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ORIGINAL ARTICLE

# Video versus ultrasound pupillometry for detecting increased pupillary diameters due to nociceptive stimuli: a prospective observational study

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## Abstract

**Purpose** Ultrasound pupillometry (UP) is a potential alternative to video pupillometry (VP) for assessing changes in patients' pupillary diameter (ΔPD) due to surgical nociception, but the reproducibility of UP and VP has been unclear. We evaluated the reproducibility of nociceptive ΔPD measured with both methods.

**Subjects and methods** This prospective observational trial with 15 healthy volunteers aged ≥ 18 years was conducted at a Japanese teaching hospital. The ΔPD due to tetanic stimuli randomly applied at 10–60 mA was measured with VP and UP. The primary outcome was the correlation between the ΔPD measured with VP and that measured with UP. The secondary outcome was the agreement between the methods. We also evaluated ΔPD pattern changes due to the raised pain intensity in each method.

**Results** The noxious ΔPD values of UP were weakly but significantly correlated with those of VP (Spearman's $\rho = 0.38$, $p < 0.001$). A significant constant error was identified between the two measurements (Bland–Altman: mean of the difference in ΔPD (VP − UP), − 0.4 [95% CI: − 0.52 to − 0.28, $p < 0.001$], generalized estimating equation: a beta estimator of ΔPD: 0.41, [95% CI: 0.26–0.56, $p < 0.001$]). The ΔPD pattern changes due to the raised tetanic stimuli were almost the same in the two methods.

**Conclusion** Due to the significant constant error, we consider the reproducibility of the measured ΔPD between UP and VP moderate.

*Trial registry number* UMIN 000047145. Prior to the subjects' enrollment, the trial was registered with the University Hospital Medical Information Network (Principal investigator: Mao Konno, Date of registration: 3.11.2022). https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000053778.

**Keywords** Nociceptive stimulus · Pupillary diameter · Ultrasound method · Video pupillometry

**Abbreviations**

NRS Numerical rating scale
PD Pupillary diameter
UP Ultrasound pupillometry
VP Video pupillometry

## Introduction

Monitoring surgical nociception in anesthetized patients remains challenging, and assessments of sympathetic responses to surgical trauma (e.g., tachycardia, hypertension, and sweating) have been reported to have potential for objectively quantifying surgical nociception [1]. Video pupillometry (VP) is one of the tools used to assess patients' increased pupillary diameter (PD) due to surgical nociception [2]. VP is an established method that is used clinically to assess the pupillary light reflex in patients with neurological issues [3], and some prospective observational/randomized studies

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have shown promising results supporting the pupillometric assessment of nociception [1, 2]. Compared to changes in patients' heart rate or blood pressure, changes in the PD are considered more sensitive to nociceptive stimuli; for example, changes in the PD due to nociceptive stimuli were detected in patients under general anesthesia while changes in their heart rate and blood pressure were not [4]. However, the use of VP to measure changes in the PD has some limitations when it is considered for use as a nociceptive monitor in the following conditions: ambient light can be quite problematic for pupillary measurements; the use of VP as continuous monitoring is impossible; and it is difficult or impossible to use VP in patients with facial or ocular injuries and those with severe eyelid swelling [1].

To counteract these limitations, ultrasound measurement of pupillary function has been proposed as an alternative to VP [5, 6]. However, the reproducibility of ultrasound pupillometry (UP) compared to VP has not been established. We thus conducted the present prospective observational study in healthy volunteers to investigate the reproducibility of nociceptive changes in subjects' PD measured with UP compared to those measured with VP.

## Methods

### Ethical approval

This prospective observational trial was conducted at Hirosaki University Hospital, Aomori, Japan. Before the subjects were enrolled, the trial was registered with the University Hospital Medical Information Network (registration no. 000047145, Principal investigator: Mao Konno, registration date: March 11, 2022) and was approved by the Institutional Review Board of the Hirosaki University Graduate School of Medicine (approval no. 2019-066, approval date Dec. 13, 2019; rinri@hirosaki-u.ac.jp).

