Early Manifestations of Postnatal Hyperoxia on the Retinal Structure and Function of the Neonatal Rat

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PURPOSE. Postnatal hyperoxia in rats causes an arrest in growth of retinal blood vessels, along with severe changes in retinal ultrastructure and function. Previous studies focused on consequences of postnatal hyperoxia at time points substantially removed from the hyperoxic insult. In this study, the earliest manifestations of this retinopathy were examined.

METHODS Newborn rats were exposed to 80% O2 from birth to postnatal day 14. The retinas were collected for vascular assessment at postnatal days 6, 9, 12, and 14, and electroretinograms were recorded at postnatal days 15, 16, 17, 19, 24, 30, and 60, after which retinal histology was performed.

RESULTS Hyperoxia significantly attenuated vascular development, especially after 6 and 9 days of exposure which resulted in 64% and 72% of normal coverage, respectively. Vascular growth continued despite hyperoxic exposure, reaching 87% of normal by postnatal day 14. Electroretinograms of hyperoxic rats retained very immature features throughout with nearly abolished b-waves and relatively preserved a-waves. Finally, while retinal structure was virtually complete in the control animals by postnatal day 15, hyperoxic rats always showed a significantly thinner outer plexiform layer (OPL) and lower horizontal cell count (P < 0.05), irrespective of the duration of exposure.

CONCLUSION The findings confirm previous reports of reduced retinal vascular coverage that accompanies the earliest manifestation of postnatal hyperoxia in rats and suggest increased retinal susceptibility to hyperoxia within the first week of life. However, despite the fact that vasculature appears to repair itself, irreversible cytoarchitectural and functional changes occur, the consequences of which are documented immediately after the cessation of hyperoxia. (Invest Ophthalmol Vis Sci. 2008;49:458–466) DOI:10.1167/iovs.07-0916

The rat model of oxygen-induced retinopathy (OIR) has been widely used as an animal model of the human form of this disease, retinopathy of prematurity (ROP). ROP is a vasoproliferative disease that, in its most severe form, can result in childhood blindness. In contrast with other animal models that have been used to study the pathophysiology of this disease, the neonatal rat offers the advantage of a highly immature retina at birth that is comparable to that of a 24- to 26-week-old human embryo. As in humans, exposure of the rat pup to postnatal hyperoxia causes severe vasoconstriction and vaso-oblation, followed by an abnormal proliferation of retinal vessels on the return to room air. Accompanying this vasculopathy are permanent structural and functional abnormalities, as documented with retinal histology and electroretinography, respectively. Of interest, however, in only a few of these studies did the researchers try to identify the earliest structural and functional manifestations of the disease process triggered by the postnatal hyperoxic shock. Therefore, the purpose of the present study was to examine first the effects of postnatal hyperoxia on vascular development throughout hyperoxic exposure and, second, to determine how early after the cessation of hyperoxia we observe changes in retinal structure and function that are known to characterize adult rats that have been exposed to the same conditions during the first 2 weeks of life.

METHODS All experimental procedures were approved by the McGill University/Montreal Children’s Hospital Research Institute Animal Care committee according to the guidelines of the Canadian Council on Animal Care and were in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Newborn litters of Sprague-Dawley rats (Charles River Laboratories, St-Constant, Quebec, Canada) were exposed to 80% oxygen immediately after birth (mixture of medical grade 100% O2 and room air measured with an oxygen meter; MaxO2 Cerametac, model OM25-ME, Medicana Inc., Montreal, Quebec, Canada), as previously described. Briefly, exposure to hyperoxia (80% O2) persisted from birth until postnatal day 14 for 22.5 hours daily, interrupted with three intervals of 30 minutes’ duration under normoxic conditions (21% O2). Animals were euthanized for vascular assessment at P6 (n = 3), P9 (n = 3), P12 (n = 3), and P14 (n = 3) throughout exposure to 80% O2 and compared with that in animals raised simultaneously in room air (21% O2, n = 3). After hyperoxic exposure, animals were assigned to one of seven experimental groups to be studied at age P15 (n = 6), P16 (n = 6), P17 (n = 6), P19 (n = 6), P24 (n = 6), P30 (n = 8), and P60 (n = 7). Data were compared with that obtained from control age-matched animals raised simultaneously in normoxic conditions (21% O2) on P15 (n = 6), P16 (n = 6), P17 (n = 6), P19 (n = 6), P24 (n = 6), P30 (n = 8), and P60 (n = 14). The rats were maintained in a cyclic lighting environment (80 lux; 12 hours dark/12 hours light). Finally, mothers of the litters were alternated between normoxic and hyperoxic conditions every 24 hours so that pulmonary complications known to arise in adult rats raised in a hyperoxic environment could be avoided.
Retinal Flatmounts

