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## Abstract

**Background.** Behavioural pain tools are used in Intensive Care Unit (ICU) patients unable to self-report their pain-intensity but need sustained efforts to educate and train the ICU team because of the subjective nature of these clinical tools. This study measured the validity and performance of an electrophysiological monitoring tool based on the spectral analysis of heart rate variability, the Analgesia Nociception Index (ANI) which varies from 0 (minimal parasympathetic tone, maximal stress-response and pain) to 100 (maximal parasympathetic tone, minimal stress-response and pain).

**Methods.** Mean-ANI (ANIm) and Instant-ANI (ANIi) were continuously recorded then compared with the Behavioral Pain Scale (BPS) before, during and after routine care procedures in critically-ill non-comatose patients.

**Results.** 969 assessments were performed in 110 patients. ANIi was the most discriminative pain tool. It was significantly correlated with BPS ($r=-0.30$; 95%CI –0.37 to –0.25; $P<0.001$). For an ANIi threshold of 42.5, the sensitivity, specificity, positive and negative predictive values were respectively 61.4%, 77.4%, 37.0%, and 90.4%. Compared with the BPS, ANIi had no significantly different ability to change during turning and tracheal-suctioning but changed significantly more during dressing change. ANIi increased independently with age, obesity and severity of illness, and controlled mechanical-ventilation, vasopressors use and analgesia. ANIi decreased independently when vigilance status and respiratory rate increased. ANIm demonstrated poor psychometric properties to detect pain.

**Conclusions.** Despite low sensitivity/specificity, ANIi$\geq$43 had a Negative-Predictive-Value of 90%. Hence ANIi may be of highest benefit for excluding significant pain. A randomized controlled trial should compare sedation-analgesia protocols based on ANIi to presently recommended behavioural-pain-tools.

**Key words**: analgesia; delirium; intensive care unit; pain; sedation

Careful pain management is associated with better patient outcomes in the ICU.[1] However, pain still remains under evaluated and under treated.[2] Probably because pain management is often challenging in the ICU setting, particularly in patients unable to communicate their pain intensity, such as sedated patients and patients with delirium.[3] In this case, clinical behavioural pain scales are used to standardise pain assessment and to adapt analgesics dose.[1 4–6] However, these methods remain subjective, depending on the nurses' education, training and ability to use the clinical tools.[7 8] Therefore, new objective tools, such as

### Editor's key points

- Accurate assessment of pain in critical care patients is important for optimal pain management.
- Standard self-reported pain assessment may be difficult, with behavioural tools often being used.
- Analysis of heart rate variability with mean or instant Analgesia Nociception Index (ANI) was assessed.
- Instant ANI may be used to exclude severe pain, although further studies are needed.

videopupillometry[9] or heart rate variability monitoring,[10] have been developed to achieve objective assessment of pain in patients unable to communicate. Analgesia Nociception Index (ANI) measures heart rate variability from ECG monitoring of the patient, providing a number from 0 to 100 through spectral analysis. This number is an estimation of the balance between parasympathetic and sympathetic outflows: 100 means a high parasympathetic modulation (low stress level=low risk of pain), 0 means extremely low parasympathetic modulation (high stress level=high risk of pain).[10] ANI has shown promising results in patients under general anaesthesia during surgery,[11] just after surgery in the recovery room[12] and recently in a small population of ICU patients who were deeply sedated.[10] ANI has not been evaluated in non-comatose ICU patients (i.e. in the largest ICU patient population, lightly sedated as recommended[1] or patients with delirium for whom pain assessment is highly challenging). Thus, we conducted an accuracy diagnosis study to answer the question: in non-comatose, non-communicative ICU patients, can ANI predict which patients are in pain according to the gold-standard (Behavioural Pain Scale, BPS≥5)?[3 4 13] Secondary endpoints were to evaluate variables that may impact ANI.

## Methods

Additional methodological details can be found in the electronic supplementary material (ESM).

### Ethics approval

The protocol was approved by the Ethics committee: Comité de Protection des Personnes (CPP) Sud Méditerranée IV (N°ID - RCB: 2014-A00337-40; Protocol Version: March 19, 2014; Consent Version: April 17, 2014).

### Patient population

The study took place in the medical-surgical ICU of the University of Montpellier Saint Eloi Hospital. All consecutive patients ≥ 18 yr-old, mechanically ventilated and/or receiving vasopressors were eligible for enrolment if they had a Richmond Agitation Sedation Scale (RASS)[14–16] above -4 and were unable to self-rate their pain intensity with the Visually Enlarged 0-10 Numeric Rating Scale (0-10 V-NRS).[17] Exclusion criteria were decision to withdraw life-support or unstable condition preventing planned routine procedures of care, and conditions precluding the use of ANI: absence of sinus cardiac rhythm, respiratory rate<10 b/min.

