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Editors key points:

- Pain shifts the balance in the autonomic tone towards the sympathetic system.
- Methods of assessing this balance include the Analgesia Nociception Index (ANI), the pupillary light reflex (PLR), and the variation coefficient of pupillary diameter (VCPD).
- The study aim was to compare the values of ANI, PLR and VCPD at postoperative VAS pain scores ≥ 4 .
- Correlations with VAS scores were strong for VCPD, moderate for PLR and weak for ANI.

Assessing Pain in the Postoperative Period: Analgesia Nociception Index™ (ANI) versus Pupillometry

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Short running Title

Postoperative pain assessment: ANI vs pupillometry

Summary

Introduction

Potential methods for objective assessment of postoperative pain include the Analgesia Nociception Index™ (ANI), a real-time index of the parasympathetic tone, the pupillary light reflex (PLR), and the variation coefficient of pupillary diameter (VCPD), a measure of PD fluctuations. Until now, the literature is divided as to their respective accuracy magnitudes for assessing patient's pain. The VCPD has been demonstrated to strongly correlate with pain in an obstetrical population. However, the pain induced by obstetrical labour is different, given its intermittent nature, than the pain observed during the postoperative period. The aim of the current study was to compare the respective values of these variables at Visual Analog Scale (VAS) scores ≥ 4 .

Methods

After approval by the Ethics Committee, 345 patients aged on average 50 ± 17 years (range: 18-91 years) of age were included. The protocols of general anaesthesia and postoperative analgesia were left to the anaesthetist's discretion. Forty minutes after endotracheal intubation VAS, ANI, PD, PLR and VCPD values were recorded.

Results

VCPD correlates more strongly ($r = 0.78$) with pain as assessed with the VAS than ANI ($r = -0.15$). PD and PLR are not statistically correlated with VAS. The ability of VCPD to assess the pain of patients (VAS ≥ 4) is strong (area under the curve, AUC: 0.92, Confidence Interval: CI: 0.89-0.95), and better than for ANI (AUC: 0.39, CI: 0.33-0.45).

Conclusion

Our study suggests that VCPD could be a useful tool for monitoring pain in conscious patients during the postoperative period.

Keywords

- analgesia
- nociception

- pain
- pain measurement: Analgesia Nociception Index™ (ANI)
- pupil, reflex: pupillary unrest, variation coefficient of pupillary diameter

Trial registry number: NCT03267979

Introduction

Pain shifts the balance in autonomic tone towards sympathetic predominance — with heart rate (HR), blood pressure (BP) and pupillary diameter (PD) all increasing. That balance may be surveyed in real time by monitoring HR variability (HRV) ¹ or the variations of PD ², and thus be used to assess pain.

Based on HRV monitoring, Analgesia Nociception Index™ (ANI), a real-time index of the parasympathetic tone ¹, has been proposed for assessing pain in the postoperative period ³, but its interest remains controversial in the literature ⁴⁵⁶.

The pupillary reflex dilation (PRD) and the pupillary light reflex (PLR) were also proposed for assessing pain ⁷⁸, but the literature is divided as to their respective abilities to assess patients' pain in the recovery room ⁹.

In an obstetrical population, it was demonstrated that the variation coefficient of PD (VCPD) strongly correlates with pain as assessed with Numeric Rating Scale (NRS) ¹⁰. However, the on-and-off nature and intensity of contractions make it impossible to prejudge the relevance of this parameter for assessing postoperative pain for all the levels of pain encountered in the postoperative period.

In this study, we propose to compare the respective abilities of ANI and the various pupillary parameters to assess postoperative pain. Our subsidiary objective was to compare the respective values of VCPD, heart rate (HR), blood pressure (BP), PLR, and ANI for assessing patients' pain (at levels ≥ 4 on the Visual Analog Scale (VAS)).

