Title:

Pupillary Unrest as an Indicator of Central Opioid Effect in Subjects 40-60 Years of Age

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ABSTRACT

Opioid-induced respiratory depression (OIRD) confers significant safety risk, but its onset can be challenging to recognize. Hypoxia and related sequelae from OIRD may present abruptly, giving the clinician insufficient time to intervene and rescue before harm reaches the patient. Previous data showed that among healthy 20-39-year-old volunteers, incremental decline and eventual obliteration of pupillary unrest in ambient light (PUAL) occurred in a consistent manner during escalating opioid concentration from remifentanil infusion. Low and often obliterated PUAL were consistent markers of high-risk remifentanil exposure and coincident episodes of hypoxic respiratory depression, even while subjects remained alert. In this young adult age group, specific PUAL values discriminated between zero or low versus high-risk intensive opioid exposure with outstanding discrimination (AUROC = 0.9671 [0.9384 – 0.9958]).[1] We anticipate PUAL will develop into a useful tool in the future to guide clinical decision-making in patients receiving opioids on matters including choice of appropriate level of monitoring, consideration of supplemental oxygen, possible opioid de-escalation, and timely pursuit of non-opioid analgesic alternatives and support when necessary. To explore the generalizability of these findings, we plan to perform a similar study among subjects in an older age range (40-60 years). Although we anticipate that the PUAL decline and opioid intensity relationship will probably be similar across age ranges, the predictive value of specific PUAL thresholds may differ in older individuals due to age-related changes in normal pupil measurements and characteristics. Recent unpublished data from ambulatory subjects showed a modest decline in resting PUAL in subjects aged 50 and older compared to younger adult subjects. The physiologic vulnerability of older patients elevates the importance of early, reliable OIRD detection. Aging is accompanied by alteration of a variety of vital protective mechanisms, including blunting of chemoreceptor-mediated ventilatory responses to hypoxia and hypercapnia.[2,3] Among subjects with sleep disordered breathing, older age is associated with more severe, prolonged desaturation episodes during upper airway obstruction.[3]

AIMS

We will establish the relationship between PUAL, estimated remifentanil concentration, and incidence and onset of OIRD indicated by decline in SpO2 < 90% in an extended age range (40-60 years). In this older age group, we will examine the magnitude and consistency of the opioid-PUAL relationship and compare risk of OIRD at various ranges of PUAL and estimated opioid effect site concentration. The purpose of doing so is to establish PUAL's validity in discriminating risk of OIRD across a broader population, and to determine whether the PUAL OIRD prediction scale requires modification or is invalid in older subjects. The overall goal is to extend the benefit of sensitive opioid monitoring across a broader patient population.

BACKGROUND AND RATIONALE

Within the past decade, opioid-related adverse events have grown at unprecedented rates. Age-adjusted opioid overdoses have risen from 3.0 to 14.9 events per 100,000 people between 2000 -2017, surpassing motor vehicles accidents and firearms as causes of accidental death in the United States.[6] In 2020, 621 citizens suffered opioid-related deaths in the city of San Francisco by December, compared 173 deaths attributed to COVID-19 at that same time-point; compared to the eight month period prior to March 2020, weekly opioid-attributed deaths increased 50% during the subsequent 8 month period.[6-9] Although the majority of opioid overdoses occur in the community, cases among hospitalized patients continue to be reported, with iatrogenic respiratory arrest from opioid mismanagement cited as a significant source of preventable harm.[10] A recent administrative database reviewing hospital-related opioid-related cardiopulmonary arrest cases showed that approximately half of such incidents occurred in the intensive care unit, despite continuous assessment and monitoring.[11] Iatrogenic opioid-related respiratory depression (OIRD) carries severe liability; a closed claim analysis showed that among reported OIRD cases, > 75% produced death or serious brain injury, 1/3 occurred during continuous pulse oximetry monitoring, and 16% occurred within 15 minutes of an uneventful nursing check.[12] These reports confirm that OIRD is difficult to recognize and predict. One favored approach currently under investigation involves remote monitoring systems to acquire and integrate vast quantities of patient data.[13] However, we ask whether nociceptive or conversational stimulation might obscure recognizable indicators of opioid toxicity, rendering common clinical parameters inadequately sensitive. We propose that an approach involving pupillary testing may be more reliable than conventional measures in assessing opioid effect. [1,14-17]

