

# Pupillary reflex dilation in response to incremental nociceptive stimuli in patients receiving intravenous ketamine

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**Abstract** Pupillometry is a non-invasive monitoring technique, which allows dynamic pupillary diameter measurement by an infrared camera. Pupillary diameter increases in response to nociceptive stimuli. In patients anesthetized with propofol or volatile agents, the magnitude of this pupillary dilation is related to the intensity of the stimulus. Pupillary response to nociceptive stimuli has never been studied under ketamine anesthesia. Our objective was to describe pupillary reflex dilation after calibrated tetanic stimulations in patients receiving intravenous ketamine. After written consent, 24 patients of our pediatric burn care unit were included. They received an oral morphine premedication (0.3 mg kg<sup>-1</sup>) 1 h before their scheduled daily dressing change. Just before the procedure, they received 1 mg kg<sup>-1</sup> of intravenous ketamine. Two minutes after this bolus, tetanic stimulations of incremental intensities were performed on the arm of each patient (5–10–20–30–40–60 mA, 60 s interval between stimulations). Pupillary diameter, heart rate and movements were recorded before and after each stimulation. Tetanic stimulations were associated with changes in pupillary diameter and heart rate. The magnitude of these changes was significantly influenced by the intensity of stimulation (ANOVA for repeated measures,  $p < 0.001$ ). Movement was associated with a 32% increase in diameter (ROC curves, AUC 0.758) with 65% sensitivity and 77% specificity. In children, pupillary reflex dilation to nociceptive stimuli persists under deep sedation obtained with 1 mg kg<sup>-1</sup> of intravenous ketamine

combined with a 0.3 mg kg<sup>-1</sup> oral morphine premedication, and its magnitude depends on the intensity of the stimulation. Our results confirm that pupillometry could be a relevant way to monitor nociception in anaesthetised subjects, including those receiving ketamine.

*Trial registration* clinicaltrials.gov, NCT 02648412

**Keywords** Pupillometry · Monitoring · Nociception · Pain · Ketamine · Anesthesia

## 1 Introduction

The monitoring of nociception in anaesthetised patients is currently one of the most challenging issues for anaesthesiologists. The finality of this monitoring is to provide the most accurate dosage of analgesics for each patient. Insufficient analgesia can result in significant hemodynamic variations, and might increase the risk of awareness. Conversely, an excessive amount of opioids might increase the incidence of general opioids-related side effects, and might be responsible for opioid-induced hyperalgesia [1, 2]. Anesthesiologists usually rely on the increase in heart rate or blood pressure to assess intraoperative nociception. But these parameters are not specific to inadequate analgesia, and many confounding factors such as hypovolemia, sepsis, anemia or medication, can interfere in their interpretation. Several monitoring techniques have been developed to provide a more precise and specific assessment of nociception. Among them, pupillometry has shown interesting results [3]. The physiological mechanism on which pupillometry is based is pupillary reflex dilation (PRD): the increase in pupillary diameter in response to a painful stimulation [4, 5]. The amplitude of pupillary reflex dilation is proportional to the intensity of nociceptive stimuli and inversely proportional to

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the amount of administered opioids, both in awake patients and in patients receiving either propofol or volatile anesthetics [6–10]. These results suggest that the monitoring of pupillary diameter may provide a useful assessment of the intraoperative balance between nociception and antinociception. However, pupillary reflex dilatation has never been investigated under ketamine anesthesia. The mechanisms of action of ketamine are very different from those of propofol or volatile anesthetics. In consequence, the pupillary reactivity profile obtained under propofol or volatile anesthetics cannot be extrapolated to patients under ketamine. Whether PRD persists under ketamine, and whether its amplitude is correlated to the intensity of the stimulus, as under volatile anesthetics or propofol, remains to be demonstrated.

Therefore, the main objective of our study was to describe PRD in response to standardized tetanic stimulations in patients receiving intravenous ketamine.

