min-pentobarbital anesthesia than with ketamine sedation and may have been due to the larger dose of ketamine used for anesthesia. In addition, the negative inotropic action of pentobarbital causes increased venous pressure, thereby increasing the IOP because of impaired aqueous outflow.

Although the increases in IOP during ketamine sedation and ketamine-pentobarbital anesthesia are statistically significant, they are small and may not be of concern in experimental situations where a slight increase in IOP does not affect the interpretation of the results of the study. It should be noted, however, that the range of responses was wide at all times, and increases in IOP up to 6.1 mm Hg were observed in Groups 1 and 2 and up to 9.1 mm Hg in groups 3 and 4. In view of these results, the use of ketamine sedation or ketamine-pentobarbital anesthesia in the rabbit is contraindicated in studies where an increase in the IOP may be detrimental to the interpretation or successful outcome of the experiment.

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From the Departments of Ophthalmology and Physiology, The Medical College of Wisconsin, and the Research Service, Wood Veterans Administration Center, Milwaukee, Wisc. This investigation was supported in part by Research Grant EY-01436 from the National Eye Institute and Research to Prevent Blindness, Inc. Also supported by the Medical Research Service of the Veterans Administration. Submitted for publication Oct. 21, 1976. Reprint requests: Dr. Diane L. Van Horn, Research Service/151, Veterans Administration Center, Wood, Wisc. 53193.

Key words: anesthetics, intraocular pressure, ketamine hydrochloride, pneumotonomography, sodium pentobarbital.

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Effect of changes in Pco2 on intraocular tension. RICHARD A. KIELAR, PENTI TERASLINNA, JAY T. KEARNEY, AND DONALD BARKER.

Elevated levels of inspired CO2 and blood Pco2 resulted in moderate elevation of IOT. A marked rapid decrease in IOT to a level less than baseline value was noted when inspired CO2 was suddenly decreased to ambient levels. Decrease in IOT was more pronounced than the decrease in Pco2, and increase in blood pH. Changes in IOT appeared related to the rate of change of Pco2 rather than the actual level of Pco2. Increased ventilatory excursions with constant inspired CO2 levels did not cause any elevation of IOT, but a minimal compensatory drop in IOT below resting values occurred when increased ventilatory excursions were discontinued. It is postulated that the changes in IOT noted are the result of sudden changes in aqueous production or ocular blood volume.

Intraocular tension (IOT) declines during rhythmic exercise involving the cardiovascular system. Concomitant with this reduction in IOT are changes in blood pH and lactate,1,2 plasma osmolality,2 and standard bicarbonate and base excess.3 It has been suggested that other factors may be responsible for the decrease in IOT noted during standardized aerobic exercise.4 It is known that Pco2 decreases during exercise, and this decrease in Pco2 may have an effect independent of the factors noted above in decreasing IOT during exercise. Therefore the present study was undertaken to determine the effect of Pco2 change on IOT at rest. In this way the influence of exercise on blood pH and lactate was eliminated.
Methods. Seven healthy male volunteers were used as subjects in the study. Baseline venous blood samples were analyzed for pH and Pco₂. Three baseline IOT measurements were done on each eye with a Draeger applanation tonometer, which was utilized throughout the study. After steady IOT control values were obtained, the subject was connected to a 13.5-liter spirometer (Warren E. Collins, Inc., Braintree, Mass.) to breathe a gas mixture of 5.8% CO₂, 24.6% O₂, and 69.6% N₂ in an open-circuit system for 10 min. IOT was measured, and venous blood samples were drawn for blood pH and Pco₂ measurements at the third, sixth, and ninth minutes of the experiments. After 10 min. of open-circuit system breathing, the system was closed so that the subject had to rebreathe the accumulated CO₂.

The closed-circuit system rebreathing was continued for 7 min., during which time oxygen was fed into the system so that its concentration resembled that of ambient air. The O₂ and CO₂ concentrations were continually monitored with a mass spectrometer (Scientific Research Instrumentation Corp.). The IOT was measured every minute, and the venous blood samples for pH and Pco₂ were drawn every 2 min. The ventilatory volume was recorded on the spirometer kymograph. At the conclusion of the 7 min. closed-circuit system rebreathing phase, the subject was allowed to breathe ambient air. IOT measurements were made every minute during the first 5 min. and every second minute for the next 10 min. during this recovery period. Blood samples for pH and Pco₂ were drawn at the second, fifth, and fifteenth minutes of recovery.

