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Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study

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Editor's key points

- Poorly controlled pain on arrival in the recovery room disrupts the handover process and may worsen patient recovery.
- Nociception reduces parasympathetic tone and this affects heart rate variability, from which the analgesia/nociception index (ANI) can be derived.
- This study shows a strong relationship between the ANI and immediate postoperative pain on arrival in the recovery room.
- The ANI may assist in optimal titration of analgesia before emergence from anaesthesia.

Background. The analgesia/nociception index (ANI) is derived from heart rate variability, ranging from 0 (maximal nociception) to 100 (maximal analgesia), to reflect the analgesia/nociception balance during general anaesthesia. This should be correlated with immediate postoperative pain in the post-anaesthesia care unit (PACU). The aim of this study was to evaluate the performance of ANI measured at arousal from general anaesthesia to predict immediate postoperative pain on arrival in PACU.

Methods. Two hundred patients undergoing ear, nose, and throat or lower limb orthopaedic surgery with general anaesthesia using an inhalational agent and remifentanil were included in this prospective observational study. The ANI was measured immediately before tracheal extubation and pain intensity was assessed within 10 min of arrival in PACU using a 0–10 numerical rating scale (NRS). The relationship between ANI and NRS was assessed using linear regression. A receiver-operating characteristic (ROC) curve was used to evaluate the performance of ANI to predict NRS$>$3.

Results. A negative linear relationship was observed between ANI immediately before extubation and NRS on arrival in PACU. Using a threshold of $<$50, the sensitivity and specificity of ANI to discriminate between patients with NRS$\leq$3 and NRS$>$3 were both 86% with 92% negative predictive value, corresponding to an area under the ROC curve of 0.89.

Conclusions. The measurement of ANI immediately before extubation after inhalation-remifentanil anaesthesia was significantly associated with pain intensity on arrival in PACU. The performance of ANI for the prediction of immediate postoperative pain is good and may assist physicians in optimizing acute pain management.

Clinical trial registration. ClinicalTrials.gov NCT01796249.

Keywords: anaesthesia, general; analgesia; nociception; pain measurement

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Severe immediate postoperative pain remains frequent after surgery, occurring in 20–40% of patients.[1] A recent study has shown that pain intensity may be high not only after major surgical procedures such as major orthopaedic surgery but also after several common minor-to-medium level surgical procedures, including haemorrhoidectomy, tonsillectomy or laparoscopic appendectomy, or cholecystectomy.[1] This study indicates that to reduce the incidence of severe postoperative pain, patients undergoing so-called minor surgery should be monitored more closely and that post-operative pain management should comply with existing recommendations.

Updated practice guidelines for acute pain management in the perioperative setting have been recently reported by the ASA Task Force on Acute Pain Management.[2] These guidelines state that anaesthesiologists should use standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side-effects caused by the therapy. In a communicating patient who is awake in the post-anaesthesia care unit (PACU), pain intensity can be assessed using a 0–100 visual analogic scale, a 1–5 verbal rating scale, or a 0–10 numerical rating scale (NRS), although the standard method is still a topic of debate.[3]

The assessment of immediate postoperative pain may be obtained in PACU using different methods such as skin conductance or pupillary reflex measurement.[4–6] We have recently reported that it may also be obtained using the analgesia/nociception index (ANI), a 0–100 non-invasive index calculated from heart rate variability reflecting the parasympathetic tone.[7] To date, ANI has been used to assess the antinociception/nociception balance during general anaesthesia in adults and children or during labour pain, showing significant changes between painful and no-pain periods.[8–11] Similarly, the measurement of ANI during the immediate postoperative period was significantly correlated with pain intensity.[7] We hypothesized that ANI may be used not only for the assessment but also for the prediction of immediate postoperative pain. Our primary objective was to investigate the performance of ANI measured at arousal from general anaesthesia in the operating theatre for the prediction of immediate postoperative pain on arrival in PACU.