Furthermore, the clinically relevant thresholds of pupillary dilatation for characterizing insufficient analgesia in anesthetized subjects are still unknown. The only available data were obtained in awake patients: in the early post-operative period, a pupillary dilation of 23% predicted a verbal pain score of more than 1 on a four point scale with 91% sensitivity and 94% specificity [9]. Anesthetized subjects have not been studied, but in this patient population the occurrence of withdrawal movements in response to a painful stimulus may be considered as a clinical sign of inadequate analgesia. As a secondary aim, to better characterize insufficient analgesia in terms of pupillometry, we investigated the threshold of pupillary dilation associated with the occurrence of movement evoked by tetanic stimulations in patients under intravenous ketamine.

## 2 Methods

### 2.1 Study design

After approval of our Institutional Review Board (Comité de Protection des Personnes Ile-de-France 5, Hôpital Saint-Antoine, 75012 Paris, France) and written informed consent of the parents (and if possible, of the child), we prospectively included children aged 1–13 years in this monocentric open study, registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT 02648412).

Recruitment took place in our pediatric burn intensive care unit. In our institution, the standard management of these patients consists of a daily antiseptic bath under ketamine anesthesia. In our standard procedure, 1 h after a standardized oral morphine premedication ( $0.3 \text{ mg kg}^{-1}$ ), boluses of  $1 \text{ mg kg}^{-1}$  of intravenous ketamine are administered to the patients to allow complete skin disinfection with antiseptic soap, and dressing change. We administer an additional  $1 \text{ mg kg}^{-1}$  ketamine bolus if the patient displays

any sign of insufficient analgesia: movement, or heart rate increase  $\geq 20\%$ . The interval between two ketamine boluses is unpredictable: it varies a lot according both to the patient, and to the intensity of the nociceptive stimulation. This intensity depends on both the extent of the burnt surface area, and on the evolution stage of the burn. The usual duration of the procedure is 30–60 min, depending on the extent and location of the burns. Spontaneous ventilation is maintained throughout the procedure, supplemental oxygen is administered via a face mask if SpO<sub>2</sub> decreases below 94%.

For this study, we included patients whose burns covered a surface area of less than 40%. We only included patients for which satisfactory daily pain management (pain scores  $< 3/8$  on the Objective Pain Scale) could be achieved with a standard analgesic regimen, consisting of scheduled oral morphine ( $0.15 \text{ mg kg}^{-1}$  every 4 h) and oral paracetamol ( $15 \text{ mg kg}^{-1}$  every 6 h). Patients were not included if their skin was damaged within 5 centimetres of the eye, or if they had any neurological, metabolic or ophthalmologic disease. Patients requiring mechanical ventilation (smoke inhalation), or patients requiring additional intravenous analgesics for pain management (other than the standardized intravenous ketamine for antiseptic bath and dressing change) were not included.

The study period began when patients were ready for their antiseptic bath, 1 h after their oral premedication. In addition to the standard monitoring (cardioscope, SpO<sub>2</sub>, Datex Ohmeda™, Helsinki, Finland), two adhesive cutaneous electrodes were placed on the ulnar surface of the inner forearm. The first electrode was positioned just above the wrist; the second electrode was positioned 3–4 cm above. These electrodes were connected to the videopupillometer (Neurolight, IDMED™, Marseille, France), which could deliver calibrated tetanic stimuli (100 Hz, 5 s). A first bolus of  $1 \text{ mg kg}^{-1}$  ketamine was injected intravenously to the patient. After 2 min, the first tetanic stimulation was performed, with an intensity of 5 mA, and maximal pupillary dilation was measured. Pupillary diameter returned to baseline within thirty seconds after the stimulation. Every 60 s thereafter another stimulation was performed (100 Hz, 5 s), with an increasing intensity of 5, 10, 20, 30, 40 and 60 mA. Thus, a maximum of 6 stimulations were performed on each patient. If any withdrawal movement occurred after one of these stimulations, the protocol was interrupted, and no further stimulation was applied to that patient. The maximal duration of the protocol for each patient was 8 min, following the ketamine bolus. During the study period, the patient was not touched; the environment was kept warm and silent. At the end of the study period (maximum 6 stimulations, 8 min), the antiseptic bath was begun.

The main outcome measure was the maximal change in pupillary diameter after the tetanic stimulations (as a percentage of pre-stimulation diameter). Secondary outcome

measures included the maximal variation of heart rate (as a percentage of pre-stimulation heart rate), and the occurrence of movements.