Methods

The study protocol was approved to both the Ethics Committee (ref: IRBN402014/CHUSTE) and the Commission Nationale de l'Informatique et des Libertés (ref: 1800890v0), and registered with ClinicalTrials.gov (ref: NCT03267979). The Ethics Committee waived the requirement for written informed consent. The study was conducted in a recovery room at the University Hospital of Saint-Etienne, between November 2014 and March 2015.

Population studied

Patients included in the study were all coming out of surgery under general anaesthesia, of full age, consenting, and fluent in French, to be able to convey their pain level using the VAS. All types of surgery conducted in our institution were included in the study, except for heart, intra-cerebral, and ophthalmologic surgeries — to avoid misinterpreting parameters. Patients coming out of emergency surgery, with heart rhythm disorders (complete arrhythmia by auricular fibrillation), or with a pacemaker were also excluded.

The protocols of general anaesthesia (whether intravenous, volatile, or a combination of both) and postoperative analgesia were left to the anaesthetist's discretion. In particular, patients could be put to sleep by intravenous injection, or through a combination of opioid with a halogenated gas, sometimes in association with a locoregional anaesthesia. The following patients were excluded from the study: patients having undergone spinal or epidural anaesthesia; patients having received ketamine, xylocaine, or magnesium, either continuously or repeatedly, to avoid misinterpreting results; patients under a vasoactive, an anti-hypertensive, or an antiarrhythmic drug; patients having required an injection of a vasoactive drug or of atropine in the recovery room.

Study design

Before being included, patients were scoped (monitoring of the electrocardiogram tracing, pulse oxymetry and non-invasive BP) in the recovery room, and extubated. They had to unerringly tell their name, birth date, and the current date, to demonstrate wakefulness. The measurements were performed at rest, without stimulating the patients. The ANI monitor was then connected to the scope and left there for 4 minutes, until equilibrium of the signal. The only ANI parameter we reported upon in this study was the instantaneous ANI (ANi), calculated for 64 seconds immediately prior to measurement.

The following parameters were then taken, all at the same time: pain as assessed with the VAS, HR, systolic BP (SBP), ANi as read directly on the monitor, and the pupillary parameters (PD, PLR and VCPD). All measurements were performed without any knowledge of the pain levels, which were assessed using the VAS. The PD recordings were made with a portable videopupillometer AlgiScan™ (iDMed, Marseille, France) that enables the ongoing recording of PD with a 0.05 mm accuracy. While the pupillometer was placed over their eye, patients were requested to focus their alternate eye at infinity — to avoid any accommodation reflex — with the surrounding light being kept at 200 Lux. The device was left in place for 6 seconds so as to reach pupillary equilibrium prior to measurement ¹¹. The variation

coefficient of PD (VCPD) is defined as the ratio of the median deviation to the median:

$$\text{VCPD} = \frac{\frac{1}{N} \sum_{i=1}^N |x_i - \text{median}|}{\text{median}}$$

It describes PD fluctuations around the median value for the 10-second recording, as previously described¹⁰. Average basic PD and VCPD were then recorded for 10 seconds, as well as PLR (pupillary decrease during a 1-second flash of 320 Lux, a luminance of 1280 Candelas.m⁻²) expressed as a percentage of PD decrease.

We also noted down each patient's demographic information (age, gender, body mass index, American Society of Anesthesiologists (ASA) score). Patients defined as "with pain" were those with a VAS ≥ 4 ¹².

Statistical Analysis

Our determination of the number of subjects to be included was based on personal data showing that the ANI of patients in the recovery room was on average of 64 ± 24 for those with a VAS < 4 , and of 56 ± 22 for those with a VAS ≥ 4 . Consistent with this, for an α -risk of 0.05 and a β -power of the statistical test of 0.90, 348 patients were needed to show a difference of 8 ANI points between the two groups, based on an estimated ANI standard deviation of 23. The statistical analysis was performed with the software SPSS (SPSS for Windows, SPSS Inc. Version 20.0), and using all the data collected. For all tests conducted, an α -risk of 0.05 was used to evidence a significant difference. No missing value was hypothesised.

