Pupillary Effects of High-dose Opioid Quantified with Infrared Pupillometry

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ABSTRACT

Background: The pupillary light reflex is a critical component of the neurologic examination, yet whether it is present, depressed, or absent is unknown in patients with significant opioid toxicity. Although opioids produce miosis by activating the pupillary sphincter muscle, these agents may induce significant hypercarbia and hypoxia, causing pupillary constriction to be overcome *via* sympathetic activation. The presence of either "pinpoint pupils" or sympathetically mediated pupillary dilation might prevent light reflex assessment. This study was designed to determine whether the light reflex remains quantifiable during opioid-induced hypercarbia and hypoxia.

Methods: Ten volunteers were administered remifentanil with a gradually increasing infusion rate and intermittent boluses, until the increasing respiratory depression produced an oxyhemoglobin saturation of 85% or less with associated hypercarbia. Subjects' heart rate, blood pressure, respiration, and transcutaneous carbon dioxide level were continuously recorded. Arterial blood gases and pupillary measures were taken before opioid administration, at maximal desaturation, and 15 min after recovery.

Results: The opioid-induced oxygen desaturation (≤85%) was associated with significant hypercarbia and evidence of sympathetic activation. During maximal hypoxia and hypercarbia, the pupil displayed parasympathetic dominance (2.5 ± 0.2 mm diameter) with a robust quantifiable light reflex. The reflex amplitude was linearly related to pupil diameter.

Conclusions: Opioid administration with significant accompanying hypercarbia and hypoxia results in pupil diameters of 2 to 3 mm and a reduced but quantifiable pupillary light reflex. The authors conclude that the pupillary examination and evaluation of the light reflex remain useful for neurologic assessment during opioid toxicity. (ANESTHESIOLOGY 2014; 121:1037-44)

THE integrity of the pupillary light reflex is of interest to clinicians caring for patients with actual or potential brain stem injury.[1–13] This includes patients with postcardiac arrest, stroke, traumatic brain injury, ruptured cerebral aneurysm, and postcraniotomy. Unfortunately, whether it is present, depressed, or absent is unknown in patients with significant opioid levels.

Many postoperative neurosurgical patients are given opioids for analgesia and for the prevention of ventilator dyssynchrony while being mechanically ventilated. A recent study reported that patients with postcardiac arrest often receive large doses of opioids after return of spontaneous circulation.[14] Furthermore, patients with acute heroin or other opioid overdose can sustain head injuries and cardiac arrest. In these diverse clinical scenarios, any effect that opioids have on the pupillary light reflex is currently viewed as a confounding factor in the clinical assessment of midbrain function. In these cases, the clinical team is often uncertain of the validity of depressed or absent pupillary reflexes given the known opioid use. Typically depressed or absent reflexes would direct the need for timely neurosurgical consult and surgical intervention in the face of known trauma.

What We Already Know about This Topic

- The pupillary light reflex is important in the evaluation of injuries to the central nervous system
- Although opioids produce miosis, they can also cause hypoxia and hypercarbia with associated sympathetic activation, and their effects on the pupillary light reflex are unknown

What This Article Tells Us That Is New

- In 10 volunteers administered remifentanil to the point of clinically significant hypercarbia and hypoxemia, there was evidence of a robust quantifiable light reflex despite small pupil size
- These results suggest that the pupillary light reflex remains a valid neurologic assessment in the presence of opioids and hypoventilation

In an effort to improve neurologic assessment of patients with both acute opioid use and the potential for mechanical or ischemic brain injury, we sought to clarify the pupillary changes brought about by opioid-induced respiratory depression, hypercarbia, and hypoxia. Although pupillary constriction is known to occur after opioid administration,[4] this clinical sign may be altered with significant opioid-induced

respiratory depression and the resultant onset of hypercarbia and hypoxia. Both hypoxia and hypercarbia activate the sympathetic nervous system, which may dilate the pupil and inhibit the light reflex.[13] Figure 1 depicts the competing effects of light excitation, physiologic stress, sympathetic input, and opioids on pupillary size.

Our hypothesis was that progressive opioid administration resulting in significant respiratory depression with associated hypoxia to an oxyhemoglobin saturation of 85%, hypercarbia with acute respiratory acidosis, and sympathetic activation would dilate the pupil above midposition (4 mm) and inhibit the light reflex.