After the rats were euthanatized, the eyes were enucleated, the anterior segments dissected, and the eyecups fixed overnight in 4% formalin. The retinas were subsequently isolated, and flatmounts were prepared for staining with adenosine diphosphatase (ADPase), as previously described.15,19,20 Specimens were mounted and photographed (40×, Axioskop microscope; Carl Zeiss Meditec, GmbH, Oberkochen, Germany). To quantify the extent of vascular coverage (in normoxia- and hyperoxia-raised animals), the ratio of total area of vascularized retina over the total retinal area was calculated (Image-Pro Plus 4.1 software; Media Cybernetics, Silver Spring, MD).

Electroretinography

Electroretinograms (ERGs) and oscillatory potentials (OPs) were recorded from a data acquisition system (Acknowledgment: Biopac MP 100WS, Biopac Systems, Inc., Goleta, CA), according to a technique previously reported by us.12–15 on rats aged 15, 16, 17, 19, 24, 30, and 60 days. After a period of 12 hours of dark-adaptation, the rats were anesthetized, under dim red light, with an intramuscular injection of ketamine hydrochloride (85 mg/kg) and xylazine (6 mg/kg). The pupils were dilated with a 1% cyclopentolate hydrochloride solution (Mydriacyl; Alcon Laboratories, Fort Worth, TX) and a DTL silver-coated conductive nylon yarn (27/7 X-Static; Sauquoit Industries, Scranton, PA) electrode was placed on the cornea to serve as the active electrode. The latter was maintained in place on the cornea with 2% hydroxymethylcellulose (Gonioscopic solution; Alcon Laboratories, Fort Worth, TX) and a DTL silver-coated conductive nylon yarn (27/7 X-Static; Sauquoit Industries, Scranton, PA) electrode was placed in the mouth (model E5 disc electrode; Grass Technologies), respectively. The rats were then placed in a light-proof recording chamber of our design that included the light electrode, Grass Technologies), respectively. Reference and ground electrodes were placed between P0 and P6 (Fig. 1E) significantly limited the vascular growth of the retinal vasculature. Hyperoxic exposure between P0 and P6 (Fig. 1E) significantly limited the vascular coverage to 46.50% ± 2.95% (Fig. 2), representing 64.9% of age-matched normal values (P < 0.05), which were not yet completely vascularized, as just mentioned. However, despite the hyperoxia regimen, the retinal blood vessels continued to grow and reached 87.90% ± 2.07% of coverage at P14, a value that was still significantly less than in the control rats (P < 0.05).

Maturation of the Scotopic ERG

Figure 3 shows representative scotopic and photopic ERG waveforms obtained at P15, P16, P17, P19, P24, P30, and P60 from control (Fig. 3A) and hyperoxic (Fig. 3B) rats, respectively. Group data are graphically reported in Figure 4. In normal rats, the scotopic ERG obtained on eye opening (P15) was of low voltage with a negative morphology, due to a prominent a-wave and underdeveloped b-wave. The ascending limb of the b-wave was also devoid of well-demarcated OPs. As the rat aged (P16–P17), the a-wave continued to dominate the response, despite the growth in amplitude of the b-wave and the appearance of easily identifiable OPs. Maximum a-wave amplitude was reached at P19. Similarly, the amplitude of the rod–cone b-wave (P19: 485.88 ± 44.45 μV; P < 0.05) from 21.24 ± 97.52 μV at P15 to a maximum of 112.11 ± 17.42 μV at P30, suggesting a delayed maturation compared with the rod Vmax. At P60, the amplitudes of the rod Vmax (609.74 ± 73.64 μV) and of the rod-cone b-wave (919.77 ± 105.65 μV)
were 89.1% and 82.0% of maximum, respectively, most probably as a result of the normal aging process, as is documented elsewhere. Postnatal hyperoxia markedly hampered the normal maturation process of the scotopic ERG signal, as exemplified in Figure 3B. As in normal rats, responses obtained from hyperoxic rats on eye opening (P15) were of negative morphology due to a prominent a-wave and a nearly absent b-wave. Again, the rising phase of the remnant b-wave was devoid of OPs. With time, there was a gradual growth in amplitude to reach maximum amplitude at P24, where the morphology of the resulting waveform was reminiscent of the ERG recorded at P17 in control rats. The increase was then followed by a gradual decline in ERG amplitude, which was most pronounced for the b-wave and OPs. Group data analysis (Figs. 4A–C) confirmed the relative resistance of the a-wave maturation process to postnatal hyperoxia. Results indicate a rapid and significant growth in a-wave amplitude to a maximum reached at P24 (P15: 166.42 ± 49.81 μV; P24: 445.23 ± 57.40 μV, P < 0.05) representing a 167.5% increase (P < 0.05).

