

The Pupillary Light Reflex

Effects of Anesthetics and Hyperthermia

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Background: The pupillary light reflex often is evaluated in the perianesthetic period to assess drug effects and brainstem function. Mild hypothermia alone or combined with isoflurane does not impair pupillary responses. Although perioperative hyperthermia is less common than hypothermia, abnormal increases in core temperature remain an important thermal disturbance. Accordingly, the pupillary effects of hyperthermia alone and hyperthermia combined with isoflurane and enflurane were evaluated. Additionally, the effects of nitrous oxide on pupillary responses were determined.

Methods: The pupillary light reflex was evaluated in 31 non-surgical volunteers participating in concurrent thermoregulatory studies. Pupillary reflexes were quantified using a portable infrared pupillometer during (1) hyperthermia alone (n = 9), (2) hyperthermia with 0.8% and 1.2% end-tidal isoflurane (n = 8), (3) hyperthermia with 1.7% end-tidal enflurane (n = 5), and (4) inhalation of 60% N₂O (n = 9).

Results: Mild hyperthermia alone (core temperature 38.5 ± 0.3° C) produced no clinically significant change in the pupillary light reflex. Pupillary responses were decreased markedly with 0.8% isoflurane, 1.2% isoflurane, and 1.7% enflurane when the volunteers were normothermic. Mild hyperthermia combined with isoflurane or enflurane dilated the pupil and increased the amplitude of the light reflex. Sixty-percent nitrous oxide decreased the pupillary reflex only 26 ± 4%.

Conclusions: Anesthetic-induced inhibition of the pupillary response to light is reversed partially by core hyperthermia. In contrast to enflurane and isoflurane, 60% N₂O has little effect on the pupil. (Key words: Anesthetics, inhaled; nitrous oxide. Anesthetics, volatile: enflurane. Hyperthermia. Hypothermia. Reflex: pupil.)

PUPILLARY diameter and amplitude of the light reflex often are measured in the perianesthetic period to help quantify anesthetic effect and neurologic function. Perioperative hyperthermia is less common than hypothermia, but does occur in infected patients, in those with blood in the fourth cerebral ventricle, after administration of mismatched blood products, and in patients who are warmed excessively.

Local ocular hypothermia alone¹ and mild systemic hypothermia during isoflurane anesthesia² only slightly impair pupillary responses. However, the extent to which pupillary reflexes are altered by hyperthermia remains unknown. Also unknown is the extent to which pupillary responses are impaired by the combination of hyperthermia and general anesthesia. Accordingly, we measured pupillary responses in volunteers made hyperthermic without anesthesia and during either isoflurane or enflurane anesthesia.

Nitrous oxide is, perhaps, the most commonly used anesthetic. Furthermore, nitrous oxide differs from the volatile anesthetics in its superior ability to preserve sympathetic tone.³ Consequently, the effects of this agent on pupillary dynamics cannot be predicted from previous studies. We therefore also determined the influence of nitrous oxide on pupillary responses.

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Methods

With approval from the University of California, San Francisco Committee on Human Research, we studied 31 volunteers. All were young, healthy, nonobese, taking no medication other than oral contraceptives, and free of eye disease. During these studies, volunteers reclined on a standard operating room table in a room maintained at $22 \pm 0.4^\circ$ C. All the volunteers fasted before induction of anesthesia and none was premedicated.

The present study was conducted concurrently with several thermoregulatory investigations.⁴⁻⁶ Because of technical difficulties, pupillary responses were not measured for every volunteer participating in the underlying studies. Furthermore, we have pupillary data from some volunteers who did not complete the multiple days required of the thermoregulatory protocols. Consequently, the number of volunteers presented here and their morphometric characteristics differ somewhat from those in the referenced underlying studies. However, all pupillary data recorded during these protocols are included in this report.

Hyperthermia Alone

Nine volunteers who participated in a thermoregulatory study⁴ were warmed with a forced-air warming blanket (Bair Hugger model 200, Augustine Medical, Eden Prairie, MN) and circulating-water blanket (Blanketrol II, Maxi-Therm blanket #276, Cincinnati Sub-Zero, Cincinnati, OH). The duration of the study was 1.8 ± 0.2 h and was terminated when the sweating rate was maximal. Pupillary reflexes were measured before warming, and when subjects reached the highest attained core temperature.

Hyperthermia with Isoflurane

Hyperthermia was induced in eight volunteers participating in a study of sweating thresholds during isoflurane anesthesia.⁴ Each participated on 2 experimental days, randomly ordered. In each case, anesthesia was induced by inhalation of nitrous oxide and isoflurane. Anesthesia was maintained at 0.8% end-tidal isoflurane on 1 study day, and at 1.2% on the other. Hyperthermia was induced as previously described for the volunteers undergoing hyperthermia alone. The

duration of the study was 2.7 ± 0.3 h at 0.8% isoflurane and 3.2 ± 0.4 h at 1.2% isoflurane. Pupillary reflexes were measured before warming and again when subjects reached the highest attained core temperature.

