Effect of Carbogen Breathing and Acetazolamide on Optic Disc Po2

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PURPOSE. Acetazolamide was previously shown to increase optic disc partial pressure of oxygen (Po2). The study was conducted to evaluate optic disc Po2 variations during normoxia, hyperoxia (100% O2), and carbogen breathing (95% O2, 5% CO2), before and after intravenous administration of acetazolamide.

METHODS. Po2 measurements were obtained at intervascular areas of the optic disc in nine anesthetized minipigs using oxygen-sensitive microelectrodes (10-μm tip diameter) placed at <50 μm from the optic disc. Po2 was measured continuously during 10 minutes under normoxia, hyperoxia, or carbogen breathing. Oxygen measurements were repeated under these conditions after intravenous injection of acetazolamide (500-mg bolus).

RESULTS. In hyperoxia, optic disc Po2 increased moderately (∆Po2= 4.81 ± 1.16 mm Hg; mean ± SD; 24%; P < 0.001) after a much larger increase in systemic PaO2. Carbogen breathing induced a significant increase in both systemic PaO2 and PaCO2, which resulted in a large increase in optic disc Po2 (∆Po2 = 13.17 ± 2.18 mm Hg; 67%; P < 0.001). Acetazolamide induced a slow and progressive increase in both systemic PaCO2 and optic disc Po2 (30 minutes ∆Po2 = 4.24 ± 2.45 mm Hg; 24%; P < 0.04). However, it was when carbogen was simultaneously administered that optic disc Po2 increased most substantially (∆Po2 = 18.91 ± 5.23 mm Hg; 90%; P < 0.002).

CONCLUSIONS. Carbogen breathing increases optic disc Po2 significantly in minipigs, more than hyperoxia. The association of acetazolamide injection with carbogen breathing could induce an additional increase in optic disc Po2 through the effect of higher systemic PaCO2.

Blood flow modifications and perturbations of the autoregulatory mechanisms of the optic nerve head (ONH) circulation have been incriminated in several ocular disorders, including glaucomatous and ischemic optic neuropathy. Knowledge of the parameters that can influence the autoregulatory responses of the ONH might improve our understanding of the pathogenesis of those diseases and might lead to new therapeutic modalities.

Blood flow can be influenced by several other chemical substances or drugs. Intravenous administration of acetazolamide has been shown to increase cerebral blood flow and has been used as a provocation test to assess cerebrovascular reserve capacity. It has also been reported to increase retinal and choroidal blood flow, as well as optic disc Po2. High PaCO2 leading to arterial vasodilation is thought to be the mechanism of increased tissue blood flow by acetazolamide. CO2-associated vasodilation is apparently mediated in the extravascular tissue through acidification of the interstitial space of the inner retina, a mechanism similar to that occurring at the cerebral cortex.

Provided there is no change in tissue oxygen consumption, tissue oxygen tension reflects corresponding blood flow variations and enables an accurate estimation of tissue oxygen supply in the physiological state or ischemic disease. Optic disc Po2 was first measured in vivo with microelectrodes in cats and in monkeys. Thereafter, Po2 measurements were obtained within the ONH tissue at various depths in minipigs and in cats. A dose-dependent significant increase in optic disc Po2 in pigs after intravenous administration of acetazolamide or dorzolamide using polarographic oxygen electrodes placed in front of the optic disc was recently described. However, the effect of carbogen inhalation on the optic disc oxygenation has not been tested. It would therefore be reasonable to see whether carbogen is sufficient to increase optic disc Po2, as well as to test the effect of the combined use of acetazolamide and carbogen on optic disc Po2. This may be useful in defining new therapeutic modalities for ischemic diseases of the optic nerve.