### 2.2 Data recording and analysis

Before ketamine injection, pain was evaluated by an Objective Pain Scale (maximal score: 8 points). Before ketamine injection, a sedation score (UMSS: University of Michigan Sedation Scale) was assessed. A score of 0 indicates that the patient is awake and alert. The maximum UMSS score is 4, and indicates that the patient is unarousable, even by significant physical stimuli [11]. A second assessment of sedation by UMSS was performed 2 min after ketamine injection, before the first stimulation. A final UMSS was assessed at the end of the study period. For each tetanic stimulation, the pupillary diameter was continuously measured starting just before until 30 s after the stimulation.

Pupillary diameter was assessed with the videopupillometer Neurolight (IDMED™, Marseille, France). This device allows the measurement of pupillary diameter using an infra-red camera that identifies, tracks, and measures the pupil. In addition, this pupillometer can deliver a calibrated tetanus (5–60 mA) via two cutaneous electrodes placed along the ulnar nerve. This electrical stimulation is coupled with the measurement of pupillary diameter changes following the tetanus. The pupillometer includes a light-occlusive rubber cup which surrounds the eye. No part of this non-invasive device ever touches the eye of the patient. Each measurement consisted of a continuous 35 s scan (5 s of stimulation, 30 s of observation). Pre-stimulation pupillary diameter was defined as the diameter at the beginning of the scan. Each measurement requires maintaining the eyelid open for about 35 s, and then it can be closed again until the next measurement. All measures were performed on the right eye of the patient. The left eye remained closed during the study period.

Changes in pupillary diameter and heart rate were assessed by comparing pre-stimulation values and maximal changes after the stimulation. Heart rate and pupillary diameter before the first stimulation (5 mA) were considered to be baseline values. Movements occurring after tetanic stimulations were recorded by the investigator, who remained at the bedside throughout the study period.

### 2.3 Statistical analysis

The primary endpoint in this study was the variation in pupillary diameter in response to tetanic stimulations. Based on previous studies investigating pupillary dilation in response to nociceptive stimuli [8, 9], the sample size was calculated to detect a difference of means of 30% with an expected standard deviation within groups of 25%. A sample size of 22 patients provided a level of significance of 0.05, and a power of 0.8.

The effects of tetanic stimulations on pupillary diameter and heart rate, and the influence of the level of tetanic intensity were tested using a two way ANOVA for repeated measures with post hoc Fisher’s LSD tests (XLSTAT 2007, Microsoft™, Redmond, WA, USA). A Spearman coefficient was calculated to characterize the relationship between tetanic intensity and pupillary dilation. Results are expressed as mean ± SD, or median [interquartile]. A p-value inferior to 0.05 was considered as significant.

To investigate the level of pupillary dilation associated with the occurrence of movements, we used the Receiving Operating Curves analysis (XLSTAT™ 2007, Microsoft, Redmond, WA, USA). Movement was considered to be a binary event: either present or absent. An area under the curve (AUC) was considered as significant and relevant if greater than 0.7.

## 3 Results

Twenty-four patients were included. Thus, 24 series of measures were performed. The demographic data are summarized in Table 1. Pain scores before the procedure were low (Objective Pain Scale < 2 points for all the patients). No patient moved after the 5 and 10 mA stimulations. Movement occurrence is detailed in Fig. 1. If any movement occurred, no further stimulation was applied to the patient. Seven measures were technically impossible to perform due to the nystagmus that may be observed after ketamine injection. Thus, 105 stimulations were analysed.

