Sympathetic Nervous System Does Not Mediate Reflex Pupillary Dilation during Desflurane Anesthesia


Background: Pupil size is determined by an interaction between the sympathetic and parasympathetic divisions of the autonomic nervous system. Noxious stimulation dilates the pupil in both unanesthetized and anesthetized humans. In the absence of anesthesia, dilation is primarily mediated by the sympathetic nervous system. In contrast, pupillary dilation in cats given barbiturate or clorazolic anesthesia is mediated solely by inhibition of the midbrain parasympathetic nucleus. The mechanism by which noxious stimuli dilate pupils during anesthesia in humans remains unknown. Accordingly, the authors tested the hypothesis that the pupillary dilation in response to noxious stimulation during desflurane anesthesia is primarily a parasympathetic reflex.

Methods: In six volunteers, the alpha-1 adrenergic receptors of the iris musculature were blocked by unilateral administration of topical dapiaprazole; six other volunteers were given unilateral topical tropicamide to block the muscarinic receptors in the iris. Desflurane anesthesia was subsequently induced in all volunteers. Sympathetic nervous system activation, with reflex dilation of the pupil, was produced by noxious electrical stimulation during 4% and 8% end-tidal desflurane, and by a rapid 4%-to-8% step-up in the desflurane concentration. Pupil diameter and the change in pupil size induced by a light stimulus (light reflex amplitude) were measured with infrared pupillometry.

Results: Dapiprazole drops produced a Horner’s miosis, but pupils were equally small after induction of anesthesia. Pupillary dilation after noxious stimulation and desflurane step-up was identical in the unblocked and dapiprazole-blocked pupils. After tropicamide administration, the pupil was dilated and the light reflex was completely inhibited. Noxious stimulation nonetheless produced a slight additional dilation.

Conclusions: During desflurane anesthesia, pupillary dilation in response to noxious stimulation or desflurane step-up is not mediated by the sympathetic nervous system (as it is in unanesthetized persons). Although inhibition of the pupil-constrictor nucleus may be the cause of this dilation, the mechanism remains unknown. (Key words: Autonomic nervous system. Pupil: light reflex. Anesthesia: desflurane).

PUPIL size is determined by an interaction between the sympathetic and parasympathetic divisions of the autonomic nervous system. Noxious stimulation dilates the pupil in both unanesthetized and anesthetized humans. In the absence of anesthesia, this response has been called the ciliospinal reflex and is primarily mediated by the sympathetic nervous system in both humans and cats. In contrast, pupillary dilation in cats given barbiturate or clorazolic anesthesia is mediated solely by inhibition of the midbrain parasympathetic nucleus. The mechanism by which noxious stimuli dilate pupils during anesthesia in humans remains unknown.

We recently observed pupillary dilation during combined epidural/general anesthesia when a tetanic electric stimulus was applied cephalad to the level of sensory block, whereas none was detected when the stimulus was applied within the blocked dermatomes.
PUPILLLARY DILATATION DURING ANESTHESIA

Clinical use of this test to evaluate sensory block level during combined epidural/general anesthesia may be facilitated by a better understanding of the mechanism by which noxious stimuli dilate pupils. For example, if this reflex is primarily sympathetically mediated, determination of sensory block level might fail if the sympathetic nervous system were compromised, by either a sufficiently high epidural or spinal block or by intravenous administration of sympathetic drugs.

Accordingly, we wanted to better define the mechanism of reflex pupillary dilation in anesthetized humans by observing the effects of topical autonomic blocking drugs on pupillary dilation in response to noxious stimulation. Our hypothesis was that pupillary dilation in response to noxious stimulation and sympathetic nervous system activation during desflurane anesthesia was primarily a parasympathetic reflex, and thus susceptible to anticholinergic drugs yet resistant to sympathetic agents.

Methods

With approval of the Committee on Human Research of the University of California, San Francisco and written informed consent, we administered 13 anesthetics to 12 volunteers. All volunteers were young, healthy, taking no medications, and had no history of ocular disease. None had evidence of anisocoria in either dim or bright light.

Protocol

Six volunteers were treated with the alpha-1 adrenergic blocking agent dapiprazole. Two drops of 0.5% dapiprazole (approximately 0.7 mg) were administered topically into one randomly chosen eye, and the same dose was repeated 5 min later. An additional treatment with dapiprazole was given 10 min after induction of anesthesia. Dapiprazole is a competitive antagonist but binds so tightly to the adrenergic receptors in the iris that it can overcome even the dilation induced by topical solutions of potent alpha-1 agonists. It has no significant affinity for beta-adrenergic or alpha-2 receptors. Only small amounts of dapiprazole are detected in the plasma after topical application, and administration of the drug produces no detectable effect on the contralateral pupil. With the 0.5% solution, reversal of phenylephrine-induced mydriasis is complete after 1 h and the effect lasts 4 to 5 h.