Based on these considerations, we sought in the present study to evaluate the variations of optic disc Po2 during normoxia, systemic hyperoxia (breathing of 100% O2), and carbogen breathing (95% O2, 5% CO2), before and after intravenous administration of acetazolamide.
MATERIALS AND METHODS

Experiments were conducted in one eye of 9 minipigs (Arare Animal Facility, Geneva, Switzerland) weighing 10 to 12 kg. The advantage of using the minipig is the anatomic similarity of its optic nerve to the optic nerve of the primates, except that the retinal arteries arise from the ciliary circulation. All the experiments were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Animal Preparation

Minipigs were prepared for the experiments, as previously described. In brief, after the minipigs received intramuscular injection of 2 mL (10 mg) of the tranquilizer midazolam maleate (Dormicum; Roche Pharma, Reinach, Switzerland), 3 mL (120 mg) of the tranquilizer azaperon (Stresnil; Janssen Pharmaceutica, Beerse, Belgium), and 1 mL (0.5 mg) of atropine, anesthesia was induced with 2 to 3 mg thiopental sodium (Pentothal; Abbott AG, Baar, Switzerland) injected into the ear vein. Curarization was performed with 2 mL (4 mg) of pancuronium bromide (Pavulon; Organon SA, Pfäffikon, Switzerland). The animals were intubated and artificially ventilated. After arterial, venous, and bladder catheterization, anesthesia and myorelaxation were maintained throughout the experiment by continuous perfusion of thiopental and pancuronium, respectively.

Each animal was ventilated at approximately 18 strokes/min, with a continuous flow of 20% O2 and 80% N2O, through a variable-volume respirator. Systolic, diastolic, and mean arterial pressures were monitored through the femoral artery with a transducer. Temperature was maintained between 36°C and 37°C with a thermoblanket. PaO2, PaCO2, PacO2, and pH were measured intermittently from the same artery with a blood gas analyzer (Labor-system; Flukiger AG, Menziken, Switzerland) and kept under control by adjusting ventilatory rate, stroke volume, and composition of the Inhaled gas.

A head-holder was used to avoid movements due to respiration. Upper and lower eyelids were removed, as well as a rectangular area of skin surrounding the eye; the bulbar conjunctiva was detached; the sclera was carefully cleaned to 5 mm from the limbus; the superficial scleral vessels were thermocauterized; the globe was fixed with a metal ring sutured around the limbus; and a sclerotomy at the pars plana was performed. The pupil was dilated with 1% atropine eye drops and the fundus was observed using an operating microscope (Carl Zeiss Surgical GmbH, Oberkochen, Germany).

PO2 Measurements

Optic disc PO2 measurements were obtained using double-barreled, recessed oxygen-sensitive microelectrodes with a 10-μm tip diameter, as previously described. The microelectrodes were prepared in our laboratory according to a technique described in detail in previous papers. They were calibrated before insertion into the eye and again after withdrawal in a buffered saline solution at 35°C, which was equilibrated with air. The microelectrodes were inserted into the vitreous cavity through a sclerotomy placed 2 to 3 mm posterior to the limbus, aided by an electronic micromanipulator. The microelectrode tip was positioned at a distance of less than 50 μm from the optic disc surface, the reference barrel recorded a sudden negative DC potential shift of several millivolts. At the moment of contact, the position display was zeroed, and the microelectrode was then withdrawn less than 50 μm from the optic disc surface.

The timeline of PO2 measurements was as follows: Baseline measurements under normoxia and a stable continuous recording for at least 10 minutes preceded inhalation of 100% O2 (hyperoxia) for 10 minutes. Then normoxia was again induced, with the purpose of obtaining a stable recording for at least 10 minutes. This recording was considered the baseline before inhalation of carbogen for 10 minutes. Each condition was confirmed by corresponding PO2, PacO2, and pH measurements. PO2 had to be high during hyperoxia, whereas both PO2 and PacO2 had to be high during carbogen breathing. The timeline of measurements was performed before and after intravenous injection of acetazolamide (500 mg bolus; Diamox; Vifor SA, Fribourg, Switzerland). Though higher than that used in clinical practice, the dose of 500 mg was chosen in accordance with previous results, studies in which various doses had been tested and the dose of 500 mg had been the lowest one to produce maximum effects on optic disc PO2.

Nitrous oxide (N2O) was present in the breathing gas during normoxia, whereas it was absent during hyperoxia or carbogen breathing. However, this was not considered to affect the results, as we have previously tested the effect of the presence or absence of N2O in the breathing gas during normoxia and we have not found any differences in pH, PO2, PaCO2, or optic disc PO2 (data not shown).

The mean ± SD of optic disc PO2, PacO2, PaCO2, and pH were calculated at baseline and 7 minutes after initiation of hyperoxia or carbogen breathing in each case.