Methods

Study design

This prospective observational study was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Est III, study identifier CPP 2012-052 B, ClinicalTrials.gov identifier NCT01796249) and performed between October 2012 and April 2013 at Édouard Herriot Hospital, Lyon, France. The methodology followed the recommendations of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[12] After written informed consent was obtained, ASA physical status I–III patients undergoing halogenated-based and remifentanil general anaesthesia in the room where the ANI monitor was placed were included. The procedures performed were ear, nose, and throat (ENT) surgery or orthopaedic lower limb surgery. The exclusion criteria were age <18 yr or >75 yr, arrhythmia, preoperative use of β-blockers, administration of anticholinergic drugs or neuromuscular block reversal in the previous 20 min, preoperative pain treated with opioids, psychiatric diseases, autonomic nervous system disorders, epilepsy, and inability to understand the verbal rating pain scale.

Anaesthetic technique

Alprazolam 0.1 mg kg^{-1}, hydroxyzine 1 mg kg^{-1}, or both were administered orally 1 h before induction of anaesthesia. After arrival in the operating theatre, patients were monitored with a three-lead electrocardiogram (ECG), non-invasive arterial pressure measurement and pulse oximetry. The anaesthetic induction was then performed using i.v. ketamine (0.1–0.5 mg kg^{-1}) to prevent postoperative hyperalgesia, propofol 2.5 mg kg^{-1} and remifentanil 1 μg kg^{-1} in 1 min if cisatracurium (0.15 mg kg^{-1}) was used or 2–4 μg kg^{-1} in 1 min to provide optimal intubation conditions in the absence of neuromuscular block.[13–15] The use of neuromuscular blocking agent was used at the discretion of the attending anaesthesiologist. After tracheal intubation, mechanical ventilation was initiated with a mixture of 60–70% O_2 and 30–40% air and adjusted to keep end-tidal CO_2 pressure between 30 and 35 mm Hg. Maintenance of anaesthesia was performed at the discretion of the anaesthesiologist with sevoflurane or desflurane adjusted to keep the minimal alveolar concentration between 0.8 and 1.2 and remifentanil 0.1–0.3 μg kg^{-1} min^{-1} in continuous infusion. In the case of use of cisatracurium, neuromuscular block was monitored by train-of-four (TOF) stimulation. Multimodal analgesia was provided at the discretion of the attending anaesthesiologist using i.v. paracetamol, ketoprofen, nefopam, tramadol, and morphine 0.1–0.2 mg kg^{-1} in combination according to respective contraindications.[2] In some cases, regional analgesia was used (peripheral nerve blocks or wound infiltration). At the end of the procedure, remifentanil and halogenated agents were discontinued, and 100% O_2 was given with a 10 litre min^{-1} fresh gas flow. To prevent residual paralysis if cisatracurium was used, spontaneous recovery from neuromuscular block at emergence from anaesthesia was assessed by a TOF ratio of ≥ 0.9.[16] In the case of a TOF ratio of <0.9, neostigmine 30–40 μg kg^{-1} and atropine 15–20 μg kg^{-1} were administered i.v. after four twitches were visible and patients were withdrawn from the study. Tracheal extubation was performed when the patient was alert, with a respiratory rate between 12 and 30 cycles min^{-1} and a temperature of $>36.5^{\circ}$C, and then the patient was sent to PACU.

Study protocol and ANI measurement

At arousal from general anaesthesia, ANI was recorded immediately before tracheal extubation using the PhysioDoloris® monitor (MDoloris Medical Systems, Loos, France). It is a non-invasive device that takes an ECG analogue output from the patient monitor and displays an average measurement of ANI made over the previous 2 min. Details of ANI calculation have been previously described.[8 17] The ANI is a 0–100 index derived from the high-frequency component of heart rate variability reflecting the analgesia/nociception balance.[8] Briefly, local minima and maxima in the normalized high-frequency RR series of the QRS complex are automatically detected and the surface between the lower and upper envelopes is measured in four sub-windows, with area under the curve $(AUC)_{min}$ defined as the smallest sub-surface.[8] Then, ANI is computed in order to express a fraction of the total window surface (having a maximum possible value of 12.8 s), leading to a measure varying from 0 to 100 displayed continuously as a short-term average more than 2 min using the following formula: $ANI = 100*[(5.1 \times AUC_{min} + 1.2)/12.8]$.[8] Higher ANI values indicate prominent parasympathetic tone, as observed during adequate analgesia.[18] In the case of nociception, the sympathetic tone increases and the parasympathetic tone decreases, leading to decreased ANI values.[18]