It is worth mentioning that, although delayed by 5 days, the maximum a-wave amplitude reached in hyperoxic rats is not significantly different from that reached in normal rats (445.23 ± 57.40 μV and 485.88 ± 44.45 μV, respectively; P > 0.05). At P60, the amplitude of the a-wave (314.21 ± 47.29 μV) was 70.6% of that measured at P24 and 85.8% of that measured in age-matched control animals. Similarly, the amplitude of the rod V_{max} increased from nonrecordable at P15 to a maximum of 290.70 ± 99.52 μV at P24 (42.5% of age-matched control amplitude; P < 0.05), whereas the rod–cone b-wave was augmented by 295.2% (P < 0.05) from 121.35 ± 52.41 μV at P15 (57.1% of control amplitude) to a maximum of 479.55 ± 101.32 μV at P24 (47.2% of age-matched control amplitude; P < 0.05).

**Maturation of the Photopic ERG**

Similar to the results reported for the scotopic ERG parameters, the course of maturation of the photopic b-wave did not occur at the same rate among animals raised in the different oxygen environments (Fig. 3).

In normal rats, the photopic ERG obtained on eye opening (P15) was identifiable, though it was of low voltage and lacking well-demarcated OPs. As the rat aged, the amplitude of the photopic b-wave and OPs grew gradually to reach a peak at P30, after which it declined. As shown in Figure 4D, there was a significant (529.7%) increase in amplitude of the photopic b-wave from eye opening to age P30 (P15: 41.50 ± 21.18 μV; P30: 261.34 ± 31.77 μV, P < 0.05). At P60, the amplitude of the photopic b-wave (230.82 ± 19.50 μV) declined to 88.3% of the maximum.

Again, postnatal hyperoxia markedly halted the normal maturation process of the photopic ERG signal as shown in Figure 3B. From nearly undetectable at eye opening (P15), the photopic b-wave grew gradually to reach maximum amplitude at P24, at which point the morphology of the resulting waveform was reminiscent of that recorded at P17 in control rats (Fig. 3A). As with the scotopic responses, the photopic ERG recorded at the end of the second month of life (P60) was smaller than that obtained 1 month earlier (P30). Group data analysis...
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Figure 2. Graphic representation of retinal vasculature coverage (ordinate) as a function of age (days, abscissa) in the normoxic-cohort (open symbols, dashed line) compared with that observed in the hyperoxic-cohort (shaded symbols, solid line). Results are expressed as a percentage of completely vascularized retinas at P14 (control) ± 1 SD. *Significant differences from control at a given age; the Student’s t-test (P < 0.05).

Figure 3. Representative scotopic (mixed rod–cone, flash intensity: 0.60 log cd·s·m⁻²) and photopic (flash intensity: 0.9 log cd·s·m⁻², background: 30 cd·m⁻²) ERGs obtained from animals raised in normoxia (21% O₂, top tracings, A) and hyperoxia (80% O₂, bottom tracings, B) from postnatal day 0 through 14. Recordings were obtained at postnatal days 15, 16, 17, 19, 24, 30, and 60, respectively. Calibrations: horizontal, 20 ms; vertical, 200 μV for scotopic mixed rod–cone responses and 50 μV for photopic responses. All tracings include a 20-ms prestimulus baseline; vertical arrows: flash onset.