Under static levels of ambient light, the normal human eye exhibits continuous, bilaterally synchronous pupil size fluctuation.[18,19] Within specific frequency bands, Fourier waveform analysis converts these oscillations to a measure known as pupillary unrest in ambient light (PUAL).[20] By convention, PUAL is expressed in arbitrary units (AU); additional details on the measurement appear in previous publications.[17,21-22] When an alert subject is in a dark environment,[23] or undergoes general anesthesia,[24] these oscillatory movements are abolished. Although its origins are unproven, PUAL appears to be mediated by fluctuating inhibitory activity within the parasympathetic Edinger Westphal nucleus, possibly driven indirectly by the locus coeruleus. [25,26]

Previous authors have cited variable decline in PUAL among surgical patients after a single 1 mcg/kg dose of fentanyl before surgery.[20] Others have noted correlation between decline in numeric pain scale and higher PUAL values after a single dose of opioid, suggesting that once the PUAL declines to low values, further analgesic benefit from opioid may be limited.[21] However, these studies only involved a single dose of opioid, and did not systematically increase opioid exposure to the point at which respiratory depression was likely to be reached.

In a study of 150 unmedicated ambulatory participants recruited from the waiting area of the UCSF preoperative clinic, average PUAL was modestly but significantly lower in subjects in older age categories. We present below the results of the previously mentioned study showing a significant relationship between PUAL decline in conjunction with opioid increase and incremental risk of respiratory depression in 20-39-year-old subjects. We therefore intend to verify the relationship between PUAL, opioid exposure and ventilatory depression in subjects in aged 40-60 years. To ensure realistic demographic representation of San Francisco at large, we will strive to enroll at least 40-60% female, 25% black or Latinx, and 35-40% Asian/Pacific Islander subjects.

PRELIMINARY DATA

We cite a case report in which low or absent PUAL was observed in a patient with OIRD and very high PUAL was observed in a patient undergoing opioid withdrawal.[17]

Subsequently we studied 20 healthy volunteers aged 20-39 years, to determine whether progressive decline of PUAL to zero or a lower limiting value would occur consistently as opioid exposure increased to the point of respiratory depression.[1] Participants received an intravenous infusion of remifentanil, an ultra-short acting opioid medication. As the dose and effect site concentrations incrementally rose, serial pupillary measures were taken every 2.5 minutes, including at times coinciding which clinically significant respiratory depression. We sought to determine whether PUAL declines consistently to zero or near zero in all subjects as opioid concentration builds to the point of respiratory depression. We found that in this group of participants aged 20-39, PUAL declined significantly over the course of the remifentanil infusion and rose significantly during recovery ($p < 0.0001$). Nearly all subjects reached 90% or greater PUAL suppression. PUAL showed outstanding discrimination in

distinguishing higher versus absent-moderate opioid exposure (AUROC = 0.957 [0.929 to 0.985] in all runs). For exploratory purposes this study had two infusion sequences, one conducted under normal "quiet" conditions, and the other during stimulating "interactive" conditions to estimate what if any role environmental stimulation may play in delaying or mitigating OIRD. Findings in younger subjects used for subsequent comparison to the older group will use the data from the control ("quiet") arm, or from both infusion sequences as appropriate.

In a separate study, to estimate normative ranges of PUAL in the general population across age groups, we evaluated 150 de-identified ambulatory subjects, collecting information only on age-range, (18-29, 30-49, 50-69, and ≥70 years), diabetes, and use of opioid or beta-blocker medication in the previous 24-hour period. In that cohort we found a modest but statistically significant impact of age on PUAL, where subjects ≥ 50 years of age had lower median PUAL values versus subjects under 50 years of age.

