

## Isoflurane, but Not Mild Hypothermia, Depresses the Human Pupillary Light Reflex

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The pupillary light reflex is often evaluated in the perioperative period as a measure of cranial nerve and midbrain integrity. Although surgical concentrations of some anesthetic agents and severe hypothermia qualitatively alter the light reflex, confounding factors frequently present during postanesthetic recovery have not been specifically quantified. We therefore studied 12 volunteers to determine the effects of residual isoflurane concentrations and typical (mild) hypothermia on the human pupillary light reflex. Young, healthy volunteers were assigned to one of three treatments: 1) normothermic isoflurane-oxygen anesthesia; 2) isoflurane-oxygen anesthesia with  $2.2 \pm 0.5^\circ\text{C}$  central hypothermia; and 3) central hypothermia ( $1.6 \pm 0.3^\circ\text{C}$ ) without anesthesia, induced by internal jugular infusion of iced lactated Ringer's solution. In normothermic anesthetized volunteers, the amplitude of the light reflex was depressed 80-90% at end-tidal concentrations greater than 0.5% isoflurane: reflex (percent of control) =  $14 - 67 \cdot \log(\text{percent isoflurane})$ ;  $r = -0.92$ . In the mildly hypothermic anesthetized volunteers, pupillary responses were not statistically different from those in anesthetized normothermic volunteers: reflex (percent of control) =  $16 - 62 \cdot \log(\text{percent isoflurane})$ ;  $r = -0.97$ . Hypothermia alone did not alter the magnitude of the light reflex. Our data suggest that mild hypothermia does not depress the light reflex but that isoflurane reversibly depresses the light reflex in a dose-related manner. (Key words: Anesthetics, volatile: isoflurane. Hypothermia. Reflex: pupil.)

THE PUPILLARY LIGHT REFLEX is often evaluated in the perioperative period as a measure of cranial nerve and midbrain integrity.<sup>1</sup> Although surgical concentrations of some anesthetic agents and severe hypothermia can alter the light reflex,<sup>2,3</sup> confounding factors frequently present during postanesthetic recovery have not been specifically evaluated. We therefore studied 12 volunteers to determine the effects of residual postanesthetic isoflurane concentrations and typical (mild) hypothermia on the human pupillary light reflex.

### Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and

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written informed consent, we studied 12 volunteers, who were distributed into three groups of four. All were young, healthy, taking no medication, and free of eye disease. Central temperatures in each group were measured using a tympanic membrane thermocouple (Mon-a-Therm®, Inc., St. Louis, MO). Volunteers were studied during a control period and then during normothermic isoflurane anesthesia ( $n = 4$ ), hypothermic anesthesia ( $n = 4$ ), and hypothermia without anesthesia ( $n = 4$ ).

In the first group, anesthesia was induced by inhalation of 1-2% isoflurane and 70% nitrous oxide in oxygen *via* face mask. Nitrous oxide was then discontinued; the trachea was intubated without the use of muscle relaxants; and isoflurane anesthesia was continued for 3 h. Tympanic membrane (central) temperature was maintained within  $0.2^\circ\text{C}$  of control values using a Bair Hugger® forced-air warmer (Augustine Medical, Minneapolis, MN). Approximately 1 h after induction, a vecuronium bromide infusion ( $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) was given as part of a separate muscle relaxant study.<sup>4</sup> This infusion was stopped in the 3rd h of anesthesia; the residual neuromuscular blockade was not antagonized.

Anesthesia was induced in the same manner in a second group of volunteers whose central temperatures were allowed to decrease passively by approximately  $2^\circ\text{C}$ . These subjects also received an infusion of vecuronium bromide ( $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) as part of the same muscle relaxant study. Neuromuscular blockade was antagonized using a mixture of glycopyrrolate (0.6 mg) and neostigmine (3 mg). Total anesthetic time was 4-5 h.

