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BRIEF COMMUNICATION

Infrared pupillometry helps to detect and predict delirium in the post-anesthesia care unit

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Abstract This study evaluates the capability of pupillary parameters to detect and predict delirium in the post-anesthesia care unit (PACU-D) following general anesthesia. PACU-D may complicate and prolong the patient's postoperative course, consequently increasing hospital costs. After institutional approval, 47 patients undergoing surgical interventions with general anesthesia were included in the study. We measured the pupillary reflexes at signing of informed consent, during surgery 20 min after intubation and when the primary inhaled anesthetic was turned off, and 15 and 45 min after PACU admittance and upon discharge from the PACU. We evaluated patients for delirium using the confusion assessment method for the intensive care unit (CAM-ICU) score after 15 and 60 min in the PACU. We chose receiver operating curve (ROC) and area under the curve (AUC) to compare the performance of non-pupillary parameters to pupillary parameters, such as pupil diameter, percent constriction, and dilation velocity, to detect and predict PACU-D. Percent constriction (AUC = 0.93, optimal threshold = 18.5%) and dilation velocity (AUC = 0.93, optimal threshold = 0.35 mm/s) showed excellent ability to detect and predict delirium persisting throughout the PACU stay. These pupillary measures showed superior performance compared to other pupillary measures and features commonly associated with delirium, e.g., age (AUC = 0.73), total opioids (AUC = 0.56), or length of surgery (AUC = 0.40). Our results suggest that pupillometry and the parameters derived from the recording may identify delirious patients in the PACU. This information can help to efficiently structure their care in a timely manner, and potentially avoid adverse complications for the patient and financial consequences for the hospital.

Keywords Delirium · Reflex · Pupillary · Delayed emergence from anesthesia · Anesthesia recovery period · Anesthesia · General

1 Introduction

In order to prevent the development of adverse postoperative cognitive outcomes such as delirium, a timely identification of patients at risk is essential. Delirium, in general, is associated with a worsening of dementia [1], increased hospital costs [2], and increased mortality [3]. Postoperative delirium (POD), occurring in the days to weeks after surgery, has also been linked to cognitive decline and increases in mortality, particularly in elderly patients [4–6]. POD also increases hospital costs, exceeding $38 billion annually [2], partly due to increasing the length of hospital stay [6, 7] or unanticipated admission to the hospital following ambulatory surgery. On a more acute time scale, hours after regaining consciousness, delirium occurring in the recovery room or post-anesthesia care unit (PACU-D) has received less research attention than POD, but may be just as harmful. PACU-D is associated with increased risk

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of POD [8], increased rates of institutionalization after hospital discharge [9], and longer hospitalizations [7]. These outcomes have major financial impact on patients and their families as well as healthcare providers and hospitals.

Structured assessment of postoperative cognition is becoming frequently used to evaluate clinical outcomes in the perioperative situation [10]. Here, we introduce the capability of infrared pupillometry to screen for patients with PACU-D. Patients undergoing general anesthesia are at risk for several potential adverse outcomes in the PACU besides PACU-D [11, 12] such as breathing difficulties [13], arrhythmias [14], pain [15], and postoperative nausea/vomiting [16]. The published guidelines for post anesthesia care recommend several standard monitors intended to quickly identify potential acute postoperative cardiac or respiratory issues [17]. Unfortunately, it is more difficult to objectively evaluate neurologic symptoms (e.g., cognitive impairments, pain) in patients acutely recovering from general anesthesia, and consistency varies greatly from provider to provider [18]. Patients living with dementia and patients with impaired verbal communication due to either pre-existing disease (i.e., tracheostomy) or surgery (e.g., ENT/oral surgery) are particularly difficult to evaluate postoperatively, resulting in undertreatment of pain and confusion [19–21]. Currently, no tool or monitor is validated to screen for PACU-D. The Confusion Assessment Method Intensive Care Unit (CAM-ICU) has been used to screen for delirium in the ICU; and due to its short duration, ease of use, and high sensitivity and specificity across multiple hospital settings is ideally suited for use in the PACU [10, 22, 23]. CAM-ICU is a highly specific test to evaluate patients for delirium based on observation and task performance scores [24].