A comparison was made between two sub-groups of the population by means of Student's *t*-test, after normality was checked through a Shapiro-Wilk test.

The correlations between VAS and respectively HR, SBP, each pupillary parameter, and ANI were studied by calculating the Pearson's coefficient of correlation, after testing the normality of the distribution.

The optimal cut-off was determined using the Youden technique¹³. Finally, the ability of the various parameters to assess patients' pain levels (VAS ≥ 4) was determined using the ROC curves and their Area Under the Curve (AUC). The ROC curves were all compared with one another by Delong's method¹⁴.

Results

Between November 2014 and March 2015, 345 patients, comprising 175 men and 170 women, aged on average 50 ± 17 years (range: 18-91 years), were included. Their average body mass index was $26.6 \pm 5.4 \text{ kg.m}^{-2}$ (range: 16.2-45.3 kg.m^{-2}).

The patients' ASA scores were distributed as follows: ASA 1: 145 patients (42% of the population), ASA 2 : 160 patients (46.4%), ASA 3 : 38 patients (11%), ASA 4: 2 patients (0.6%).

Patients came from the following surgical specialties: orthopaedics (44.1%), endoscopy (15.4%), otorhinolaryngology (13.3%), digestive surgery (9.6%), neuro-spinal surgery (9.6%), gynaecology (2.9%), urology (2.3%) and vascular surgery (2.8%).

On the 345 patients included, 15 were under beta-blockers, and none under amiodarone.

The average time between a patient's arrival in the recovery room and his/her measurement was 42 ± 35 min.

The first line of Table 1 shows the recorded clinical parameters for all 345 patients.

The effect size of correlation, as defined according to Cohen's guidelines¹⁵, is strong between VAS and VCPD ($r = 0.78$; $p < 0.0005$), weak between VAS and ANli ($r = -0.15$; $p = 0.006$), and mild between VAS and HR ($r = 0.24$; $p < 0.0005$), as well as between VAS and SBP ($r = 0.26$; $p = 0.001$). PD and PLR are not statistically correlated with VAS. Figure 1 shows VCPD for all 345 patients as a function of their VAS.

The abilities of VCPD, PLR, and ANli to assess pain ($\text{VAS} \geq 4$) were then evaluated using the ROC curves and their AUC. The AUC of VCPD (0.92, Confidence Interval (CI): 0.89-0.95, $p < 0.0005$) is statistically different from the AUC of both PLR (0.69, CI: 0.63-0.75, $p < 0.0005$), and ANli (0.39, CI: 0.33-0.45, $p = 0.001$) (Figure 2).

The patients were then divided according to their pain levels into two groups (VAS < 4 versus VAS ≥ 4). Their recorded clinical parameters (the last two lines of Table 1) show a significant statistical difference between the two groups, except for basic PD. We calculated the optimal cut-off to dichotomise the population (VAS < 4 or VAS ≥ 4) according to Youden's method, which evidences a best cut-off of 6.4. A VCPD variation of more than 6.4 is associated with a VAS ≥ 4 with a sensitivity of 0.92, a specificity of 0.73, a positive predictive value (PPV) of 0.93, and a negative predictive value (NPV) of 0.70. A PLR amplitude > 37% is predictive of a VAS ≥ 4 with a sensitivity of 0.32, a specificity of 0.87, a PPV of 0.75, and a NPV of 0.52. An ANli < 40 is predictive of a VAS ≥ 4 with a sensitivity of 0.91, a specificity of 0.14, a PPV of 0.81, and a NPV of 0.27.

Discussion

Our study validates VCPD as a reliable tool both for monitoring pain in conscious patients, and for discriminating those with pain in the postoperative period. VCPD correlates more strongly ($r = 0.78$) with pain — as assessed with the VAS — than ANli ($r = -0.15$), HR ($r = 0.24$), and SBP ($r = 0.26$) do.