Statistics

All PO2 levels, as well as their differences from baseline (∆PO2), were expressed as the mean ± SD. For each result presented, n represents the number of optic disc territories where measurements were obtained. An n greater than the number of minipigs means that more than one optic disc territory was analyzed in the same eye. The Wilcoxon signed-rank test was used to detect differences in mean PO2 under each condition. In addition, the Friedman test was performed to compare the respective effect of hyperoxia and carbogen breathing in the same territory at four predetermined time points (2, 5, 7, and 10 minutes). A box-plot representation was used to provide a visual summary of the median values and of the 5%, 25%, 75%, and 95% percentiles. Finally, the Wilcoxon signed-rank test was performed to compare the respective effect of hyperoxia and carbogen breathing before and after intravenous injection of acetazolamide. In all comparisons, P < 0.05 defined statistically significant differences.

RESULTS

Measurements before Administration of Acetazolamide

Under normoxia (PO2 = 104.09 ± 6.06 mm Hg; PacO2 = 35.45 ± 2.41 mm Hg; pH = 7.45 ± 0.06; n = 28), mean optic disc PO2 recorded in intervacterial areas of nine eyes was 20.11 ± 2.47 mm Hg (n = 28), a level similar to those previously described. The inhalation of 100% O2 induced a mean increase in optic disc PO2 of ∆PO2 = 4.81 ± 1.16 mm Hg or 24% (nine eyes; n = 13; Fig. 1) after 7 minutes. Under systemic hyperoxia, mean optic disc PO2 increased from 20.36 ± 2.88 to 25.18 ± 3.75 mm Hg and that difference, although moderate, was statistically significant (P < 0.001), yet disproportional to a substantial increase in PacO2 (∆PacO2 = 334.40 ± 39.36 mm Hg; ∆PaCO2 = −4.66 ± 2.27 mm Hg; ∆pH = 0.03 ± 0.01; n = 13). This increase was fully reversible after return to normoxia.

The inhalation of carbogen induced a mean increase in optic disc PO2 of ∆PO2 = 13.17 ± 2.18 mm Hg or 67% (nine eyes; n = 15; Fig. 1) after 7 minutes. Mean optic disc PO2 increased significantly from 19.89 ± 2.13 to 33.05 ± 3.45 mm Hg (P < 0.001). Under the effect of carbogen, both PacO2 and PaCO2 increased significantly (∆PacO2 = 371.72 ± 95.19 mm Hg; ∆PaCO2 = 10.31 ± 3.71 mm Hg; n = 15). The CO2 increase induced a respiratory acidosis from a mean pH of 7.45 ± 0.06 to 7.38 ± 0.07 (∆pH = −0.07 ± 0.02; n = 15). The effect was also fully reversible after return to normoxia.

Considering 12 optic disc territories of nine minipigs submitted to the same conditions at four different time points (2, 5, 7, and 10 minutes), the Friedman test revealed a statistically more significant effect of carbogen inhalation on the optic disc PO2 variations with time (P < 0.0001) than of hyperoxia (P < 0.001).
Furthermore, at each of the four analyzed times, the Wilcoxon signed-rank test showed a significantly greater effect of carbogen inhalation on the optic disc PO2 variations than that of hyperoxia ($P < 0.02$ at 2 minutes; $P < 0.003$ at 5, 7, and 10 minutes; Fig. 2).

**Measurements after Intravenous Administration of Acetazolamide**

After inducing a transient decrease in optic disc PO2 due to a transient systemic hypotension (confirmed by our arterial pressure monitoring) related to the injection, intravenous administration of 500 mg of acetazolamide led to a slow and progressive increase in optic disc PO2 (Fig. 3A) in parallel with a slow and progressive increase in PaCO2 (Fig. 3B), as previously described.10,24 In six intervascular optic disc territories of six eyes, after the injection of acetazolamide and during normoxia, the optic disc PO2 measured 30 minutes later revealed an increase ($\Delta P O_2 = 4.24 \pm 2.45$ mm Hg, or 24%). More specifically, acetazolamide had increased optic disc PO2 from a mean of $22.97 \pm 4.23$ to $35.83 \pm 5.52$ mm Hg ($P = 0.002$). In hyperoxic conditions, PaO2 increased significantly ($\Delta P aO_2 = 374.42 \pm 43.77$ mm Hg), whereas PaCO2 and pH remained practically stable ($\Delta P aCO_2 = 1.42 \pm 3.27$ mm Hg; $\Delta pH = -0.001 \pm 0.03$; $n = 10$).