We chose to use the opioid remifentanil in our model for opioid-induced respiratory depression because of its short duration of action, which allowed us to perform this volunteer study with greater safety and minimal recovery time. In addition, the autonomic effects of remifentanil given in low doses were adequately evaluated and detailed in previous studies.[2]

Materials and Methods

After institutional review board (Committee on Human Research, University of California of San Francisco, San Francisco, California) approval and informed written consent, 13 healthy volunteers were enrolled in the study. Fasting subjects were admitted to a human volunteer study room where ambient noise and lighting could be controlled and uniform, and complete monitoring, ventilation, and resuscitation equipment and supplies were readily available similar to an intensive care unit or operating room setting. A 20-gauge intravenous line and a 22-gauge radial arterial catheter were placed after an intracutaneous wheal of lidocaine. After resting for 30 min, nasal oxygen (3 l/min) was administered and baseline hemodynamic parameters and pupillary measurements were taken from the right eye using a pupillometer with an opaque rubber cup covering the eye as described below,[15] while the left eye was occluded from ambient light with a folded cloth.

Initial arterial blood gases were determined and an intravenous remifentanil infusion was begun at a rate of 0.05 μg kg^{-1} min^{-1}. After 15 min, subjects received a 0.1 μg/kg intravenous bolus of remifentanil, and the continuous infusion of remifentanil was increased by 0.025 μg kg^{-1} min^{-1}. At each 5-min interval thereafter, the continuous infusion of remifentanil was increased by 0.025 μg kg^{-1} min^{-1} and an additional escalating bolus was administered. The remifentanil bolus was increased by 0.05 μg/kg with each subsequent administration. Two board certified anesthesiologists were available at all times during each volunteer study period, as well as other personnel required for data retrieval.

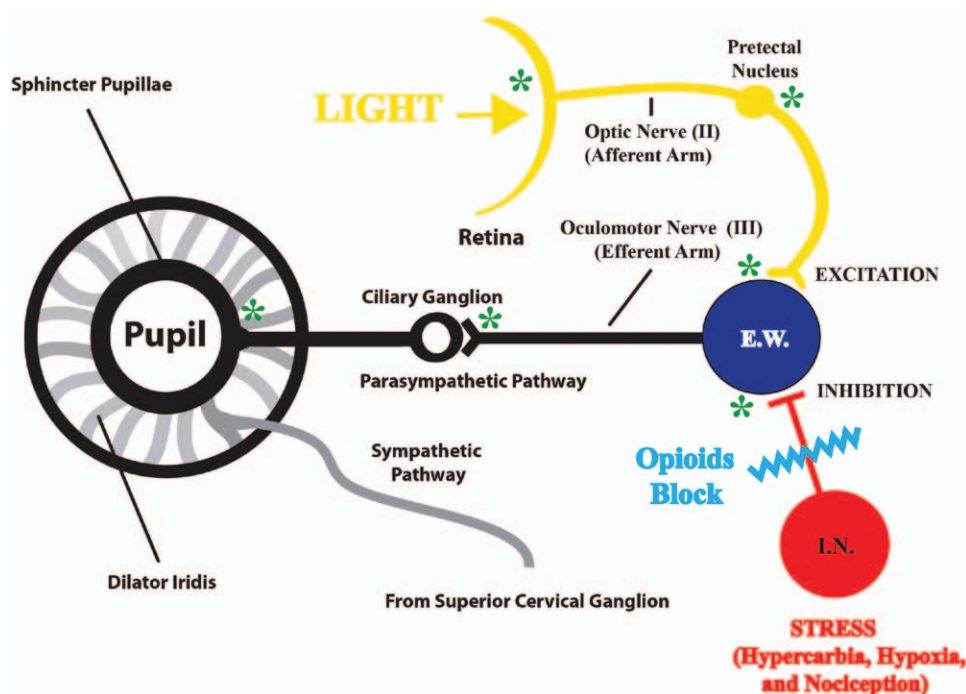We measured the following parameters: continuous blood pressure and heart rate from the arterial catheter,