EXPERIMENTAL DESIGN AND METHODOLOGY OF PROPOSED STUDY

Design:
Volunteers aged 40-60 years will be recruited to participate. All will undergo a 35-minute remifentanil infusion regimen. After an 8-hour fasting period, subjects will arrive at the UCSF Department of Anesthesia Hypoxia Lab, which will be equipped with standard resuscitative equipment and medications (including naloxone, atropine, and epinephrine). Lighting conditions (200 lux) will be strictly controlled, and the room will remain free of distracting noise. After providing written informed consent, subjects will undergo peripheral IV placement, baseline pupillary and vital-sign measurements, and will receive prophylactic antiemetic medications (aprepitant 40 mg + ondansetron 4 mg).

Measurements:
Pupillary measurements will be obtained with a hand-held infrared pupillometer (Neuroptics PLR-3000, Laguna Hills, California), with each subject looking into a dark grey single-use rubber cone-shaped eye piece with the left eye. This eye piece will be situated to exclude ambient light, while the operator's left hand will cover the contralateral eye. Since the pupil diameter does not fluctuate in darkness, a soft blurred disk of white light from a 50 µ-watt source, at approximately 350 lux illumination, will be directed at the measured eye to initiate the oscillation in pupil size, and a 10-second infrared video of the pupil will be taken. The videos will be processed *post hoc* to fast Fourier transformation to quantitate the PUAL measurement. Previous calibration of the PUAL, obtained by measuring metal holes of known diameter (2.6 – 4.8 mm), allowed subtraction of inherent noise and establishment of zero at the lower scale boundary.[17] Participants will undergo an infusion and recovery sequence with an intravenous infusion of remifentanil, in a manner similar to that used in the previous study of 20-39-year-olds (0.2 µg/k/minute x 5 minutes, then 0.3 µg/kg/minutes x 5 minutes, then off), with pupillary measures taken every 2.5 minutes, for the 10-minute

infusion and 25-minute recovery period. In addition to PUAL, the average pupil diameter (millimeters) will be recorded, and for exploratory purposes, other measurements will be taken at regular intervals (constriction velocity, light reflex, and light off response), for some measurements using a second instrument (Neuroptics NPi - 200).

Study Protocol:
In each 35-minute test sequence, vital signs will be continuously monitored with pupillary measurements taken every 2.5 minutes. During the first 10 minutes of the 35-minute sequence, remifentanil will be infused at a predetermined rate described below. Sedation assessment will be made using the Pasero Opioid-Induced Sedation (POSS) Scale.[29]

Opioid Infusion:
The remifentanil will be infused for 10 minutes- at a rate of 0.2µg/kg/minute for the first 5 minutes, followed by 0.3µg/kg/minute for the next 5 minutes. After remifentanil discontinuation, pupillary measurements will continue every 2.5 minutes for the remaining 25-minute recovery phase. To avoid the costs and stimulating effect of sequential blood drawing, or the added discomfort of arterial line placement to facilitate repeated blood sampling, we do not plan to measure remifentanil blood concentration, choosing instead to use an infusion protocol based on the Minto model that, when given to eligible subjects, should achieve an estimated maximum effect site concentration of 4-6 ng/mL, a level known to produce near-maximum isoflurane MAC reduction and high probability of apnea. [29-31]

Outcomes:
Primary outcome is the correlation between PUAL and intensity of opioid exposure (represented by time-points corresponding to progressively increasing and declining estimated opioid concentrations) and the ability to discriminate zero-moderate versus high-toxic opioid effect. The discrimination of PUAL to identify high-risk opioid exposure will be determined by construction of receiver operator characteristic (ROC) curves.

Subjects:
Eligible subjects will be 40-60 years of age, recruited from flyers posted around the UCSF campus, and from an advertisement placed on Craigslist. Exclusion criteria will include use of opioid agonist or antagonist within the prior thirty days, any cardiopulmonary or neurologic condition, baseline $SpO_2 < 95\%$, diabetes, obstructive sleep apnea (OSA), BMI > 35 kg/m2, current or previous substance use disorder, ocular disease (including glaucoma), prior ocular surgery, use of any prescription ocular medication, use of medications known to affect pupillary characteristics (see below), blindness, previous episodes of serotonin syndrome, or inability to provide written informed consent.