The second stage of the study evaluated the effects on IOT of the extremely high ventilation elicited during the closed-circuit system rebreathing, while alveolar Pco₂ was held stable. The mixed venous Pco₂ concentration at rest was determined individually with the rebreathing method of Campbell and Howell. The subject was connected with a high-velocity one-way breathing valve to a pneumotachyograph, which recorded ventilatory volume and flow, and was requested to hyperventilate at a rate comparable to the maximal volume exhibited during the closed-circuit CO₂ retention test. This was accomplished by establishing the breathing rate with a metronome and verbally encouraging the subject to adjust the tidal volume to the target value on the oscilloscope output. A gas mixture of 90% CO₂ and 10% N₂ was fed into a mixing tube attached to the inspiratory side of the valve and kept at the individually determined resting value of the mixed venous Pco₂ by monitoring with the mass spectrometer. Three baseline IOT determinations were made, and IOT measurements were again done each minute of the 7 min. period of hyperventilation and the first 3 min. of recovery.

The statistical significance for changes were estimated at the 0.05 p level with the use of procedures for correlated values.

Results. There was a slight rise in IOT from 16.0 ± 2.0 to 17.5 ± 2.2 mm. Hg when CO₂ was administered during the open-circuit phase, but
then a decline occurred to resting levels during the remainder of the open-circuit system breathing. During this time pH fell slightly from 7.389 ± 0.30 to 7.344 ± 0.018, and Pco2 rose from 35.6 ± 3.9 to 43.4 ± 4.2 mm. Hg. The changes in IOT were not statistically significant (Fig. 1).

During the closed-circuit phase IOT gradually rose from 15.8 ± 2.3 to 19.4 ± 3.5 mm. Hg, and pH continued to decrease from 7.344 ± 0.018 to 7.258 ± 0.030. The Pco2 continued to rise from 43.3 ± 4.2 to 54.4 ± 2.4 mm. Hg (Fig. 1). The change in pH and Pco2 again showed statistical significance, but the IOT change did not.

However, sudden lowering of Pco2 to the level in the ambient air was associated with a marked decrease in IOT. The IOT suddenly dropped from 19.4 ± 3.5 to 13.5 ± 2.1 mm. Hg after 1 minute of ambient air recovery and remained between 13.3 ± 2.0 and 12.8 ± 1.6 mm. Hg for the next 14 minutes. The pH rose to near baseline levels during this recovery period, reaching 7.345 ± 0.024 at the end of the recovery period. These changes in all experimental variables were statistically significant, the change in IOT being highly significant (p >0.001). The IOT stayed below baseline values in spite of near resting values obtained for blood pH and CO2 15 minutes after recovery (Fig. 1).

In the second portion of the experiment, in which the extreme physical labor of hyperventilation was separated from the effects of Pco2 by maintaining the Pco2 at resting values during hyperventilation, the changes in IOT were minimal. The maximum elevation of IOT during hyperventilation was 0.4 mm. Hg, and IOT dropped 1.2 mm. Hg below resting values during recovery. These changes in IOT were not statistically significant.

Discussion. The effect of elevated Pco2 levels on rising IOT in anesthetized animals and humans has been reported by several authors. The findings in this study are consistent with these prior studies.

The marked compensatory drop in IOT below baseline levels with a sudden return of inspired CO2 to ambient levels has not been previously reported. The changes in IOT appear related to the rate of change of Pco2 rather than the actual level of Pco2. The IOT was noted to rise initially from baseline levels during the early part of the open-circuit system phase as Pco2 rose. However, the IOT then decreased slightly during the latter part of the open system as Pco2 continued to rise slightly. Also, the change from the closed-circuit system to ambient levels of inspired air produced a marked drop in IOT below baseline values as the Pco2 decreased rapidly toward baseline values.

The rapidity in rate of change of IOT, noted with change from the closed-circuit system to ambient levels of inspired air, has also not previously been reported in humans. The mechanism of changes in IOT associated with changes in Pco2 in humans is not known. Inspiration of 10% CO2 produces a marked increase in intraocular blood volume. The associated distention of the globe may thus increase the IOT. Extracocular vascular distention and increased venous pressure occurring with increased Pco2 values may also raise IOT. Pulse and arterial blood pressure, however, do not correlate with IOT changes associated with changes in Pco2.

Another possible mechanism is increased aqueous secretion. Bill has shown in anesthetized cats that the effect of elevated Pco2 in raising IOT was associated with increased uveal blood flow. The mechanism of increasing IOT was most likely due to increased ultrafiltration associated with vasodilation and increased perfusion pressure in the ciliary processes. The effect of elevated CO2 levels on the amounts of H2CO3, H+, and HCO3 available during active secretion is unknown, and thus changes in this mechanism must also be considered. The effect of carbonic anhydrase inhibitors on the response of IOT to changing levels of Pco2 is now being investigated, which may help clarify whether or not active secretion is involved in this mechanism.