Fig. 1. Pathways and nerve centers that control pupil size and the pupillary light reflex in humans. *Colored* structures are the central nerve centers and pathways that modify the pupillary light reflex. Edinger Westphal (EW) Nucleus neurons are pacemaker cells that are modified by excitatory and inhibitory inputs. Opioids block the inhibition of the EW nucleus. *Green asterisks* (*) show locations where hypercarbia, hypoxia, and opioids might potentially interfere with the light reflex, although our analysis demonstrates that the effect of opioids on the light reflex is primarily a function of pupil size. * = locations where hypercarbia, hypoxia, and opioids might potentially interfere with the light reflex. IN = inhibitory neuron.

additional measure of heart rate and rhythm from a 5-lead electrocardiogram (leads II and V5), fingertip oxyhemoglobin saturation (Masimo Corporation, Irvine, CA; set on 2-s rapid response), respiratory rate from both an exhaled carbon dioxide tracing (Datex-Ohmeda, Inc., Madison, WI) and from a respiration transducer belt (Biopac Systems, Inc., Goleta, CA), and transcutaneous earlobe carbon dioxide (TcCO$_2$, TOSCA; Linde Medical System, Linde Basel, Switzerland). All continuous monitoring data were recorded using LabVIEW (National Instruments Corporation, Austin, TX). Arterial blood gases were sampled from the radial arterial line before opioid administration, at the time of oxygen desaturation, and 15-min after recovery. Samples were analyzed using an ABL800 FLEX (Radiometer Medical A/S, Copenhagen, Denmark). Pupil diameter, pupillary light reflex, and pupil area were measured with an infrared pupillometer (Neuroptics, Inc., Irvine, CA) before opioid administration, at the time of oxygen desaturation, and at 1, 2, 4, 6, 10, and 15-min after recovery.

The pupillary measures were obtained by using a portable infrared pupillometer. A flash of visible light with an 800-ms duration was delivered at the start of each 3.2-s scan. The pupillometer calculates the reflex amplitude as the absolute difference between the starting diameter and the minimum diameter obtained after the light flash.[10,15]

The neurological pupillary index (NPi) is a proprietary tool that displays a unitless numerical value from 0 to 5 indicating the quality of the light reflex.[3] It compares the measured pupillary light reflex to a large normal control population and is calculated from a proprietary algorithm using parameters that include latency, constriction velocity, and reflex amplitude. Zero is indexed to represent no light reflex, whereas any measure greater than 3 is considered within the normal range. Pupillary measurements with large amplitude artifacts brought about by movements of the head or hand are detected by the instrument and labeled as faulty readings. NPi has been used clinically to assess midbrain function based on pupillary parameters,[3] but has not been clinically validated at small pupil diameters after opioid therapy.

During the remifentanil infusion, the volunteers were not stimulated by voice, touch, or prompted to breathe. They were asked to remain quiet and only speak if they had a question or needed assistance. Using the described remifentanil protocol, the oxyhemoglobin saturation fell gradually over time, typically taking 30 min to reach 85%. Nasal cannula oxygen (3 l/min) was administered throughout the experiment to provide a more gradual rate of desaturation and potentially better mimic the hospitalized patient. As soon as this endpoint was reached, pupillary measurements were taken, arterial blood gases were obtained, the subjects were aroused by a verbal stimulus if they did not arouse spontaneously, and the remifentanil infusion was discontinued. This time point was labeled time "zero" and pupillary measurements were repeated at 1, 2, 4, 6, 10, and 15 min after

reaching this endpoint. If the subject's TcCO$_2$ reached 80 mmHg before reaching an oxyhemoglobin saturation of 85%, a confirmatory arterial blood gas was obtained, and this time point was considered the endpoint of maximal desaturation. At 15-min after the discontinuing the infusion, a final arterial blood gas was obtained.

Statistical Analysis

We used repeated-measures ANOVA with Tukey–Kramer *post hoc* tests to compare autonomic measures and laboratory values: (1) before initiating the remifentanil infusion (baseline); (2) at 85% saturation (time zero); and (3) 15-min after discontinuing the infusion. Paired *t* tests were used to compare differences between the maximal change in pupil diameter to maximal change in the pupillary light reflex.