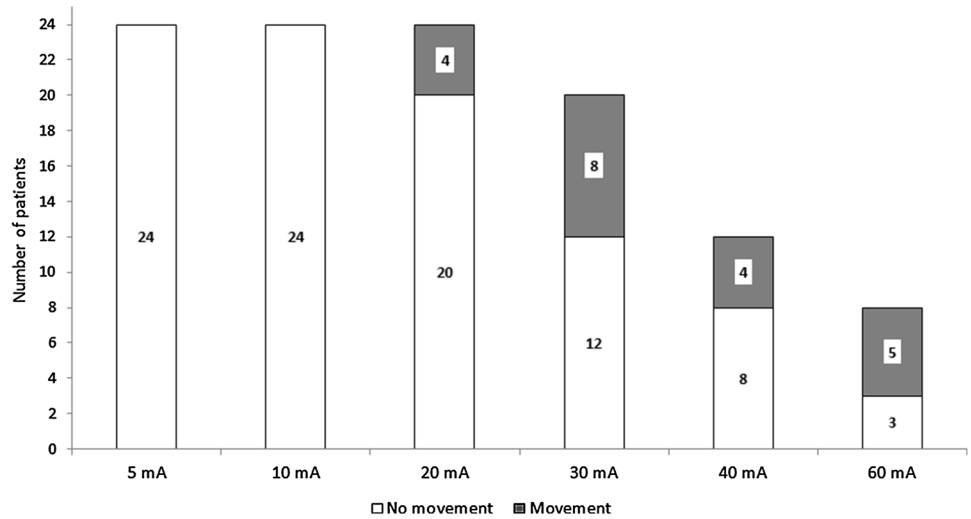
Before ketamine injection, patients were fully awake, with a median UMSS score of 0 [0–0]. Two minutes after ketamine injection, patients were deeply sedated, with a median UMSS score of 4 [4]. At the end of the study period, median UMSS was 3 [3, 4].

Baseline pupillary diameter was 3.4 ± 0.2 mm. All pre-stimulation values were not significantly different from the baseline value (Table 2), with a mean pre-stimulation diameter of 3.3 ± 0.7 mm. Tetanic stimulations were associated with significant changes in pupillary diameter (ANOVA p < 0.001). The magnitude of pupillary dilation was significantly influenced by the intensity of stimulation (ANOVA p < 0.001), with a maximal mean dilation of 39 ± 19%, occurring at 60 mA (Figs. 2, 3). Pupillary diameter increase was significantly correlated to the intensity of stimulation (Spearman coefficient r = 0.59, p < 0.001).

**Table 1** Patient’s characteristics (mean ± SD)

	N = 24
Age (years)	4.2 ± 3.7
Weight (kg)	20 ± 13
Burn surface area (% of body surface area)	17 ± 11

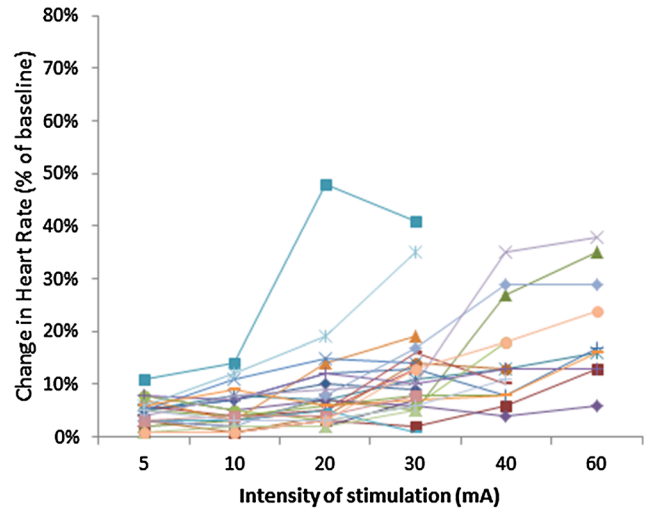
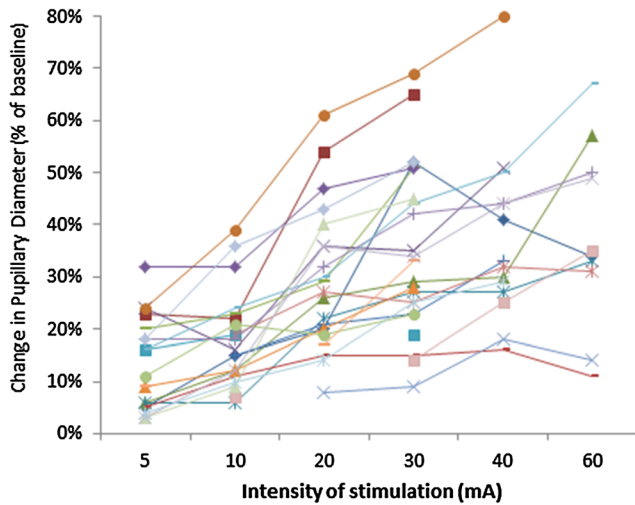
**Fig. 1** Occurrence of movement at each intensity of stimulation. White area: number of patients who did not move. Grey area: number of patients who moved. If a patient moved, no further stimulation was performed on this patient