Hyperthermia with Enflurane

We studied five female volunteers participating in a study of sweating thresholds during combined epidural/general anesthesia.⁵ Epidural anesthesia was administered *via* a lumbar epidural catheter with a 17-ml bolus followed by 12–15 ml/h of 1.5% 2-chloroprocaine. General anesthesia then was induced with no premedication by inhalation of 3–4% enflurane in 70% N₂O. Vecuronium bromide (0.1 mg/kg) was administered to facilitate tracheal intubation. Nitrous oxide was discontinued, and the end-tidal concentration of enflurane was adjusted to 1.7%. Core hyperthermia was induced by a forced-air cover and circulating-water mattress positioned below the umbilicus. Pupillary reflexes were measured before warming and again when subjects reached the highest attained core temperature.

Nitrous Oxide

During induction of anesthesia for a thermoregulatory study,⁶ nine volunteers were given 70% N₂O in oxygen by face mask. When they failed to respond to verbal stimuli, volunteers were given vecuronium bromide (0.1 mg/kg). Ventilation was controlled by face mask to maintain normocarbida. The end-tidal concentration of nitrous oxide subsequently was reduced to 60%. Pupillary reflexes were measured before induction of anesthesia and after the volunteers had breathed 60% N₂O for ≈ 10 min. Tympanic membrane temperature during the pupillary measurements was $36.8 \pm 0.2^\circ$ C.

Measurements

Core temperatures were measured at the tympanic membrane or distal esophagus. Temperatures were measured with either Mallinckrodt probes (St. Louis, MO) connected to Columbus Instruments Iso-Thermex thermometers (Columbus, OH) or YSI Series 700 thermistor probes (Mallinckrodt) connected to an Omega model 5831 thermometer (Stamford, CT). Both combinations have an accuracy near 0.1° C and a precision of 0.01° C.

Pupillary responses (pupillary diameter and light reflex amplitude) were evaluated using a portable infrared pupillometer (Applied Sciences Laboratory, Waltham, MA).** The instrument was programmed to

** RADIUS A, WELCH P, CONC EJ, HENNINGFIELD JE: A portable pupillometer system for measuring pupillary size and light reflex. *Behav Res Meth Instrum Comp* 21:611–618, 1989.

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search for a stable pupillary diameter, flash a 0.5-s light stimulus, and initiate a 2-s, 10-Hz scan at the start of the stimulus. The light stimulus is provided by two green, light-emitting diodes having a combined intensity of 130 candelas/m². All measurements were made in the same room, where ambient light was set with a dimmer switch to approximately 150 lux. To ensure a consistent visual fixation point, awake volunteers focused on the eye of the examiner during each scan, at a distance of approximately 50 cm. All measurements were taken from the right eye. An opaque bandage was used to prevent ambient light from entering the left eye.

Clinical experience has shown that three scans are sufficient in most volunteers to record a reproducible reflex pattern. We therefore recorded at least three sets of data to produce one averaged scan from which pupil diameter and reflex amplitude were calculated. The difference between the prestimulus diameter and the minimum diameter in the 2 s following the stimulus was termed the reflex amplitude.

End-tidal gas concentrations (Capnomac II, Datex, Helsinki, Finland) were analyzed continuously either from samples taken from the endotracheal tube connector while volunteers were intubated or from a tightly fitted face mask after extubation. Spurious end-tidal samples (identified by inconsistent carbon dioxide tracings) were eliminated. At least 2 min of stable end-tidal anesthetic concentrations was obtained before the averaged scans were included in the data analysis.

Data Analysis

Pupillary responses to nitrous oxide and hyperthermia alone were compared with control values using two-tailed, paired *t*-tests. Responses to isoflurane and enflurane and the additional changes induced by hyperthermia were compared using repeated-measures analysis of variance and Scheffé's *F* test. Results are pre-

Table 1. Morphometric Characteristics of the Volunteers

	Age (yr)	Weight (kg)	Height (cm)	Sex (male/total)
Hyperthermia alone	30 ± 6	72 ± 16	175 ± 9	7/9
Hyperthermia + isoflurane	28 ± 5	67 ± 10	170 ± 4	3/8
Hyperthermia + enflurane	32 ± 8	63 ± 13	160 ± 7	0/5
Nitrous oxide	26 ± 5	64 ± 9	168 ± 7	4/9

There were no statistically significant differences among the groups.