Linear regression was used to determine the relationship between pupil diameter and amplitude of the pupillary light reflex after remifentanil administration. We also examined the correlation between the initial pupil diameter (baseline) and the change in pupillary diameter between baseline and the size of the pupil at desaturation.

We used TcCO$_2$ as a surrogate measure of central opioid effect and compared it to pupil diameter and light reflex as other measures of central opioid effect. Because it is known that increased ambient light decreases pupil size linearly until pupil size reaches approximately 3 mm in diameter,[16] we performed a nonlinear fit of change in pupil size *versus* change in TcCO$_2$. Using the change in carbon dioxide allowed us to normalize for the different study subjects and perform nonlinear regression. Goodness-of-fit to determine the most appropriate nonlinear equation was assessed by plotting residuals and comparing root-mean-square error of other potential fits for both individual subjects and the entire data set.

All values are means ± SDs unless otherwise noted in the article. *P* value less than 0.05 was considered statistically significant and based on a two-tailed hypothesis testing design. Data analysis was performed using JMP 10.0 (SAS Institute, Cary, NC).

Results

Of the 13 subjects enrolled in the study, two refused to continue with the study because of an unpleasant side effect of nausea and vomiting from the remifentanil. The pupillary data from one subject were contaminated with blink artifacts, so the data from this subject were not used. We therefore present data from the 10 subjects who participated to the end of the study.

Subjects included four women and six men with a mean age of 29 ± 3 yr, mean weight of 71 ± 9 kg, and mean hemoglobin of 12.9 ± 1.1 g/dl. All measured parameters were significantly altered by oxygen desaturation with remifentanil (table 1). Graphic illustration of the changes that occurred in measured variables is shown in figure 2.

All subjects reached the endpoint of 85% saturation except one who reached an arterial carbon dioxide level (Pa_{CO_2}) of 80 mmHg at only 90% saturation and this point was taken as the point of maximal desaturation. Of the measured vital parameters, respiratory rate was most profoundly depressed as a percentage of the control value (decreased 95 ± 2%) at the point of maximal desaturation (respirations 0.7 breaths/min) and then noted significant recovery with an increase to 6 breaths/min only 1-min after the remifentanil infusion was discontinued. In addition to discontinuing the remifentanil infusion, a verbal stimulus reminded the volunteer to breathe (time zero on fig. 2). No stimulus other than verbal was needed to initiate a subject breath after the maximal (85%) saturation level was reached, and no assists with ventilation or other resuscitation measures were needed in any of the subjects. After the verbal stimulus, all oxygen saturation values returned to greater than 95% hemoglobin saturation before the 1-min measurement.

There was evidence of sympathetic activation of the cardiovascular system with significant increases in heart rate during the progressive desaturation, but parasympathetic effects on the pupil were dominant. All subjects were noted to have pupillary diameters less than 3 mm at the point of maximal desaturation. Although pupil diameter and area are related by a simple mathematical relationship, we provided both measures in the results because although diameter is a more familiar clinical measure, the flux of light is more directly related to the pupil area. The fractional decrease in the light reflex (decrease of 84 ± 4%) noted at desaturation was similar to the decrease in pupil area (decrease of 81 ± 5%) with both significantly diminished compared with both predrug baseline and 15-min postinfusion values ($P < 0.05$; fig. 2). A comparison of the pupil light reflex with pupil diameter for all measurements noted a significant linear relationship ($P < 0.0001$). The quality of the light reflex as assessed by NPi was only minimally altered at all recovery time intervals. As the pupil enlarged during the recovery phase, the light reflex amplitude increased, but NPi at desaturation was only decreased by 6.7 ± 2.5% compared with the predrug baseline measurement. The light reflexes

at each time interval for a single representative individual are shown in figure 3.