Effect of Hyperoxia on Retinal Cytoarchitecture

The maturation-induced changes in retinal function described earlier were also accompanied by changes in retinal structure. Representative retinal cross sections obtained at postnatal days 15, 17, 19, and 24 from control and oxygen-exposed animals are shown in Figure 6. Given that our previous studies showed that postnatal hyperoxia affects only the thickness of the outer plexiform layer (OPL) and the horizontal cell (HC) count, data analysis was limited to these two cytoarchitectural features. Group data are graphically reported in Figure 7. In control rats, the thickness of the OPL grew slightly, but not significantly, from eye-opening to P24 (P15: 6.82 ± 0.09 μm, P24: 9.62 ± 1.06 μm; P > 0.05). In contrast, the OPL of the...
The hyperoxic-cohort reached maximum thickness at P16, after which a gradual and significant thinning occurred (P16: 5.42 ± 0.84 μm, P24: 2.39 ± 1.44 μm, P < 0.05). Furthermore, animals that were raised in 80% O2 always showed a thinner OPL than that in age-matched control rats, which reached significance at P16 (68.1% of control at P15 to 24.8% of control at P24; P < 0.05), confirming our previous demonstration of OPL susceptibility to postnatal hyperoxia.12,14,15 This hyperoxia-induced OPL thinning was also accompanied by a significant reduction in the total number of HCs, as reported in Figure 6. In control rats, we noticed a slight but significant attrition of the HC count with age (P15: 3.53 ± 0.12 cells, P24: 2.40 ± 0.35 cells; 68.0% of P15, P < 0.05). The above contrasts with the severe reduction in HC count noted in the hyperoxic cohort from P15: 0.93 ± 0.23 cells (26.3% of age-matched control HC count, P < 0.05) to P24: 0.28 ± 0.25 cells (11.7% of age-matched control HC count, P < 0.05).

**DISCUSSION**

Previous studies have shown that postnatal exposure to hyperoxia severely damages retinal structure (e.g., significant thinning of the OPL and attrition of the HC count) and function (significant reduction in amplitude of photopic and scotopic ERGs).15–18 These irreversible sequelae are preceded by a typical and reversible vasculopathy reminiscent of that known to characterize the human form of this retinal disorder, retinopathy of prematurity (ROP). Although previous studies have also evidenced significant reductions in vascular coverage after postnatal hyperoxia in rats,5,8,9,19,26–28 few studies have examined the differential susceptibility of retinal vasculature to postnatal hyperoxia as a function of the degree of vascular maturity reached at the time of hyperoxic exposure. To our knowledge, however, our study is the first to show that despite the damage that is observed within the first week or so of exposure (e.g., P0–P6 and P0–P9 in Figs. 1 and 2), the retinal vascular growth process appeared to fight this oxidative stress, to achieve nearly full coverage while remaining under hyperoxic exposure throughout the first 2 weeks of life. The window of blood vessel plasticity described by Benjamin et al.29 would further support our findings, in which early postnatal exposure to hyperoxia (P4–P6) similarly resulted in vaso-oblitration. This phenomenon is explained by the increased susceptibility of immature vessels that have not yet acquired pericytes at such an early age, whereas vessels that are more mature appear to better withstand an equivalent stress that occurs later on.29 Furthermore, VEGF has been shown to play a pivotal role in vascular development and retinal coverage, and hyperoxia counteracts its expression, which inevitably results in underdeveloped retinal vasculature.30 In fact, exogenous VEGF administration has been shown to act as a vascular survival factor, rescuing vasculature from hyperoxia-induced