In keeping with the literature^{7 16}, we did not find any correlation between basic PD and pain as assessed with the VAS, in constant ambient light. Basic PD does not appear to be significantly influenced by a constant pain in the postoperative period. Similarly, Aissou found no change in basic PD before and after morphine titration in the postoperative period⁷. According to Dualé, that is probably due to the residual effect of the opioid used during operation¹⁷.

The pupillary reflex dilation (PRD) performs however better in the literature^{18 19}, but it requires applying a painful stimulus. In a more recent study on PRD responses to pressures applied in the immediate postoperative period to wound edges, a DP increase of more than 23% was associated with both a high probability of a verbal rating scale value warranting morphine titration and a high probability of strong pain, corresponding to a value higher or equal to 2 on a 0-to-4 simple verbal pain rating scale⁷. In that study, PD increase correlated markedly with the simple verbal rating scale ($r = 0.88$). In a previous study conducted on parturients in the delivery room, PD was also shown to increase proportionally to the pain induced by

upon uterine contractions, mildly correlating with the NRS ($r = 0.42$)¹⁰. Such a measurement of pain, however, requires a nociceptive stimulus: it does not allow for assessing pain in the absence of a nociceptive stimulus, as for instance a constant pain in a patient in the recovery room.

The pupillary light reflex (PLR) is one of the tools that may be used for investigating pain without resorting to painful stimulation. We showed it: (1) to exhibit slightly superior values, albeit clinically non relevant, in patients with the most pain ($VAS \geq 4$), and (2) not to correlate with VAS, possibly as a result of the residual effect of opioids, and of the sympathetic activity induced by the capnia variations associated with respiratory depression induced by residual anaesthesia²⁰. In an obstetrical study, in which PLR was measured both in the absence ($NRS = 0$) and at the peak of a uterine contraction ($NRS = 8$), PLR was shown to correlate with pain as assessed with the NRS ($r^2 = 0.26$)⁸. However, the pain induced by obstetrical labour is different, given its intermittent nature, than the constant pain observed during the postoperative period.

The ANli of patients with pain was statistically shown to — significantly although weakly — inversely correlate with the VAS ($r = -0.15$, $p = 0.006$). As for HR and SBP, the ANli difference between the patients with pain and those without pain is too small and clinically irrelevant. Again, the lessened ANli values might be attributable to anaesthesia-related residual respiratory depression. Notwithstanding its usefulness under general anaesthesia for monitoring the nociception-antinociception balance^{1 21}, the ANli becomes ineffective during apnea, as it is based on the interaction between HR and ventilation²².

Fifteen of the patients in our study were taking beta-blockers. We did exclude patients taking beta-blockers as our intention was for our study to reflect clinical reality. Moreover, many recent studies on ANI do not consider the long-term use of beta-blockers to be an exclusion criterion.^{23 24 25} That was also the case for studies involving conscious patients^{26 27}. Furthermore, when we excluded from analysis the data from patients taking beta-blockers, the results on the heart rate and ANli do not change (data not shown). Our findings support Boselli's proposal to use ANli for monitoring pain immediately after surgery²⁸: in his study Boselli included 200 patients anaesthetized with an halogenated agent or with propofol/remifentanyl "at the discretion of the anaesthesiologist." He showed that the performance of ANI for the detection of moderate to severe pain was also very good for patients under anaesthesia with an halogenated compound. In contrast, other authors have reported a low performance of ANli for postoperative pain

assessment of halogenated-anaesthetised patients⁴. We decided at the outset not to limit the scope of our study to intravenous anaesthesia — as that is only one of several different anaesthetic techniques in use. We proposed to demonstrate that a simple parameter, usable at the patient's bed in daily clinical practice, allows for the discrimination between the patients “with pain” and those “without pain”, regardless of the type of anaesthesia used.