### Subjects and data measurements

Healthy volunteers aged ≥ 18 years who provided written informed consent were eligible, and those with a history of any ophthalmologic disease and/or the use of any drugs that could affect their PD were excluded. Age, gender, and measured PD values were collected.

### Applied standardized noxious stimuli

A standardized cutaneous tetanic stimulus using TOF Watch® (Inmed Equipments, Gujarat, India) was applied to the marked median nerve of the subject's elbow randomly at 100 Hz with an amplitude of 10–60 mA for 5 s. The subjects evaluated the pain intensity of the randomly applied tetanic stimuli by using a self-reporting numerical rating scale (NRS).

### Video pupillometry

The subject was relaxed in a sitting position. Changes in the PD due to an applied tetanic stimulus were recorded with the use of an infrared video system (the DK-2000™ electronic pupillometer, Scalar Corp., Tokyo). The minimum measurable distance of this device was 0.1 mm. The subject's measured eye was kept covered with a detachable opaque rubber cup throughout the procedure in order to keep the measured eye in the dark so that ambient light could not affect the pupillary measurement (Fig. 1a) [7]. In contrast, the unmeasured eye was covered with an eye patch to reduce the effect of the consensual light reflex due to ambient light coming into the unmeasured eye, since ambient light was reported to impact pupil parameters in a prospective observational study with 280 pupillary measurements of healthy and critically ill subjects [8]. First, the baseline value of the subject's PD was measured, and after each cutaneous tetanic stimulus was randomly applied, the PD's changes were automatically captured, recorded, and analyzed (Fig. 1b).

### Ultrasound pupillometry

We used a SonoSite M series ultrasound system with an L25x, 6- to 13-MHz ophthalmology-compatible linear probe (FujiFilm Corp., Tokyo). After the subject was relaxed in a sitting position, a linear probe was gently placed on the subject's closed eye (Fig. 1c) and was tilted until the pupil was visualized as a circle in a trans-palpebral tangential image (Fig. 1d, e). Both eyes were kept closed to minimize the effects of ambient light coming into subject's eyes. The measured eye was covered with an eye patch to prevent contact between the subject's eye and the sonographic gel; the unmeasured eye was closed without an eye patch. The measurement time was within 5 min at the adjusted mechanical index ≤ 0.26 according to the 'as low as reasonably achievable' principle [9]. First, the baseline value of the PD was measured. Each cutaneous tetanic stimulus was then randomly applied. The maximum PD within 10 s after the applied noxious stimulus was manually captured and recorded, since we considered that the PD changes were complete within 2–3 s after a stimulus. The pupil has been reported to dilate within a 2- to 3-s period after the pupillary light reflex begins [10]. The minimum measurable distance of the ultrasound system was 1 mm. We manually measured the PD of recorded pupillary images with a ruler so that we could measure changes in the PD with a 0.1-mm minimum measurable distance in the UP method as well.