### Conduct of the study

After having obtained consent from the surrogate decision maker and having enrolled the patient into the study, investigators planned different procedures of care with the bed-side nurse including: 1) a central venous catheter or arterial catheter dressing change, 2) a complete turning of the patient on both sides in order to wash the back and change the bed sheets, and 3) a tracheal suctioning if relevant (intubated patients).

### Data handling

Pain was measured in two different ways: 1) clinically, using the BPS performed by the clinical investigator, 2) electrophysiologically, using ANI which was continuously recorded by the PhysioDoloris® monitor (MDoloris Medical Systems, Lille, France) at an acquisition frequency of 60 Hz. ANI data were subsequently extracted and analysed by an independent research investigator, based on procedure timings reported on the ANI monitor at bedside. The investigator who performed the BPS and the ANI analyst were unaware of each other's measurements. Further details of ANI measurement are provided in ESM. Briefly, ANI is a non-invasive device that takes an ECG analogue output from the patient ICU monitor and displays an average measurement.[18] Two ANI values provided by the monitor were analysed after data extraction: 1) Mean-ANI (ANIm), an average calculated over the previous 4 min, and 2) Instant-ANI (ANIi), an average calculated over a shorter period of time (64 s).

Pain assessments were made under three conditions for each patient: 1) at rest, before any procedure; 2) during the procedure of care; and 3) after the procedure. Study design is shown in ESM (Supplementary Fig. E1).

### Statistics

1) Primary endpoint: ANI performance to detect pain defined as a BPS≥5

Sensitivity, specificity, positive predictive value and negative predictive value were calculated according to standardized definitions. To determine relevant ANI thresholds, Receiving Operator Characteristics (ROC) curves were constructed based on the definition of pain as a BPS≥5. This threshold was chosen because it is the lower limit of the interquartile range in ICU patients during a painful procedure,[3 7] and because this threshold is now used in routine protocols that have been shown to be feasible and safe in the ICU setting, such as analgesia based sedation protocol[19] and protocol for procedural analgesia[4]. These protocols are provided online in French and in English as additional files in Critical Care Forum (http://ccforum.biomedcentral.com/articles/10.1186/cc12683).[4] BPS was used as the Gold-standard to measure pain in the present population of ICU patients unable to communicate according to guidelines.[1 20] With the Critical Care Pain Observation Tool (CPOT),[21] BPS has demonstrated the best psychometric properties among different behavioural pain tools,[1] and high responsiveness well adapted for research.[7] The Youden index was used to determined the ANI threshold.[22] The graphic correlation with BPS was also shown and measured using Spearman's test.

2) secondary endpoint: variables associated with ANI

To explore patients' baseline variable and variables associated with critical illness that could impact on ANI, a mixed linear regression model was used to determine which would be associated with a greater or a lower ANI value by univariate and multivariate analysis. Variables whose *P* value were under 0.15 (univariate analysis) were considered for a multivariate

analysis. Forward selection (according to Akaike Information Criterion) was used to determine the final regression model.

3) Post-hoc analysis

A post-hoc analysis was performed to explain the performance of ANI compared with the BPS. While recommended for clinical practice, BPS remains an "imperfect" gold-standard because of its subjective nature and the impossibility of monitoring it continuously (punctual measurements). Thus, we used the procedure itself rather than the BPS to define the gold-standard. This was done to show the performance of each tool (ANI and BPS) according to the three different procedures. ROC curves were constructed using the procedure as the Gold standard and Hawley and McNeil's method was used to compare ROC curves.[23]

4) Number of patients and procedures necessary to include for analysis

Expecting ANI to have a sensitivity of at least 80% based on previous data in patients studied in a postanaesthesia care unit,[12] and expecting that 75% of patients would have a BPS≥5 during a procedure of care,[3] with an estimation of plus or minus 7% (half-distance of the 95% Confidence Interval), 102 paired measurements of ANI and BPS were necessary for each procedure of care, that meant including at least 102 patients undergoing each procedure.

5) Presentation of data

Quantitative data are shown as medians and $25^{th}$-$75^{th}$ percentiles. A Pvalue of ≤ 0.05 was considered statistically significant. Data were analysed using the SAS Enterprise Guide version 7.12 (2016) (SAS Institute, Cary, NC) and the R software version 3.3.1 (21 June 2016).