During carbogen inhalation under the effect of acetazolamide, the greatest increase in optic disc PO2 was recorded ($\Delta P O_2 = 18.91 \pm 5.23$ mm Hg, or 90%; six eyes; $n = 10$; Fig. 4) after 7 minutes, from a mean of $21.90 \pm 5.03$ to $40.81 \pm 7.70$ mm Hg ($P < 0.002$). Carbogen breathing induced a significant increase in both $P aO_2$ and $P aCO_2$ ($\Delta P aO_2 = 404.14 \pm 117.01$ mm Hg; $\Delta P aCO_2 = 71.92 \pm 15.03$ mm Hg).
36.82 mm Hg; \( \Delta \text{Paco}_2 = 10.42 \pm 4.05 \) mm Hg; \( n = 10 \), leading to a deeper systemic acidosis from pH = 7.37 ± 0.06 to 7.30 ± 0.06 (\( \Delta \text{pH} = -0.07 \pm 0.02; n = 10 \)).

With the Friedman test, the effect of hyperoxia and carbogen breathing was analyzed at four different time points (2, 5, 7, and 10 minutes) and in nine optic disc territories of six minipigs placed in the same conditions after acetazolamide injection (Fig. 5). This test revealed the statistically significant effect of both hyperoxia or carbogen inhalation on the optic disc PO\(_2\) variations with time at all four analyzed time points (\( P < 0.0002 \)). Furthermore, the Wilcoxon signed-rank test demonstrated a significantly greater effect of carbogen inhalation on the optic disc PO\(_2\) variations compared with hyperoxia (Fig. 5), at all time points (\( P < 0.02 \)) except 2 minutes (\( P < 0.07 \)).

In addition, with the Friedman test, the effect of hyperoxia was analyzed at four different time points (2, 5, 7, and 10 minutes) and in the same eight optic disc territories of six minipigs tested before and after acetazolamide injection (Fig. 6). This test revealed a significantly greater effect of hyperoxia after acetazolamide injection on optic disc PO\(_2\) variation with time (\( P < 0.0005 \)), compared with hyperoxia before acetazolamide injection (\( P < 0.04 \)). That effect of hyperoxia after acetazolamide injection was confirmed by the Wilcoxon signed-rank test, at all four time points (\( P < 0.02 \)).

Finally, with the Friedman test, the effect of carbogen inhalation was analyzed at four different time points (2, 5, 7, and 10 minutes) and in the same seven optic disc territories of six minipigs tested before and after acetazolamide injection (Fig. 7). This test revealed a statistically significant effect of carbogen before and after acetazolamide injection on optic disc PO\(_2\) variation with time (\( P < 0.002 \)). Furthermore, the Wilcoxon signed-rank test demonstrated a significantly greater effect on optic disc PO\(_2\) variation with time of carbogen breathing after acetazolamide injection than of carbogen breathing before acetazolamide injection, at all four time points (\( P < 0.03 \)).

**DISCUSSION**

Nutrition and oxygenation of the ONH depends on its blood flow, which is proportional to the perfusion pressure in the ONH and inversely proportional to the resistance to flow. Resistance is closely dependent on PaO\(_2\) and PaCO\(_2\). As a result, elevated PaO\(_2\) decreases ONH blood flow,\(^{36,37}\) whereas elevated PaCO\(_2\) increases ONH blood flow,\(^{37}\) to ensure a constant supply of the ONH in oxygen.

Previous findings in minipigs indicate regulation of retinal blood flow during systemic hyperoxia, maintaining preretinal

![Figure 3](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933437/)

**FIGURE 3.** (A) Continuous typical recording of optic disc PO\(_2\) during 30 minutes of normoxia after intravenous injection of acetazolamide. Optic disc PO\(_2\) increased progressively in a linear pattern under the effect of acetazolamide. (B) Optic disc PO\(_2\) mean variation and PaCO\(_2\) mean variation during 90 minutes of normoxia after intravenous injection of acetazolamide. Optic disc PO\(_2\) increased progressively, in parallel with an increase in PaCO\(_2\), in a linear pattern, after treatment with acetazolamide.