Pupillometry is a non-invasive quantitative measurement of dynamic changes in pupil size in reaction to light stimuli. Pupillary reactivity not only provides insight into the balance between the sympathetic and parasympathetic nervous systems, but also help to evaluate patients during acute neurologic disease [25], titration of anesthetic dose [26] and possibly postoperative recovery from anesthesia, the focus of this study. Previous studies using pupillary light reflex (PLR) in the perioperative environment have focused on intraoperative and postoperative pain [27–29], because of the inverse relationship of pupil diameter and administered opioid dose in perioperative patients [29–32]. One study highlights the potential of pupillometry to quantify subtle changes in neurocognitive states of arousal [25].

PLR has been extensively studied in evaluating patients in both psychiatric and neurologic settings [25] and it is an effective parameter to identify cognitively impaired patients [33, 34]. Our study shows that PLR measures can help to screen for PACU-D and they may provide a tool to reduce long term complications associated with PACU-D, including a complicated postoperative course, increased risk for escalation of care, or increased hospital costs.

2 Materials and methods

The study protocol was approved by the local Institutional Review Board (Emory University School of Medicine, Atlanta, GA, USA, approval number 63456). Written informed consent was obtained from each patient. The study took place at Emory University Hospital Midtown (Atlanta, GA, USA).

2.1 Study design and patients

This prospective observational study investigated patients during the preoperative, perioperative, and postoperative periods, until discharge from the PACU. Every patient older than 18 years of age undergoing surgery at Emory Midtown Hospital was considered eligible. Non-inclusion criteria were patients with ocular issues, surgeries involving the area above the neck or in the prone position, Monitored Anesthesia Care, poor health literacy, and refusal to participate. A total of 47 ambulatory surgery patients were included in the study.

2.2 Pupillary assessment

Pupillary assessment was measured with a NeurOptics PLR-200™ portable infrared pupillometer (NeurOptics, Irvine, CA, USA). The pupillometer included a pre-formed silicone membrane surrounding the orbit under investigation, to minimize the influence of ambient light on the PLR. Each assessment consisted of a five second video recording of the pupil diameter in response to a light stimulus lasting 802 ms with a pulse intensity of 180 μW. The pupillary parameters, extracted from PLR, recorded by the device were maximal pupil diameter, minimal pupil diameter, percent constriction [(maximal pupil diameter − minimal pupil diameter)/maximal pupil diameter], latency (time of onset of constriction), average constriction velocity, maximal constriction velocity, average dilation velocity, and time taken for pupil to recover to 75% of its initial resting size (T75).

We measured these parameters at six time points for each patient: (i) after signing informed consent, (ii) 20 min after intubation, (iii) upon turning off primary maintenance inhaled anesthetic, (iv) 15 min and (v) 45 min after PACU admittance, and (vi) at time of PACU discharge.

We performed pupillometry on the left eye unless contraindicated due to surgical position or previous unilateral ocular disease. In that case we measured the right eye.

During the recording, we instructed the patient to look straight ahead, towards an object greater than 3 m away to prevent the accommodation reflex from interfering with the measurement of the PLR. For the initial measurement, we applied the pupillometer to the orbit, and instructed the patient to cover their contralateral eye with their hand. When the patient was not able to cover the contralateral eye, the investigator closed it by applying gentle downward traction on the superior eyelid. This procedure was described by Kantor et al. [31]. If the patient blinked during the critical measurement period, we stopped the scan and discarded the measurement. Then, we repeated the measurement after waiting for at least 30 s to allow the pupil to fully recover from the previous light stimulus. Pupillary assessments were conducted by the research investigators, who were trained on proper technique prior to making measurements.

2.3 Intraoperative assessments

We recorded the time and dose of administered opioids and other drugs throughout the course of anesthesia. Pupillary measurements were not revealed to the surgical, anesthesia, and nursing staff during the perioperative period, so as to not alter administered patient care during the study. The anesthetic and analgesic procedure was not standardized, but left to the anesthesiologist of record in order to reflect the normal administration of anesthesia. All patients received inhalational anesthesia (either sevoflurane or desflurane). We used the anesthesia protocols of the surgical interventions to extract the information regarding the expired inhaled anesthetic concentrations. We calculated the MAC equivalents as described in the review article by Aranake, Mashour and Avidan [35].