Unilateral pharmacologic blockade of the cholinergically (muscarinic) innervated sphincter muscle was induced in six additional volunteers. Two drops each of 1% tropicamide were instilled topically into one randomly chosen eye, and the dose was repeated 5 min later. Subsequently, we applied tropicamide drops every 30 min throughout anesthesia. One percent tropicamide produces 60 to 80 min of competitive inhibition of muscarinic (receptor subtype M_{3}) transmission at the pupillary sphincter. One volunteer who initially received tropicamide was given an additional desflurane anesthetic. In this case, both tropicamide and dapiprazole drops were instilled into one eye. The timing of drug administrations and the anesthetic protocol was the same for this volunteer as in the other studies, except that both ocular medications were given.

General anesthesia was induced 30 min after instillation of tropicamide and 60 min after dapiprazole treatment. Intravenous propofol (2 mg/kg) was followed by vecuronium bromide (0.1 mg/kg). The trachea was intubated and desflurane was administered to an end-tidal concentration of 4%. Sufficient additional vecuronium was administered to maintain one mechanical twitch in response to supramaximal train-of-four stimuli applied to the ulnar nerve at the wrist. Anesthesia was initially maintained with 4% end-tidal desflurane in a 50:50 mixture of air and oxygen. The volunteers’ lungs were mechanically ventilated to maintain end-tidal P_{CO}_{2}, between 35 and 45 mmHg. A forced-air (Augustine Medical, Eden Prairie, MN) warming blanket was used to maintain distal esophageal temperature at 36 to 37°C.

Fifteen minutes after the end-tidal desflurane concentration stabilized at 4%, we induced reflex pupillary dilation by applying a 100-Hz, 65- to 70-mAmp, 5-s-long electrical stimulus (DiGi Stim II, NeuroTec, Houston, TX) to the T9 dermatome via stainless steel needle electrodes inserted in the anterior midline. Seventeen minutes later, the sympathetic nervous system was activated by rapidly increasing the end-tidal desflurane concentration to 8%, using a previously described protocol. Ten minutes after the desflurane concentration stabilized at 8%, a similar electrical stimulus was applied again.

The desflurane concentration was subsequently reduced to 2 to 4% and neuromuscular function was allowed to recover partially. Neostigmine (2.5 mg) and glycopyrrolate (0.5 mg) were administered, desflurane was discontinued, and the trachea was extubated.

Thirty minutes after awakening, two drops of 2.5% phenylephrine were instilled into both eyes of volunteers who had been treated with dapiprazole. Two drops of 1% pilocarpine were instilled into both eyes of the first volunteer given tropicamide. Because pilocarpine induced ciliary spasm of his unblocked eye, pilocarpine was administered only to the tropicamide-treated eye in the remaining volunteers. These drops were administered to test the adequacy of the sympathetic and muscarinic blockade.

**Measurements**

Standard anesthetic monitors were used in all volunteers, including a pulse oximeter (Nellcor, Hayward, CA), electrocardiogram (Tektronix, Houston, TX), esophageal temperature (Mon-a-Therm; Mallinckrodt Anesthesiology, St. Louis, MO), and oscillometric blood pressure (Modulus CD; Ohmeda, Salt Lake City, UT). Throughout the study, end-tidal oxygen, carbon dioxide, and desflurane concentrations were measured using a Capnomac Ultima (Datex Medical Instruments, Tewksbury, MA). Values were recorded at 5-min intervals throughout. In addition, heart rate and blood pressure were recorded at 1-min intervals for 8 min after noxious stimulation and the desflurane step-up.

Pupil size was measured bilaterally using two calibrated portable infrared pupillometers (Fairville Medical Optics, Amersham, UK). Pupil size and the change in pupil size after a light stimulus (light reflex amplitude) were evaluated before and after instillation of eye drops, electrical stimulation, and desflurane step-up. Scans were 2 s long in the volunteers given dapiprazole and 5 s long in those given tropicamide. Measurements were taken immediately before, and 0 (elapsed time zero), 0.5, 1, 1.5, 2, 2.5, 4, and 8 min after electrical stimulation and desflurane step-up. Ambient light was excluded using rubber eye cups attached to the optical units. We previously described the details of infrared pupillary measurements. Absence of a light reflex in the tropicamide-treated eyes was determined using previously described criteria.