Immediate postoperative pain intensity was assessed within 10 min of arrival in PACU by using a 0–10 NRS (0=no pain and 10=worst pain imaginable), with NRS$\leq$3 corresponding to no or mild pain and NRS$>$3 corresponding to moderate-to-severe pain.[19] All patients were educated about NRS before surgery. Patients experiencing NRS$>$3 received i.v. morphine titration

or peripheral nerve block until pain returned to an NRS of ≤3.[2 20] Patients experiencing an initial NRS of ≤3 did not receive morphine titration. The use of non-opioid agents for multimodal postoperative analgesia during PACU stay was left to the discretion of the anaesthesiologist.[2] All anaesthetic data including ANI measurements were recorded using the DIANE® 4.4.5 software (Bow Médical, Amiens, France) for further analysis.

Statistical analysis

The number of patients during the study period determined the sample size. Statistical analysis was performed using MedCalc® 12.1.4.0 (MedCalc Software, Mariakerke, Belgium). For the comparison between patients with NRS≤3 (adequate analgesia) and NRS>3 (pain), the Student's *t*-test was used for normally distributed quantitative data (Kolmogorov–Smirnov test), the Mann–Whitney *U*-test for non-normally distributed data, and the χ^2 test for quantitative data. We hypothesized that ANI at arousal from general anaesthesia immediately before extubation would have a linear relationship with initial NRS in PACU. The linear relationship and the coefficient of determination (r^2) were assessed using linear regression. A receiver-operating characteristic (ROC) curve was built by plotting the sensitivity, or true-positive rate, as a function of the false-positive rate (100−specificity) at different ANI points. The software generated the ANI value with the highest sensitivity and specificity (Youden index) to conclude that a patient had immediate postoperative pain (NRS>3) requiring supplemental analgesia. The performance of a diagnostic test with an ROC curve AUC of >0.8 can be classified as good.[21] The results were expressed as mean (SD), median interquartile range (IQR) or *n* (%). The threshold for statistical significance was set at $P=0.05$.

Results

Of the 495 patients potentially eligible, 16 missed the invitation to participate or declined to be invited, 64 received spinal anaesthesia, 12 received peripheral nerve block, 58 received total i.v. anaesthesia with propofol and remifentanil for endoscopic procedures (suspension laryngoscopy), and 48 received opioids other than remifentanil (alfentanil or sufentanil), leaving 297 patients examined for eligibility (Fig. 1). Of these patients, 60 were excluded and of the 237 patients included, 37 were withdrawn from study, leaving 200 patients for analysis (Fig. 1). In these patients, ANI was measured at arousal from general anaesthesia immediately before extubation and pain intensity was assessed using NRS within 10 min of arrival in PACU. Measurements were correctly performed in all these patients without any missing values.

Considering pain evaluation, 130 patients (65%) had no or mild pain (NRS≤3), all of them having received effective i.v. or regional analgesia during surgery, and 70 patients (35%) had moderate-to-severe pain (NRS>3) requiring i.v. morphine titration or peripheral nerve block. Gender, body mass index, ASA class and the chosen halogenated agent were similar between patients with NRS≤3 and NRS>3 (Table 1). More patients with NRS>3 underwent orthopaedic procedures than patients with NRS≤3 (70% *vs* 37%, respectively, $P<0.01$).

Mean (SD) ANI values were statistically higher between patients with initial NRS≤3 and NRS>3 [68 (18) *vs* 42 (12), respectively, $P<0.01$]. The median [IQR] morphine consumption during PACU stay was statistically higher ($P<0.01$) in patients with initial NRS>3 in comparison with patients with NRS≤3, (4 mg [3–6] *vs* 0 mg [0–0], respectively, $P<0.01$). In total, 33 patients received intraoperative regional analgesia (mostly bilateral infraorbital nerve block for nose surgery), 26 of them (79%) having NRS ≤3 and a median [IQR] ANI of 62 [51–84] on arrival in PACU (Table 1). More patients with NRS>3 received postoperative regional anaesthesia techniques (mostly femoral nerve block) for pain management in PACU in comparison with patients with NRS≤3 (36% *vs* 10%, respectively, $P<0.01$).