## Results

During the study period, a total of 969 pain measurements were done in the 110 patients included in the analysis. A consort flow chart of patient enrolment is shown in ESM (Supplementary Fig. E2). Table 1 summarises patients' characteristics and medical characteristics. The prevalence of pain (BPS≥5) was 76% during suctioning, 49% during turning and 5% during catheter dressing. The overall prevalence of pain during all procedures was 43%.

### ANI performance (primary endpoint)

The ROC curve (Fig. 1) for ANIm was close to the central line with an Area Under the Curve (AUC) of 0.57 (95% CI: 0.53 to 0.62). AUC for ANIi was greater: 0.73 (95% CI: 0.68 to 0.77). For an ANIi threshold of 42.5, the sensitivity and specificity were 61.4% and 77.4%, respectively, the positive predictive value was 37.0%, and the negative predictive value was 90.4%. Figure 2 shows the correlation between BPS and ANI. The correlation between BPS and ANIi (r=–0.30; 95% CI: –0.37 to –0.25; $P<0.001$) was greater than for the ANIm.

### Variables associated with ANI (secondary endpoint)

Supplementary Table E1 in the ESM shows univariate and multivariate analyses of variables associated with ANIi values. The timing of measurement (before and after the procedures compared with during the procedure) was independently associated with a greater ANIi value (estimate coefficients, EC = 23.0 [95% Confidence Interval (CI) 20.1-26.0] and 24.2 [21.3-27.1], respectively), as were three patient characteristics or medical variables (age, obesity, and severity of illness; EC = 0.2 [0.1-0.3], 8.8 [6.0-11.6] and 0.2 [0.1-0.2], respectively) and three therapeutic variables (assist controlled ventilation, vasopressors use, and analgesia with acetaminophen; EC = 8.7 [2.0–15.4], 2.7 [0.1–5.4] and 5.7 [2.1–9.2], respectively). Two physiological variables were independently associated with a lower ANIi value: RASS level, and respiratory rate (EC=–1.2 [–2.5 to –0.0] and –0.3 [–0.5 to –0.1], respectively).

### Distribution of ANIm, ANIi and BPS according to the procedure

Figure 3 shows the median scores of ANIm, ANIi and BPS in different situations. ANIm and ANIi decreased while BPS increased during the three procedures. When the medians and interquartile ranges measured during the procedures were compared with those measured before or after the procedures, it appeared that ANIi was the most discriminative pain tool while ANIm was poorly discriminative (Fig. 3).

### Post-hoc analysis

To compare the ways in which ANIi and BPS change during a given procedure, the ROC curves were also constructed using each of the three procedures as the Gold standard. The AUCs were not significantly different between ANIi and BPS for turning and suctioning (Supplementary Fig. E3). For dressing change, ANIi had a significantly greater AUC than the BPS.

## Discussion

The main findings of this study are that ANIi is effective to detect pain during nursing procedures in critically ill patients. ANIi changes more frequently than BPS during dressing change and is moderately but significantly correlated with BPS. An ANIi≥43 has a negative predictive value of 90% to not be associated with a BPS≥5. Several medical, physiological and therapeutic parameters impact on ANIi value independently, but much less so than the painful procedure itself. Unlike to ANIi, ANIm is not a reliable tool to detect pain in ICU patients.

Pain is one of the most stressful events experienced by patients during their ICU stay.[24] Along with delirium, pain is another neuropsychological event for which rigorous screening is highly recommended in ICU patients.[1] Improved pain management based on an accurate assessment of patient's pain intensity is associated with better patient outcomes.[1] This could be partly explained by a reduced use of sedatives and a greater use of analgesics.[25] There is no doubt that pain management in the ICU is a challenge, and determining the most valid and reliable tool is paramount before any implementation of an analgesia protocol by a multidisciplinary team.[1] Team's preferences regarding the choice of a pain tool should be taken into account, but a consensus is difficult to reach because of the subjective nature of these tools.[7]

Electrophysiological pain monitoring needs to be considered for pain management to avoid issues related to inter-rater agreement, especially in the ICU setting where a high number of caregivers work together sharing the same patients. Also, some electropysiological tools, such as videopupillometry, are more sensitive to detect physical stimulation than clinical behavioural tools.[26] However, literature is contrasted regarding the ability of videopupillometry to detect pain related to nursing procedures in ICU patients.[27] Unlike videopupillometry, ANI is an electrophysiological tool that allows for continuous monitoring. The present study shows that ANIi has the best discriminant property compared with BPS, given that the medians and interquartile range of values were more clearly different during