2.4 Postoperative assessments

We assessed PACU-D as measured by CAM-ICU for each patient at 15 and 60 min after PACU admittance. We recorded the dose and time of opioid and other analgesics that were administered by the PACU nurse.

PACU-D assessments were conducted by the research investigators, who were trained on proper technique prior to making measurements.

2.5 PACU discharge criteria

We used our standard discharge criteria from the PACU. Patients had to be awake, and oriented and at their preoperative level of consciousness. They had to demonstrate the ability to follow commands and to respond appropriately. Additional discharge criteria included:

Stable vital signs, ability to maintain a patent airway and ability to swallow, respirations that are deep, even and unlaboured, adequate oxygenation defined by >90% saturation on room air, ability to move all extremities or at baseline, temperature of $\geq 36\,^{\circ}C$, pain score of ≤ 5 out of 10, with controlled or absent nausea and/or vomiting.

A Richmond Agitation and Sedation Score of 0–1 and modified Aldrete Score of 9–10 were required prior to discharge.

2.6 Statistical analysis

We used the R 3.1.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria) for statistical analysis. We used the pROC package 1.8 for R [36] to calculate receiver operating curves (ROCs) and the area under the curve (AUC) with according 95% confidence intervals (2000-fold bootstrapping) for different pupillary and demographic parameters. AUC is equivalent to dichotomous prediction probability, a measure often used to evaluate the performance of depth of anesthesia monitoring systems [37]. According to the traditional academic point system, AUC values, adjusted to the [0.5–1] interval, can be interpreted as excellent: $1 \geq AUC \geq 0.9$; good: $0.9 > AUC \geq 0.8$; fair: $0.8 > AUC \geq 0.7$; poor: $0.7 > AUC \geq 0.6$; or fail: $AUC < 0.6$.

In order to define possible thresholds that can be used for distinguishing between patients with and without PACU-D, we determined a modified Youden's index (sensitivity + specificity − 1), a measure that describes the performance of a diagnostic test. Here, we determined the thresholds by iterating across all thresholds that would yield sensitivity greater than or equal to 0.8, that is 80% of patients with the PACU-D would be detected by a test using such a threshold, and finding the threshold corresponding to the largest Youden's index. The usefulness of these thresholds in evaluating patients with and without PACU-D was also expressed by calculating the negative predictive value (NPV), the ratio of true negatives to all negatives for a certain test, and positive predictive value (PPV), the ratio of true positives to all positives for a certain test.

We performed a Mann–Whitney *U* test to detect possible differences in the demographic data of the patients with and without PACU-D. We checked for differences between the surgical techniques the patients underwent as well as their ASA status of patients with and without PACU-D using a Chi-squared test. We set the confidence level for all tests to 95%, i.e., $p < 0.05$.

Multiple regression analysis was used to assess for possible confounders. A multiple logistic regression model was first created using PACU-D as the outcome, a pupillary measure as the exposure variable, and a confounder of interest. A second simple logistic regression model was then created removing the confounder of interest, but keeping PACU-D as the outcome and the pupillary measure as

the exposure variable. The percent difference between the beta coefficients for the exposure variable (pupillary measures) under investigation between the two models was then calculated. For generation of the figures we used MATLAB (MATLAB R2015a, The MathWorks®, Natick, MA, USA) and Inkscape 0.91. Beeswarm plots were generated with the MATLAB-based *plotSpread* function (MATLAB File Exchange).

3 Results

Out of 47 patients, 10 patients had a positive CAM-ICU score, measured after 15 min in the PACU. No patients in the study were diagnosed with PACU-D at 60 min after a negative CAM-ICU score at 15 min. Of the ten patients with PACU-D at 15 min, six had persistent PACU-D, (i.e., a positive CAM-ICU score at 15 min and at 60 min). All cases of PACU-D could be sub-categorized as hypoactive delirium (RASS < -1).

We did not find significant differences in the patient demographics between patients with and without PACU-D, except age. Patients expressing PACU-D at 15 min were significantly older. There was also no significant difference in the types of surgery between the groups. PACU-D patients were older 65 (12) years (median and interquartile range IQR) versus 49 (22) years. They also underwent longer surgical procedures 119 (91) min versus 57 (74) min. Table 1 contains the detailed information.