A statistically significant negative linear relationship (ANI=68.1−4.2×NRS, $r^2=0.33$, $P<0.01$) was observed between ANI immediately before extubation and NRS on arrival in PACU, with 33% variations of ANI explained by NRS (Fig. 2). The ROC curve determining the performance of ANI for predicting NRS>3 is shown in Figure 3 [AUC=0.89, 95% confidence interval (CI) 0.84–0.93]. At the threshold of <50, the sensitivity and specificity (95% CI) of ANI to discriminate between patients with NRS≤3 and NRS>3 were 86% (75–93) and 86% (79–92), respectively, with 77% (66–89) positive predictive value and 92% (85–96) negative predictive value (Table 2). In a subgroup analysis (Table 2), a higher performance of ANI for predicting NRS>3 was observed in orthopaedic patients (ROC curve AUC=0.93) than in ENT patients (ROC curve AUC=0.83). The frequency of patients with NRS>3 was higher in patients undergoing orthopaedic procedures than in those undergoing ENT surgery (51% *vs* 20%, respectively, $P<0.05$).

Discussion

The results of this study demonstrate that there is a negative linear relationship between ANI measured at arousal from general anaesthesia before extubation and immediate postoperative pain on arrival in PACU, with ANI<50 corresponding to the subjective threshold of moderate-to-severe pain (NRS>3). With an ROC curve AUC of 0.89 (and of 0.93 for painful procedures such as lower limb orthopaedic surgery), the performance of ANI for the prediction of immediate postoperative pain may be classified as good.[21] Moreover, with a high negative predictive value, ANI≥50 may predict that 92% of patients will have adequate analgesia (NRS≤3) on arrival in PACU, therefore not requiring morphine titration or regional anaesthesia, which might be of importance to optimize the treatment of immediate postoperative pain.

Indeed, although the benefits of optimal pain management are well recognized, treatment of postoperative pain continues to be a major challenge. Extensive studies have demonstrated that despite improvements in pain management, many patients still experience moderate-to-severe postoperative pain.[1] Severe pain is associated with decreased patient satisfaction, delayed postoperative ambulation, the development of chronic postoperative pain, and increased morbidity and mortality;

