inflammation as part of the ocular irritative response to a variety of noxious stimuli.

Materials and Methods

Male and female Dutch-Belted rabbits (1.5–3.0 kg) were placed in rabbit boxes without restraint. The ARVO Resolution on the Use of Animals in Research was followed. One drop of 0.5% proparacaine hydrochloride (Alcon Laboratories, Fort Worth, TX) was applied topically to each conjunctival sac. A floating tip pneumotonometer (Alcon Laboratories) calibrated with the standard calibrator (Alcon) was used to measure the IOP in conscious animals.\(^27\) Five in vivo baseline measurements and biomicroscopic observations were then made on each eye to characterize the time course of inflammation as described previously.\(^3,28\) Briefly, aqueous flare and cellular response in the anterior chamber were assessed using a slit lamp. The response was rated from 0 to 3+; 0: no tindall effect, 1+: slight tindall effect, 2+: moderate to dense tindall effect, 3+: dense tindall effect with fibrin clots. Iris hyperemia was rated from 0 to 3+ based on engorgement and prominent vascularity.


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of the iris tissue. Cells were judged on high-power slit-lamp examination and graded; 0: no cells apparent, 1+: few cells, 2+: many cells, and 3+: cell clumps. Pupillary diameter was measured with a pupil gauge in millimeters. Conjunctival effects were rated grossly; 1+: conjunctival hyperemia only, 2+: hyperemia and chemosis of the bulbar conjunctiva, and 3+: prolapsing conjunctival chemosis and upper lid swelling. After these baseline observations, the animals were anesthetized with intramuscular ketamine hydrochloride (100 mg/ml) and acepromazine (10 mg/ml). As in a previous study, for all animals the anesthesia was identical. Five animals each were assigned to the laser, cryopexy or endotoxin group. CW Nd:YAG light (1-5 J) was generated by a self-calibrating laser unit (SLT, Malvern, PA) and transmitted through a quartz fiber optic cable. A pencil-shaped hand-piece carried a rounded sapphire crystal measuring 2.2 X 1.5 mm. The right eye of each animal was gently proptosed. The crystal was brought into conjunctival contact 6-7 mm posterior to the limbus and the beam was directed toward the opposite equator along the equatorial plane. Thirty applications were given for 360° with 1.5 J being the mean energy at a constant exposure of 0.5 seconds. In a second group of five animals, a Keeler-Amoils cryo unit (Acu 220, Broomall, PA) was connected by a cable to a hand-held probe with a tip measuring 2.2 mm in diameter. The right eye of each rabbit was gently proptosed and the tip of the cryo probe was brought into direct conjunctival contact (6-7 mm) posterior to the limbus. Six applications of confluent cryopexy were given to the superior 180°, carefully avoiding the lids and nictitating membranes. Each application was carried out at 80°C for 60 seconds. In a third group of five animals, after establishing the baseline parameters, the right eye was proptosed. Ten µg of endotoxin of Serratia marscescens (given to Wills Eye Hospital by Dr. A. Nowotny) suspended in 0.05 ml of normal saline solution were injected intravitreally. The right eye was entered at the pars plana with a 30-gauge needle attached to a tuberculin syringe. Central location of the tip of the needle was verified by indirect ophthalmoscopy. Following laser, cryopexy or endotoxin treatment, IOP readings and other biomicroscopic observations were repeated immediately after the injury and at ½ hr, 1, 2, 4, 7, 24 hr, 1, 2, 3, 5, 7, 10, 14, 17, 19, 20 and 21 days. The last three measurements were averaged to obtain a more objective end point at 3 weeks. For each data point the mean and standard deviation of the difference of five experimental and five control eyes ± SD.

Fig. 1. Effects of CW Nd:YAG contact laser (a, b) and cryopexy (c, d) applied 6-7 mm posterior to the limbus of pigmented rabbits and of intravitreal injection of endotoxin (e, f) on IOP and flare. Each data point is based on the mean of the difference of five experimental and five control eyes ± SD.
**Results**

**Biomicroscopic Observations**

The ocular response to CW Nd:YAG laser applied 6 mm posterior to the limbus: Following posterior (equatorial) application of contact CW Nd:YAG laser in pigmented rabbits, the IOP rose slightly to +5.3 ± 5.2 mm Hg at 30 min (range 0–12 mm Hg) and decreased thereafter to reach a minimum at 2 days (Fig. 1a). From 2 days to 3 weeks there was a trend towards normal pressures and IOP was −7.5 ± 7.7 mm Hg at day 21 (Fig. 1a). The aqueous flare mirrored the pressure behavior. Maximum flare was seen at 2–3 days when the pressure was lowest and decreased thereafter as the pressure rose (Fig. 1b). Miosis, iritis, cells and conjunctivitis were mild after posterior contact laser application (Fig. 1g–j).