**Statistical Analysis**

Pupil size in the unblocked and blocked eyes was compared using two-tailed, unpaired t tests. Pupil size and hemodynamic responses before and after instillation of eye drops, and before and after electrical stimulation or autonomic activation induced by desflurane step-up, were compared using two-tailed, paired t tests. As suggested by Matthews and colleagues, we restricted analysis of the pupil size versus time data to a relevant "curve descriptor," maximum pupil size. Results are presented as means ± SD; P < 0.05 was considered statistically significant.

### Results

Table 1 shows demographic and morphometric data. There were no statistically significant differences between the volunteers treated with dapiprazole and those given tropicamide. Noxious electrical stimulation and the desflurane step-up produced substantial and statistically significant increases in mean arterial blood pressure and heart rate. Because the hemodynamic responses were similar, results from the dapiprazole- and tropicamide-treated volunteers were combined (Table 2).

Dapiprazole eye drops induced a typical "Horner's miosis," associated with conjunctival injection, and ptosis. Induction of anesthesia markedly reduced pupil size bilaterally, abolishing the anisocoria. Reflex dilation in response to electrical stimulation during 4% and 8% desflurane, and in response to the desflurane step-up, was identical in the unblocked and dapiprazole-blocked pupils. A power analysis indicated that we had a 85% chance of detecting even a 1-mm difference in stimulation-induced dilation in the blocked and unblocked pupils at an unpaired alpha level of 5% (combining the three stimuli). Postanesthetic administration of phenylephrine did not increase the size of the dapiprazole-treated pupil, but it did increase the size of the untreated pupil by 2 mm (Fig. 1, Table 3).

The tropicamide-treated pupil of one volunteer constricted 0.5 mm after receiving pilocarpine eye drops. The data from this volunteer were thus excluded from analysis, although his responses to noxious stimulation were similar to those in the other five volunteers. Pilo-
Table 2. Hemodynamic Responses

<table>
<thead>
<tr>
<th></th>
<th>4% Desflurane</th>
<th>4–8% Stepup</th>
<th>8% Desflurane</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Prestimulus</td>
<td>%Δ</td>
<td>Prestimulus</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 11</td>
<td>28 ± 21</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>73 ± 10</td>
<td>19 ± 14</td>
<td>75 ± 7</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110 ± 8</td>
<td>11 ± 7</td>
<td>107 ± 10</td>
</tr>
</tbody>
</table>

Prestimulus and maximum percent increase (%Δ) in heart rate, mean arterial blood pressure (MAP), and systolic blood pressure (BP) at an end-tidal desflurane concentration of 4% desflurane, during the 4–8% concentration stepup, and at an end-tidal desflurane concentration of 8% desflurane. Results are presented as mean ± SD and include results from both the dapiprazole- and tropicamide-treated volunteers. All increases were statistically significant.

carpine administration decreased pupil size by less than 0.1 mm in the remaining volunteers.

Pupils were dilated and nonreactive after tropicamide, and the light reflex was completely blocked by the treatment. Induction of anesthesia decreased size of the unblocked pupil approximately 4.5 mm and decreased size of the blocked pupil 0.9 ± 0.1 mm (table 4). However, the blocked pupil still dilated slightly after each stimulus (fig. 2, table 4). The size of the tropicamide-blocked pupil was larger in all volunteers at the end of the 5-s tetanic stimulus than at the beginning of the stimulus.

The single volunteer given two anesthetics exhibited comparable pupillary responses during each anesthetic. With tropicamide only, pupillary dilation in response to electrical stimulation with 4% desflurane, during the desflurane step-up, and in response to electrical stimulation with 8% desflurane were 0.3, 0.6, and 0.3 mm, respectively. When the study was repeated

Table 3. Pupil Diameters during Desflurane Anesthesia in Dapiprazole-treated Volunteers

<table>
<thead>
<tr>
<th></th>
<th>Unblocked (mm)</th>
<th>Blocked (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before dapiprazole</td>
<td>6.5 ± 1.0</td>
<td>6.6 ± 1.0</td>
</tr>
<tr>
<td>After dapiprazole</td>
<td>6.2 ± 1.3</td>
<td>3.7 ± 1.2*†</td>
</tr>
<tr>
<td>During anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% desflurane</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Poststimulation maximum</td>
<td>4.7 ± 1.9†</td>
<td>4.8 ± 2.4†</td>
</tr>
<tr>
<td>4% desflurane</td>
<td>1.7 ± 0.4</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Post-stepup maximum</td>
<td>6.6 ± 1.4†</td>
<td>6.4 ± 1.6†</td>
</tr>
<tr>
<td>8% desflurane</td>
<td>2.1 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Poststimulation maximum</td>
<td>5.7 ± 2.5†</td>
<td>5.4 ± 2.3†</td>
</tr>
<tr>
<td>After anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before phenylephrine</td>
<td>5.9 ± 1.3</td>
<td>4.0 ± 1.2*</td>
</tr>
<tr>
<td>After phenylephrine</td>
<td>7.9 ± 1.4†</td>
<td>3.7 ± 1.0*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. The column labeled "Blocked" contains data from the eye to which dapiprazole was administered; however, the eye was not yet blocked in the first row, labeled "Before Dapiprazole." * Statistically significant differences between the blocked and unblocked pupils (unpaired t tests; P < 0.05).
† Significant differences before and after eye drops, and before and after sympathetic stimulation (paired t tests, P < 0.05).
Table 4. Pupil Diameters during Desflurane Anesthesia in Tropicamide-treated Volunteers