3.1 Pupillary assessments for PACU-D

Pupillary measures did not reveal significant differences between the PACU-D and non-PACU-D group in the preoperative and intraoperative measurements, but after 15 min in the PACU, several pupillary parameters significantly deviated between PACU-D and non-PACU-D group. The percent constriction and the dilation velocity assessed after 15 min in the PACU showed "excellent" performance in predicting PACU-D at 60 min and were superior to other, non-pupillary predictors linked with delirium in previous studies (e.g., age, length of surgery, and preoperative administration of midazolam). The ROC presented in Fig. 1 visualizes the superior performance of the pupillary measures compared to other predictors of delirium. Percent constriction was 13% (5%) in the patients with PACU-D at 60 min versus 26% (11%) for non-PACU-D patients. The dilation velocity in PACU-D patients was 0.25 mm/s (0.21 mm/s) compared to 0.53 mm/s (0.36 mm/s).

Figure 2a shows the distribution of the percent constriction, the parameter with the highest AUC to predict PACU-D at 60 min, of the PACU-D and non-PACU-D patients at various assessment times. The detailed distribution of age and length of surgical intervention is presented in Fig. 2b. Further, the exact results of the AUC analyses are presented in Table 2.

The predictive values of the four pupillary parameters with the highest AUC values are presented in Table 3. The presented parameters show very high negative predictive values (NPV). For example, patients with a percent constriction magnitude of greater than 18.5% are almost certain not to develop persistent PACU-D in the PACU (NPV = 0.95).

4 Discussion

Delirium after general anesthesia comes in many forms: emergence delirium, PACU-D, postoperative delirium [38]. The clinical impact of these different manifestations is not well described, as clinical research has in part been hindered by the lack of a consensus definition of the different entities. However, PACU-D has been shown to be associated with future delirium, cognitive decline, and institutionalization at discharge [9].

Our results show that pupillometry may serve as a reliable method to detect and predict PACU-D. A recent review of the utility in pupillometry in anesthesia practice suggests that this technology is being underutilized in situations that its application may be useful [39]. Our findings show that the processed parameters, percentage constriction and dilation velocity, recorded after 15 min in the PACU were excellent predictors for longer lasting PACU-D. They outperformed non-pupillary parameters, like midazolam usage, age or duration of the anesthesia. Based on the determined thresholds, several pupillary measurements show high predictive power in identifying patients with a low suspicion of developing PACU-D (NPV > 0.94). This information could potentially be used to provide alternate (accelerated recovery) PACU clinical pathways for patients with low risk of developing PACU-D and consequently have additional time to identify and monitor patients with higher risk of developing PACU-D.

Deiner et al. and Fong et al. showed that early treatment of patients that develop POD may enable healthcare providers to minimize the severity of possible future cognitive decline, and reduce the number of future cognitive related hospital readmissions [3, 4, 6]. The prevention of rapidly developing cognitive complications following POD could drastically cut hospital costs and improve efficiency in the perioperative arena [6], to the benefit of hospital administrators, physicians, and patients alike. In this context, pupillometry could help to counteract cognitive decline by supporting timely identification of post-anesthetic PACU-D development.

Table 1 Patient demographics and surgery characteristics of the patients without PACU-D and patients that expressed PACU-D at 15 min and patients that exhibited persistent PACU-D (PACU-D at 60 min)