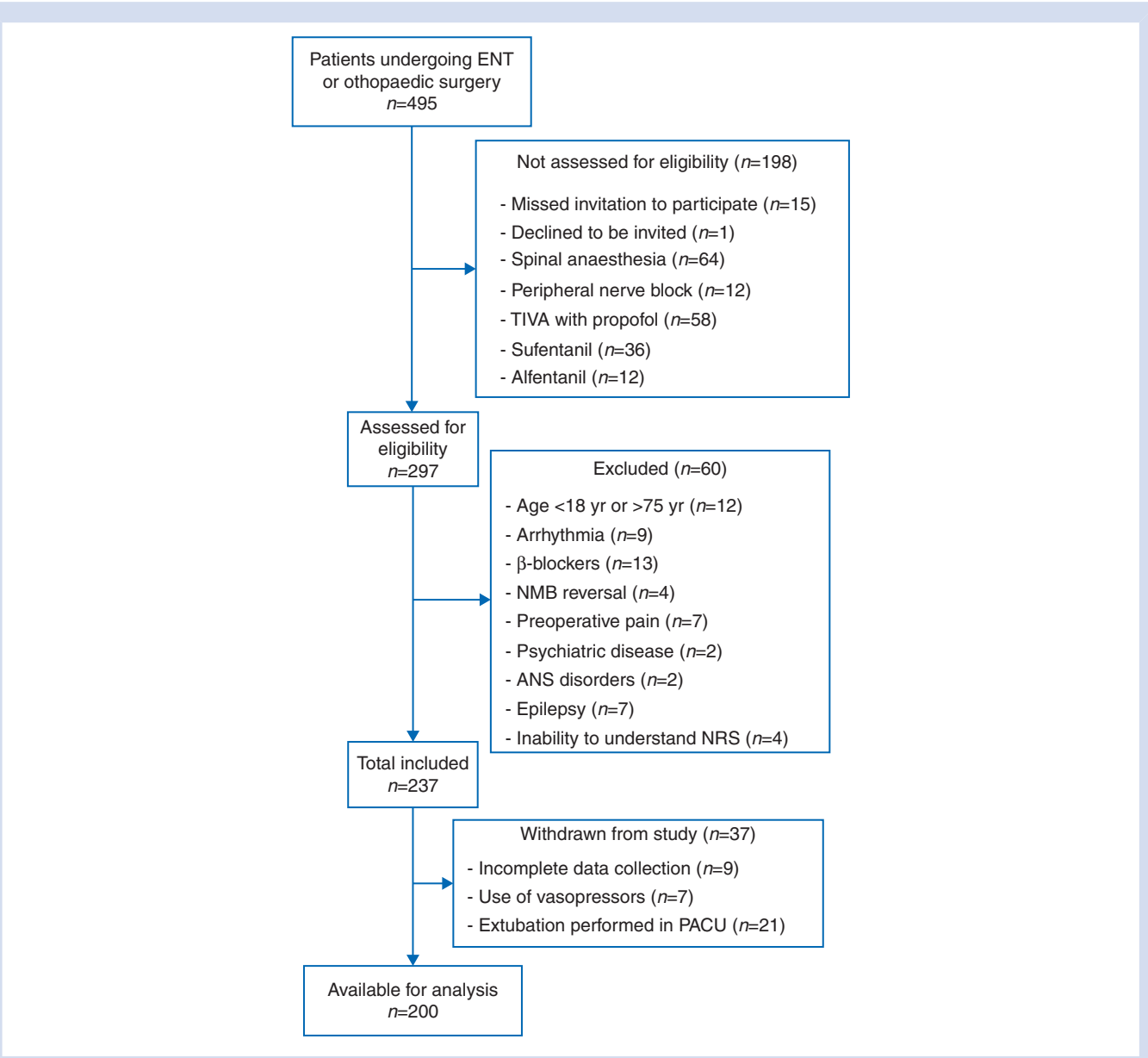

Fig 1 Flow diagram. ANS, autonomic nervous system; ENT, ear-nose-throat; NMB, neuromuscular block; NRS, numerical rating scale; PACU, post-anaesthesia care unit; TIVA, total intravenous anaesthesia.

therefore, it is of great importance that optimal analgesic strategies are used to improve pain management.[1 2]

The recent study by Gerbershagen and colleagues[1] showed that pain scores are often high on the first day after surgery and that many operations considered minor procedures are associated with considerable pain, probably because physicians and nurses may underestimate the patient's requirement for analgesic medication. Therefore, relief of acute pain during the immediate postoperative period, using multimodal analgesia, i.v. morphine titration, or peripheral nerve block, is an important task for anaesthesiologists.[2 20] In the current study, similar to previous reports, 35% of patients experienced immediate postoperative pain (NRS>3) with higher pain scores observed in orthopaedic patients. The prediction of postoperative pain before arrival in PACU using ANI at arousal from general anaesthesia may be helpful to anticipate adequate analgesia and thus to improve postoperative pain management.

We have previously described a negative linear relationship between ANI and NRS values on arrival in PACU in patients undergoing ENT surgery.[7] The differences between the current study and our previous study appear in Supplementary Table S1. In this study, the performance of ANI for the assessment of immediate postoperative pain after remifentanil and halogenated-based general anaesthesia was good, with an ROC curve AUC of 0.82. An ANI value of ≤57 provided the best sensitivity (76%) and specificity (73%) to discriminate between patients with NRS≤3 and NRS>3, which was less than in the

Table 1 Characteristics of study subjects. Values are given as mean (SD), median [IQR], or *n* (%). ANI, analgesia/nociception index; BMI, body mass index; ENT, ear, nose, and throat; NRS, 0–10 numerical rating pain scale; PACU, post-anaesthesia care unit; RA, regional analgesia