<table>
<thead>
<tr>
<th></th>
<th>Unblocked (mm)</th>
<th>Blocked (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before tropicamide</td>
<td>6.5 ± 0.6</td>
<td>6.6 ± 0.4</td>
</tr>
<tr>
<td>After tropicamide</td>
<td>6.4 ± 0.7</td>
<td>8.8 ± 0.6*†</td>
</tr>
<tr>
<td><strong>During anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% desflurane</td>
<td>1.8 ± 0.4</td>
<td>7.7 ± 0.6*†</td>
</tr>
<tr>
<td>Poststimulation maximum</td>
<td>6.6 ± 0.4†</td>
<td>8.1 ± 0.7*†</td>
</tr>
<tr>
<td>4% desflurane</td>
<td>1.6 ± 0.4</td>
<td>7.7 ± 0.7*†</td>
</tr>
<tr>
<td>Post-stepup maximum</td>
<td>7.2 ± 1.2†</td>
<td>8.3 ± 0.9†</td>
</tr>
<tr>
<td>8% desflurane</td>
<td>1.9 ± 0.3</td>
<td>8.0 ± 0.8*†</td>
</tr>
<tr>
<td>Poststimulation maximum</td>
<td>6.9 ± 1.7†</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td><strong>After anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before pilocarpine</td>
<td>—</td>
<td>8.6 ± 0.7</td>
</tr>
<tr>
<td>After pilocarpine</td>
<td>—</td>
<td>8.6 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD. The column labeled “Blocked” contains data from the eye to which tropicamide was administered; however, the eye was not yet blocked in the first row, labeled “Before Tropicamide.”

* Statistically significant differences between the blocked and unblocked pupils (unpaired t tests, P < 0.05).
† Significant differences before and after eye drops, and before and after sympathetic stimulation (paired t tests, P < 0.05).

using both dapiprazole and tropicamide eye drops, the three sympathetic nervous system stimuli produced dilation of 0.4, 0.5, and 0.4 mm, respectively.

Discussion

Pupil size is determined by smooth muscles in the iris that are innervated by the two divisions of the autonomic nervous system. Briefly, cholinergic (muscarinic) innervation of the iris originates exclusively in the midbrain (pupilloconstrictor nucleus) whereas sympathetic innervation, mediated by alpha-1 adrenergic receptors, arises in the first few thoracic segments of the spinal cord.

Dapiprazole markedly decreased pupil size before induction of anesthesia. However, blocked and unblocked pupil sizes were equal during desflurane anesthesia. Dilation in response to noxious electrical stimulation and desflurane step-up were virtually identical with and without dapiprazole drops. These data suggest that sympathetic contribution to pupil size is negligible during the anesthetized state. This result is in distinct contrast to the unanesthetized state in which stimulus-induced dilation (the ciliospinal reflex) is primarily sympathetically mediated. It is unlikely that our conclusion is confounded by inadequate sympathetic block because even topical administration of concentrated phenylephrine proved incapable of producing dilation when the study was complete.

Activation of unblocked beta or alpha-2 adrenergic receptors does not account for the dilation that we observed. The beta-adrenergic antagonist esmolol does not diminish the dilatory response. Timolol, a non-specific beta antagonist, also does not block epinephrine-induced pupillary dilation. Topical clonidine, an alpha-2 agonist, does not dilate the human pupil. Some topical alpha-2 agonists dilate the pupil slightly, but this effect is thought to be mediated by the alpha-1 adrenergic receptor. In rabbits, for example, mydriasis induced by topical clonidine is blocked by alpha-1 adrenergic antagonists. Furthermore, the alpha-2

![Graph showing pupil size before and after desflurane administration](image-url)
antagonist yohimbine does not block the mydriatic response to norepinephrine in rabbits, indicating that the mydriasis is produced by stimulation of the alpha-1 adrenergic receptor.19