	PACU-D assessment at 15 min		p	PACU-D assessment at 60 min		p
	No PACU-D	PACU-D		No PACU-D	PACU-D	
Total	37	10		40	6	
Age (years)	49 (23–84)	65 (46–81)	**0.01**	52 (23–84)	65 (46–81)	0.07
Sex (male)	24 (65%)	9 (90%)		26 (65%)	6 (100%)	
BMI (kg/m^2)	33 (15–54)	33 (19–45)	0.61	33 (15–54)	34 (19–39)	0.77
ASA class						
Class 1	3 (8%)	0 (0%)		3 (8%)	0 (0%)	
Class 2	16 (43%)	5 (50%)		18 (45%)	2 (33%)	
Class 3	17 (46%)	5 (50%)		18 (45%)	4 (67%)	
Class 4	1 (3%)	0 (0%)	0.76	1 (3%)	0 (0%)	0.74
Type of surgical procedures						
General	10 (27%)	3 (30%)		12 (30%)	1 (17%)	
Gynecological	6 (16%)	2 (20%)		7 (18%)	1 (17%)	
Orthopedic	21 (57%)	5 (50%)	0.92	21 (53%)	4 (67%)	0.77
Benzodiazepine premedication (mg)	2 (0–2)	0.5 (0–2)	0.08	2 (0–2)	0 (0–2)	0.13
Airway device (ETT)	30 (81%)	9 (90%)		34 (85%)	5 (83%)	
Neuromuscular blockade reversal	18 (49%)	7 (70%)		22 (55%)	3 (50%)	
Duration of surgery (min)	57 (7–197)	119 (48–187)	0.03	67 (7–197)	66 (48–187)	0.47
Duration in PACU (min)	73 (30–155)	65 (60–101)	0.26	73 (56–155)	68 (60–101)	0.62
Intraoperative opioids[a]	250 (50–783)	308 (183–400)	0.29	263 (50–783)	333 (183–400)	0.38
Intraoperative opioids per surgery minute[b]	4.8 ± 1.8	2.5 ± 0.6	0.07	4.2 ± 1.9	3.4 ± 1.5	0.7
Postoperative (in PACU) opioids[a]	50 (0–273)	58 (0–167)	0.67	67 (0–273)	50 (0–167)	1
Total opioids[a]	350 (75–883)	363 (250–550)	0.46	350 (75–883)	363 (300–550)	0.64
Medical history						
Cardiovascular disease	23 (62%)	4 (40%)		25 (63%)	2 (33%)	
Any alcohol use	20 (54%)	4 (40%)		21 (53%)	2 (33%)	
History of smoking	12 (32%)	1 (10%)		11 (28%)	1 (17%)	
Respiratory disease	3 (8%)	2 (20%)		3 (8%)	2 (33%)	
Neurological disease	2 (5%)	0 (0%)		2 (5%)	0 (0%)	
Diabetes mellitus	5 (14%)	1 (10%)		5 (13%)	1 (17%)	
History of cancer	3 (8%)	1 (10%)		4 (10%)	0 (0%)	
Renal disease	4 (11%)	1 (10%)		4 (10%)	1 (17%)	
Prior cognitive impairment	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Anesthetic concentration						
Avg endtidal (%)	2.0 (1.4–7.3)	2.1 (1.5–2.5)	0.95	2.1 (1.4–7.3)	2.0 (1.5–2.5)	0.65
MAC equivalent	1.0 (0.7–1.3)	1.0 (0.8–1.2)	0.72	1.0 (0.7–1.3)	1.0 (0.8–1.2)	0.83

Values are expressed as median (range) or number of subjects (%). Age was the only pre-operative characteristic that differed significantly between those with and those without PACU-D 15 min after PACU admission. Length of surgery was the only intraoperative characteristic significantly different among these groups. None of these patient or surgical factors differed when comparing the patients with versus patients without persistent PACU-D (after 60 min in PACU)

[a] μg of fentanyl equivalents

[b] μg of fentanyl equivalents min^{-1}

Generally speaking, a formal delirium assessment is not part of discharge criteria for patients who have received general anesthesia. Since the 1970s, the Aldrete score [40] has commonly been applied to assess readiness for discharge in patients recovering from the sedative effects of anesthesia. Our work is consistent with others [10] hat demonstrates that patients might be discharged from the PACU while still screening positive for PACU-D via CAM-ICU. The assessment of consciousness in the Aldrete score varies among institutions and among providers. Vague

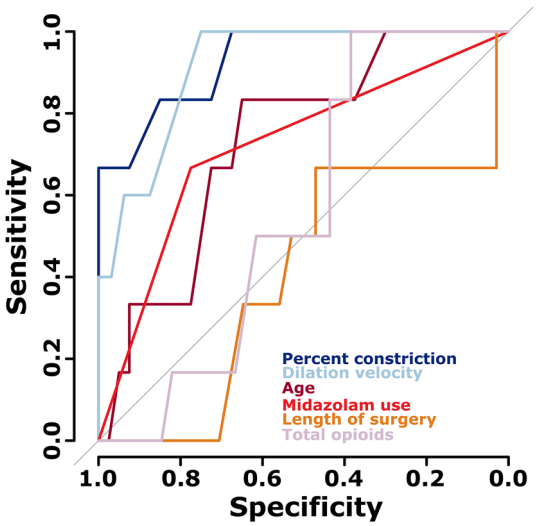

Fig. 1 ROC plot for the pupillary parameters percent constriction (AUC (95% confidence interval): 0.93 (0.83–1)) and average dilation velocity (0.92 (0.81–1)), as well as the non-pupillary parameters age (0.73 (0.53–0.93)), the total amount of opioids (0.56 (0.37–0.75)), length of surgery (0.40 (0.14–0.67)), and use of midazolam (0.72 (0.50–0.94)), in predicting PACU-D at 60 min. The curves of the pupillary parameters demonstrate a larger AUC than the curves of the non-pupillary parameters. The corresponding predictive values are presented in Table 3