Volunteers in the third group were given no sedative or anesthetic drugs. These individuals were cooled centrally by infusions of iced lactated Ringer's solution ( $\approx 3^\circ\text{C}$ ) at a rate of  $1.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 15 min, followed by  $0.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 30 min. Infusions were given *via* an internal jugular catheter placed prior to the study period using standard techniques. We have previously shown that this rate of cold intravenous infusion induces clinically significant hypothermia (a  $1-2^\circ\text{C}$  decrease in central temperature) within 30 min.<sup>5</sup>

Pupillary reflexes (light reflex amplitudes and pupillary diameters) were evaluated using a recently developed portable infrared pupillometer (Fairville Medical Optics, Inc., Amersham, England).§ The instrument was pro-

§ RADIUS A, WELCH P, CONE EJ, HENNINGFIELD JE: A portable pupillometer system for measuring pupillary size and light reflex. *Behavior Research Methods Instruments and Computers* 21:611-618, 1989

grammed to search for a stable pupillary diameter, flash a 0.5-s light stimulus, and then 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/m<sup>2</sup>. All measurements were made in the same room, where ambient light was set with a dimmer switch to approximately 150 lux.

Baseline pupillary and temperature measurements were taken in each group prior to the administration of the anesthetic or iced saline. In the two groups receiving isoflurane these baseline measurements were averaged and considered the preinduction values. Pupillary responses during hypothermia alone were averaged during the 20 min of lowest body temperature and compared with those obtained during the control period. To ensure a consistent visual fixation point, during each scan the awake volunteers focused on the eye of the examiner at a distance of approximately 50 cm. All measurements were taken from the right eye. Ambient light was excluded from the left eye, by covering the eye with a hand in the awake volunteers and by taping the eyelid closed in the anesthetized volunteers.

Clinical experience has shown that three scans are sufficient in most subjects to record a reproducible reflex pattern from which the parameters of the light reflex can be analyzed. We therefore averaged at least three sets of data to produce one (averaged) scan, from which pupil size and reflex amplitude were recorded. The difference between the prestimulus diameter and the minimum diameter in the 2 s following the stimulus was defined as the reflex amplitude.

Volunteers in the normothermic and hypothermic anesthetized groups were monitored for blood pressure and tympanic temperature and for hemoglobin oxygen saturation by pulse oximetry. End-tidal isoflurane and end-tidal carbon dioxide (infrared analyzer, Datex, Finland) were continuously analyzed from samples taken from the endotracheal tube connector while the volunteer was intubated and from a tightly fitted face mask after the trachea had been extubated. Spurious end-tidal samples (identified by inconsistent carbon dioxide recordings) were eliminated. Volunteers' lungs were mechanically ventilated until the return of muscular function, and thereafter the volunteers breathed spontaneously. Pupillary responses were measured at 0.5- to 5-min intervals beginning approximately 1 h before isoflurane was discontinued. Volunteers had their tracheas extubated while fully anesthetized to minimize sympathetic stimulation, and then isoflurane administration was discontinued. Subjects then breathed a mixture of air and oxygen from a face mask, and measurements were continued except during periods of coughing or straining. At least 2 min of stable end-tidal isoflurane concentrations were obtained before the averaged scan was included in the data analysis.

The effects of residual isoflurane concentrations during recovery from isoflurane anesthesia were compared using analysis of variance of regression coefficients among groups.<sup>6</sup> Two-tailed paired *t*-tests were used to compare pupillary responses during hypothermia alone to control values. Results are reported as means  $\pm$  standard deviations; *P* < 0.05 was considered significant.

### Results

The morphometric characteristics, ages, and changes in central temperature in each group are shown in Table 1. The only significant differences were the decreases in central temperature in the hypothermic anesthetized and hypothermic awake groups as compared to the normothermic anesthetized group. In the two hypothermic groups, the decrease in tympanic membrane temperature was not statistically significantly different between those who were anesthetized and those who were not.

