



The Analgesia Nociception Index is More Strongly Associated with Anxiety Than with Pain in Conscious Male Patients Undergoing Hernia Repair Under Combined Spinal-epidural Anaesthesia

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Abstract

Objective: The Analgesia Nociception Index (ANI), derived from heart rate variability, is a non-invasive marker of the nociception-analgesia balance. Its validity and validity in conscious are uncertain because activity may also psychological factors, particularly anxiety. This exploratory study examined the among ANI, pain, and anxiety in male patients undergoing hernia repair with combined spinal-epidural anaesthesia (CSEA).

Methods: Twenty-four male patients with American Society of Anesthesiologists physical status I-II undergoing hernia repair under CSEA were enrolled. Self-reported visual analogue scale for Anxiety (VAS-A), pain (VAS), and continuously recorded ANI were assessed at four procedural stages: lateral positioning (T1), local anaesthetic infiltration (T2), epidural puncture (T3), and two minutes post-puncture (T4). Within-patient (primary), patient-level, and observation-level correlations were and the two within-patient correlations involving ANI were formally compared.

Results: At the within-patient level, ANI correlated negatively with anxiety ($r=-0.794$, $P < 0.001$) and with pain ($r=-0.515$, $P < 0.001$); the ANI-stronger than the ANI-pain correlation. The association between ANI and anxiety was significantly stronger than that between ANI and pain (Hotelling-Williams $t=4.10$, $P < 0.001$). The patient-level ANI-pain analysis was clearly underpowered (post-hoc power ≈ 0.18).

Conclusion: Clinicians should therefore avoid interpreting a low ANI value as evidence of inadequate analgesia alone and should consider concurrent assessment of both pain and anxiety. These findings should be regarded as hypothesis-generating and require confirmation in larger, sex-balanced, multicentre studies. Trial registration: ClinicalTrials.gov (NCT05053633), registered 22 September 2021.

Keywords: Analgesia Nociception Index, combined spinal-epidural anaesthesia, anxiety, pain, heart rate variability

Main Points

- Within individual patients, Analgesia Nociception Index (ANI) showed a significantly stronger association with anxiety than with pain during combined spinal-epidural anaesthesia. These findings support the interpretation that ANI in conscious patients is influenced by both emotional and nociceptive autonomic activity, with anxiety showing a stronger association.
- These associations were attenuated and were not consistently significant at the patient (between-patient) level, likely owing to limited statistical power at the between-patient level and to stable between-patient differences in baseline autonomic function.

Introduction

Assessing pain in conscious patients psychological and emotional factors.¹ Objective physiological have increasingly been investigated as complementary tools to traditional.^{2,3} Derived from heart rate variability (HRV) signals, the Analgesia Nociception Index (ANI) primarily reflects parasympathetic nervous system activity⁴ and has been proposed as an indicator of the balance between nociceptive input and analgesic effect.

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Received: March 24, 2026 **Accepted:** August 19, 2026 **Epub:** October 15, 2026

Cite this article as: Guo S, Wen H, Yang J. The analgesia nociception index is more strongly associated with anxiety than with pain in conscious male patients undergoing hernia repair under combined spinal-epidural anaesthesia. *Turk J Anaesthesiol Reanim*. [Epub Ahead of Print]



Previous studies have demonstrated the potential utility of ANI during general anaesthesia and postoperative pain assessment.^{5,6} However, its in conscious individuals remain uncertain, with the literature across studies.⁷ Because ANI reflects autonomic nervous system activity, it may be influenced not only by nociceptive stimuli but also by emotional states such as anxiety. Emerging evidence suggests that autonomic indices may reflect.^{4,8}

Combined spinal-epidural anaesthesia (CSEA) provides a clinically relevant model for examining patients because patients remain awake and able to while experiencing predictable procedural stimuli. Despite this few studies have specifically examined the interplay among ANI, intensity, and anxiety during regional anaesthesia.

The primary aim of this exploratory prospective observational investigate the associations among ANI, pain intensity, and anxiety in male patients undergoing hernia repair under CSEA. We hypothesized that patients. ANI would be more strongly associated with anxiety than with pain, indicating that emotional responses may contribute substantially to ANI fluctuations in conscious patients.

Methods

Study Design and Participants

This prospective, observational, exploratory study was approved by the Capital Medical University Beijing Chao-Yang Hospital Institutional Ethics Committee (approval number: 2021-ke-490, date: September 2021), and written informed consent was obtained from all enrolled participants. The study was registered at ClinicalTrials.gov (NCT05053633). Adult male patients aged 18-80 years with American Society of Anesthesiologists (ASA) physical status I or II scheduled for inguinal, umbilical, or incisional hernia repair under CSEA were screened for eligibility. The study cohort was restricted to male patients because, during the study period, hernia repair under CSEA at our institution was performed almost exclusively in male patients; female patients undergoing hernia repair were not excluded by protocol but were too few to support a balanced sex-stratified analysis or a meaningful sex-by-anxiety interaction test. Because HRV and emotional-autonomic responses are known to differ by sex, the generalizability of our findings to female patients should be considered limited; this is explicitly addressed in the Discussion.