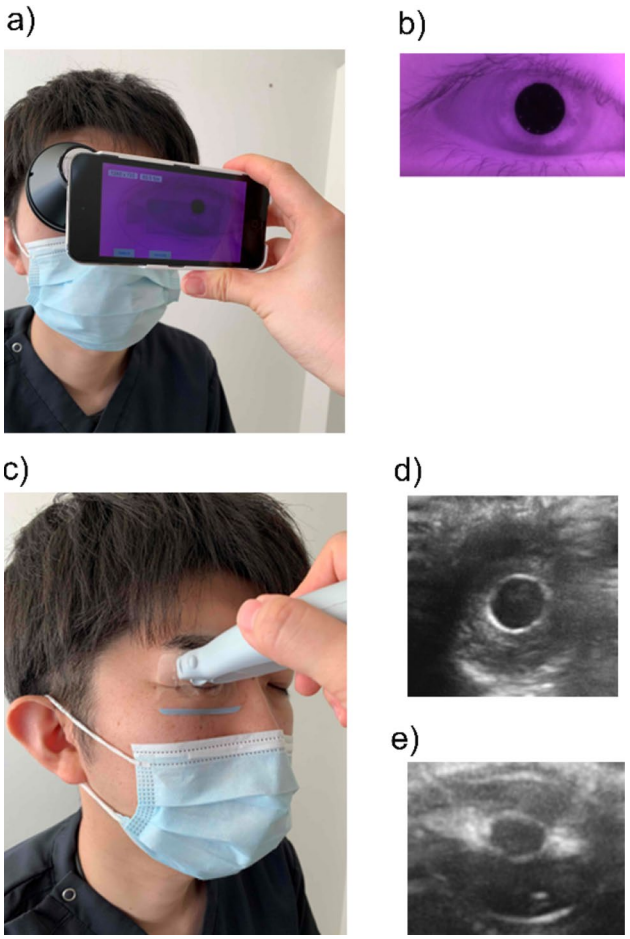


**Fig. 1** Photo of the video/ultrasound pupillometry probe and images of the captured pupil by the video pupillometry (VP) and ultrasound pupillometry (UP) methods. **a** The subject's measured eye was covered with a detachable opaque rubber cup throughout the procedure to keep the measured eye in the dark. **b** After each cutaneous tetanic stimulus was randomly applied, the pupillary diameter (PD) changes were automatically captured, recorded, and analyzed. **c** After the subject was relaxed in a sitting position, a linear probe was gently placed on the subject's closed eye covered with an eyepatch. **d** The ultrasound probe was tilted until the pupil was visualized as a circle in a trans-palpebral tangential image. **e** Some ultrasound images of the pupil captured by the UP method were oval rather than perfectly circular

## The changes in the pupillary diameter

Changes in the subject's PD between the maximal and basal values were calculated as ΔPD = maximal value − basal value. The basal value was measured for every ΔPD calculation. Each measurement with a tetanic stimulus was conducted at ≥ 5-min intervals. The measurements of the PD were performed by the same investigator (M.K.) with the use of VP or UP in a quiet room with standardized dimming lights. For all subjects, the VP measurements preceded the UP measurements, and the UP measurements were obtained within 7 days after the subjects' VP measurements.

## The relationship between the applied tetanic noxious stimulus and the subjects' NRS reports

The pain intensity of the randomly applied tetanic stimuli was reported by the subjects on an NRS. To confirm whether the subjects experienced appropriate pain for the applied tetanic stimulus, we investigated the relationship between the current values of all tetanic stimuli applied and the reported NRS values ($n = 210$ reports).

## The primary and secondary outcome measures

The primary outcome of this study was the correlation between the ΔPD value measured with VP and that measured with UP, analyzed by obtaining Spearman's rank correlation coefficient. The secondary outcomes were as follows. (1) The agreement between the ΔPD measured by the VP and UP methods was analyzed by the Bland–Altman method. (2) The estimated effectiveness of the use of the UP method on the repeatedly measured ΔPD was analyzed with the use of generalized estimating equation (GEE) models. (3) The correlation between ΔPD and the pain intensity (i.e., the TOF Watch stimulus' amplitude and the NRS values) in each pupillometry method was analyzed using Spearman's rank correlation coefficient. (4) The changes in the ΔPD pattern due to the raised noxious stimulus in VP/UP methods were evaluated by comparing each increased ΔPD to the basal value using the Friedman test with Bonferroni correction.

## Sensitivity analysis for the primary outcome

To validate the present data analysis, we performed a sensitivity analysis of the primary outcome with the assumption that ΔPD values measured with VP or UP were normally distributed. The correlation between the ΔPD measured with VP and that measured with UP was evaluated using Pearson's product-moment correlation coefficient.