The pupillary measurements during the isoflurane study took  $2.8 \pm 0.7$  h. End-tidal isoflurane plateaus lasting more than 2 min were observed on 50 occasions in the eight anesthetized volunteers. The duration of the stable measurement periods are shown in table 2. Isoflurane depressed the light reflex so that at end-tidal concentrations greater than 0.5%, the amplitude of the reflex was reduced to approximately 10% of the awake values (figs. 1 and 2); at lower concentrations, the reflex rapidly regained amplitude. The reflex, however, was not totally abolished even at an end-tidal concentration of 2%. A linear relationship was observed between the logarithm of the isoflurane concentration and the decrease of the light reflex amplitude; the slope of this relationship was not different in the two anesthetized groups (fig. 2). Typical pupillary responses during anesthesia are shown in figure 3; as the isoflurane concentration increased, the amplitude decreased. Prestimulus diameter was also related to isoflurane concentration in the normothermic anesthetized group ( $r = -0.93$ ), but the data were scattered ( $r = -0.5$ ) in the hypothermic anesthetized group (fig. 4).

TABLE 1. Morphometric and Temperature Data for Each Study Group

	n	Age (yr)	Height (cm)	Weight (kg)	$\Delta$ Temperature ( $^{\circ}$ C)
Normothermic anesthesia	4	$25 \pm 2$	$170 \pm 10$	$65 \pm 11$	$0.1 \pm 0.1$
Hypothermic anesthesia	4	$28 \pm 6$	$168 \pm 7$	$70 \pm 16$	$-2.2 \pm 0.5^*$
Hypothermia alone	4	$30 \pm 6$	$171 \pm 4$	$72 \pm 9$	$-1.6 \pm 0.3^*$

\* Represents significant differences from normothermic anesthesia.

TABLE 2. Durations of Stable Isoflurane Concentrations

	Time (min)				
	2-4	4-8	8-12	12-16	>16
Normothermic anesthesia	3	5	10	3	5
Hypothermic anesthesia	3	7	8	3	3

The light reflex at the time glycopyrrolate and neostigmine were administered was small (0.1–0.2 mm). This small reflex was unchanged in amplitude in two volunteers 5 min after the reversal agents were given. The effect of these drugs in the other two volunteers of this group was inconclusive because unstable end-tidal isoflurane concentrations precluded reliable measurements.

Central temperature decreased rapidly in response to cold intravenous infusions. Within 20 min, tympanic membrane temperature was  $1.6 \pm 0.3^\circ\text{C}$  below control values. At the lowest central temperature, the light reflex amplitude was unchanged in two volunteers, decreased by 9% in a third, and decreased by 4% in the fourth (fig. 5). These changes were not statistically significant. The scans for all four subjects in this group were pooled to form a composite scan (fig. 6). The amplitude of the light reflex was similar during normothermia and hypothermia, independent of anesthesia.

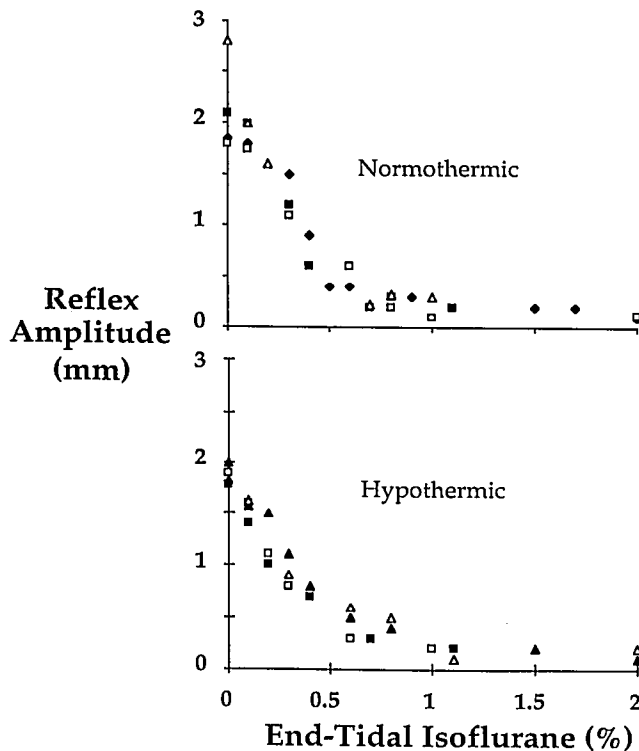


FIG. 1. Reflex amplitude as a function of end-tidal isoflurane concentration in normothermic and hypothermic groups. Each group had four volunteers, represented by different symbols.