Blood gas measurements of Pa_{CO_2} were within 10% of the measured $TcCO_2$ measurements taken at the same time. We therefore used the continuous $TcCO_2$ as a measure of remifentanil-induced respiratory depression (as values were continuously recorded and available for all time points of pupillary measure) and evaluated the central respiratory effect of increasing opioid (as measured by $TcCO_2$) on pupil diameter (fig. 4). After examining several potential fits, including linear, second-order polynomial and bilinear equations, a basic reciprocal form with a parameter for minimal pupil size was the best fit for the data. The relationship between $TcCO_2$ and pupil size for all 10 subjects is shown in figure 4A using a nonlinear reciprocal fit. An increase in $TcCO_2$ was associated with decreasing pupil size. Regardless of the increase in carbon dioxide, only minimal pupillary change was noted below 3 mm diameter. The mean minimal pupil diameter at maximal desaturation (85%) was 2.5 mm with a narrow range of 2.2 to 2.8 mm. The nonlinear fit of the data resulted in a minimum pupil diameter corresponding to 2.3 mm (fig. 4A equation).

A nonlinear reciprocal fit was also used to evaluate the relationship of decreasing pupillary light reflex with increasing central respiratory depression ($TcCO_2$), as shown in figure 4B. In all subjects, the light reflex remained intact and quantifiable using infrared pupillometry. A mean light reflex value of 0.4 mm at the nadir (desaturation to 85%) corresponded to a mean minimum pupil diameter of 2.5 mm at this same time point. The reciprocal nonlinear fit of the data resulted in a similar value of 0.3 mm for the parameter corresponding to the minimum pupil reflex (fig. 4B).

Discussion

This is the first study to measure pupillary responses with objective pupillometry during high-dose opioid administration associated with significant hypercarbia and hypoxia. Our primary findings demonstrate that even with opioid doses resulting in severe respiratory depression, the pupil should

Table 1. Changes in Autonomic Measures after Remifentanil Infusion (n = 10)

Physiologic Parameter	Predrug Baseline	Oxygen Desaturation	15-min Postdesaturation	P Value
Heart rate (beats/min)	61 ± 10‡	97 ± 24	83 ± 25	0.0001
Systolic BP (mmHg)	130 ± 17	137 ± 24	141 ± 16	0.13
Pupil diameter (mm)*	5.6 ± 0.9	2.5 ± 0.2	4.1 ± 1.2	<0.0001
Pupil light reflex (mm)*	2.5 ± 0.4	0.4 ± 0.1	1.4 ± 0.6	<0.0001
NPi	4.6 ± 0.2†	4.3 ± 0.2†	4.4 ± 0.4	0.0049
Pupil area (mm^2)*	24.9 ± 8.2	4.9 ± 0.9	13.9 ± 7.3	<0.0001
$TcCO_2$ (mmHg)	40.4 ± 3.4	73.0 ± 9.2‡	43.9 ± 6.2	<0.0001
Respiratory rate (breaths/min)	15.2 ± 3.2	0.7 ± 0.3‡	13.1 ± 3.8	<0.0001