Subjects will be instructed to fast for at least 8 hours prior to arrival for the study. The study team will instruct the subjects on which if any prescription medications should be taken on the day of the study prior to arrival. Failure to adhere to fasting instructions will disqualify the subject from participation.

The following classes of medication exert known impact on resting pupil size and use of any of the following will preclude participation:[32]
1/ Alpha blockers, primarily used for their ability to relax the bladder and prostate smooth muscle to address lower urinary tract symptoms (tamsulosin, alfuzosin, terazosin, doxazosin), although may also be used to treat hypertension or hair loss (labetalol, saw palmetto);
2/ Anticholinergic medications, including medication used for chronic obstructive pulmonary disease (ipratropium) and overactive bladder (including oxybutynin, tolterodine, solitenacin, darifenacin, fesoterodine, and mirabegron);
3/ Antidepressant medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, selective-norepinephrine reuptake inhibitors, MAO-I, and mianserin.
4/ Antipsychotic or mood stabilizing medications, which mostly act by postsynaptic blockade of D2 receptors. Examples include first generation (haloperidol, thioridazine, thiothixene) and second generation (olanzapine, quetiapine, risperidone) drugs;
5/ Phosphodiesterase inhibitors, including tadalafil, sildenafil, and tadalafil;
6/ Stimulant or appetite-suppressant medications, including dextroamphetamine, phentermine, or methylphenidate;
7/ Antihypertensive or antiarrhythmic medications, including clonidine, beta blockers, alpha blockers, and calcium channel blockers.
8/ Topical eye medications used for glaucoma, including dorzolamide, latanoprost, and timolol.

One important element of the evaluation is to identify conditions that may predispose the subject to adverse cardiovascular outcome. The current consensus guidelines from the American Heart Association and American College of Cardiology on preoperative evaluation of the patient prior to noncardiac surgery state that even for patients with one or multiple procedural or medical risk factors for adverse postoperative cardiovascular outcome, those able to perform > 4 METS of work may reasonably proceed to surgery without additional cardiovascular testing.[33] To determine functional capacity, we will ask potential subjects to undergo a modified 4-item Duke Activity Scale Index questionnaire to indicate the likelihood of VO2max > 16 mL/kg/minute, which translates to the ability to perform ≥ 4.6 METS of work.[34,35] To determine risk of obstructive sleep apnea (OSA), an 8-item STOP-BANG score (validated screening tool for presence and severity of OSA) will be administered.[36] A Subjects must have a modified DASI score of 4 and STOP-BANG score of < 3 to qualify for participation.

<u>Inclusion criteria are as follows:</u>

Age 40-60 years of age
Able to read and understand the informed consent
Able to follow NPO instructions
Must have a responsible adult to escort subject home from UCSF after the study

Must show proof of COVID vaccination and negative COVID PCR test obtained ≤ 72 hours prior to the study

Exclusion criteria are as follows:

BMI > 35 kg/m2
Current or previous opioid or other substance use disorder
Current or recent (within prior 30 days) use of any μu- opioid agonist, partial agonist, or antagonist
Significant or uncontrolled gastroesophageal reflux disease (GERD)
History or symptoms of ischemic heart disease (pain or pressure in the chest/arm/jaw, shortness of breath or light-headedness with moderate exertion; previous myocardial infarction; any coronary intervention or revascularization)
Known or suspected arrhythmias (atrial fibrillation, atrial flutter, palpitations associated with light-headedness, syncope or light-headedness with exercise)
History of heart failure, pulmonary hypertension, or congenital heart disease
Known or suspected obstructive sleep apnea (confirmed diagnosis on sleep study, or STOP-BANG score ≥ 5 if untested)
Current or recent use (within 7 days) of antihypertensive medication (beta blocker, calcium channel blocker, clonidine, ACE inhibitor, angiotensin-receptor blocker)
Use of any alpha-adrenergic blocking medication for urinary symptoms or anticholinergic medications
History or ocular surgery (ie, cataract surgery, vitrectomy), ocular disease (ie, glaucoma), or use of topical eye medications
Use of mood stabilizers or antidepressant medications (including serotonin-reuptake inhibitors or MAO-inhibitors) within past 30 days
Use of stimulant medications (amphetamines, including medications used for appetite suppression or attention deficit disorder)
Use of phosphodiesterase inhibitor medications (usually given for erectile dysfunction) within the past 7 days
Inability to read or understand English
Any condition prohibiting delivery of oxygen by nasal cannula
Anxiety or panic disorders
Severe motion sickness or intractable vomiting after prior anesthesia
Fever, upper respiratory infection, or illness of any variety within 8 weeks of participation