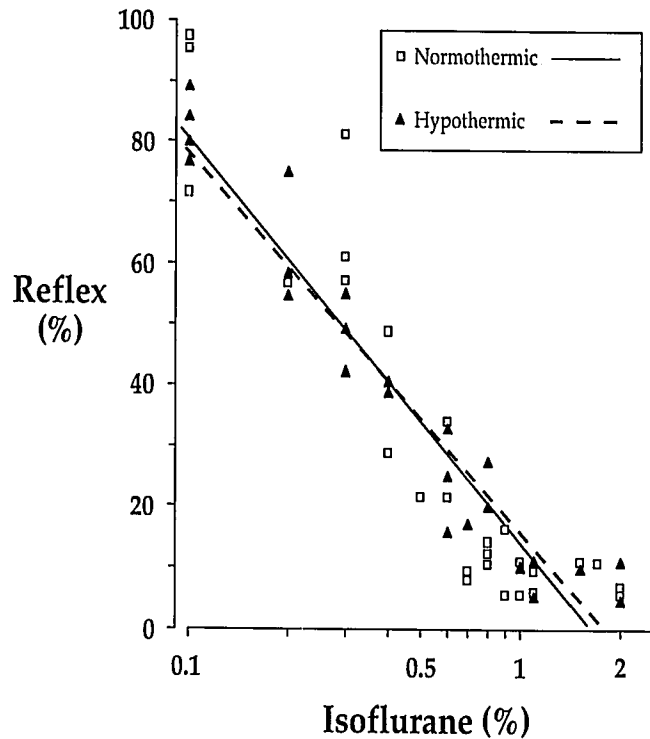


FIG. 2. Relationship between percent of preinduction reflex amplitude and end-tidal isoflurane for normothermic (squares) and hypothermic (triangles) volunteers. Regression line for normothermic group (solid line) is: reflex (% control) =  $14 - 67 \cdot \log(\text{isoflurane } \%)$ ;  $r = -0.92$ , and for the hypothermic group (dashed line) is Reflex (% control) =  $16 - 62 \cdot \log(\text{isoflurane } \%)$ ;  $r = -0.97$ . The slopes are not significantly different.

Discussion

The pupillary response to light is commonly used in the perianesthetic period to assess brainstem function. Because hypothermia and residual anesthetic are common in the postoperative period, it is important to know if these factors depress the light reflex. The recent introduction of a portable infrared pupillometer provides a noninvasive method for objective analysis of the reflex with a uniform light source.

We studied the effect of isoflurane during emergence from anesthesia, when anesthetic concentrations were decreasing rapidly. Our dose-response curves were constructed only from concentrations that were stable for at least 2 min. This limited the data to about six points for each volunteer, but a clear linear relationship was found between the decrease in reflex amplitude and the logarithm of the end-tidal isoflurane concentration. Although isoflurane markedly depressed the light reflex, a reflex was still measurable at end-tidal concentrations commonly encountered during surgery (*i.e.*, 1 MAC). These data are consistent with a previous study of pupillary responses during isoflurane administration.<sup>2</sup>

The cause of a reduced light reflex during general anesthesia is unknown. Anesthesia decreases pupil size, thereby limiting the range of pupillary movement. Decreased size alone, however, does not account for the observed loss of reflex amplitude, because the pupil could regain its size during emergence while the reflex remained depressed (fig. 3; compare 0.8% vs. 0.05%). During emergence, the hypothermic anesthetized volunteers all shivered and exhibited myoclonic activity; this was often associated with pupillary dilation. Perhaps because of this, the relationship between end-tidal isoflurane and pupil diameter was different in this group as compared to the normothermic anesthetized volunteers, who demonstrated little muscular activity during emergence from anesthesia. Even though the pupil occasionally dilated prematurely during emergence in this hypothermic group, the light reflex remained depressed.