**Table 1** Patient characteristics and medical characteristics of the 110 patients included for analysis. Continuous data are expressed in median [25th-75th percentiles]. ICU, Intensive Care Unit; SAPS II, Simplified Acute Physiological Score II; SOFA, Sequential Organ Failure Assessment score; RASS, Richmond Agitation Sedation Scale. *Major opioids included sufentanil ($n$=30) and remifentanil ($n$=1). †Percent sum differs from 100% because some patients might receive several analgesics

| **Medical history and characteristics upon admission to ICU** | |
|---|---|
| Age (yr) | 61 [51–68] |
| Sex (F/M) | 34/76 |
| BMI (kg m$^{-2}$) | 25 [22–30] |
| BMI $\geq$ 30 kg m$^{-2}$, *n* (%) | 27 (25%) |
| Arterial Hypertension, *n* (%) | 42 (38%) |
| Diabetes, *n* (%) | 24 (22%) |
| Chronic pain syndrome, *n* (%) | 14 (13%) |
| Reason for admission to the ICU | |
| Medical, *n* (%) | 58 (53%) |
| Surgical (from operating room), *n* (%) | 43 (39%) |
| Surgical (from ward), *n* (%) | 9 (8%) |
| SAPS II score | 47 [36–58] |
| SOFA score | 9 [6–12] |
| **Characteristics upon enrolment into the study** | |
| Time between admission to ICU and enrolment (days) | 2 [1–5] |
| Vigilance status | |
| Median RASS level | −1.50 [−3.00; −1.00] |
| RASS level= 0, *n* (%) | 13 (12%) |
| RASS level> 0, *n* (%) | 2 (2%) |
| RASS level< 0, *n* (%) | 95 (86%) |
| Physiological parameters | |
| Heart Rate (b/min) | 90 [70–101] |
| Systolic arterial pressure (mm Hg) | 127 [116–139] |
| Diastolic arterial pressure (mm Hg) | 64 [57–70] |
| Mean arterial pressure (mm Hg) | 86 [78–92] |
| Respiratory Rate (b/min) | 20 [16–24] |
| Oxygen saturation (%) | 99 [97–100] |
| Therapeutics | |
| Invasive mechanical ventilation, *n* (%) | 103 (94%) |
| Assist Control Volume, *n*/*N* (%) | 37/103 (36%) |
| Pressure Support Ventilation, *n*/*N* (%) | 66/103 (64%) |
| Tidal volume (ml/kg of Ideal Body Weight) | 7 [6–9] |
| Plateau pressure (cm $H_2O$) | 16 [14–22] |
| Positive End Expiratory Pressure (cm $H_2O$) | 6 [5–8] |
| Vasopressors, *n* (%) | 51 (46%) |
| Dose (μg kg$^{-1}$ min$^{-1}$) | 0.2 [0.1–0.4] |
| Sedation, *n* (%) | 58 (53%) |
| Propofol, *n*/*N* (%) | 53/58 (91%) |
| Dose (μg kg$^{-1}$ min$^{-1}$) | 21.5 [16.4–34.5] |
| Midazolam, n/N (%) | 4/58 (7%) |
| Dose (μg kg$^{-1}$ min$^{-1}$) | 2.9 [2.3–4.5] |
| Ketamine, *n*/*N* (%) | 1/58 (2%) |
| Dose (μg kg$^{-1}$ min$^{-1}$) | 8.0 [8.0–8.0] |
| Analgesia, *n* (%) | 71 (65%) |
| Sufentanil, *n*/*N* (%)† | 30/71 (42%) |
| Dose (μg kg$^{-1}$ h$^{-1}$) | 0.1 [0.1–0.2] |
| WHO's step I-II analgesics | |
| Acetaminophen, *n*/*N* (%)† | 14/71 (20%) |
| Dose (mg kg$^{-1}$ d$^{-1}$) | 51.9 [47.1–64.5] |
| Nefopam, *n*/*N* (%)† | 25/71 (35%) |
| Dose (mg kg$^{-1}$ d$^{-1}$) | 1.6 [1.4–1.9] |
| Tramadol, *n*/*N* (%)† | 26/71 (37%) |
| Dose (mg kg$^{-1}$ d$^{-1}$) | 5.1 [4.4–6.5] |

