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Analgesia nociception index: evaluation as a new parameter for acute postoperative pain

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Editor's key points

- Development of objective pain measures would be useful in situations where verbal communication is impaired.
- The analgesia nociception index (ANI) uses heart rate variability (HRV) as a surrogate pain measure.
- After sevoflurane anaesthesia there was a small statistically significant negative correlation between ANI and pain.
- Changes in ANI did not seem useful in differentiating between minor and severe pain.

Background. A means of identifying the presence and severity of pain that is not reliant on the subjective assessment of pain is desirable whenever a patient self-rating of pain cannot be easily obtained (e.g. sedated patients, very young children, individuals with learning difficulties). The heart rate variability based analgesia nociception index (ANI) has been proposed to reflect different levels of acute pain. The aim of this study was to compare ANI scores with a numeric rating scale (NRS, 0–10) based on self-assessment of pain in the recovery room.

Methods. One hundred and twenty patients after non-emergency surgery were included. On arrival in the post-anaesthesia care unit (PACU) and subsequently at 5 min intervals, patients were asked to rate their level of pain on a 0–10 NRS. ANI values 0–100 points (low values indicating higher levels of pain) were recorded simultaneously.

Results. Eight hundred and sixteen pain ratings from 114 patients were included in the analysis. A small but statistically significant negative correlation was found between ANI and the NRS scores ($\rho = -0.075$; $P = 0.034$). A small but significant difference in ANI was found comparing the extremes of pain [mean (SE): NRS 0: 63 (1.4) *vs* NRS 6–10: 59 (1.4); $P = 0.027$]. However, a receiver-operating analysis testing the value of ANI to distinguish between NRS 0 and NRS 6–10 revealed only low sensitivity and specificity.

Conclusion. ANI did not reflect different states of acute postoperative pain measured on a NRS scale after adult sevoflurane-based general anaesthesia.

Keywords: analgesia, postoperative; pain, postoperative

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Freedom from pain is a basic human right and also impacts on patients' postoperative outcomes. As pain is by definition a subjective experience, patient self-rating based pain scales such as the numeric rating scale (NRS) or the visual analogue scale (VAS) are considered the gold standard for assessing acute pain in adult postoperative patients. However, these scales are bound to fail in individuals with communication impairment such as those patients who are sedated, demented, or very young. In these instances, a cooperation-independent monitor for pain would be highly desirable.

In the past, measures of sympathetic activity, such as skin conductance monitoring or the HRV based surgical pleth index (SPI) have shown some association with acute pain, however without being sufficiently accurate to recommend their use in clinical practice.[1 2]

Most recently, an ANI (Metrodoloris, France) has been promoted world-wide by its manufacturer as a potential tool to aid the assessment of acute nociception and pain. The ANI has been developed as a joint venture project by the University Lille, France and the Clinical Investigation Centre 807 for Innovative Technology of Lille, France. It is based on ECG data derived from two single-use ANI electrodes applied in V1 and V5 positions to the chest. The ANI is finally computed from a frequency domain-based analysis of the high frequency component (HF: 0.15–0.5 Hz) of HRV which also incorporates the respiration rate (RR) as a potential confounder. It is displayed as a score from 0–100 with low values reflecting low and high values high parasympathetic predominance in autonomic cardiac control.[3 4]

A study investigating its correlation with the VAS during labour showed a negative linear relationship between the two scores, with ANI values below 49 indicating pain scores >30 (VAS 0–100).[3]

The primary aim of our study was to prospectively investigate the association between the ANI and the NRS in adult patients after sevoflurane-based anaesthesia for non-emergency

surgery. Secondary aims were to investigate the influence of sedation and opioid administration on ANI scores, and the clinical applicability of ANI as a measure of acute pain.