	NRS≤3 (*n*=130)	NRS>3 (*n*=70)	*P*-value
Age, yr	44 (18)	51 (17)	<0.01
BMI, kg m^{-2}	25 (5)	26 (5)	0.19
Gender, *n* (%)			
Male	68 (52)	40 (57)	0.61
Female	62 (48)	30 (43)	
ASA class, *n* (%)			
I	71 (55)	26 (37)	0.06
II	52 (40)	38 (54)	
III	7 (5)	6 (9)	
Halogenated agent, *n* (%)			
Desflurane	94 (72)	56 (80)	0.30
Sevoflurane	36 (28)	14 (20)	
Cisatracurium, *n* (%)	13 (10)	14 (20)	0.08
Type of procedure, *n* (%)			
ENT surgery	82 (63)	21 (30)	<0.01
Lower limb orthopaedic surgery	48 (37)	49 (70)	
ANI values			
All patients	68 (18)	42 (12)	<0.01
Patients with intraoperative RA	62 [51–84] (*n*=26)	49 [47–63] (*n*=7)	0.09
Morphine consumption in PACU, mg	0 [0]	4 [3–6]	<0.01
Peripheral nerve block in PACU, *n* (%)	13 (10)	25 (36)	<0.01

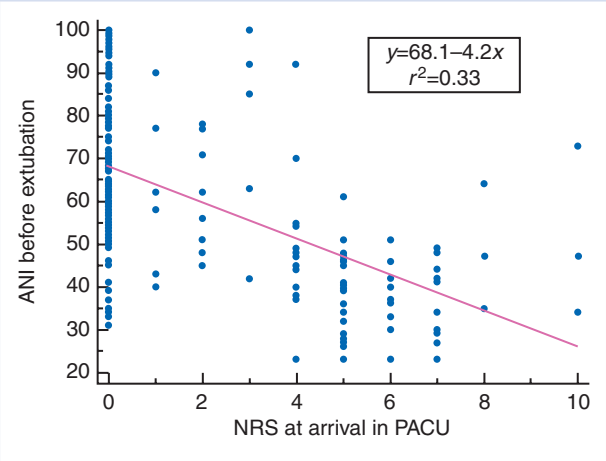

Fig 2 Negative linear relationship between ANI and NRS. ANI, analgesia/nociception index; NRS, numerical rating scale.

current study. These differences may be explained by the fact that many factors other than pain commonly encountered in PACU are known to increase sympathetic activity, such as stress and anxiety, and therefore may influence ANI response.[22 23] More recently, a study very similar to our previous study showed very different results, with both sensitivity and specificity of ANI found to be only ~50% and an area under ROC curve of 0.434.[24] The differences might be partly explained by

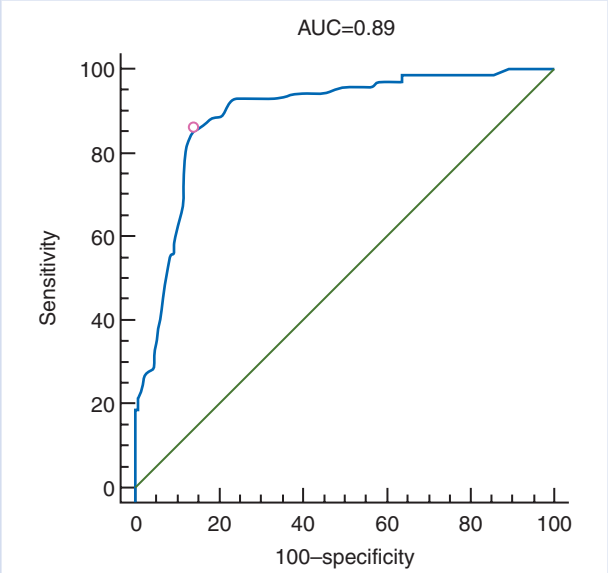

Fig 3 ROC curve showing the relationship between sensitivity (true-positive rate) and 100−specificity (true-negative rate) determining the performance of ANI measured immediately before extubation to predict immediate postoperative pain (NRS>3). The open circle represents Youden index. ANI, analgesia/nociception index; AUC, area under the curve; ROC, receiver-operating characteristic.