Other causes of a reduced light reflex during general anesthesia are purely speculative. Natural sleep and other states of decreased vigilance depress the light reflex<sup>7</sup>; it

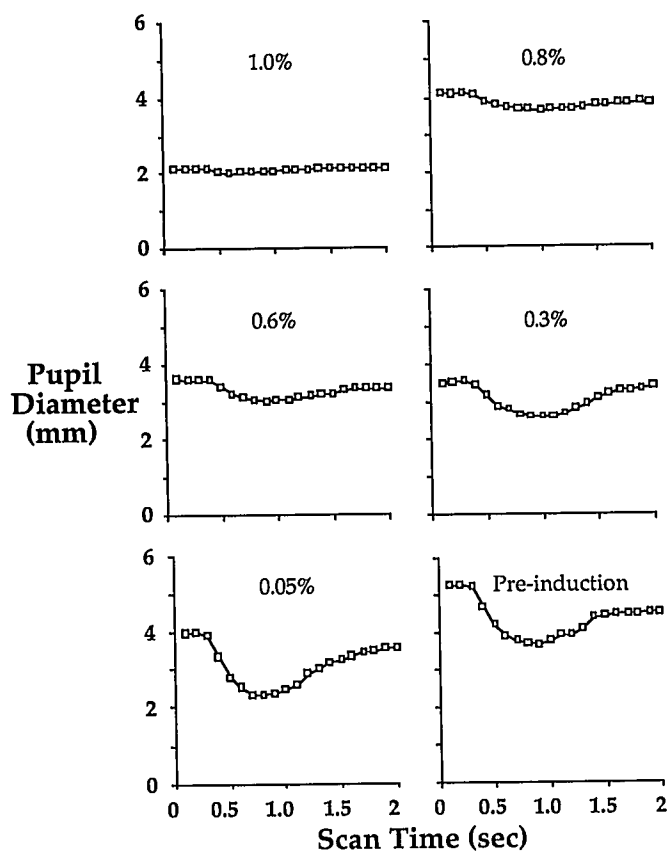


FIG. 3. Average light reflex scans at various end-tidal concentrations in a hypothermic volunteer. The light stimulus was given between 0 and 0.5 s. Note that in addition to the decrease in reflex amplitude, there is an increase in latency and a decrease in constriction velocity as the isoflurane concentration increased.