Exclusion criteria involving opioid use or substance use disorder will be determined by self-report from the potential subject.

DATA COLLECTION

Subject data including subject number, initials, age, sex, race, height and weight, along with time-stamped drug administration and vital signs, will be collected on a source document anesthetic record, which will be scanned and stored on a HIPAA-compliant secure location. Pupillary measures will be collected on a Neuroptics PLR-3000 device, and the date and times of the scans will be correlated to the times of each subject's data. The pupillary scans will be downloaded by Bluetooth to a csv file that will be stored on an encrypted laptop computer.

DATA ANALYSIS

We plan to test 20 subjects aged 40-60 under paired conditions- absent versus uninterrupted conversational interaction- over a 35-minute period. Interim analysis is planned after 10 subjects are studied.

Correlation between PUAL and opioid concentration:
We will examine PUAL and estimated opioid effect site concentration during both drug infusion (0-10 minutes, where opioid concentrations progressively increased) and recovery (10-35 minutes, where opioid concentrations progressively decline). Each 2.5-minute point will be treated as an ordinal variable "time", and opioid effect-site concentrations will be calculated at each time point according to the Minto pharmacokinetic model estimates.[29] The effect of time (as surrogate for opioid concentration) on PUAL will be assessed using a linear mixed effects model.

Distinguishing between zero-low risk versus high-risk, toxic opioid conditions by PUAL:
We will collect PUAL data at times when estimated opioid effect site concentrations in all subjects are consistently low (< 2.0 ng/mL) versus high (>2.4 ng/mL). A receiver operating characteristic analysis using dichotomized PUAL values will be constructed to determine PUAL's ability to distinguish between low-risk versus high-risk opioid exposure in the 40-60-year-old subjects. This ROC curve will be compared to that of subjects in the 20-39 year-old range, and interval likelihood ratios that identify high, indeterminant and low risk will be reported.

SAMPLE SIZE CALCULATION

The primary objective of this study is to assess PUAL's ability to identify high-risk opioid effect in older adults. In the previous study in younger adults, we used a remifentanil infusion that consistently produced zero to moderate opioid effect at 2 time points (baseline and 2.5 minutes) and high opioid effect at 4 time points (5.0, 7.5, 10.0, and 12.5 minutes). We assessed the ability of PUAL to discriminate using the area under the ROC curve (AUROC).

In that study the AUROC was slightly *lower* under quiet vs. interactive conditions (0.95 vs 0.97), and the standard error of the summary AUROC was 0.01. If the discrimination is substantially lower in older adults, we would expect an AUROC of 0.875. A sample size of 20 participants would produce a 95% confidence interval of width 0.12 (0.81 to 0.93) and a standard error of 0.0275.[37] The standard error of the difference in AUROCs would be 0.03 and would provide 80% power to detect a difference in AUROCs of 7.5% at the 0.05 significance level.[38]

In addition, we intend to evaluate the same PUAL intervals as found in our previous analysis of 20-39-year-old subjects:

- PUAL 0.00 to <0.04 = high-risk opioid effect, interval likelihood ratio = 14.59;
- PUAL ≥ 0.04 to 0.13 = indeterminate effect, interval likelihood ratio = 1.12;
- PUAL ≥ 0.14 = zero or low risk opioid effect, interval likelihood ratio = 0.02.

We will calculate interval likelihood ratios in the 40-60-year-olds.[39] For high opioid effect, we expect an interval likelihood ratio of approximately 10. Our sample size of 20 should allow estimation with a 95% confidence interval 3.3 to 30.

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