It might be argued that we failed to detect sympathetic dilation of the pupil because our stimuli insufficiently activated the sympathetic nervous system. However, the tetanic stimulus we used is a known potent noxious stimulus,20 and the protocol we used for the desflurane step-up is associated with substantial increases in muscle sympathetic nerve activity, serum catecholamine concentrations, and heart rate and blood pressure.10,21,22

It is surprising that the sympathetic component of reflex dilation is absent during desflurane anesthesia, because sympathetic reflexes persist with this agent. The cardioaccelerator fibers remain functional during desflurane anesthesia,22,23 and these fibers originate from the same thoracic segments as those that, in persons who are awake, activate the radial muscle of the iris. The pupillary sympathetic reflexes, however, are unique in that the central pathways traverse rostral areas (thalamus, possibly cortex) of the brain,23 whereas other sympathetic reflexes, such as the somatosympathetic reflex, are elicited by pathways traversing the lower brain stem24 and can even be observed in brain-dead patients.25 This paradox may therefore be explained by Lowenfeld's theory that the rostral brain centers that maintain consciousness are required for the presence of sympathetic pupillary reflexes.26 That anisocoria in the dapiprazole-treated volunteers did not return until they were awake and oriented supports this theory.

Studies in animals show that inhibition of the pupilloconstrictor nucleus accounts for pupillary dilation during anesthesia.6,5 Thus we expected tropicamide to block pupillary dilation in response to noxious stimulation during anesthesia. Nonetheless, noxious stimulation and desflurane step-up dilated the tropicamide-blocked pupil. Magnitude of the dilation in the blocked pupil was small because it was already near its anatomic maximum size.

We therefore failed to define precisely why the pupil dilates in response to noxious stimulation in anesthetized humans. If the tropicamide-treated pupil did not dilate after the stimuli, we could conclude that the dilation occurred, just as in animals, by inhibition of the pupilloconstrictor nucleus. However, the pupils did dilate and because pupil sizes were unequal before the stimulus, it is impossible for us to assess relative contributions of parasympathetic nucleus inhibition and residual dilation that was not blocked by tropicamide.

Lack of sympathetically mediated dilation was confirmed by continued dilation of the tropicamide-treated pupil in the single volunteer also treated with dapiprazole. Our data thus do not support sympathetically mediated dilation. Residual dilation in the tropicamide-blocked pupil might be due to inadequate cholinergic block, although residual cholinergic activity seems unlikely because the light reflex—which also requires muscarinic transmission—was completely inhibited. Furthermore, pilocarpine did not induce constriction of the pupil at the end of the study (in five of the six volunteers given tropicamide).

An alternative explanation for dilation of the tropicamide-blocked pupil during anesthesia is a previously undescribed nonadrenergic, noncholinergic mechanism. If there is such an action involved in pupillary dilation during anesthesia, our data do not allow us to speculate as to what this transmitter might be or about its neural pathway into the eye.

A shortcoming of this study is that we did not evaluate the potential contribution of central adrenergic transmission to pupillary dilation during desflurane anesthesia. Alpha-2 adrenergic receptors are widely dispersed within the central nervous system27 and could be involved in afferent or efferent components of reflex pupillary dilation.11 Dilation of the cat pupil by noxious stimuli, for example, is thought to be mediated by alpha-2 adrenergic inhibition within the pupilloconstrictor nucleus.28 Consistent with this theory, alpha-2 adrenergic agonists, such as clonidine, dilate the cat pupil.29 In contrast, alpha-2 agonists produce miosis in humans,29 suggesting that species differences in pupillary control may be substantial and that animal data should be extrapolated to humans with considerable caution.

We evaluated the mechanism of reflex pupillary dilation during desflurane anesthesia by using topical agents to block the action of norepinephrine and acetylcholine at the iris musculature. Dapiprazole drops produced a Horner's miosis, but pupils were equally small after anesthesia was induced. Pupillary dilation after noxious stimulation and desflurane step-up was identical in the unblocked and dapiprazole-blocked pupils. After tropicamide administration, the pupil was dilated and the light reflex was completely inhibited. Noxious stimulation nonetheless produced small but significant additional dilation of the pupil. Our results suggest that during desflurane anesthesia, pupillary di-
lation in response to noxious stimulation or desflurane step-up is not mediated by the sympathetic nervous system (as it is in unanesthetized persons). Instead, it appears to involve either inhibition of the pupilloconstrictor nucleus or a previously undescribed noncholinergic, nonadrenergic synapse at neuromuscular junctions within the iris.

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References


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