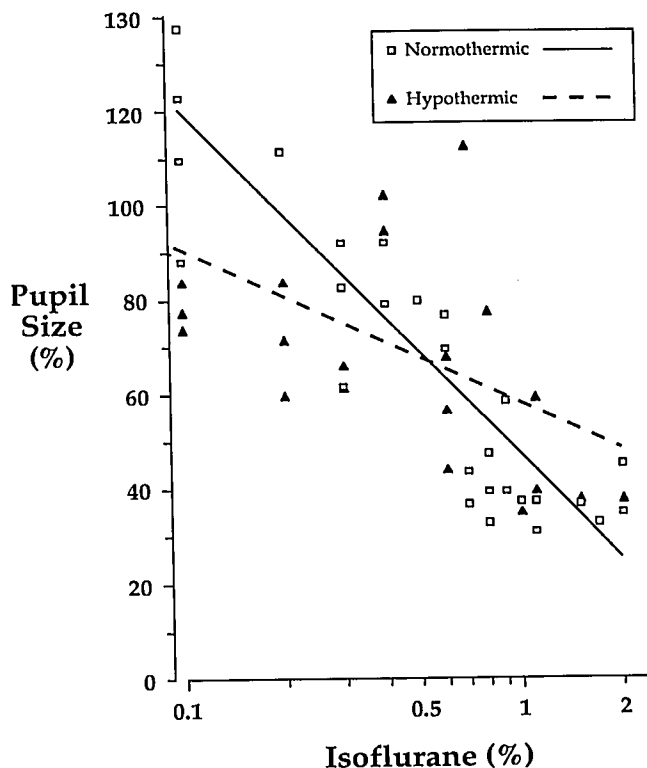


FIG. 4. Relationship between percent of preinduction pupil size and end-tidal isoflurane (percent) for normothermic (squares) and hypothermic (triangles) volunteers. The regression equations for the normothermic group (solid line) is: size (% control) =  $47 - 73 \cdot \log(\text{isoflurane } \%)$ ;  $r = -0.93$ , and for the hypothermic group (dashed line) is: size (% control) =  $57 - 32 \cdot \log(\text{isoflurane } \%)$ ;  $r = -0.50$ .

is possible that anesthetic drugs and natural sleep inhibit areas of the central nervous system that facilitate the light reflex. Visual evoked potentials also are depressed by isoflurane.<sup>8</sup> Because the retina is the receptor for both the visual evoked potential and the light reflex, it is possible that both pathways are blocked primarily by an action within the retina.

Central hypothermia alone did not decrease the reflex amplitude. Previous studies reporting the action of hypothermia on the light reflex are confounded by concomitant use of sedative agents. For example, Fischbeck and Simon<sup>3</sup> reported that 30% of mildly hypothermic patients had a sluggish or absent light reflex, but many of their patients became hypothermic while under the influence of recreational drugs or ethanol. Huet *et al.*<sup>9</sup> reported sluggish or absent light reflexes in most patients undergoing hypothermic cardiopulmonary bypass; however, large doses of sufentanil had been given during induction of anesthesia, and the hypothermia was profound. Fay and Smith<sup>10</sup> studied neurologic reflexes during hypothermia induced by surface cooling and demonstrated sluggish light reflexes when central temperatures were

below 35°C. However, they had used rectal bromethol for sedation. Our data were obtained by central cooling and may differ from those obtained during similar hypothermia induced by surface cooling. That is, surface cooling may lower the temperature of the iris musculature more than central temperature. Local cooling of the iris might directly depress the muscular component of the light reflex while leaving midbrain responses intact.

Additionally, we found that hypothermia did not potentiate the depressant action of isoflurane on the light reflex. A limitation of this study is that the normothermic anesthetized group received no reversal agents, whereas the hypothermic anesthetized group was given glycopyrrolate and neostigmine. The light reflex is mediated through muscarinic receptors that are known to be affected by topical antimuscarinic agents and cholinesterase inhibitors.<sup>11</sup> With two of our volunteers, intravenous administration of these agents did not alter the light reflex, but we do not consider this an adequate sample. Although reversal agents might have had a separate action on the light reflex, the curves representing the relationship between the decrease in reflex amplitude and isoflurane concentrations were markedly similar (figs. 1 and 2). It is unlikely that two separate factors (hypothermia and the use of reversal agents) would have equal but opposite effects.

It should also be noted that the duration of anesthesia was different in the anesthetized groups. We did not think