![Figure 4](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933437/)

**FIGURE 4.** Continuous typical recording of optic disc PO\(_2\) under hyperoxia or carbogen breathing after intravenous injection of acetazolamide. The corresponding table shows the mean ± SD of the blood gas levels and the optic disc PO\(_2\) variation in each condition. Both hyperoxia and carbogen breathing led to a significant increase in optic disc PO\(_2\) under the effect of acetazolamide, but carbogen breathing induced a greater increase in optic disc PO\(_2\) than did hyperoxia. Both hyperoxia and carbogen induced an increase in PaO\(_2\), whereas carbogen also induced a more marked increase in PaCO\(_2\) and a deeper systemic acidosis.

<table>
<thead>
<tr>
<th>Inhaled gas</th>
<th>( n )</th>
<th>PaO(_2)</th>
<th>PaCO(_2)</th>
<th>pH</th>
<th>( \Delta \text{PO}_2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxia</td>
<td>10</td>
<td>475.60 ± 44.27</td>
<td>42.82 ± 4.81</td>
<td>7.39 ± 0.05</td>
<td>12.86 ± 4.08</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Carbogen</td>
<td>10</td>
<td>505.50 ± 35.32</td>
<td>56.88 ± 5.52</td>
<td>7.30 ± 0.06</td>
<td>18.91 ± 5.23</td>
<td>&lt;0.002</td>
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PO₂ at a constant level despite the elevation of PaO₂. In addition, previously published data demonstrated that, although juxta-arteriolar tissue PO₂ of the ONH increases (due to direct O₂ diffusion from the arteriolar wall), intervascular tissue PO₂ within the ONH and in front of the optic disc remains practically unchanged. In our experiments, systemic hyperoxia significantly increased PaO₂. This high PaO₂ induced a slight increase in optic disc PO₂, probably due to O₂ diffusion from the arterioles (Fig. 1).

The slight increase in optic disc PO₂ recorded in our experiments during systemic hyperoxia may be related in part to the tip diameter of the microelectrode used. Juxta-arteriolar and intervascular PO₂ in the vitreous are significantly different at 50 μm from the vitreoretinal interface. Given the microelectrode’s properties, a small tip diameter ensures an intervascular PO₂ measurement at that distance. Investigations involving a tip diameter of 3 to 6 μm found no increase in optic disc PO₂ over intervascular areas during systemic hyperoxia. Because our electrode had a 10-μm tip diameter, it is likely that we also recorded a small part of the O₂ diffusing directly from the ONH arterioles; however, after the initial PO₂ increase, the PO₂ remained constant throughout measurements under hyperoxia.

Carbogen breathing induces a simultaneous increase in PaO₂ and PaCO₂, affecting the retinal and ONH arteriolar reactivity. Elevated PaO₂ induces arteriolar vasoconstriction, whereas elevated PaCO₂ induces a vasodilation similar to that observed in cerebral arterioles. In retinal circulation, due to the vasodilatory effect of elevated PaCO₂, carbogen breathing leads to less reduction of retinal blood flow compared with systemic hyperoxia.

Assuming similar reactivity of the ONH arterioles, carbogen breathing should lead to a less important arteriolar vasoconstriction at the level of the ONH compared with hyperoxia. Indeed, in our experiments, optic disc PO₂ increased significantly during carbogen breathing (Fig. 1), more than after systemic hyperoxia (67% vs. 24%), as also confirmed by statistical comparison. Our results are in agree-
ment with those observed in normal retinas of newborn and adult rats and in normal and ischemic intervascular retinal territories of minipigs.

In addition to blood flow changes induced by carbogen, the blood CO₂ increase and the resultant pH decrease should affect the ability of hemoglobin to bind oxygen. Elevated PaCO₂ induces a rightward shift of the oxyhemoglobin dissociation curve, which reflects decreased affinity of hemoglobin for oxygen, meaning that oxygen is released from hemoglobin more readily, increasing oxygen availability in the tissue. Thus, the optic disc PO₂ increase measured in our experiments during carbogen breathing reflects both the effect of carbogen on the ONH circulation and the increased oxygen delivery to the ONH tissue due to a rightward shift of the oxyhemoglobin dissociation curve.

Intravenous administration of acetazolamide increases cerebral, retinal, and choroidal blood flow, with simultaneous increase in PaCO₂. This PaCO₂ increase is due to significant bicarbonate losses in the renal tubules, resulting in hyperchloremic metabolic acidosis. The CO₂ produced by cells cannot be eliminated by carbonic anhydrase and so increases PaCO₂ by diffusing in the blood through the basement membrane.