procedures than during rest times (Fig. 3). ANIi is also more sensitive than BPS to change during some procedures (dressing change) but it changes very similarly to BPS during patients' turning and tracheal suctioning (Supplementary Fig. E3). Dressing change has recently been recognized as a painful procedure in critically ill patients, even though less painful than mobilization and suctioning.[28 29] The two latter procedures are the most common painful procedures experienced by the patient during an ICU stay.[2] A multidisciplinary quality-improvement study based on clinical pain tools along with an analgesia protocol showed that decreased incidence in severe pain while turning ICU patients was associated with fewer adverse outcomes.[4] Thus, future studies should measure the impact of analgesia protocols based on ANIi monitoring compared with the standard of care (BPS or CPOT). If ANIi is more sensible than BPS, this could lead to an increased use of analgesics and a decreased use of sedatives. In addition to better pain relief for patients, this could also improve their outcomes because sedatives are associated with delirium,[30 31] and prolonged mechanical ventilation and length of ICU and hospital stay.[1 32] On the other hand, an excessively sensitive pain tool might be associated with an overuse of analgesics including opioids and their related side-effects. Such randomized controlled trials would answer the question of which strategy has the best benefit/risk ratio for the patients. They should also take into account the feasibility for ICU teams of protocols based either on subjective or objective pain tools.

The main limit of ANI is that heart rate variability is an indirect unselective measurement of stress, including various sources of stress such as pain but also anxiety and fear. A recent study in 20 healthy volunteers reported a significant decrease in ANI values, after different types of nociceptive stimuli including a placebo stimulation or even the information of the stimulation alone without any effective stimulation.[33] It was not possible to assess anxiety in the present study because inclusion criteria required that the patients could not use a self-report 0-10 NRS. The 0-10 NRS is the most feasible tool that can be used to assess anxiety and emotional distress in critically ill patients.[24 34] Most of the patients had decreased vigilance status (Table 1) and anxiety or emotional distress would be unlikely at baseline. However, there was a small but significant decrease in ANIi as the RASS level increased, (i.e. when patient's awareness increased) (ESM, Supplementary Table E1). Thus, ANI clearly depends on awareness. Also, the impact on ANI of a stimulation, lighter than the care procedures investigated in the present study, such as talking to the patient, needs further investigation. Heart rate variability has been used recently in this way to construct a prototype aimed at monitoring sedation in ICU patients.[35] The link between awareness and possible anxiety or emotional distress had not been shown before because the only recent study already published in ICU patients excluded lightly sedated patients, enrolling 41 deeply sedated patients.[10] In this study, ANI changed significantly during the procedure (turning) without any significant correlation between ANI and BPS.[10] This could be explained by the inclusion of comatose patients in whom pain behaviour is drastically impaired.[26] It is probably more important to treat pain in non-comatose patients because the patient is more likely to be aware of pain, with a possible link between pain and other stressors such as anxiety, insomnia and delirium.[24] Another explanation is that ANI could be modified by delirium or impaired cognition, but a study showed that heart rate variability was not significantly different in ICU patients with and without delirium.[36] A recent study investigating ANI in 20 patients with burns who were able to self-report their