Methods

After registration with the Australian New Zealand Clinical Trials Registry (ACTRN12612001193864; https://www.anzctr.org.au/registry/trial_review.aspx?ID=363258) and approval by the Ethics Committee of the Royal Perth Hospital (EC 2012–050), 120 adult patients undergoing non-emergency surgery were included after giving written informed consent. All patients received maintenance of anaesthesia with sevoflurane and fentanyl. Patients receiving β-receptor blockers, ketamine, clonidine, or any vasoactive substance (i.e. metaraminol, ephedrine) and patients receiving neostigmine, atropine or glycopyrrolate were excluded. The study commenced after operation upon admission to the post-anaesthesia care unit (PACU).

As soon as sufficiently responsive, patients were asked by a PACU nurse (blinded at all times to the ANI scores) to rate their pain at rest on a 0–10 point NRS. If pain was rated as NRS 0–3 (not requiring urgent treatment), the rating was repeated after 10 min. If pain was NRS 4–10 (requiring urgent treatment), 20 μg i.v. fentanyl was administered and the pain rating repeated at 5 min intervals until the NRS was rated 0–3. Once rated NRS 0–3, the rating was repeated at 10 min intervals.

ANI scores were obtained by an independent observer immediately preceding each pain rating. The NRS scores were obtained directly after the ANI scores. To monitor ANI scores, a commercially available stand-alone ANI monitor (MetroDoloris, Lille, France) was used. With the ANI electrodes in V1 and V5 ECG position, ANI was continuously recorded and displayed. Pain scores, postoperative nausea and vomiting and sedation scores and opioid administration were logged as events on the ANI monitor. Sedation was recorded at each pain rating on a −5 (unconscious) to +5 (severe agitation) score, with 0 reflecting a conscious and calm patient. Coinciding with above ANI/NRS ratings, blood pressure (BPsyst), heart rate and RR were also recorded.

The observation period ended with PACU discharge.

Statistical analysis

After a pilot study including 30 subjects a sample size of 113 subjects was estimated to detect a minimum difference of four ANI points between NRS 0 (no pain) and NRS 6–10 (severe pain) with 80% power and an alpha error of 5% [based on an estimated ANI standard deviation (SD) of 15]. In order to allow for potential drop outs and missing data, 120 patients were recruited.

For the comparison of mean ANI scores between different states of pain [no (NRS 0), mild (NRS 1–3), moderate (NRS 4–5), or severe (NRS 6–10)] a linear mixed model approach was used to account for the different numbers of repeated measurements per patient. All data were tested for normal distribution (Kolmogorov–Smirnov test) and are provided as mean (SD or SE) or median (percentiles), as appropriate. Spearman's rho coefficient was used to investigate the correlation between ANI and NRS values. To calculate the sensitivity and specificity of ANI to distinguish different states of pain an analysis of receiver-operating characteristics (ROC) was used.

Table 1 ANI at different states of pain measured on a NRS. *$P<0.05$ (*vs* NRS 0)

NRS score	ANI [mean (SE)]	95% CI
0	62.9 (1.4)	60.2–65.6
1–3	59.0 (1.4)	56.3–61.7
4–5	59.1 (1.5)	56.1–62.0
6–10	59.2 (1.5)*	56.2–62.2

Results

Data of 114 [79 male, 35 female; aged 35 (14) yr] patients were analysed. Six patients were excluded because of technical difficulties with the monitor (problems with placement of the adhesive electrodes) or protocol violation.

Eight hundred and sixteen NRS-ANI readings were obtained from above patients after different types of surgery (48 plastic, 38 orthopaedic, 21 general, 7 other). Overall, pain was rated as 'no' (NRS 0; $n=236$), 'mild' (NRS 1–3; $n=199$), 'moderate' (NRS 4–5; $n=168$) or 'severe' (NRS 6–10; $n=213$).