Our videopupillometer was equipped with an automated VCPD measuring device. In a previous study with labouring parturients¹⁰, VCPD was associated with a NRS ≥ 4 , with an area under the ROC curve of 0.97 (CI: 0.93-1.0), and both a specificity and a negative predictive value of 0.97. The calculation method of VCPD may however be questionable. VCPD is calculated as the median of the absolute values of the deviations to the median for the duration of the recording, at the sampling frequency of the videopupillometer. During a uterine contraction, PD increases till the peak of the contraction, and then decreases. That variation of the PD base line may induce a VCPD increase that is unrelated to PD fluctuations. That may have led to the VCPD high values obtained during the contractions in the labour room and the higher cut-off of 9.0 which was observed. In this study, the pain recorded in the postoperative period is constant for the duration of the measure: the VCPD calculation can not therefore be overvalued or artificially increased due to base line variations.

In this paper, we proposed to validate VCPD both in a broader population of conscious patients and in the postoperative period, a time during which the residual effects of general anaesthesia may obfuscate the assessment of pain. We sought to evidence a correlation between VCPD and pain as assessed with the VAS. VCPD, a punctual measure of the dispersion of pupillary fluctuations around their median value, allows for assessing pain without either nociceptive (PRD) or light stimulation (PLR). We found the AUC of the VCPD ability to assess pain to be high (0.92), albeit slightly lower than the value previously found with labouring parturients (0.97)¹⁰. In that previous study, the pain levels were very high during uterine contractions (VAS up to 7.5 ± 1.2), and very low in the absence of contractions (VAS up to 1.1 ± 1.0). In this study, the pain levels assessed with the VAS in the recovery room are continuous and distributed between 0 and 10, which probably explains why VCPD is observed to be less discriminating in the postoperative period.

Just as happens with other parameters derived from the autonomous nervous system, the basic pupillary diameter (PD) does not suffice to discriminate the patients with pain from those without pain: the PD is

essentially linked to the surrounding lighting. By contrast, its variation (delta PD) correlates far better with pain⁸. We showed that, using VCPD, the sensitivity/specificity of the PD variability (PDV) is even better¹⁰. The same was demonstrated for the heart rate (HR), whose base value is not correlated with pain. By contrast, its variation (delta HR) correlates with pain, and its variability (HRV) even much more so.

It has been recently shown that opioids decrease pupil size variation in healthy volunteers²⁹, and that pupil size variation predicts opioid efficacy in the postoperative care unit³⁰. It may be that the patients with the lowest VCPD in our study were those who had received the highest opioid doses. Nonetheless, PD and its fluctuations do not result solely from the opioid concentration. The pupil size variation depends on both the pain level (due to nociceptive stimulations) and the opioid concentration. It reflects the persistent pupillary reactivity to stimulation after opioid-induced blocking, and allows for the quantification of the residual pain. In a recent paper, PD has been proposed as a clinical feedback resulting from the balance between the intensity of the nociceptive stimulus and the effects of anaesthetic drugs³¹. VCPD could likewise become an integrated parameter for assessing pain.

We disregarded the types of pain induced by the surgeries performed: visceral pain, bone pain, pain caused by nerve injuries, or inflammatory pain due to the release of algogenic substances on the surgery site, or their combination. Of the patients included in the study, 44.1% had had an orthopaedic surgery, 14.8% a visceral surgery (digestive, gynaecological, or urologic), and 9.6% a spinal surgery: bone surgery thus appears to be overrepresented. We did not divide evenly the types of pain attributable to the various surgeries performed. However, all the pain levels between 0 and 10 are represented: the results were obtained on the basis of the whole range of pain levels.

The limitations of this study are first and foremost those which are inherent to pupillometry¹¹. Many anaesthetic drugs affect the pupil and its measurement. Likewise, postoperative anxiety, drowsiness, nausea and vomiting — frequent after general anaesthesia — may have rendered their assessment of pain with the VAS more difficult. We disregarded any such possible effects. Patients' ability to self-assess their pain may have been altered by the sedative residual effects of hypnotics³². We mitigated that by performing the measurements on a same level of wakefulness, waiting for patients from the operating room to be extubated and able to answer simple questions before assessing their pain. The patients' pain levels

were measured, alongside all parameters, only once at a given moment. However a patient's pain level in a post-operative care unit may change rapidly. It would have been valuable to get an average of 2 or 3 scores for pain and all parameters, every 5 minutes, so as to diminish the dispersion of the measurements obtained.