Although the blood pH was inversely proportional to the IOT, it is obviously not a sensitive, nor determining factor in regard to IOT change but reflects the resulting respiratory acidosis from increased inspired CO2 levels.

Previous reports of decreased blood pH in exercise were believed to be important factors in decreasing IOT; however, others reported decrease in IOT without concomitant changes in blood pH. This present report shows that blood pH can fall with a concomitant rise in IOT.

Increased ventilatory excursions, with constant inspired CO2 levels, did not cause any elevation of IOT. A minimal drop in IOT below resting values was noted when the increased ventilatory excursions were discontinued. These findings are consistent with the above view that the changes in IOT are related to sudden rates of change in Pco2 levels and not to rate of ventilation.

The rapid changes in IOT associated with changes in Pco2 may have important clinical implications. The accurate assessment of the IOT in children who require general anesthesia may be dependent upon accurate knowledge of the alveolar Pco2. A rapidly changing alveolar Pco2 level during periods of apnea or during hyperventilation by bag-breathing will have to be taken into consideration in assessment of the child's IOT. Increased Pco2 levels in patients undergoing procedures under local anesthesia, with the usual confined breathing space due to draping of the face, may result in elevation of IOT to unsafe levels.
From the Departments of Ophthalmology and Physical Education, University of Kentucky, and the Department of Medicine, Veterans Administration Hospital, Lexington, Kentucky. Submitted for publication Aug. 18, 1976. Reprint requests: Dr. Richard A. Kielar, Department of Ophthalmology, University of Kentucky Medical Center, Lexington, Ky. 40506.

Key words: intraocular tension, blood pH, blood Pco2, inspired CO2, aqueous secretion.

REFERENCES

Intraocular axial swelling produced by partial, immediately retrobulbar ligature of optic nerve. Jonathan D. Wittschafter, Donald E. Slagel, William J. Fox, and Frank J. Rizzo.

This is the first report of an experimental intraorbital ligature producing papilledema characterized by axonal swelling and accumulation of mitochondria in the lamina retinalis of the optic disc of rhesus monkeys subjected to immediately retrobulbar ligature of a portion of the optic nerve. This is an improved technique for investigating the pathogenesis of papilledema and optic neuropathy.

Previous experimental methods of producing papilledema have relied on increasing intracranial pressure, systemic toxicity, and hypertension or on ocular hypotony. Here we report an experiment which has been designed to produce retrobulbar axoplasmic stasis in a portion of the optic nerve of the rhesus (Macaca mulatta) monkey.

Methods and procedures
Surgical procedures. The procedure was performed under general anesthesia with halothane and appropriate control of respiration, blood pressure, and temperature. A lateral orbitotomy was performed with the operating microscope. The posterior ciliary arteries were identified and observed to pulsate. A double-armed suture 6-0 black silk suture with a GS-9 needle (Ethicon) was placed so as to penetrate the lateral aspect of the optic nerve at its deepest point, and the other arm was passed through the optic nerve sheaths under the posterior ciliary arteries so as not to disturb these vessels. Flow through the central retinal vessels was confirmed by fluorescein angiography and qualitative ophthalmodynamometry. Indirect ophthalmoscopy and fundus photography were always performed immediately before and after surgery, daily for the first 3 days, twice weekly thereafter, and immediately prior to sacrifice.

Histological study. Animals were sacrificed with perfusion of 2.5% glutaraldehyde in 0.05M cacodylate buffer at pH 7.3 given in the superior vena cava. After perfusion, the eye was removed and immediately placed in precooled 2.5% glutaraldehyde fixation solution during microdissection. The tissues were post-fixed in 1% osmium tetroxide in 0.1M cacodylate buffer dehydrated in ethanol, treated with propylene oxide, and embedded in Epon resin 812. Thick sections of 1 to 2 μ were cut and stained with toluidine blue and paraphenylenediamine.

The measurements of the axonal cross-sections were made from photographic prints of electron micrographs, with a Bausch & Lomb magnifier; more than 50 measurements were used for each layer of the disc. The axons were identified by their characteristic neurotubules and lighter cytoplasm. In longitudinal sections the measurements were made at the greatest distance noted on a line perpendicular to the inner surface of the plasma membrane for any given axon. All identifiable axons were measured, but this method tends to exclude the smaller, more eccentric cuts of axons which could not be identified with cer-