descriptions such as: arousable to voice, fully awake, approaching baseline typically suffice for fulfilling post-anesthetic discharge criteria. The CAM-ICU was designed for use in the ICU with patients receiving sedation. It is important to note that the CAM-ICU is a functional assessment rather than a laboratory value. Medications and adverse reactions to administered medications are often an etiology for delirium; however morphine-induced delirium is still delirium. Despite sedation and analgesia in a patient, some may and some may not still function well enough while sedated that they do not screen positive for PACU-D by CAM-ICU. To further illustrate this point, although higher opioid doses might be more likely to produce an adverse reaction, there is no blood concentration of opioid that represents the threshold for developing delirium. At this point, it is impossible to determine if our CAM-ICU screen is identifying patients with a delay in reorganization of arousal circuits and/or a heightened sensitivity to low-dose anesthesia; but future studies may be able to provide insight to these mechanistic questions.

4.1 Depressed pupillary reflexes at PACU discharge

Our work with pupillometry in the PACU reveals that readiness for PACU discharge does not consistently correlate with complete recovery of baseline tone of the autonomic

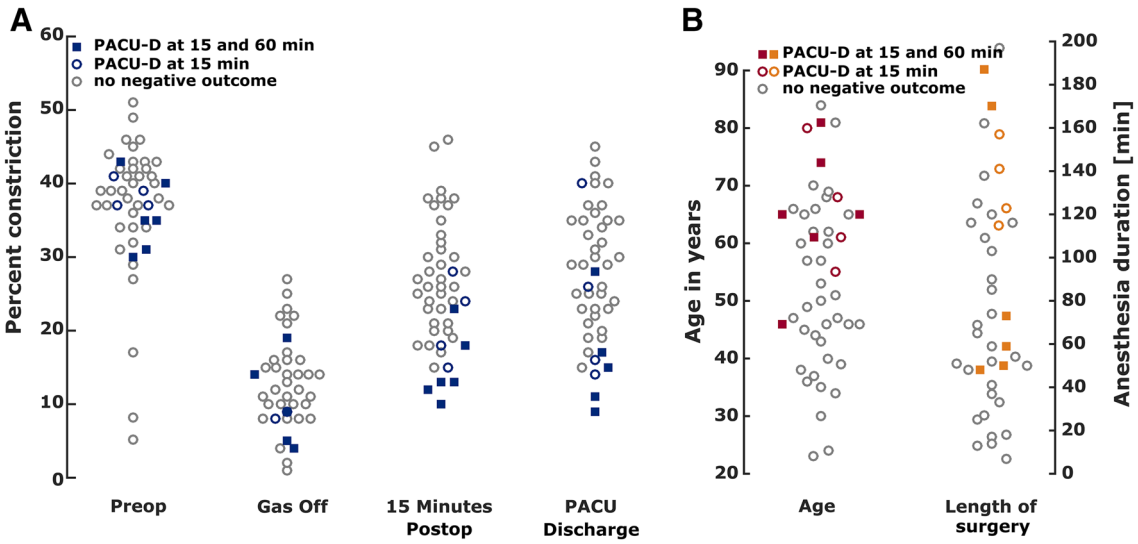

Fig. 2 Beeswarm plots for the pupillary parameter percent constriction and the other predictors age and length of surgery. **a** Percent constriction, for each patient at the different recording time points. The *gray circles* represent patients that did not develop PACU-D, while the *blue circles* indicate the patients that were tested positive for PACU-D at 15 min. The *blue filled squares* indicate patients with PACU-D at 15 and at 60 min, i.e., persistent PACU-D. This plot shows the accumulation of the percent constriction of the patients with PACU-D at low percent constriction values during the measurements in the PACU that led to the high AUC of 0.93 (95% CI 0.83–1). At the preoperative recording and at "gas off", the PACU-D patients' parameter values were mixed in. **b** Age and surgery length for each patient. The *gray circles* represent patients that did not develop PACU-D, while the *red* (*orange*) *circles* indicate the age (surgery length) of patients that were tested positive for PACU-D at 15 min. The *red* (*orange*) *filled squares* indicate age (surgery length) of patients with PACU-D at 15 and at 60 min, i.e., persistent PACU-D. The parameter values of the patients with PACU-D are blended in the parameter values without PACU-D leading to the low AUC values presented in Table 2