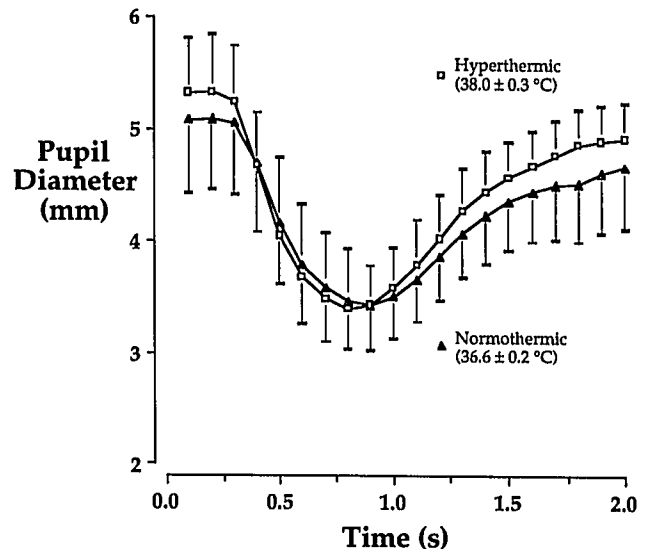


Fig. 1. Systemic hyperthermia ($38.0 \pm 0.3^\circ\text{C}$) without anesthesia slightly increased pupil diameter and the light reflex amplitude, but the changes were not significant.

sented as means \pm SD; differences were considered significant when $P < 0.05$.

Results

The morphometric characteristics of each study group are shown in table 1. There were no significant changes in either the light reflex or diameter of the pupil during hyperthermia without anesthesia (fig. 1). Pupillary responses were depressed significantly by both isoflurane and enflurane. Hyperthermia during anesthesia significantly increased the diameter of the pupil and the light reflex (table 2).

Inhalation of 60% N₂O slightly decreased pupil diameter ($5 \pm 2\%$) and the pupillary light reflex amplitude ($26 \pm 4\%$). Although the decreases were statistically significant, they were not clinically important (fig. 2).

Discussion

The pupil has been used to estimate anesthetic depth for more than a century.⁷ Although Hewitt illustrates a pupillometer in his 1907 textbook,⁸ and Geudel⁹ wrote extensively on pupillary diameter, it was Flagg who first emphasized the importance of the pupillary light reflex in estimating the anesthetic level.¹⁰ His 1916 textbook includes a lengthy discussion of pupil-

Table 2. Pupillary Effects of Anesthetic Induction and Subsequent Core Hyperthermia

	Temperature (° C)	Pupil Diameter (mm)	Reflex Amplitude (mm)
No anesthesia			
Control	36.6 ± 0.2	5.1 ± 0.8	1.7 ± 0.6
Hyperthermia	38.0 ± 0.3*	5.3 ± 0.5	2.0 ± 0.5
Isoflurane (0.8%)			
Control	36.3 ± 0.3	5.5 ± 0.8	1.8 ± 0.4
Anesthesia	36.5 ± 0.3	1.6 ± 0.2†	0.4 ± 0.1†
Hyperthermia	39.4 ± 0.2*	4.1 ± 2.0*	0.9 ± 0.4*
Isoflurane (1.2%)			
Control	36.6 ± 0.4	6.0 ± 0.6	2.0 ± 0.5
Anesthesia	36.4 ± 0.2	1.7 ± 0.4†	0.2 ± 0.1†
Hyperthermia	39.4 ± 0.2*	4.1 ± 1.4*	0.5 ± 0.3*
Enflurane (1.7%)			
Control	36.5 ± 0.4	5.8 ± 0.9	2.2 ± 0.6
Anesthesia	36.8 ± 0.5	2.2 ± 0.5†	0.3 ± 0.4†
Hyperthermia	40.3 ± 0.3*	4.5 ± 1.2*	0.9 ± 0.4*

* Statistically significant differences produced by hyperthermia.

† Statistically significant differences from control values.

lary physiology and describes the influence of ether on pupil diameter and the light reflex. Other authors, such as Poe,¹¹ Doglietti,¹² and Gillespie,¹³ agreed with Flagg that the light reflex was not abolished until deep levels of ether anesthesia were attained.

Our data are consistent with previous observations: the pupillary response to light remained detectable at 1 minimum alveolar concentration (MAC) isoflurane or enflurane. However, the magnitude in both cases was small, *e.g.*, 0.2 mm. Steady-state response to 0.8% and 1.2% isoflurane did not differ significantly from those we reported previously during recovery from anesthesia.² Interestingly, pupil diameter and reflex amplitude were similar during 1 MAC of isoflurane and enflurane. These data suggest that these volatile anesthetics alter pupillary dynamics similarly.