**FIGURE 4.** Graphic representation of a-wave (A), rod V<sub>max</sub> (B), rod-cone b-wave (C), and photopic b-wave (D) amplitudes (ordinate in microvolts) obtained at postnatal days 15, 16, 17, 19, 24, 30, and 60, respectively (abscissa in days). Amplitudes from control animals raised in normoxia (open symbols, dashed line) are compared with those obtained from animals raised in hyperoxia (shaded symbols, solid line). *Significant differences between normoxia- and hyperoxia-reared groups for each given age; Student’s t-test (P < 0.05). Significant differences within normoxic or hyperoxic cohorts were identified with a one-way ANOVA followed by a post hoc Tukey test. Values found to be significantly different from those obtained at P15, or the time at which the earliest recordable response was obtained (P < 0.05). Results are given as the mean amplitude ±1 SD.
more rapid revascularization than those that are returned to a maintained in a continuous hyperoxic environment undergo a greater extent in rats exposed to hyperoxia from P7 to P9 than role for VEGF. For example, vaso-obliteration occurred to a suppressed paradoxically results in an enhanced revascularization process,19,32 thus placing less of an emphasis on a permanent structural and functional damage inevitably occurs. Nevertheless, previous studies, in addition to our findings reported herein, have shown that despite full vascular coverage, destruction.31 Of interest, however, other studies have also shown that prolonged hyperoxia (during which VEGF levels are suppressed) paradoxically results in an enhanced revascularization process,19,32 thus placing less of an emphasis on a role for VEGF. For example, vaso-obliteration occurred to a greater extent in rats exposed to hyperoxia from P7 to P9 than in those exposed from P7 to P12.19 Similarly, mice that are maintained in a continuous hyperoxic environment undergo more rapid revascularization than those that are returned to room air after exposure, thought perhaps to result from the preservation of astrocytes and Müller glia in these conditions.32 Concomitant increases in NO levels via increased eNOS expression with early hyperoxia-induced vaso-obliteration and with subsequent revascularization after prolonged hyperoxia have also suggested a cytotoxic and cytoprotective role for NO, respectively, in each of these conditions.32 Whether similar mechanisms are responsible for enabling the retina to overcome vascular deficits that are initiated early on in our model of continuous exposure, however, requires further elucidation. Nevertheless, previous studies, in addition to our findings reported herein, have shown that despite full vascular coverage, permanent structural and functional damage inevitably occurs.10–15 It is important to keep in mind, however, that many of the results referred to from previous studies were obtained from mature or nearly mature animals (ranging from P18 to P60) and at a time interval remote from the cessation of the oxidative insult. With this study, we confirm that the pathological sequence of events that ultimately yields the clinical picture described earlier was initiated while the rats were still in the hyperoxic regimen, at least when the retinal cytoarchitecture is considered. Given that these cytoarchitectural anomalies appear to be limited to OPL thinning and reduced HC counts, it is not surprising that there is no evidence of significant functional deficits, as determined with the ERG a-wave in the first 2 days or so after the opening of the eyes (and consequently after the cessation of the hyperoxic regimen, as per our protocol), while scotopic and photopic b-waves already tend to be attenuated in amplitude. These findings would therefore suggest that OIR is initiated at a postreceptor level, where both outer retinal structure and function remain intact, whereas synaptic impairment at the level of the OPL prevents signal transmission to the inner retina. Our results are in accord with previous studies that documented early differences between control and hyperoxia-exposed animals on eye opening at P13 and P14, 2 days after and immediately after the cessation of hyperoxic exposure, respectively.17,18 While hyperoxia resulted in attenuated b-wave amplitudes compared with those in control rats raised in room air, the a-wave appeared to be either similarly17 or less18 affected. Evaluation at further time points revealed even greater scotopic b-wave attenuations in hyperoxic rats compared with control as evidenced at P17,11 P18,17 and at P21,18 whereas the a-wave amplitude improved with age, reaching values virtually identical with the control at P18,17 at P21, and beyond.18 These findings of impaired postreceptor function that occur shortly after the hyperoxic episode may therefore be explained by the thinning of the OPL, which we have identified as early as eye opening (P15).