**Table 2** Pupillary diameter (mm) before and after each stimulation (mean ± SD)

	5 mA	10 mA	20 mA	30 mA	40 mA	60 mA
Pre-stimulation	3.6 ± 0.9	3.3 ± 0.8	3.4 ± 0.8	3.2 ± 0.7	3.1 ± 0.6	3.4 ± 0.7
Post-stimulation (maximal)	3.7 ± 0.9	3.7 ± 0.9	4.1 ± 0.8	4.2 ± 0.9	4.2 ± 0.8	4.5 ± 1.0
Pupillary dilation	13 ± 9%	18 ± 9%	29 ± 13%	35 ± 17%	36 ± 17%	39 ± 19%

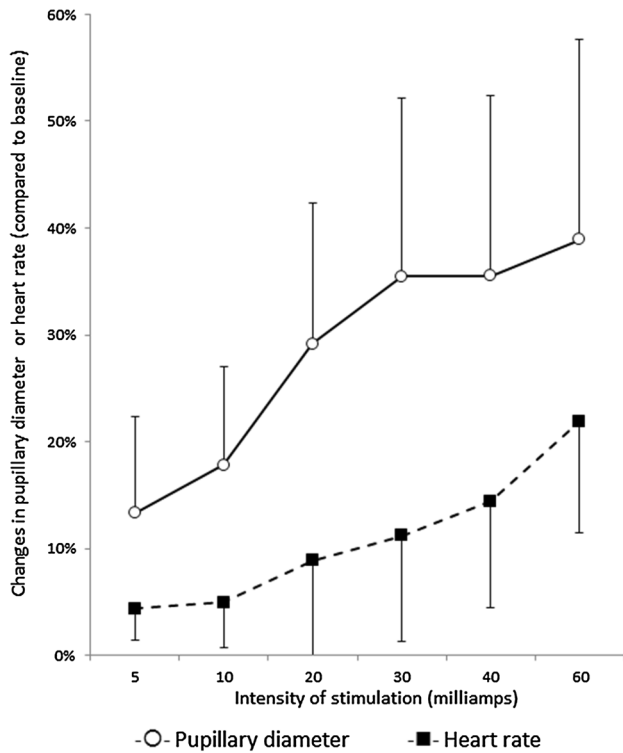
mA milliamps



Each line represents a patient.  
 Missing measures are due to nystagmus  
 Interrupted lines are due to movement occurrence  
 mA : milliamps

**Fig. 2** Individual variations of pupillary diameter and heart rate at the different intensities of stimulation, expressed as a percentage of increase compared to baseline. Each line represents a patient. Missing pupillary diameters correspond to impossible measures due to

the presence of a nystagmus (n=7). Interrupted lines correspond to patients who moved before the 60 mA stimulation (n=16). mA milliamps