Data are mean ± SD. Repeated-measures ANOVA with Tukey–Kramer honestly significant difference for multiple comparisons.
* All time points significantly different. † Significantly different from each other. ‡ Significantly different from other time points.
BP = blood pressure; NPi = neurologic pupil index; $TcCO_2$ = transcutaneous carbon dioxide.
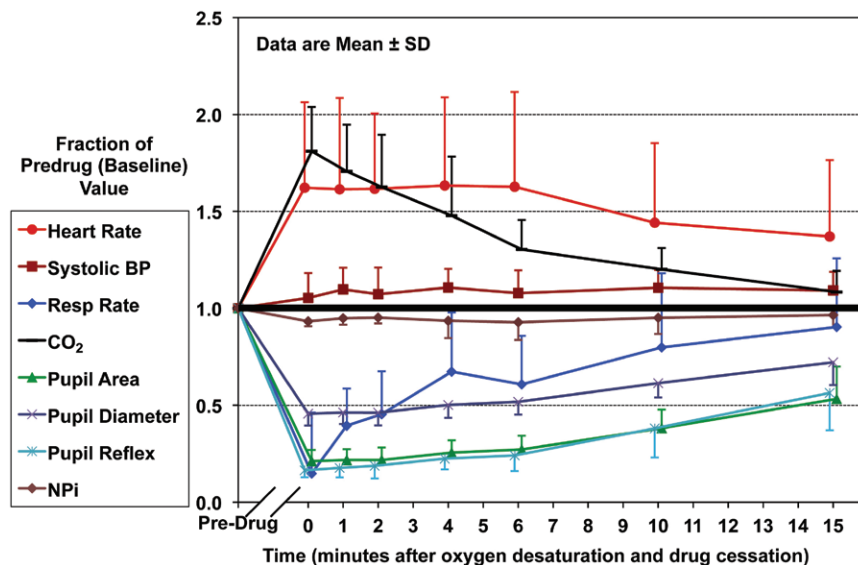
Fig. 2. Fractional changes in the measured physiologic parameters at the time of desaturation (time zero) and during the 15-min recovery phase. Values are displayed as a fraction of predrug baseline values. Values are displayed as means ± SD. Statistical comparisons were only performed between baseline, nadir, and after 15-min of recovery, and the statistical results are summarized in table 1. Note the close correlation between changes in the pupil reflex and pupil area. BP = blood pressure; CO_2 = carbon dioxide; NPi = neurologic pupil index.
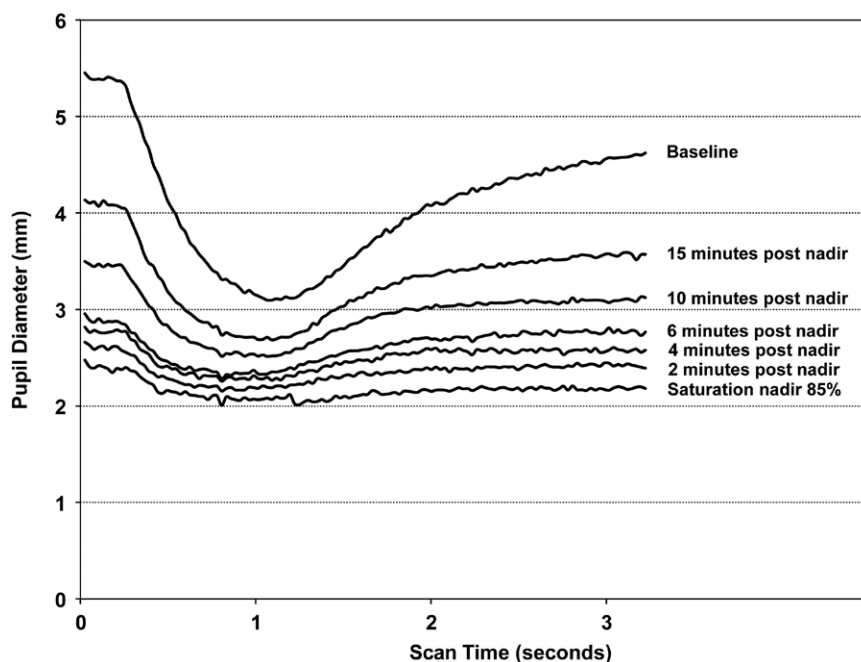

Fig. 3. Example of quantitative pupillary light reflexes obtained by a pupillometer displayed over a 3.2-s scan in a single study subject. The opposite eye was covered with an opaque cloth. A flash visible light was delivered for 800 ms at the start of each scan. Each line follows the pupil diameter as it changes during the scan. The lines displayed note baseline, desaturation to 85% oxyhemoglobin at time zero, and multiple time points between time zero and 15-min postdesaturation.

not be characterized as a dimensionless point (*i.e.*, pinpoint pupil) and the light reflex remains present and quantifiable even in the presence of significant narcotic-induced hypoxia and hypercarbia (fig. 3).