## Statistical analyses

We determined the mean ± standard deviation (SD) for continuous variables with normal distributions. The median (and first and third quartiles) are presented for variables that were not normally distributed. Probability ($p$) values < 0.05 were accepted as significant. The Shapiro–Wilk test was used for checking the normality of the distributions of the variables. We calculated Spearman's rank correlation coefficient to evaluate the correlation between variables that were not normally distributed. The Bland–Altman method was

applied for assessing the agreement between the ΔPD measured with the VP method and that measured with the UP method. Repeated-measured continuous variables without a normal distribution were analyzed using the Friedman test with Bonferroni correction and the GEE models. We used GEE models with a linear link function, an exchangeable working correlation matrix, and a Huber–White sandwich estimator variance–covariance matrix to estimate how the UP method affects the repeatedly measured ΔPD, adjusted for potential confounders. Pearson's product-moment correlation coefficient was used for the evaluation of the correlation between variables with normal distributions.

A priori sample size calculations for the primary outcome were done using G*Power 3 software [11]. A power analysis was performed by using the correlation coefficient with an effect size of 0.3 (i.e., medium effect size) and the power of 0.80 at a two-sided alpha level of 0.05. A total of 84 measurements was needed for a medium effect size. We planned to perform seven measurements per subject. The total number of 15 subjects (105 measurements) was thus sufficient in accord with the current power analysis. All statistical analyses were conducted with IBM SPSS® statistics ver. 22.0 software (IBM, Tokyo).

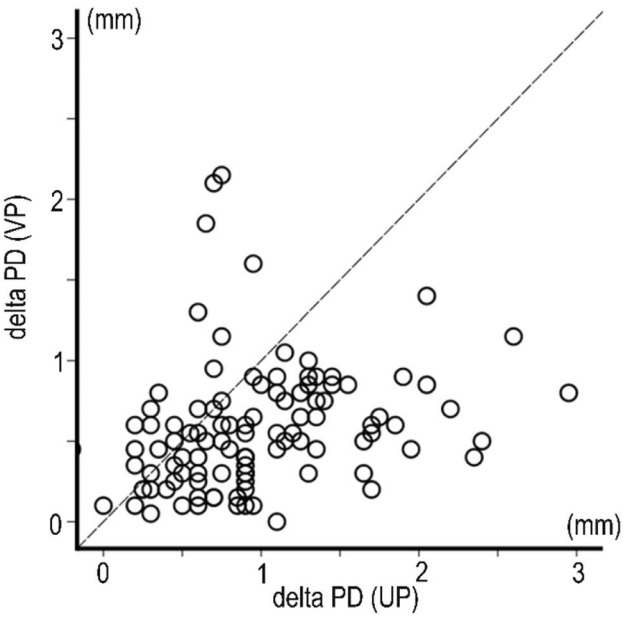


**Fig. 2** The correlation between changes in the PD measured with VP and that measured with UP. Changes in the PD between the maximal and basal values were calculated as ΔPD = maximal value − basal value. A significant but weak positive correlation was observed between the ΔPD values obtained by the two methods (Spearman's $\rho = 0.38$, $p < 0.001$). The graph was created using Adobe Photoshop 2022 software and IBM SPSS® statistics ver. 22.0 software

## Results

A total of 15 healthy volunteers (12 males/3 females) aged 31 [28, 32] [median (first and third quartiles)] years old were enrolled. The study was well-powered with 105 calculated ΔPD values analyzed.

### The relationship between the applied tetanic pain intensity and the reported NRS value

The NRS of each tetanic noxious stimulus was as follows, as the median value [first and third quartiles]. Current at 0 mA: 0 [0, 0], 10 mA: 2 [1, 2.3], 20 mA: 2 [1, 2.3], 30 mA: 2.5 [2, 3], 40 mA: 3 [2, 5], 50 mA: 4 [3, 5.3], and 60 mA: 4.5 [4, 6]. A highly significant positive correlation was identified between the current values of the tetanic stimuli and the subjects' NRS values (Spearman's $\rho = 0.82$, $p < 0.001$).