The pupillometry technique we used to measure VCPD on our 345 patients proved to be very well tolerated, easily applied at the patient's bed, without much constraints and quickly applied (6 seconds to obtain the equilibrium of the pupil, and then 10 seconds for measuring). No adverse event due to that technique occurred. The measures can be taken by a physician or a nurse. Furthermore, contrary to HRV and to ANI, the pupillometry results are independent of the patient's heart regularity, ventilation or apnea condition.

Although the pupillary responses to pain have been known for more than two millennia^{33 34}, automatized pupillometry has been in use for only about fifteen years in anaesthesia. It gave rise to many studies seeking to provide caregivers with a dependable and objective tool for monitoring pain, especially for non-communicative patients. The dynamic pupillary parameters (PD increase in response to a painful stimulus: PRD, PD decrease in response to a light stimulus: PLR) appear to correlate more strongly with pain than mere static PD measures. But they do enable an assessment of a constant pain: they only allow for comparing two phases ("after stimulation" vs. "before", or "after analgesic treatment" vs. "before").

The present study had compared the respective values of ANIi, PLR and VCPD for assessing postoperative pain. This paper shows that VCPD, which records the permanent fluctuations of PD around their median value, correlates more strongly with pain — as assessed with the VAS — than ANIi. The cut-off we determined needs to be prospectively validated in a new population. This study performed in the recovery room must however be corroborated by further studies carried out in other clinical conditions, most notably to assess nociception/antinociception balance under general anaesthesia.

Conflicts of interest

The authors declare no competing interests.

Disclosure of funding

The University Hospital of Saint-Etienne assumed the biomedical research proponent's third-party liability insurance contract.

Authors' contributions and authorship

D.C., D.Z., S.M.: Study conception and design; M-C.V., A.M-B., M.C.: Patient recruitment and data collection; V.P., F.V.: Analysis and interpretation of data; D.C., S.M.: Drafting the article; F.V., F.R., S.M.: Revising the article.

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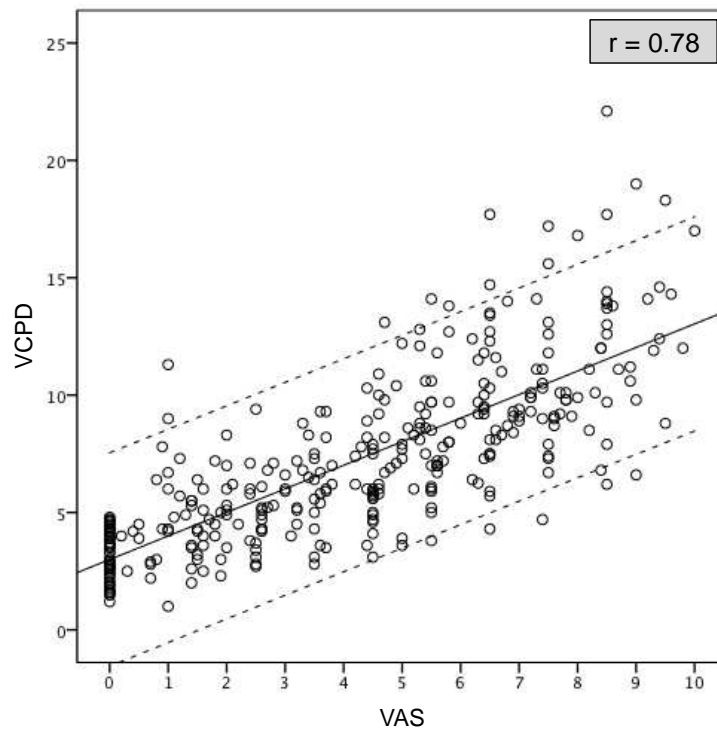


Figure 1: Graph showing the correlation between VAS and VCPD. r : Pearson's coefficient of correlation. The dotted lines represent the confidence interval at 95%.