These data show that sympathetic activation by hypercarbia and hypoxia overcomes the previously described parasympathetic hemodynamic effects of remifentanil that often include bradycardia and hypotension.[17–19] Similar levels of acute hypoxia in humans have previously been demonstrated to significantly increase sympathetic nerve activity.[20] Surprisingly, the pupil data in our study continued to show predominately parasympathetic effects (miosis) throughout,
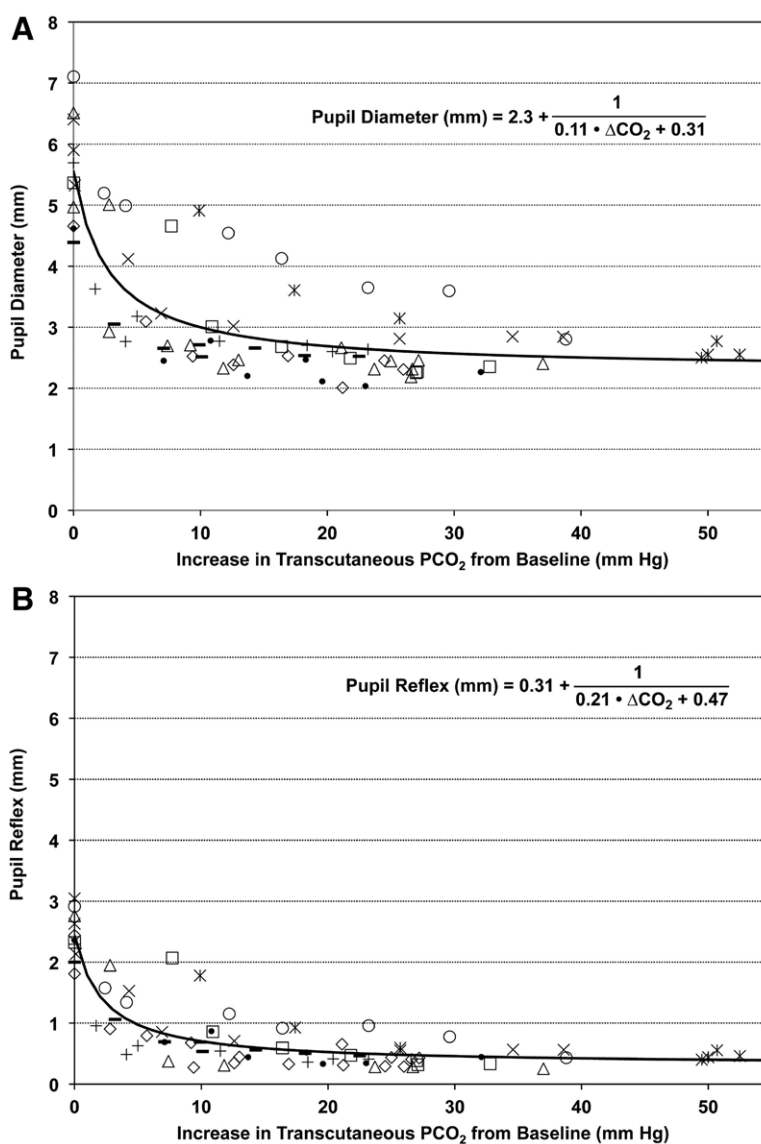
Fig. 4. Pupil diameters (*A*) and pupillary reflex (*B*) in relation to transcutaneous carbon dioxide measurements. Individual study subjects are shown with different symbols. Nonlinear reciprocal fits are displayed in each figure. P_{CO_2} = partial pressure of carbon dioxide.

thus demonstrating the autonomic nervous system has disparate responses to an increasing dose of opioid (remifentanil).

The data revealed that the pupil did not continue to constrict past a mean of 2.5 mm even with the large doses of remifentanil that we administered. It is known that the pupil has the ability to constrict further and will constrict to diameters below 1 mm (pinpoint) with topical application of miotic agents and with organophosphate poisoning.[21]

One explanation of the failure to achieve further pupillary constriction (*i.e.*, a pinpoint pupil) was because sympathetic tone to the dilator muscle was augmented sufficiently to produce mild dilation but not strong enough to obtund the light reflex or to produce pronounced mydriasis (fig. 1).

Another explanation for our failure to observe pinpoint pupils might be that our measurements were taken without ambient light. However, when we added a light stimulus,

pupil size decreased only 0.3 mm, constricting the pupil to mean diameters that remained greater than 2 mm. It should be noted however that no authors have documented "pinpoint pupils" or pupils less than 2.0 mm diameter after opioid therapy while using infrared pupillometry to objectively document pupil size.[22–26]

Our results reveal an opioid-constrictive effect on pupil size similar to that described for light. With increasing ambient light, pupil size is directly related to light intensity until the pupil reaches a diameter of approximately 2.5 to 3.0 mm at which point the mechanical properties of the iris begin to restrict further constriction (fig. 4A).[16] It is noteworthy that in all of our subjects, oxygen desaturation did not occur until this plateau was reached.