### The primary outcome measure

There was a significant but weak positive correlation between the ΔPD measured with VP and that measured with UP (Spearman's $\rho = 0.38$, $p < 0.001$) (Fig. 2).

### The secondary outcome measures

As shown by the Bland–Altman plot in Fig. 3, a significant fixed error existed between the values measured by the two pupillometry methods, with the mean of the difference in the ΔPD (value = VP − UP) at − 0.40 (95% confidence interval [CI]: − 0.52 to − 0.28, $p < 0.001$). The 95% limit of agreement was − 1.62 to 0.81. A significant proportional error was also observed between the values measured by the two methods ($p = 0.007$).

The GEE models were applied to estimate how the use of UP affected the repeatedly measured ΔPD, adjusted for the subjects' age and gender. The results of the analysis with the GEE model demonstrated that the use of UP was associated with a significantly larger ΔPD [beta (β) estimator of ΔPD: 0.41, 95% CI: 0.26–0.56, $p < 0.001$], but neither age ($p = 0.95$) nor gender ($p = 0.4$) was associated with a significantly larger ΔPD.

For the VP method, there was a significant, strong, and positive correlation between the ΔPD and each amplitude of the TOF Watch (Spearman's $\rho = 0.50$, $p < 0.001$) and between the ΔPD and the pain intensity reported on the NRS (Spearman's $\rho = 0.57$, $p < 0.001$), whereas the corresponding correlations for the UP method were weak (TOF: Spearman's $\rho = 0.34$, $p < 0.001$, NRS: Spearman's $\rho = 0.39$, $p < 0.001$). The increase in the ΔPD due to tetanic stimuli measured by UP showed a pattern that was nearly identical to that obtained with VP, and a significant increase in the ΔPD compared to that at 0 mA was detected at the amplitudes > 40 mA in both methods. However, in our multiple

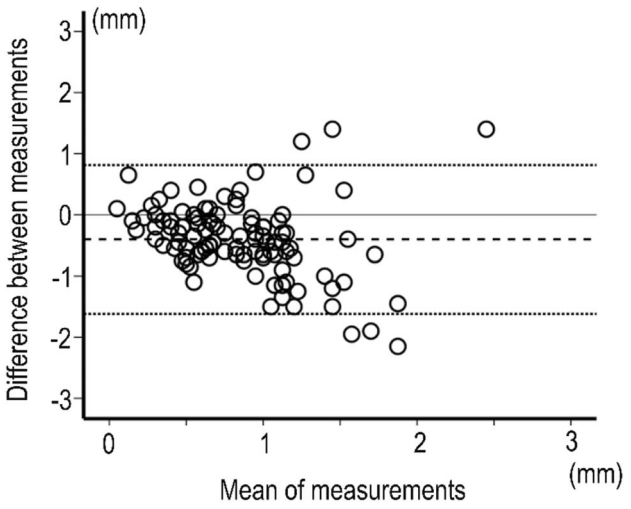


**Fig. 3** The Bland–Altman plot assessing the agreement between changes in the PD measured with VP and that measured with UP. Changes in the PD between the maximal and basal values were calculated as ΔPD = maximal value − basal value. *Large-dashed line:* the error (i.e., the mean value of the difference in the values measured by each pupillometry method). *Small-dashed line:* the 95% limits of agreement. A fixed error existed between the measured values of the two methods, since the mean of the difference in ΔPD of the VP-measured values to that of the UP-measured values was − 0.4 [95% CI: − 0.52 to − 0.28, $p = 0.000$]. The proportional error was also found between the values obtained by the two methods ($p = 0.007$). The graph was created using Adobe Photoshop 2022 software and IBM SPSS® statistics ver. 22.0 software

comparisons of the ΔPD with Bonferroni correction, the significant increase was observed at the amplitudes of 40, 50, and 60 mA in the VP method but at only 40 and 60 mA (not 50 mA) in the UP method (Table 1).