**Fig. 3** Pupillary diameter and heart rate increase at the different intensities of stimulation (mean ± SD)

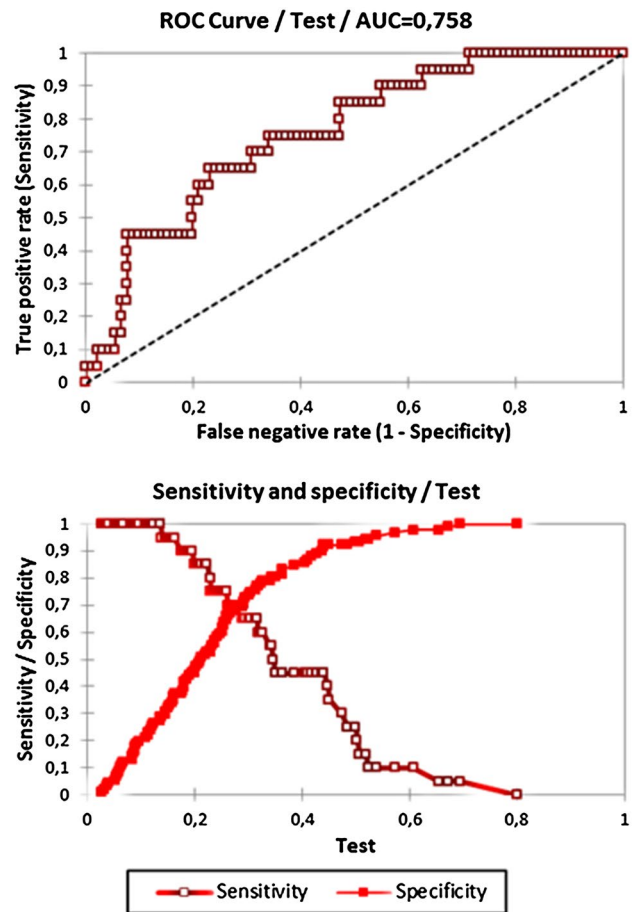
Baseline heart rate was  $115 \pm 31$  beats per minute, all pre-stimulation values were not significantly different from the baseline value. Tetanic stimulations were associated with moderate but significant changes in heart rate ( $p < 0.001$ ). The magnitude of heart rate changes was significantly influenced by the intensity of stimulation ( $p < 0.001$ ), with a maximal mean increase of  $22 \pm 10\%$ , occurring at 60 mA (Figs. 2, 3).

Regarding the threshold of pupillary dilation associated with the occurrence of movement, the ROC curves are detailed in Fig. 4. We found that movement was associated with a pupillary dilation of 32% (AUC = 0.758), with a sensitivity of 0.65, and a specificity of 0.77.

#### 4 Discussion

Using tetanic stimulations, we have demonstrated that in children, pupillary dilation in response to nociception persisted after  $1 \text{ mg kg}^{-1}$  of intravenous ketamine combined with a  $0.3 \text{ mg kg}^{-1}$  oral morphine premedication, and that the magnitude of pupillary dilation increased with the intensity of stimulation.

Pupil size results from the opposing action of smooth muscles in the iris innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system. The



**Fig. 4** Probability of movement associated with pupillary dilation in response to nociceptive stimulation: ROC curves

parasympathetic system of the iris originates exclusively in the midbrain, innervates the circular fibres of the iris, and has a constrictive action. In contrast, the polysynaptic sympathetic system innervates the radicular fibres of the iris and dilates the pupil. In awake subjects, the stimulus-induced dilation is primarily sympathetically mediated and the amplitude of pupillary dilation has been demonstrated to correlate with pain perception [6, 9, 12]. This pupillary dilation in response to noxious stimulation is also observed in subjects anaesthetised with propofol or volatile agents. However the persistence of this reflex after a local  $\alpha 1$  adrenergic blockade in subjects anaesthetised with desflurane suggests that in that context, the sympathetic contribution to pupil size is negligible [13]. Despite these physiological differences, the persistence of pupillary dilation in response to nociceptive stimulation under general anaesthesia makes pupillometry a potentially interesting tool to monitor intra-operative nociception.

We have previously demonstrated, in children under sevoflurane, receiving no muscle relaxants, that skin incision was associated with a fast and ample pupillary dilation (200%

increase in pupillary diameter), although no movement or significant hemodynamic changes occurred. The pupillary dilation was rapidly inhibited by a bolus of alfentanil [5]. Several other publications have described a similar pupillary reactivity to nociceptive stimulation under volatile halogenated agents (sevoflurane, desflurane and isoflurane) [4, 7, 13–15]. Ketamine was used in combination with inhaled general anaesthesia in one of these studies: under desflurane 4–5%, the injection of 1 mg kg<sup>-1</sup> of ketamine to healthy adults did not modify baseline pupillary diameter [15]. Our study provides the first evidence that pupillary reflex dilation to nociceptive stimulation persists under intravenous ketamine anaesthesia, when no other general anaesthetics are administered to the patient.

Regarding the influence of ketamine, used as a sole anesthetic agent, and pupillary diameter, very few data are available. The effects of ketamine on the autonomous nervous system are still not fully understood. A shift of the cardiac sympatho-vagal balance towards its sympathetic component has been suggested in patients receiving intravenous ketamine [16]. In anaesthetised dogs, a moderate increase of pupillary diameter has been demonstrated after intravenous ketamine [17], but these results have not been confirmed in humans. There are no published data about the possible influence of ketamine on the pupillary reactivity to noxious stimulations.