Small, but statistically significant negative correlations were found between ANI and NRS scores ($\rho=-0.075$; $P<0.05$) and ANI and BPsyst ($\rho=-0.136$; $P<0.01$). ANI was significantly higher at states of deep sedation compared with at full consciousness [mean (SE): 73.4 (14.6) *vs* 58.7 (15.1); $P<0.001$].

ANI scores before and 5 min after a bolus of fentanyl did not differ significantly [ANI pre-fentanyl: 52 (14) *vs* ANI post-fentanyl: 54 (15); n.s.].

In general, ANI scores did not differ between different levels of pain, although lower ANI scores were found in 'severe' *vs* 'no' pain (Table 1). This association was not significantly influenced by the degree of sedation.

ROC were used to describe the sensitivity and specificity for ANI to distinguish between these extremes of the pain scale (NRS 0 *vs* NRS 6–10). Both sensitivity and specificity of ANI were found to be only around 50% (area under ROC curve 0.434).

Discussion

Our study was unable to reproduce the findings of a strong relationship between ANI and patient self-rated pain described by Le Guen and colleagues.[3] In contrast, though statistically significant, we found the correlation between the two parameters to be weak in patients after general anaesthesia. This discrepancy may be explained by the different setting of the two investigations: Le Guen and colleagues[3] included fully conscious subjects during labour pain

whereas our study took place in PACU after sevoflurane-based anaesthesia. Therefore, the presence of anaesthetic drugs and associated sedation of postoperative patients are likely to have influenced ANI scores. This is supported by our results showing higher ANI scores in deeply sedated patients. More specifically recovery after sevoflurane-based anaesthesia may be associated with higher sympathetic activity (higher noradrenaline plasma levels) and a higher total power in the frequency domain analysis of HRV when compared with recovery after total i.v. anaesthesia (TIVA) with propofol.[5] Despite this foreseeable confounder we opted to investigate patients after sevoflurane-opioid-based anaesthesia as this regime appears to be far more commonly used than TIVA, and thus reflecting clinical reality in PACU more accurately. However, to date all studies investigating ANI in the perioperative context included only patients after TIVA,[6] and our investigation is the first to focus on patients after volatile-based anaesthesia. In addition to anaesthetic drugs, many other factors are commonly encountered in PACU (arousal, anxiety, agitation, and noise) known to increase sympathetic activity. This plethora of potential confounders in the PACU setting is well described and has been previously suspected to impair the accuracy of other monitors of pain/nociception such as skin conductance or SPI.[7 8] The relationship between acute postoperative pain and associated autonomic stress response may be far less linear than commonly assumed.[9] The latter would obviously significantly influence the performance of any monitor for pain or nociception which is based on the assessment of sympathetic or vagal activity.

However, because the ANI has shown, albeit weakly, to correlate with acute pain, it may perform better in the confounder-reduced setting of general anaesthesia. The ANI has been shown to potentially be of value in predicting an imminent haemodynamic stress reaction,[6] and it has also been described to predict treatment success for tourniquet-related hypertension.[10] Under general anaesthesia with desflurane and remifentanil, ANI was found to be more reactive than skin conductance monitoring to different levels of remifentanil infusions in children.[11] The latter suggests that different monitors are not simply exchangeable, even though they may also be based on the assessment of autonomic responses to acute pain/nociception. Hence research may need to be directed to identify the ideal monitor or combination thereof for specific clinical settings.

Though we are unable to comment on its value in this context, the matter is worthy of further investigation.

We conclude, that ANI only weakly reflects states of postoperative pain in patients after sevoflurane-based anaesthesia. With a sensitivity and specificity of around 50% in distinguishing between 'no' *vs* 'severe' pain, the monitor cannot currently be recommended for use in this clinical context. Whether ANI may be more valuable in anaesthetized patients requires further investigation.

Author's contributions

T.L. is the principal investigator and author of the manuscript. W.S.T., C.L., B.W., T.F., and N.P. significantly contributed to the manuscript preparation (Methods, Results) and language editing.

Declaration of interest

None declared.

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