Table 2 Performance of ANI for the prediction of immediate postoperative pain (NRS>3). ANI, analgesia/nociception index; ANI, analgesia/nociception index; AUC, area under the curve; ENT, ear, nose, and throat; NRS, 0–10 numerical rating pain scale; ROC, receiver-operating characteristic. Values in square brackets are 95% confidence intervals

	All patients	ENT surgery	Lower limb orthopaedic surgery
n	200	103	97
Patients with NRS>3	70 (35%)	21 (20%)	49 (51%)
ROC curve AUC	0.89 [0.84–0.93]	0.83 [0.75–0.90]	0.93 [0.86–0.97]
ANI threshold (Youden index)	50	50	52
Sensitivity (%)	86 [75–93]	81 [58–95]	92 (80–98)
Specificity (%)	86 [79–92]	83 [73–90]	90 [77–97]
Positive predictive value (%)	77 [66–89]	55 [36–73]	90 [78–97]
Negative predictive value (%)	92 [85–96]	94 [86–99]	92 [79–98]
Positive likelihood ratio	6.2 [4.0–9.6]	4.7 [3.8–6.0]	8.8 [7.8–10.0]
Negative likelihood ratio	0.2 [0.1–0.3]	0.2 [0.1–0.6]	0.1 [0.0–0.3]

the fact the authors used fentanyl in their study, whereas remifentanil was used in ours, probably exhibiting different properties affecting heart rate variability.

In the current study, ANI measurements were performed at arousal from general anaesthesia, immediately before extubation, that is, at such a time as supposedly avoids stress and anxiety when sympathetic activity should theoretically be mainly related to pain. This might in part explain why the global performance of ANI measured at arousal from anaesthesia to predict postoperative pain is somewhat better than ANI measured in awaken patients in PACU to assess postoperative pain. However, in our previous study, ANI performance was significantly better after propofol i.v. anaesthesia than after halogenated-based anaesthesia (ROC curve AUC=0.93 with 89% sensitivity and 87% specificity for ANI≤57 to assess NRS>3).[7] It has been shown that the choice of anaesthetic may influence the intraoperative stress response during halogenated-based or total i.v. anaesthesia, with a marked reduction of heart rate variability for both techniques and a more distinct decrease in total power using sevoflurane rather than propofol.[25] The different impact of the chosen anaesthetic agents on heart rate variability might also in part explain the differences between ANI used for the assessment or for the prediction of postoperative pain.

Our study presents, however, some limitations. First, many patients were excluded, including patients with arrhythmia or using medications known to alter heart rate variability (e.g. β-adrenoreceptor antagonists, atropine, vasopressors, or antiepileptic drugs) which may cause concern for the use of ANI in these patients.[26 27] Moreover, in the current study, the administration of neuromuscular blocking drugs was closely monitored, allowing residual paralysis to be prevented without the use of neostigmine and anticholinergic medications that could have interfered with heart rate variability in the majority of patients.[28 29] Our results may not be extrapolable to curarized patients when reversing neuromuscular block with an acetylcholinesterase inhibitor rather than spontaneous recovery is chosen, which is a frequent option.[16] Other factors such as age and sex, inspiratory oxygen fraction, or the choice of anaesthetic agent (propofol or halogenated) or technique (spinal or general anaesthesia) may influence the autonomic nervous system regulation and alter the response of heart rate variability to nociception.[30–33] Moreover, the influence of tracheal tube stress before extubation on ANI remains to be determined. Last, the opioid used in the current study was remifentanil because of its specific short-acting pharmacokinetic and pharmacodynamic properties, but our results may not be extrapolable to general anaesthesia using fentanyl or sufentanil, which may have a different impact on heart rate variability.[34 35] Further studies are thus needed to assess the usefulness of ANI in various anaesthesia conditions and in different patient groups.

In conclusion, the measurement of ANI at arousal from remifentanil and halogenated-based general anaesthesia immediately before extubation is significantly correlated with pain intensity on arrival in PACU. In our study population, an ANI value of <50 was predictive of moderate-to-severe pain (NRS>3) with good performance. Considering the high negative predictive value at this threshold, the measurement of ANI at arousal from general anaesthesia immediately before extubation appears to be a simple and non-invasive method to predict adequate analgesia on arrival in PACU in patients without exclusion criteria. In this perspective, ANI may help clinicians and other healthcare providers to optimize acute pain management in the immediate postoperative period.

Supplementary material

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

Authors' contributions

E.B.: designed and conducted the study, analysed data, and prepared the manuscript. L.B. and B.A.: helped design the study and prepare manuscript. The other authors collected data and helped prepare the manuscript.

Declaration of interest

E.B. received a travel grant from MDoloris Medical Systems for a symposium presentation. None of the other authors has any existing conflicting interest, including honoraria for presentations at departmental or scientific meetings.

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