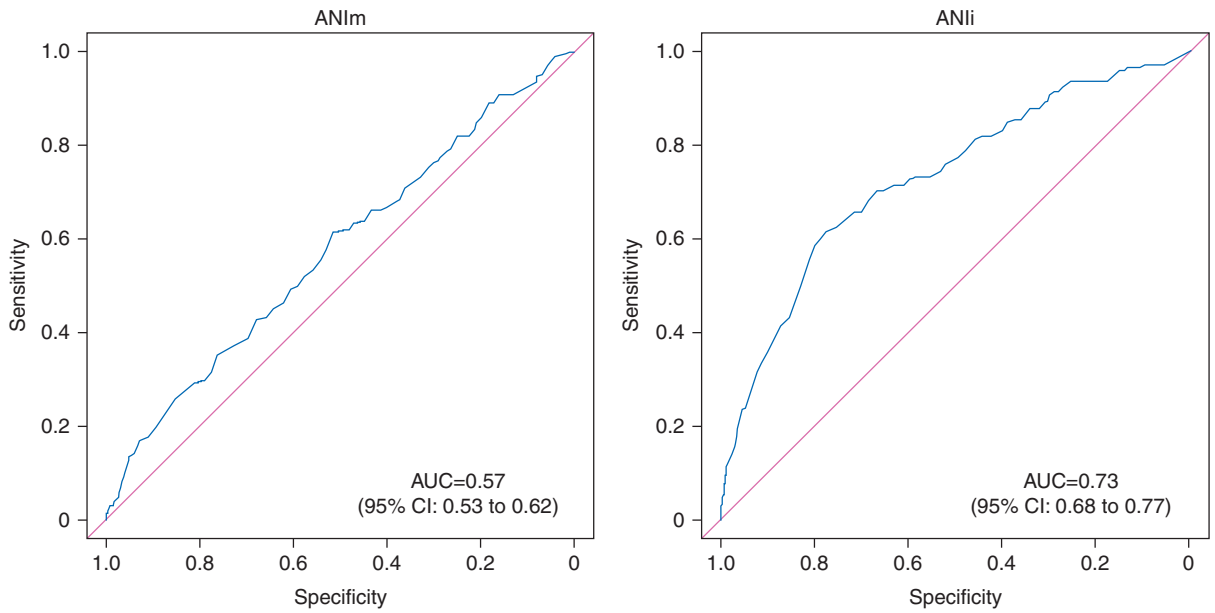


Fig 1 Receiver operating characteristics (ROC) curves for ANI associated with pain defined by a BPS score≥5. All 969 paired measurements of ANI and BPS were included for analysis. ROC curve for ANIm (left panel) demonstrated that ANIm was poorly predictive of pain defined by a BPS ≥ 5 (sensitivity 61.4%, specificity 51.5%, positive predictive value 21.3%, negative predictive value 86.2%, at a mean ANI threshold of 62.5). ROC curve for ANIi (right panel) demonstrated that ANIi was more predictive than ANIm (sensitivity 61.4%, specificity 77.4%, positive predictive value 37.0%, negative predictive value 90.4%, at an ANIi threshold of 42.5). ANI, Analgesia Nociceptive Index; ANIm, mean ANI; ANIi, instant ANI; BPS, Behavioural Pain Scale; AUC, Area under the curve.

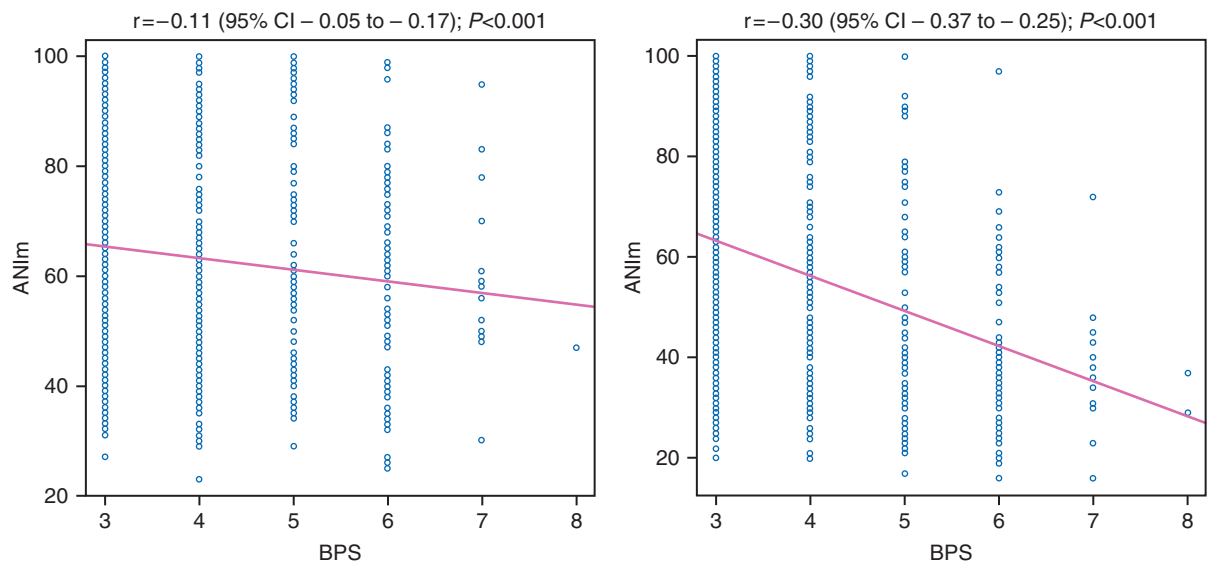


Fig 2 Correlation between ANI and BPS. This figure shows the correlation graph between ANIm and BPS (left panel) and ANIi and BPS (right panel). Both demonstrated significant but low to moderate correlations with BPS (Spearman's test). ANIi demonstrated a better correlation than ANIm. All 969 paired measurements of ANI and BPS were taken into account for analysis. ANI, Analgesia Nociceptive Index; ANIm, mean ANI; ANIi, instant ANI; BPS, Behavioural Pain Scale.