Table 2 The table contains the AUC values and 95% confidence intervals for pupillary and non-pupillary parameters to detect PACU-D after 15 and 60 min in the PACU

	PACU-D assessment at 15 min	PACU-D assessment at 60 min
Pupillary parameters		
Percent constriction after 15 min in PACU	***0.87 (0.74–0.1)***	**0.93 (0.83–1)**
Dilation velocity after 15 min in PACU	**0.90 (0.79–1)**	**0.92 (0.81–1)**
Maximal constriction velocity after 15 min in PACU	***0.88 (0.77–1)***	***0.89 (0.78–1)***
Average constriction velocity after 15 min in PACU	***0.85 (0.72–0.99)***	***0.89 (0.72–1)***
Pupil latency after 15 min in PACU	*0.80 (0.65–0.94)*	***0.85 (0.69–1)***
Time to 75 after 15 min in PACU	***0.81 (0.63–0.99)***	*0.72 (0.51–0.92)*
Maximal pupil diameter after 15 min in PACU	0.71 (0.56–0.87)	0.71 (0.52–0.90)
Minimal pupil diameter after 15 min in PACU	*0.6 (0.42–0.78)*	*0.44 (0.19–0.70)*
Other predictors		
Length of surgery	0.73 (0.55–0.91)	*0.40 (0.14–0.67)*
Age	0.77 (0.62–0.92)	0.73 (0.53–0.93)
Midazolam use	*0.64 (0.47–0.82)*	*0.72 (0.50–0.94)*
Administered opioids intraoperatively	*0.61 (0.44–0.78)*	*0.62 (0.39–0.84)*
Length of PACU stay	*0.59 (0.39–0.79)*	*0.50 (0.22–0.78)*
ASA	*0.52 (0.35–0.69)*	*0.6 (0.40–0.80)*
Administered opioids postoperatively	*0.54 (0.33–0.76)*	*0.50 (0.21–0.80)*
Total administered opioids	*0.58 (0.41–0.75)*	*0.56 (0.37–0.75)*

Bolded AUC values indicate "excellent" performance and bold and italic values indicate "good performance". Regular values indicate "fair" performance that is significant by means of the 95% CI. Italicized values are not significant

Table 3 Predictive values of the best performing pupillary measures recorded at 15 min to predict PACU-D assessed after 60 min in the PACU

	Percent constriction	Average constriction velocity	Maximal constriction velocity	Dilation velocity
Optimal threshold	−18.5%	−0.99 mm/s	−1.17 mm/s	0.35 mm/s
Sensitivity	0.83 (0.44–1)	1 (0.50–1)	0.83 (0–1)	1 (0.40–1)
Specificity	0.85 (0.61–1)	0.7 (0.58–0.95)	0.90 (0.60–0.98)	0.75 (0.59–0.97)
PPV	0.46	0.33	0.56	0.27
NPV	0.95	0.97	0.95	0.94
Youden index	0.68	0.7	0.73	0.75

nervous system, as many patients displaying depressed pupillary reflexes [39] during their PACU stay continued to have depressed reflexes at discharge from the PACU. Due to the importance of the autonomic system in various bodily functions, autonomic imbalance may predispose patients to certain morbidities due to inability to maintain systemic homeostasis. Both the short term and long term effects of discharging patients prior to complete autonomic recovery warrant further investigation.