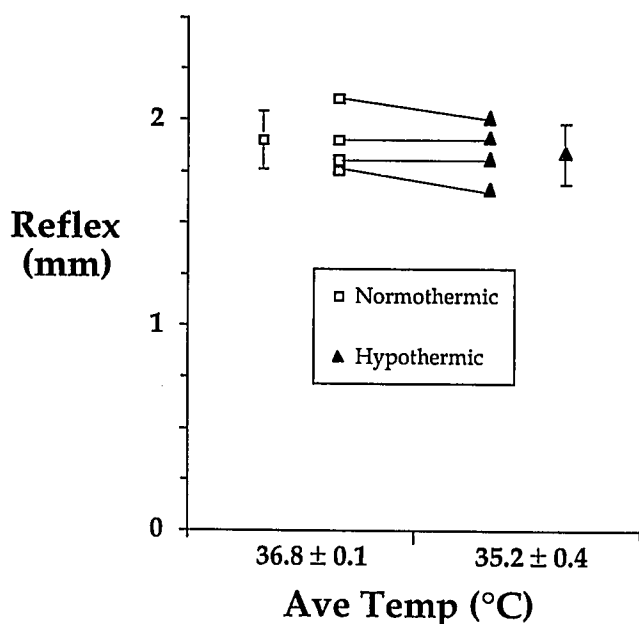


FIG. 5. Light reflex amplitude before (squares) and after (triangles) induced hypothermia in four volunteers. Mean tympanic temperature before and after hypothermia is shown on the abscissa.

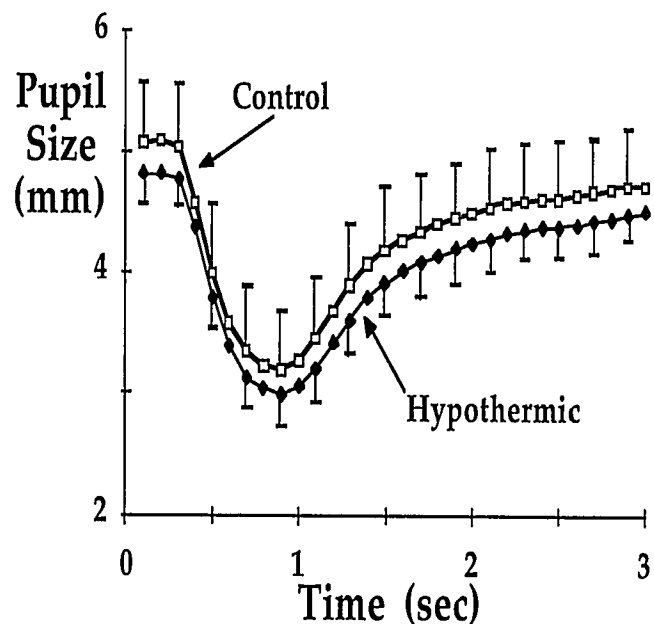


FIG. 6. Pupil size following a 0.5-s flash of light in four volunteers before and after reduction of central temperature by  $1.6 \pm 0.3^\circ\text{C}$ .

that this would alter the relationship between end-tidal isoflurane and reflex amplitude; a previous study could detect no difference in the action of isoflurane on the light reflex between the 1st and 5th h of anesthesia.<sup>2</sup> However, we cannot dismiss the possibility that adaptation was occurring as the anesthetic progressed.

Volatile anesthetics and hypothermia are not the only variables that might affect the light reflex in the perioperative period. Anesthetic adjuvants, such as neuroleptic agents<sup>12</sup> and opioids,<sup>§</sup> also may influence the light reflex. Stimulation of the sympathetic nervous system can alter both the extent and the shape of the light reflex.<sup>13</sup> We did not study the effects of these factors. Therefore, until more is learned about the pupil, the light reflex cannot be advocated as a measure of "depth of anesthesia." Nevertheless, in the absence of surgical stimulation or sympathetic activation, the light reflex is an easily obtained measure that correlates as well, and perhaps better, with isoflurane concentration as do other autonomic measurements, including blood pressure, heart rate, and esophageal contractility.<sup>14</sup>

In summary, we studied the influence of two variables on the pupillary light reflex in the perioperative period. Isoflurane markedly depressed the light reflex, whereas

§ Pickworth WB, Welch P, Henningfield JE, Cone EJ: Opiate-induced pupillary effects in humans: Methods and findings in experimental clinical pharmacology 11:759-763, 1989

mild hypothermia neither depressed this reflex nor augmented the depressant effect of isoflurane.

Mon-a-Therm<sup>®</sup>, Inc. donated the thermocouples. The authors also greatly appreciate the loan of a Datex Capnomac<sup>®</sup> from Datex Medical Instrumentation, Inc.

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