The relationship between the intensity of nociceptive stimulation and the magnitude of pupillary dilation in anesthetized patients was suggested in a study by Barvais [8]: in patients anaesthetised with propofol, a standardized nociceptive stimulus (60 mA, 10 s, 100 Hz tetanus) was performed at different levels of analgesia, obtained with increasing effect site target concentrations (Ce) of remifentanyl. For remifentanyl Ce comprised between 0 and 3 ng ml<sup>-1</sup>, the authors describe a linear relationship between remifentanyl Ce and post-stimulation pupillary diameter: for an identical stimulus, pupillary dilation decreases when remifentanyl concentration increases. There were two possible (and non-exclusive) explanations to these results: the weaker pupillary dilation could either be attributed to the enhanced analgesia provided by higher concentrations of remifentanyl, or merely to the direct dose-dependent miotic effects of remifentanyl. Our results support the former hypothesis (less dilation explained by a more powerful analgesia). In contrast with Barvais et al. our variable parameter was the intensity of nociception, not the amount of opioids. Taken together, our findings and those by Barvais et al. suggest that the analgesia-nociception balance might be adequately monitored by pupillometry in anaesthetized subjects.

The pupillary diameters we measured might have been influenced by the previous administration of morphine to our patients. Baseline pupillary diameters and post-stimulation pupillary diameters might have been decreased by

oral morphine. However, morphine administration was standardized for all patients, both as an oral premedication (0.3 mg kg<sup>-1</sup> 1 h before the antiseptic bath) and as a scheduled oral analgesic medication for the remainder of the day (0.15 mg kg<sup>-1</sup> every 4 h). No other drug known to influence pupillary diameter was administered. Because of the interindividual variability in opioid sensitivity, standardized doses of oral morphine might have affected pupillary diameters differently between our patients. Despite this potential bias, which might have theoretically blunted pupillary response to nociceptive stimuli, our results have reached statistical significance.

Another factor which might have influenced our measurements was that it was not possible, in practice, to standardize ambient light for all measurements. Thus, pupillary diameters might have been influenced by ambient light during the 1–2 s between eyelid opening and light occlusive pupillometer placement. However, this potential bias applies to all patient measurements, as all data collection took place in the same room, between 9.00 and 12.00 AM.

The consistent pupillary response observed in our population (maximal mean dilation 39 ± 19%) occurred while the amplitude of heart rate variation was smaller (maximal mean increase 22 ± 10%), and while movement response was inconstant. Compared to the increase in heart rate, the wider range of pupillary diameter variation in response to nociceptive stimuli has been reported in numerous other studies, both in children [5] and in adults [7]. In these studies, the interpretation of this phenomenon was that pupillometry provided a more sensitive assessment of intraoperative nociception than heart rate variations.

Pupillary dilation, heart rate increase and movement responses to nociception imply sub-cortical structures located at nearby but different anatomic levels: the mid-brain for pupillary reflex, the lower half of the brainstem for heart rate and the spinal level for movement. Thus, the current study supports the assumption previously suggested [14], that the dissociation between heart rate, movement and pupillary responses may be explained by different sensitivities to anesthetic drugs of the brain structures involved in these processes. With volatile anesthetics, more specifically with sevoflurane, different Minimum Alveolar Concentrations (MACs) have been determined in children for abolition of pupillary dilation (MAC PUP = 4.8%), blunting of adrenergic response (MAC BAR = 3.6%), movement inhibition (MAC = 2.5%), and return to consciousness (MAC AWAKE = 0.45%) [14, 18–20]. Hence, under sevoflurane, the MAC is higher than the MAC AWAKE: when depth of anesthesia decreases, movement will be restored before consciousness. Although the sensitivity of different areas of the central nervous system to ketamine has not been clearly established, we considered movement as a clinical sign that ketamine anesthesia was becoming insufficient to match

the nociceptive input elicited by the tetanic stimulations, although our patients were still unconscious. Therefore, no patient received a higher stimulation than the one inducing a motor response.