Because of this nonlinearity in the pupil response to opioids, it is apparent that pupil diameter can only be used to

evaluate the pharmacodynamic effects of μ-opioids if the pupil diameters remain within the dynamic the range of the iris, for example, from pupillary diameters of approximately 3 to 7 mm (fig. 4A).[27] Pharmacodynamic studies of opioid effect using the pupil measurement should therefore be conducted with subjects that have diameters approximately greater than 5 mm in the dark so that ample range is available for constriction before the pupil reaches this nonlinear plateau. Older subjects are therefore not ideal candidates for pupillary diameter studies of this nature because they start with relatively small pupils. Due to a smaller dynamic range, the incorrect conclusion might therefore arise that older subjects are resistant to the central effects of opioids,[22] when in fact they are usually thought to be more sensitive.[28,29]

The effect of opioids on the pupillary light reflex in animals and humans has been studied previously with inconclusive results. In cats and dogs, opioids depress the light reflex,[30,31] whereas in rabbits, the light reflex is enhanced.[4] In anesthetized humans, the light reflex is not depressed after alfentanil opioid administration with controlled ventilation,[25] but the effects of the combination of opioid and significant sympathetic activation induced by the respiratory depression were previously uncertain.

Our study confirms that although opioid-induced respiratory depression decreases pupillary diameter, the light reflex remains intact and can still be ascertained. The decrease in pupil diameter/area limits the mechanical range of the iris and diminishes the intensity of the retinal light flux. The relationships displayed in figure 2 demonstrate that the decreased light reflex amplitude is closely related to the decreased size of the pupil at the time of the light stimulus (brought about by remifentanil administration) and similar to the same relationship in humans not administered opioids.[32] The quality of the light reflex as measured by the NPi was essentially unchanged by the drug administration, even during significant hypercarbia and hypoxia. Because NPi was determined from a large population of unmedicated healthy volunteers, this finding argues against a significant effect of hypercarbia and hypoxia on the light reflex during opioid toxicity.

Detecting the presence of a normal light reflex in an obtunded patient is a clinically significant finding. An active light reflex immediately rules out brain death and argues against structural lesions of the midbrain that commonly obliterate the light reflex.[18] It should be noted that visual appreciation of light reflexes in miotic pupils is difficult and infrared pupillometry is advised when attempting to assess the light reflex at small diameters. As a measure of brain stem function the light reflex is unique because, unlike other clinical tests such as cough, gag reflex, breathing, grimace, and calorics, the light reflex can function with complete paralysis of striated muscles by neuromuscular-blocking agents.[33] The pupillary light reflex is also not depressed by sedation with dexmedetomidine[34] or benzodiazepines.[35] However, overdose of some anesthetic agents such as propofol severely obtunds the reflex.[36,37]

The clinical relevance of this study is that a pinpoint, sluggish pupil is not an essential component of the opioid toxidrome. There is no evidence that the pupil will continue to constrict as the subject progresses further into asphyxia. Thus a small, reactive but not pinpoint pupil near 2.5 to 3 mm diameter may be present with significant opioid toxicity.

Limitations to this study are that remifentanil was given without noxious stimulation such as might occur during the perioperative period or with concurrent trauma. Nociception would be expected to overcome some of the respiratory depressant effects of remifentanil and it also might exaggerate the sympathetic effects on the cardiovascular system. This study examined only young healthy subjects and other drugs were not combined with the opioid. Remifentanil is structurally unique compared with other opioids and contains ester linkages that allow rapid breakdown in the plasma. However, it exhibits typical μ-agonist pharmacologic effects and these study results should be relevant to all μ-selective opioids except for meperidine, a drug that has anticholinergic effects on the pupil.[38] Our methodology documented the single effect of one drug alone as a first step toward understanding the effect of opioids on the pupil.

Conclusion

In summary, during significant opioid-induced respiratory depression, an intact light reflex was observed in small but not pinpoint pupils. This information is relevant to health professionals involved in the perioperative care and resuscitation of patients with potential brain stem injury, because assessment of midbrain function depends significantly on evaluation of pupil size and reactivity, and many of these patients have also received opioids.

Acknowledgments

Competing Interests

The authors declare no competing interests.

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