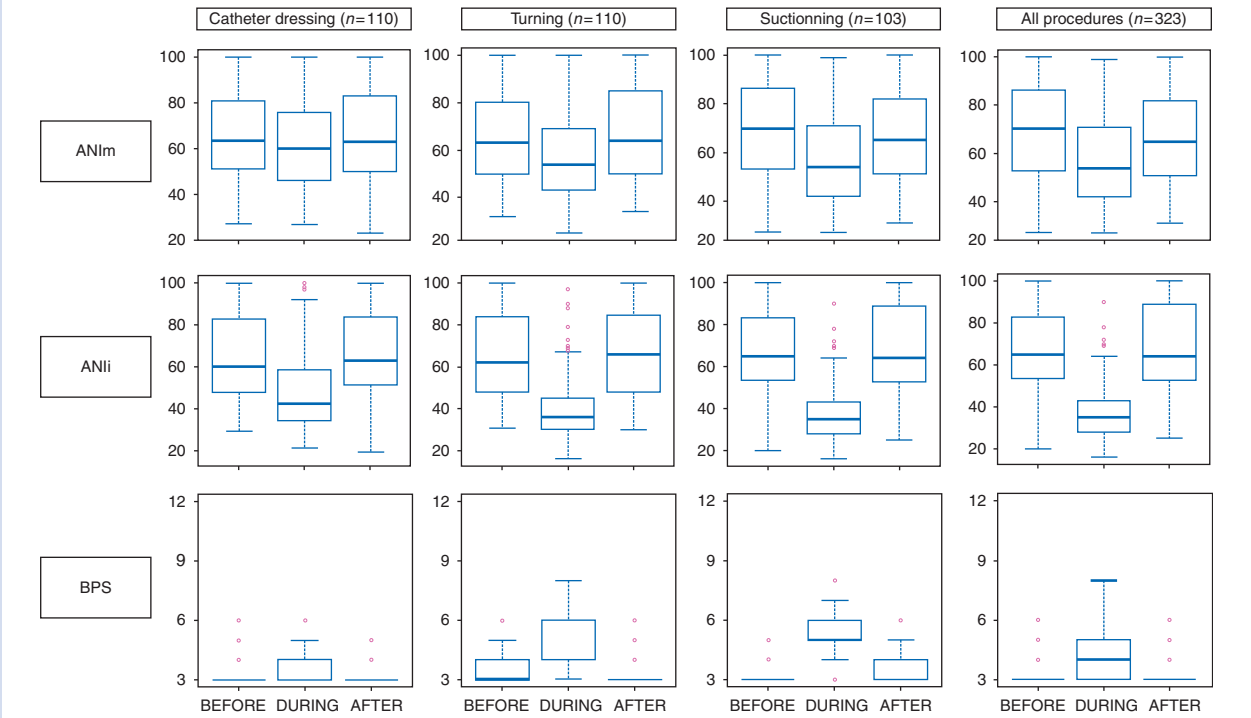


Fig 3 Median values of ANIm, ANIi and BPS before, during and after three different care procedures. This figure shows the median scores of the 3 tools according to different situations: before, during and after 3 different care procedures: a dressing change of a central venous or arterial catheter (all patients, $n$=110), a patient's turning for washing and changing sheets (all patients, $n$=110) and a tracheal suctioning in intubated patients ($n$=103). The right figures show pooled data from the three procedures. Considering the box plots, ANIi demonstrates a good discriminative validity during procedures while ANIm was poorly discriminative. ANI, Analgesia Nociceptive Index; ANIm, mean ANI; ANIi, instant ANI; BPS, Behavioral Pain Scale.

pain intensity on a 0-10 NRS, during scheduled wound treatment procedures, reported findings similar to the present study with a sensitivity and a specificity of ANI to detect pain of 67% and 70%, respectively.[37]

The present study showed other factors that were independently associated with ANI (ESM, Supplementary Table E1). However, all significant factors impacting on ANI, including RASS as discussed above, impacted much less than the painful procedure itself. This should reinforce the validity using ANI in ICU patients. We analysed these factors in an exploratory way in order to find a possible physiological explanation. ANI value was significantly lower when respiratory rate increased. This is consistent with the nature of ANI that decreases when pain, stress response, and sympathic tone increase. Beside, ANI is determined by changes in the parasympathic tone related to ventilation cycle (sinus arrhythmia).[18 38] The consequence is that ANI needs a respiratory rate$\geq$10 b/min to be accurate; this was the case in patients enrolled in our study. Heart rate variability is affected mostly by changes in intrathoracic pressure rather than by respiratory rate itself.[38] In the present study, airway pressure and Tidal volume were not independently associated with ANI values contrary to respiratory rate and spontaneous ventilation. Therefore, the association shown between ANI value and respiratory rate could be explained by a higher stress response in patients breathing spontaneously,[39] and/or with a higher respiratory rate.