VAS: Visual Analog Scale, VCPD: variation coefficient of pupillary diameter.

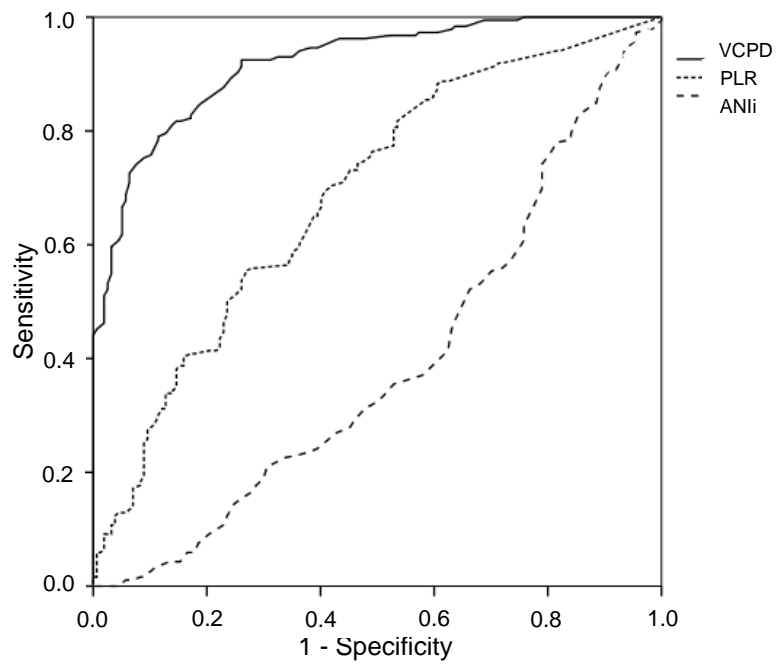


Figure 2 : ROC curves of the abilities of VCPD, PLR and ANIi to detect a VAS ≥ 4 (solid line: VCPD, dotted line: PLR, stippled line: ANIi).

VAS: Visual Analog Scale, VCPD: variation coefficient of pupillary diameter, PLR: pupillary light reflex, ANIi: instantaneous Analgesia Nociception Index™.

	VAS	VCPD	HR (bpm)	SBP (mmHg)	PD (mm)	PLR (%)	ANli
n = 345	4.2 ± 2.8	7.2 ± 3.7	75 ± 16	125.4 ± 18.3	3.6 ± 1.0	31.3 ± 9.8	61 ± 17
VAS < 4 (n=159)	1.5 ± 1.3	4.6 ± 1.9	73 ± 16	120.8 ± 16.1	3.6 ± 1.1	30.0 ± 8.3	64 ± 18
VAS ≥ 4 (n=186)	6.6 ± 1.5	9.4 ± 3.3	76 ± 16	127.8 ± 19.0	3.5 ± 0.9	32.4 ± 10.9	58 ± 15
<i>p</i>	< 0.0005	< 0.0005	0.002	0.018	NS	0.026	< 0.0005

Table 1: Parametric variations. The first line shows the recorded clinical parameters for all 345 patients. The two following lines show the recorded clinical parameters for the two sub-groups (VAS < 4 and VAS ≥ 4).

Values: averages ± standard deviations, n: population, VAS: Visual Analog Scale, VCPD: variation coefficient of pupillary diameter, HR : heart rate, SBP: systolic blood pressure, PD: pupillary diameter, PLR: pupillary light reflex, ANli: instantaneous Analgesia Nociception Index™.

The two groups averages were compared using Student's *t*-tests. NS: not significant.