Hyperthermia alone had minimal effects on the light reflex in unanesthetized volunteers, but dilated the pupil and increased the amplitude of the light reflex in volunteers given enflurane and isoflurane anesthesia. It is possible that anesthetics intensify a mild inhibitory action brought about by hyperthermia on the pupilloconstrictor nucleus. Alternatively, this difference between the unanesthetized and anesthetized groups

might result simply from a greater core temperature increase in the anesthetized volunteers.

The pupillary response to hyperthermia was just as dramatic during enflurane anesthesia when cutaneous thermal sensitivity was blocked by epidural anesthesia as it was when isoflurane with no epidural block was given. This finding implies that the pupil dilates during hyperthermic anesthesia in response to increased core temperature rather than augmented skin temperature. It is unlikely that similar pupillary changes would have occurred without hyperthermia because we have shown previously that the pupil remains small and relatively nonreactive during similar durations of isoflurane² or enflurane^{††} anesthesia during either normothermic or hypothermic conditions.

It also is unlikely that systemic absorption of 2-chloroprocaine would result in dilation of the pupil: this agent is metabolized rapidly in the plasma, and local anesthetics never have been shown to dilate the pupil during anesthesia. We therefore conclude that core hyperthermia, *per se*, causes pupillary dilation and an increase in the light reflex during both enflurane and isoflurane anesthesia.

We studied nitrous oxide at only one end-tidal concentration and thus were unable to construct a dose-response curve. Nevertheless, at 0.55 MAC, nitrous oxide reduced the light reflex amplitude only 26%; in contrast, comparable MAC-fractions of isoflurane have

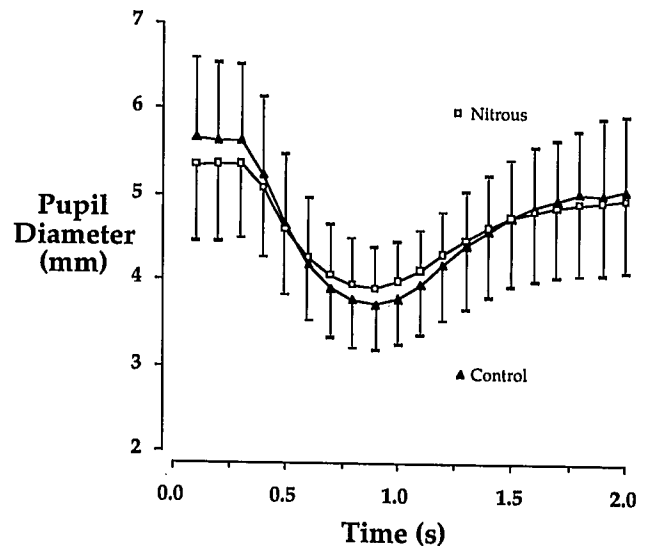


Fig. 2. Inhalation of 60% N₂O slightly decreased pupil diameter (5 ± 2%) and reflex amplitude (26 ± 4%). Although the decreases were statistically significant, they were not clinically important.

†† Belani KG: Unpublished observations.

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been shown to reduce the light reflex 70%.² Similarly, we would have expected 60% N₂O to reduce pupil diameter 30% but observed essentially no change.

Whereas our previous research measured the effects of isoflurane during emergence,² this study considered the effects of nitrous oxide during induction of anesthesia. Because our volunteers were not premedicated, preganglionic sympathetic activity may have been greater during the induction period than subsequently. Nevertheless, sympathetic tone generally may be preserved better by nitrous oxide administration than by the other anesthetics we tested.³ Consistent with this hypothesis, others have documented *increased* pupil diameter when nitrous oxide was added to halothane.¹⁴

Skeletal muscle relaxation was provided in all of our anesthetized volunteers by administration of vecuronium bromide. However, iris contraction is not mediated by nicotinic receptors and presumably is not influenced by skeletal muscle paralysis.

None of our volunteers was undergoing surgery or comparable painful stimulation. We demonstrated previously that painful electrical stimulation during isoflurane anesthesia markedly dilates the pupil and increases amplitude of the light reflex.¹⁵ Thus, our current data should be applied only to relatively unstimulated patients or those in whom surgical pain is prevented by simultaneous regional blockade. Similarly, opioids significantly diminish pupillary diameter and likely alter anesthetic dose-response relationships considerably.

In summary, we demonstrated that mild hyperthermia without anesthesia produced no important changes in pupillary responses, whereas mild hyperthermia during isoflurane or enflurane dilated the pupil and increased the light reflex amplitude. In contrast, inhalation of 60% N₂O only slightly decreased the light reflex amplitude.

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