The pharmacokinetics/pharmacodynamics profile of ketamine is not clearly elucidated, especially in terms of sedative and analgesic effects in children [21–23]. Some authors reported a median of 16 min of total sedation after 1 mg kg<sup>-1</sup> of IV ketamine in children [24] with arousal concentrations close to those described in adults [22]. The peak effect of ketamine in the central nervous system is expected within one minute after IV administration [25]. For that reason, in our study, the first tetanic stimulation was provided 2 min after the IV bolus.

Because we did not provide a continuous infusion of ketamine during our 8 min study period, the patients could not be considered as in a steady-state of analgesia and sedation. The effects of the initial bolus of ketamine certainly decreased over time. However, 10 min after an IV administration of 1 mg kg<sup>-1</sup> of ketamine, most children are expected to have a serum concentration above 0.1 mg l<sup>-1</sup>, which is associated with analgesia in adults [25]. Moreover, this continuous decrease in analgesia reinforces our findings: the fact that PRD increases when less analgesia is provided (greater dilation explained by less analgesia) is in accordance with the fact that PRD increases when the stimulation is more intense (greater dilation explained by greater nociceptive input). In both circumstances, the balance between nociception and analgesia is shifted towards nociception. In other words, our results suggest that under ketamine anaesthesia, PRD increases with the level of nociception. The consequence of these findings, in clinical practice, is that intravenous ketamine may not preclude the use of pupillometry monitoring to assess the nociception-antinociception balance in anesthetized patients.

The 32% pupillary dilation associated with movement provides the first data regarding a hypothetical “pupillary threshold” indicating insufficient analgesia. This value was obtained under intravenous ketamine anesthesia, after an oral morphine premedication, and might be different when other anesthetic agents or different opioids doses are used. However, it is close to the 23% dilation threshold predicting a verbal pain score of more than 1 on a four point scale described by Aissou in awake patients [9]. If validation studies confirm the relevance of this strategy, this result might prove useful to guide intraoperative administration of analgesics: as already suggested by Guglielminotti [10], opioid infusion rate could be targeted to keep pupillary diameter response amplitude below a predefined threshold.

One of the limitations of our study was the lack of randomization of the tetanic intensities. As already discussed, we chose incremental tetanic intensities for ethical reasons; indeed we intended to avoid any stimulation above the

intensity that would induce movement. This design might have induced a certain degree of habituation leading to a decrease of nociceptive responses; however the amplitude of the pupillary responses suggested that the influence of this potential bias may be weak.

Another limitation of our study could be the use of tetanic stimulations (5–60 mA, 5 s) to generate nociception. Tetanic stimulations have been used in numerous studies investigating monitors of the nociception-antinociception balance. For example, Barvais used a 100 Hz, 60 mA, 10 s tetanus [8], Larson a 65–70 mA, 100 Hz, 5 s tetanus [4, 13]. Other studies evaluating both short duration (5 s) and long duration (30 s) bursts of tetanic stimulation found that only longer duration impulses appeared to correspond to surgical stimulation; the authors suggest that short duration stimuli affect only superficial nociceptive structures, whereas longer duration stimuli affect the deeper tissues as well [26]. In our study, we chose short duration tetanic stimulation as a standardized nociceptive stimulus. Whether the demonstrated relationship between nociceptive intensity and pupillary dilation also applies to other kinds of nociceptive stimulations, and especially surgical stimulations, remains to be demonstrated.

Finally, we did not record pupillary diameter, heart rate or blood pressure in awake children before ketamine injection, so we cannot describe the effect of ketamine on these variables.

In conclusion, this study adds two elements to the increasing collection of published data on pupillometry: in children, nociception-induced pupillary reflex dilation persists under deep sedation obtained with 1 mg kg<sup>-1</sup> of intravenous ketamine combined with a 0.3 mg kg<sup>-1</sup> oral morphine premedication, and the magnitude of pupillary reflex dilation depends on the level of nociception. Our results confirm that pupillometry could be a relevant way to monitor nociception in anaesthetised subjects, including those receiving intravenous ketamine.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comité de Protection des Personnes CPP Ile de France 5, Hôpital Saint-Antoine, Approval Number: 10923 on March 8th 2011, chairman V.G. Levy.) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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