Previous studies of ours also suggested a normal age-related decline in amplitude of scotopic and photopic ERG parameters between P30 and P60,12–15,25 findings that are corroborated with results reported herein (Fig. 4). Of interest, only the a-wave showed a similar age-dependent amplitude attenuation after exposure to hyperoxia, whereas the rod Vmax, rod-cone b-wave, and photopic b-wave did not. A study by Penn et al.18 revealed a similar decline in the scotopic b-wave amplitude (by 10–40%) between control animals aged 5 and 9 weeks (from P35 to P63), time points that resemble those used in the present study, whereas no such findings were evident in the hyperoxic cohort. No other significant gain or decline in amplitude was observed in recordings obtained throughout 16 weeks of age (P112), thereby excluding the likelihood of any delay in this age-related decline. On the other hand, the a-waves obtained from animals raised in the different oxygen environments within that age-range were both similarly attenuated, and when taken together with the results just reported, further support our current findings. These results collectively suggest that whereas normal developing animals are subjected to a decline in retinal function [which is also accompanied by a normal thinning of the retinal layers between the time of eye opening (approximately P15) through adulthood],35 a different picture emerges after exposure to hyperoxia. The thinning of the retina, which is likely to be at the root of the functional attenuation that takes place with age, most probably occurs through apoptotic mechanisms or otherwise, as a part of the normal aging process. As described earlier, hyperoxia that occurs from birth throughout P14 is of only little consequence on the a-wave, suggesting that the photoreceptor layer is resistant to this stress. Consequently, the normal cellular refinement of the outer retina that occurs with time (between P30 and P60) can still progress under conditions of excess oxygen. In contrast, hyperoxic exposure culminated in a compromised b-wave along with considerable damage to the generating cells, and of note, the irreversible reorganization of retinal structure and/or cell death that occurred in the postreceptor retinal layers of exposed animals appeared to be stationary once maximum amplitude was attained. This finding suggests that the damage triggered by hyperoxia precludes further deterioration of the retina, such as that which occurs in the normal aging process. The steps involved in this “protective” mechanism remain to be fully understood. Unlike precocial species (such as humans, for example) that are born with eyes opened and relatively mature retinal struc-
ature and function, altricial animals (such as the rat and mouse) are born with their eyes closed and a relatively immature retina comparable to a prematurely born human infant at 24 to 26 weeks of gestation. Consequently, the susceptibility of the different retinal elements to the oxidative insult could depend on the level of maturity that they reached at the time of the hyperoxic exposure and/or the duration of the hyperoxic exposure that they suffered (also dependent on their birth date). For example, it has been shown in mice that cones, ganglion cells, amacrine cells, and HCs are the first identifiable retinal cells at E14, whereas rods and Müller cells appear at birth. In a normal environment, this results in a well-organized maturation of retinal function, where development of saturated rod a- and b-wave amplitudes has been shown to occur between P12 and P30, which is related to rod outer segment (ROS) length and rhodopsin content levels. Similarly, photopic OPs have also been shown to reach maturity much later (P30) compared with the earlier maturation of scotopic OPs at P17. Results obtained in our present study are in accordance with these findings, given that we observed a peak in the normal rod $V_{max}$ amplitude at P24, whereas that of the photopic b-wave occurs at P30. Surprisingly, however, the peak for both parameters after hyperoxic exposure is found at P24, suggesting that despite the attenuation in both rod and cone responses, the rod $V_{max}$ still follows a normal developmental time course after hyperxia, in contrast to the cone and rod-cone b-waves whose maturation peaks tend to fall short of normal. Furthermore, the attenuation in the cone b-wave amplitude at the height of maturation (as a function of normal, as per Fig. 5) is significantly more pronounced than that of the rod $V_{max}$. When taken together with the normal process of retinal cellular development, these findings suggest that the earliest existing structures (cones and HCs, for example) are those that are most susceptible to maturation-induced changes that follow postnatal hyperxia. This concept could also explain the more severe impact of oxidative stress on HCs and the OPL (the layer of synaptic contact between photoreceptors and HCs and bipolar cells), as the former are more developed at birth, and would consequently be exposed to the hyperoxic regimen for a longer duration. Of interest, previous studies have described a role for free radicals in generating the pathogenesis of OIR. It has also been suggested that endogenous antioxidant defense systems may differ between rods and cones, rendering the latter system more sus-
ceptible in the face of reactive oxygen species induced by hyperoxia, or FeSO₄ for example. Furthermore, our finding of a more potent effect of Trolox C, a vitamin E analogue with antioxidant capacity, on cone-mediated function in the hyperoxic retina, suggests to us that treatment is targeted to the areas that need it most. Collectively, these results support the hypothesis whereby devastation of the cone pathway (which begins its development in utero) occurs to a greater extent than that of the rod pathway (which begins its development postnatally).

Our ability to demonstrate altered retinal function (with the exception of the a-wave) immediately after cessation of hyperoxic exposure would put less emphasis on the contribution of neovascularization to these manifestations, since this aggravated angiogenic process is known to be triggered after recovery in room air. Although in the present study we have not tried to quantify the level of neovascularization, our findings suggest that it may play a negligible role in the initial impairment of retinal function (at birth) compared with the devastating structural consequences (e.g., retinal detachment) that it could cause, should it fully manifest itself. If the above scenario also applies to the human counterpart, care will have to be taken when evaluating the functional consequences of hyperoxic exposure in human premature infants, despite the lack of significant evidence of underlying neovascularization.

In conclusion, posthyperoxia events, including the return to normoxia (e.g., relative hypoxia), and the resulting neovascularization have been deemed largely responsible for the pathogenesis of OIR and its human form, ROP. The results obtained with the present study suggest that alterations in retinal cytoarchitecture concurrent with hyperoxic exposure in addition to the arrest in functional maturation that directly follows the exposure regimen in neonatal rats may play an equally important role. Whether the above are induced as a result of the vasculopathy or occur independently remains to be further elucidated.

References

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