In our experiments, acetazolamide injection induced a slow and progressive increase in optic disc PO₂ in association with a slowly and progressively increasing PaCO₂, as previously described. This probably reflects, as in the case of carbogen, a vasodilatory effect of acetazolamide on the ONH arterioles and an increased dissociation of oxygen from hemoglobin, both due to the elevated PaCO₂. Rightward shift of the oxyhemoglobin dissociation curve with increased oxygen availability under the effect of acetazolamide has also been described in the treatment of myocardial ischemia. Moreover, our results indicated that concomitant administration of acetazolamide and carbogen can increase optic disc PO₂ more significantly than the association of the former with hyperoxia (90% vs. 58%). This effect is apparently due to the additive action of acetazolamide and carbogen on the elevation of PaCO₂. Indeed, PaCO₂ was higher when acetazolamide was associated with carbogen than with hyperoxia.

To our knowledge, this is the first time that concomitant administration of acetazolamide and carbogen has been tested for the ONH. This is important, as one can extrapolate that carbogen inhalation, especially in association with intravenous injection of acetazolamide, may improve oxygen delivery to a hypoxic ONH. In disturbed perfusion through the ONH capillaries, this association improves the oxygenation of the ONH by increasing O₂ diffusion from the ONH arterioles. In that case, the association would be beneficial as a treatment modality for disorders related to ONH ischemia or dysregulation of the ONH blood flow, such as glaucoma and nonarteritic anterior ischemic optic neuropathy (NAION).

Regarding glaucoma, acetazolamide is being used for its intraocular pressure (IOP)-lowering action, which increases the perfusion pressure in the ONH, but the double effect of elevated PaCO₂ described herein is also possible. Flammer and Drance gave oral acetazolamide in patients with glaucoma and observed visual field improvement without correlation with the IOP reduction and without change in perfusion pressure, suspecting improved ONH blood flow from decreased vascular resistance. In addition, the presence of relative vasoconstriction has been shown in patients with glaucoma, at least partially reversed by hypercapnia. Finally, carbogen breathing was reported to improve visual fields of patients with normal-tension glaucoma, postulated to reverse an initial vasoconstriction.

Regarding NAION, no established treatment exists. Intravenous acetazolamide was administered by Hayreh in patients with NAION and progressive loss of vision or visual fields, pretreatment IOP < 20 mm Hg, and (in some of them) angioGraphic evidence of poor perfusion in posterior ciliary artery system; further deterioration was prevented. Hayreh actually wanted to lower IOP to improve the perfusion pressure in the ONH, whereas, retrospectively, a beneficial effect through elevated PaCO₂ also seems possible.

In clinical practice, if acetazolamide alone, or associated with carbogen breathing, can exert a beneficial functional effect through increased oxygenation, this should also be reflected in the results of functional tests. However, acetazolamide attenuates the amplitudes of ERG responses. Moreover, under hypercapnic conditions, the b-wave of ERG is depressed as a result of reduction in extracellular K⁺. In addition, recent studies have shown either no effect or decreased contrast sensitivity by CO₂. Thus, a blood flow increase by acetazolamide and/or carbogen breathing does not necessarily mean a functional benefit resulting from increased

![Figure 7](https://via.placeholder.com/150)
oxygenation of the ONH. The beneficial effect of increased ONH oxygenation by carbogen inhalation with concomitant intravenous acetazolamide injection remains to be confirmed by clinical findings.

In conclusion, the present study shows that carbogen breathing increases optic disc PO$_2$ significantly in minipigs, more than systemic hyperoxia. Moreover, it shows that a much more important increase in optic disc PO$_2$ can be obtained by concomitant use of carbogen breathing and intravenous injection of acetazolamide, through the effect of elevated PaCO$_2$, most probably inducing ONH arteriolar vasodilation and increased dissociation of O$_2$ from hemoglobin. The association of intravenous injection of acetazolamide with carbogen breathing can improve the oxygenation of the ONH substantially and could be a good therapeutic modality in cases of ischemia or dysregulation. This would be of particular interest, as acetazolamide is already being used in the treatment of glaucoma. Clinical studies are needed, however, to confirm these speculations.

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References