On the other hand, ANI increased with acetaminophen use, age and obesity. The effect of acetaminophen could be explained because of a significant analgesic effect in ICU patients,[40] but also because patients only treated by acetaminophen would be less likely to be in pain before the study procedure than patients receiving more effective analgesics.[2] The association between age, obesity and ANI could be explained by an impaired regulation of the neurovegetative system (dysautonomy) in older and/or obese patients. However, if there is a statistical trend in univariate analysis in the association between ANI and potential cofactors related to dysautonomy (hypertension and/or diabetes), only age and obesity were significant after multivariate analysis (ESM, Supplementary Table E1). Greater ANI values could be explained by higher pain thresholds in older,[41] and in obese patients.[42] Obese patients may experience lower pain intensity because of a protective effect of fat against pressure pain,[43] or a possible anti-nociceptive effect of obesity related hormonal changes related to obesity.[44] Finally, ANI increased with severity of illness, and the use of vasopressors, as previously reported.[10] In the present study, patients receiving vasopressors had a significantly lower RASS level than others: -2 [-3 to -1] vs. -1 [-2 to -1], $P$<0.001. This could be explained by the fact that the most critically ill patients were also more sedated with a decreased perception of stress. However, vasopressors use was independently associated with higher ANI in the present study after adjustment on RASS level.

Other factors such as sepsis might explain this result, as heart rate variability is modified early in infected patients.[45]

Our study has several limitations. As mentioned above, because of the observational design of the study, explanation of factors associated with ANI can only generate some hypotheses pending the results of physiological studies that would address these questions. Secondly, our study could not assess all factors impacting on ANI. However, the study was not calibrated on this secondary endpoint. Only predefined factors that we considered particularly relevant were assessed with a multivariate analysis. Some of these factors (use of vasopressors, mechanical ventilation . . .) while common, reflect the heterogeneous nature of ICU patients. Nevertheless, our population was strictly selected on the pertinence of using a behavioural or electrophysiological pain assessment method (i.e. non comatose but non communicant patients suffering from critical illness). Moreover, these factors had a little impact on ANI compared with painful procedures and seemed to be surrogate markers of pain sensitivity/analgesia rather than factors influencing the physiology of ANI. Another limit of our study inherent to the selected population was inability to assess anxiety in these non communicant patients, even though anxiety, as previously stated, can impact on ANI. Thirdly, randomized controlled trials are mandatory to measure the impact of ANI, compared with behavioural pain tools that are presently recommended but less sensitive than electrophysiological methods to detect changes during procedures. Fourthly, because ANI provides a value calculated over a large period of time (one to four min), the modest correlation between ANI and BPS could be explained by a possible imperfect match between the time of pain measurement using BPS and the time of measure by ANI recording. To match ANI and BPS timings to the best, the ANI analysts, who were unaware of the BPS result, could not be blinded to the procedure. Thus, ANI analysts could have been biased to some extent by their knowledge. An external validation cohort of ANI monitoring over a longer period of time is needed as a second step to confirm the present findings, through an independent analysis of ANI capacity to detect painful procedures, blinded to the procedure timing.

## Conclusions

Contrary to anaesthesia care, ANIm is not a reliable tool to detect pain in critically ill patients and should not be used in the ICU setting. On the other hand, ANIi is effective to detect pain during common procedures of care in ICU patients (turning, tracheal-suctioning). ANIi is more sensitive to change during smaller stimulations (dressing change) than recommended clinical behavioural pain tools such as the BPS.

In addition to age, obesity, severity of illness, use of vasopressors and mechanical ventilation that significantly impact ANIi, ANIi significantly decreased with a higher patient's awareness. This could be partly explained by the fact that ANIi measures unselective sources of stress including pain and anxiety. Therefore, randomized controlled trials are needed to measure the impact of a sedation-analgesia protocol based on ANIi, compared with recommended behavioural pain tools (standard of care) on sedation use and its related outcomes (delirium, duration of mechanical ventilation, length of stay in the hospital). Also, this study needs to be replicated on patients receiving neuromuscular blocking agents because behavioural pain tools cannot be used and it is paramount that these patients do not suffer any pain. Though sensitivity and specificity of ANIi in the reflection of pain were low, the Negative-Predictive-Value of ANI$\geq$43 was 90%. Hence ANIi may be of highest benefit for the exclusion of significant pain.

## Authors' contributions

Study design/planning: G.C., T.T., A.R., S.J.
Study conduct: T.T., A.R., A.P.
Data analysis: N.M., A.D.J.
Writing paper: G.C., T.T., A.R., S.J.
Revising paper: all authors

## Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.


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