4.2 Limitations of the study

This is the first study to investigate pupillometry as an objective measurement to predict PACU-D. A larger study is necessary to properly evaluate the potential association of PACU-D with POD and other adverse outcomes. Opioid administration can affect pupil measurements, but our small study determined that opioid administration was not associated with PACU-D (Tables 1, 2); however the influence of opioid administration acutely on pupil measurements was not considered in our study. When adjusting for possible confounders in a logistic regression prediction model, moderate changes (greater than 25%) in the beta coefficients of percent constriction and dilation velocity parameters at 15 min were observed with total opioid and intraoperative opioid administration. However, due to the small sample size of this study, creation of a valid logistic regression model to account for possible confounding factors in our study was not feasible [41]. Although opioid administration likely contributes in a complex way to both PACU-D and pupillometry measures, the AUC analysis reveals that opioid administration itself is not a good predictor of PACU-D

as presented in Fig. 1. Nevertheless, we showed that independent from these possible confounding factors, PACU-D can be predicted by a pupillometry-based method. In addition, all patients presenting with PACU-D in this study were hypoactive delirium patients. Hyperactive or mixed delirium [42, 43] patients may present differently from hypoactive delirium patients after surgery, and this would need to be evaluated further in future studies. Due to our small sample size, our findings may only be generalizable to hypoactive PACU-D [42, 43] occurring in relatively short surgeries with planned extubations. However, our observations are consistent with the findings of several previous studies [10, 44–46], which have demonstrated that hypoactive delirium is the most prevalent delirium subtype, while also the most often underdiagnosed. Hypoactive delirium is more common in the elderly and associated with worse outcomes [43, 45], so early detection is paramount to improve perioperative patient care. While CAM-ICU is a simple and reliable tool for most patients, limitations may preclude it from being useful in certain patient populations. Namely, the CAM-ICU incorporates subjective evaluation of level of consciousness, which may cause great inter-rater variability, particularly when used by non-trained providers [47]. As such, a standard assessment of PACU-D for the entire patient population including patients with pre-existing dementia is still an ongoing challenge [48, 49]. Our observational study was also limited by not sampling blood to accurately measure levels of analgesics, volatile anesthetics, or other drugs in our patients. Typically, our CAM-ICU observations in the PACU occurred over 30 min after the patient first achieved MAC-awake, likely corresponding to volatile anesthetic concentrations much lower than MAC-awake but not quite zero. Generally, the time to complete elimination of the substance in vessel rich tissues, like the brain, would be several hours after PACU discharge. Future studies will be required to determine why some patients test positive and others negative for delirium screens in the presence of minimal levels of anesthesia. The sympathetic and parasympathetic nervous systems can influence pupillary reactions. Although our results indicate a strong effect of PACU-D on the pupillary parameters, a possible relationship between PACU-D and changes to the sympathetic/parasympathetic balance has to be investigated in the future. We further performed the assessment of delirium in the PACU and did not do any follow up assessments, since the procedures analyzed were outpatient procedures. Whether our findings for PACU-D persist after leaving the PACU has to be evaluated in the future. Another point to be considered in future studies would be the investigation of appropriate treatment strategies for PACU-D. Recent interest in anesthesia reversal agents represents a potentially promising clinical research strategy [50, 51].

4.3 Overall conclusions

Over the past 50 years, monitoring of surgical patients by members of the anesthesiology team has become increasingly more sophisticated. The recent interest in adverse cognitive consequences in the perioperative period [38] has many considering alternative monitoring modalities to predict or detect cognitive problems early. Our work supports pupillometry as a convenient, non-invasive, and objective method for early detection of PACU-D in at-risk patients. Usage of pupillary assessment for evaluation of postoperative recovery from anesthesia can help clinicians identify patients requiring increased attention and care in the PACU, and may help reduce patient readmissions, unnecessary escalation of care, hospital costs, and future cognitive decline.

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Author contributions EY performed experiments, analyzed the data, wrote the manuscript. MK analyzed the data, wrote the manuscript. SH analyzed the data, helped to write the manuscript. PD conducted experiments, helped to write the manuscript. SCL designed the experiments, helped to conduct experiments. PSG designed the experiments, wrote manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors report a conflict of interest.

Disclosure Disclosure of potential conflicts of interest.

Research involving human or animal participants The Research involved human participants (patients). The study protocol was approved by the local Institutional Review Board (Emory University School of Medicine, Atlanta, GA, USA, approval number 63456).

Informed consent Written informed consent was obtained from each patient. The study took place at Emory University Hospital Midtown (Atlanta, GA, USA).

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