The ocular response to cryopexy applied 6 mm posterior to the limbus: Following posterior (equatorial) cryopexy, the IOP rose dramatically reaching a peak of 16 ± 9.6 mm Hg at 1 hr, the range of pressure increases being 6–30 mm Hg, compared to the control eye. The IOP fell thereafter, reaching a minimum at 10–14 days after which there was a trend towards recovery. The pressure reduction at 21 days was −14.2 ± 6.0 mm Hg (Fig. 1c).

Aqueous flare was noted immediately following cryopexy. It reached a peak at 24 hr and decreased thereafter. Flare was significantly larger in extent compared to posterior laser at 1 day (Fig. 1b, d). Even though the iris was remote from the site of cryopexy, dramatic miosis occurred (Fig. 1k). The pupillary diameter was comparable to the control eye after 4 hr. Iritis, cellular and conjunctival reaction were moderate to severe following posterior cryopexy.

The ocular response to intravitreal injection of 10 μg of endotoxin: Following central intravitreal injection of 10 μg of endotoxin in 0.05 ml buffer the pressure rose transiently due to the added volume (Fig. 1e). The IOP rose again from 1–7 hr and fell as flare developed (Fig. 1f). The pressure remained low despite decreasing flare and was −17.9 ± 2.8 mm Hg at 21 days. At 3 weeks the lowest IOP was obtained with endotoxin injection followed by cryopexy and laser (Fig. 1e, c, a). The lowest IOP was accompanied by the most flare, followed by cryopexy and laser, re-
respectively (Fig. 1f, d, b). After endotoxin injection the iris became miotic at 1–2 hr, as the flare rose (Fig. 1o) however, failed to redilate due to massive uveal engorgement. Both iritis and cellular exudation were the most pronounced of the three models studied (Fig. 1p, q), while the conjunctival reaction was mild.

Morphologic Observations

Posterior contact laser: On gross examination corneal edema and posterior synechiae were noted in one case each. The ciliary body was grossly intact in all cases (Fig. 2a). Mild cataracts and posterior vitreous traction bands were uniformly present. The equatorial scars were sharply circumscribed and pigmented; some carried yellowish vitreous condensations as evidence of old hemorrhage. Histologically the ciliary bodies were found to be intact and unremarkable. The sites of laser applications at the equator showed atrophic thin retina attached to a fibrous chorioidal scar (Fig. 2b). The sclera appeared compressed and featured fibroblastic hypercellularity.

Posterior cryopexy: On gross examination large confluent chorioretinal scars extended for 180° along the equator 5–7 mm in width, sometimes reaching the ora serrata (Fig. 2c). The ciliary body was grossly intact. Mild cataracts were found. The vitreous was fibrous and condensed with vitreous strands attached to the chorioretinal scars. Histologically the ciliary body and iris were normal. In the area of retinal cryopexy the retina was reduced to a gliotic band (arrow, Fig. 2d) overlying atrophic and hypovascular chorioidal connective tissue. The sclera appeared normal in thickness and cellularity.

Intravitreal endotoxin: Grossly, posterior synechiae were found in two eyes. On cut surface the vitreous was liquid and cataracts were seen in all eyes. Two eyes showed shallow retinal detachments surrounding a whitish intravitreal nodule. The uvea appeared diffusely thickened (Fig. 2e). Histologically the chorioidal vessels were engorged and the stroma edematous (Fig. 2f). A mild mononuclear infiltrate was present throughout. The retina showed cellular invasion, with reactive gliosis compared to controls, especially in two eyes where gliotic epiretinal nodules were associated with dense inflammatory infiltrates. The sclera did not show any changes.

Discussion

In this study we compared three animal models of inflammation and their resultant ocular hypotension. Care was taken to keep the injurious agent away from the ciliary body, i.e., in the equatorial plane. Our histological studies confirmed that there was no direct cyclodestruction while chorioretinal lesions were found in all. Contact laser had more scleral effects than cryopexy.