### The sensitivity analysis

The results of the sensitivity analysis conducted to validate the primary outcome were similar to those obtained with the original results. The correlation between ΔPD measured with VP and that measured with UP evaluated using Pearson's product-moment correlation coefficient showed a weak but significant correlation (Pearson's $r = 0.24$, $p = 0.014$).

## Discussion

This prospective observational study was conducted to evaluate the reproducibility of changes in subjects' PD due to nociceptive stimuli measured with UP compared to VP. The primary outcome results demonstrated that there was only a weak positive correlation between the ΔPD measured with UP and that measured with VP. The results of the Bland–Altman analysis and GEE model indicated that there was a significant constant error between the ΔPD measured by UP and VP. However, we observed a significant correlation between ΔPD and pain intensity (i.e., the TOF amplitude and the subjects' NRS values) in both the UP and VP methods, although the correlation was weaker in the UP method compared to the VP method. The pattern of the increased ΔPD measured with UP was almost the same as that measured with VP.

A prospective observational study with 100 subjects that assessed the reduction in the PD due to a light stimulus in different age groups revealed that normal pupillary values measured with B-mode ultrasound clearly detected changes in the PD; the reported pupillary values measured with UP [5] were similar with those measured with VP reported in

**Table 1** The measured pupillary diameter values

| TOF, mA | VP (pupillary dia., mm) | | | UP (pupillary dia., mm) | | |
|---|---|---|---|---|---|---|
| | Max | Min | ΔPD | Max | Min | ΔPD |
| 0 | 4.6 ± 0.9 | 4.3 ± 0.8 | 0.2 [0.1, 0.3] | 8.8 ± 1.8 | 7.8 [6.9, 8.9] | 0.3 [0.2, 0.9] |
| 10 | 4.5 ± 1.0 | 4.1 ± 1.0 | 0.5 [0.3, 0.6] | 9.1 ± 1.6 | 7.4 [6.9, 8.8] | 0.8 [0.6, 1.3] |
| 20 | 4.7 [4.0, 4.9] | 4.0 ± 1.0 | 0.4 [0.3, 0.6] | 9.2 ± 2.4 | 7.8 [6.6, 8.8] | 0.8 [0.6, 0.9] |
| 30 | 4.8 ± 0.9 | 4.3 ± 0.7 | 0.6 [0.4, 0.7] | 9.1 ± 1.4 | 8.2 ± 1.6 | 0.9 [0.8, 1.1] |
| 40 | 5.2 ± 1.1 | 4.3 ± 0.9 | 0.9 [0.5, 1.0]*** | 9.5 ± 1.8 | 8.1 ± 1.7 | 1.3 [0.9, 1.8] *** |
| 50 | 4.9 ± 0.7 | 4.2 ± 0.7 | 0.7 [0.5, 0.8]*** | 9.3 ± 1.7 | 8.0 [7.0, 8.7] | 1.2 [0.6, 1.3] |
| 60 | 4.9 ± 1.0 | 4.2 ± 1.1 | 0.6 [0.5, 0.9]*** | 8.4 [7.8, 10.8] | 7.4 [6.8, 8.9] | 1.1 [0.8, 1.4]** |
| Spearman's ρ (ΔPD versus TOF) | | | $0.50^{\#\#\#}$ | Spearman's ρ (ΔPD versus TOF) | | $0.34^{\#\#\#}$ |
| Spearman's ρ (ΔPD versus NRS) | | | $0.57^{\#\#\#}$ | Spearman's ρ (ΔPD versus NRS) | | $0.39^{\#\#\#}$ |

Max: maximum, Min: minimum, NRS: numerical rating scale, TOF: train of four, UP: ultrasound pupillometry, VP: video pupillometry, ΔPD: delta pupillary diameter = max. pupillary diameter value – min. value