In a previous study we described the ocular irritative response for identical amounts of contact laser and cryopexy applied directly to the ciliary body.3 Apart from differences in extent, the response of IOP, flare, pupil, iritis, aqueous cells and conjunctiva were identical, i.e., apparently independent of location. These findings suggest that chorioretinal and intravitreal noxious stimuli caused the ocular hypotension using indirect mediation rather than direct destructive effects on the ciliary body. As for laser and endotoxin, it is apparent that the stimuli differ quantitatively and qualitatively. Judging by biomicroscopic parameters, the endotoxin stimulus seemed most severe, followed by cryopexy and then laser. The qualitative mode of cellular injury was also different comprising heat, cold and toxic damage. While it was difficult to create quantitatively equivalent stimuli, each stimulus regardless of etiology initiated an ocular irritative response. This response had a certain phenotype, part of which was IOP, as had also been shown for topical nitrogen mustard and intravitreal copper sulfate.28,29

In all of our models, initial hypertension was followed by protracted hypotension, which seemed to be closest related to flare. Hypotension first appeared when flare rose and decreased concomitant with flare. The highest flare had the lowest pressures and vice versa. At 3 weeks, the lowest pressure was found in the endotoxin model, followed by cryopexy and then laser. The endotoxin model also had the most flare, followed by cryopexy and then laser. This inverse relationship had been previously appreciated,6,9,10,20 in particular, the importance of proper location of the probe had been questioned by Boles-Carenini and Orzalesi in the rabbit.20

Most studies on cryopexy in the rabbit applied the cryoprobe 3 mm posterior to the limbus8–11 and lesions were often difficult to find.7,20 In humans, the edge of the probe was placed 3 mm11,13,37 and 4–6 mm17,34,35 posterior to the limbus. Even though with cryopexy there is considerable spreading effect, the ciliary body may not always have been frozen sufficiently to cause tissue necrosis. Noncontact laser has been focused in the rabbit at 1 mm,36 and at 1–2 mm,13,18 in humans, 3 mm,37 3.5 mm,31–23 and 3–6 mm11 posterior to the limbus. It was the experience of Alfred Vogt that the rear margin of the corona ciliaris was reached 2 mm posterior to the margin of the cornea.20 We have confirmed this observation in eye bank eyes and, in addition, make our incision for pars plana vitrectomy at 3.5 mm posterior to the limbus, aiming the blade posteriorly to penetrate the cortical gel and base of the vitreous. Laser applications at 3.5
Fig. 2. Gross (a, c, e) and microscopic (b, d, f) findings 3 weeks after transscleral laser retinopexy (a, b), retinocryopexy (c, d), and intravitreal injection of endotoxin (e, f). Since the ciliary body in laser and cryoretinopexy was normal, the site of contact retinal application is shown in (b, d), while the ciliary body is shown in (f).

mm with a retro focus of 3.8 mm, therefore, in all likelihood coagulate vitreous base structures. Similarly, nonpenetrating cyclodiathermy has been applied 5–8 mm posterior to the limbus\textsuperscript{24–26} and cycloelectrolysis 6–7 mm posterior to the limbus.\textsuperscript{38,39} It is not surprising that in the latter cases at this distance vitreous occasionally presented through a puncture hole. Vogt reasoned that the loss of vitreous was not only unavoidable but that it was even desirable that a little vitreous would trickle out.\textsuperscript{38} These reports in the literature\textsuperscript{13,17,21–26,34,37–39} as well as our own observations during vitrectomy and in the laboratory support the concept that the ciliary body was not always directly involved in clinically successful cases of "cyclodestruction." Furthermore, it indicates that the response of primates, including humans, may be similar to our rabbit models of posterior laser or cryopexy.
Recent evidence suggests that inflammatory mediators may influence uveoscleral outflow in primates. This is an attractive finding since conventional outflow is often impaired in patients undergoing ablation. The clinical inflammation will eventually subside even though there are signs of a prolonged breakdown of the blood–aqueous barrier in many patients. Our experiment does not address the question of long-term effects of ablation; however, it is tempting to speculate that in the absence of a neuroepithelial barrier, outflow might take place through the choriotiretinal scars (Fig. 2a–d), enlarging the total area of transscleral outflow routes. This would be enhanced by the large transscleral pressure head commonly found in glaucoma patients. In this context, it would not matter whether the neuroepithelial defect is at the corona ciliaris, pars plana or in peripheral retina. Evidence of long-term pressure-lowering after xenon and argon photocoagulation of the retina would support this concept.41

In conclusion, all ablative procedures initiate an ocular irritative response and neuroepithelial defect, both of which are related to the intensity of the ablation. A review of the literature of contact and noncontact ablation shows that aiming has been highly variable with almost uniform clinical success even focused away from the ciliary processes. In our experiments, with the ciliary body left intact, breakdown of the blood–ocular barrier, observed as flare, correlated best with the pressure-lowering effect, suggesting that the lowering of intraocular pressure may be a result of complex mediation (possibly via transscleral routes) rather than mere anatomic cyclodestruction.

Key words: CW Nd:YAG laser, contact transscleral laser, cyclophotocoagulation, cyclophotocoagulation, cyclophotocoagulation, retinopathy, inflammation

References