$^{**}p < 0.01$, $^{***}p < 0.001$ versus ΔPD at 0 mA, $^{\#\#\#}p < 0.001$ for the correlation between ΔPD and the TOF or NRS

early literatures [12, 13]. Another prospective non-randomized study comparing the pupillary light responses in UP with that in VP in 26 critically ill patients (212 pupillary measurements) showed a strong positive correlation between a reduction in the PD obtained by VP and that shown by UP ($r = 0.926$, 95% CI: 0.893–0.949, $p < 0.001$) [3]. In contrast, our present results demonstrated that the reproducibility of UP was moderate, due to a weak correlation between the ΔPD measured by the two methods, with a significant constant error. Despite this inconsistency, our findings indicating that UP can detect a noxious increase in the PD similarly to VP supports the possibility that UP can be used as an alternative to VP for pupillometric assessments of nociception in clinical settings; the ΔPD measured with UP as well as that measured with VP was significantly correlated with the subjects' reported pain intensity. The use of UP as well as that of VP detected a significantly increased ΔPD at > 40 mA of nociceptive stimuli.

Our present results are not consistent with those of the above-cited studies [3, 5]. We speculate that this inconsistence is due mainly to technical error, since UP requires a manual measurement of the PD [3, 5]. Experience is necessary to obtain accurate measurements with UP [5], whereas VP automatically captures, records, and analyzes the pupillary diameter's changes [1, 3]. Indeed, we observed that some of the ultrasound images of the pupils' shape were oval rather than perfectly circular in the UP method (Fig. 1d, e), probably because the ultrasound probe on the eyelid could not be placed at a right angle to the pupil. The recorded PD values obtained with the UP method were thus larger than those obtained with VP in the present study.

There are some study limitations to consider. (1) For the evaluation of the reproducibility of UP compared with VP, both UP and VP should have been performed in the same sessions for the subjects; one pupil should have been measured with UP while the other was measured with VP. However, this strategy was technically difficult for the single examiner. In a prospective study comparing the pupillary light responses in UP with that in VP, high reproducibility between UP and VP was reported although the two methods were not conducted at the same time [3]. (2) This study was conducted in fully conscious healthy volunteers who were not under general anesthesia. Caution is necessary when evaluating changes in the PD of anesthetized patients by UP as well as VP since several anesthetic agents, opioids in particular, influence the PD of anesthetized patients [1, 2]. However, some randomized clinical trials conducted to evaluate the clinical usefulness of VP-guided anesthesia conducted in patients receiving opioid-based anesthesia reported a significant reduction of opioid doses with VP guidance [14, 15]. Those results indicate the potential clinical usefulness of UP in anesthetized patients. (3) The technical barrier presented by UP measurement is addressed above. In this study, the same examiner measured the subjects' PD values by the UP method, which may have resulted in the constant errors. However, such a technical error is often encountered in clinical settings. Our results indicate that UP measurements along with technical errors can be clinically acceptable as an alternative to VP. (4) This study was conducted with a small number of healthy volunteers ($n = 15$). Further studies with a larger number of anesthetized patients are needed to determine the precise clinical usefulness of nociceptive assessments by UP.

## Conclusion

Our findings demonstrated that ultrasound pupillometry provided moderate reproducibility of nociceptive changes in subjects' PD compared to VP, probably due to the technical barrier. Ultrasound pupillometry may be an alternative to video pupillometry for pupillometric assessments of nociception in clinical settings.

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**Authors' contributions** MK: Obtained the subjects' written informed consent, data collection, and drafting and revising the manuscript. HN: Analysis of the data and drafting and revising the manuscript. MK: Study design and revising the manuscript critically for important intellectual content. KH: Revising the manuscript critically for important intellectual content, and supervision of the study. All authors approved the final version of the manuscript.

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**Data availability** The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval** The Hirosaki University Graduate School of Medicine Institutional Review Board approved this study (approval no. 2019–066).

**Consent to participate** Informed consent was obtained from all individual subjects included in the study.

**Prior presentations** None.

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