Exclusion criteria included chronic pain, cardiovascular disease, arrhythmia, dysautonomia, pacemaker implantation, or use of medications affecting autonomic function (β -blockers, anxiolytics, opioids, or antidepressants). Patients with cognitive impairment, with contraindications to CSEA, or with prior exposure to similar procedures were also excluded to minimize potential confounding effects on the perception of pain and anxiety.

Measurements

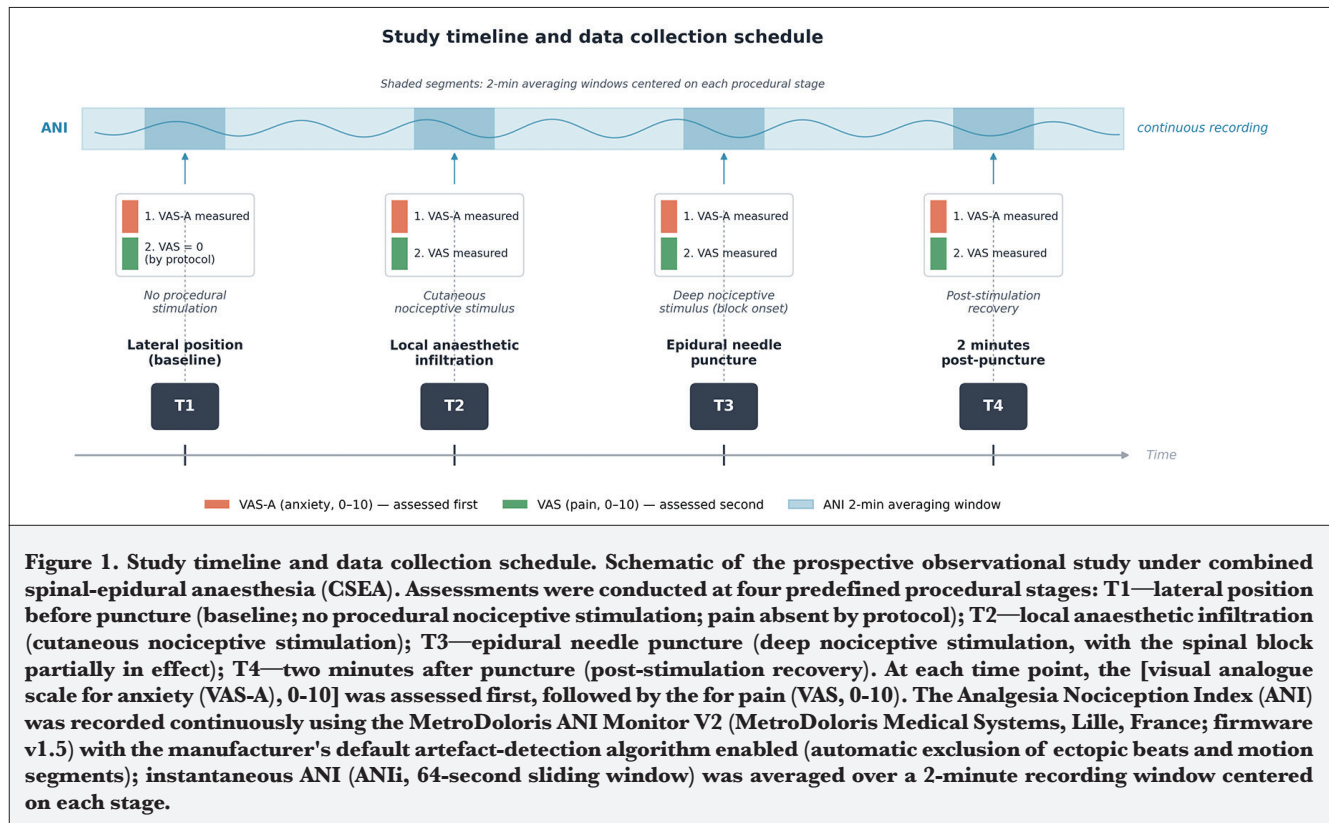
Before surgery, all participants were familiarized with the study procedures and assessment scales. During CSEA, self-reported pain and anxiety were assessed while ANI was recorded continuously. Pain intensity was assessed using the [visual analogue scale (VAS); 0-10] and anxiety using the (VAS-A; 0-10).

Measurements were obtained at four predefined procedural stages: T1 (lateral positioning before any procedural stimulation), T2 (local anaesthetic infiltration), T3 (epidural needle puncture), and T4 (two minutes after puncture). At each time point, anxiety (VAS-A) was assessed first, followed by pain (VAS). The rationale for this order was to prevent acute nociceptive ratings from priming subsequent anxiety reports; however, we acknowledge that the inverse priming effect (anxiety reports priming pain) cannot be excluded, and we address this in the Discussion. The study timeline and data collection schedule are presented in Figure 1.

ANI was monitored using the MetroDoloris ANI Monitor V2 (MetroDoloris Medical Systems, Lille, France; firmware version 1.5) with electrodes placed on the chest according to the manufacturer's recommendations. The instantaneous ANI (ANi, computed over a 64-second sliding window) was used as the primary outcome and averaged across a 2-minute recording window centered on each procedural stage to signal stability and minimise transient noise. The device's built-algorithm automatically excluded ectopic beats and motion-related signal segments from ANI computation. In addition, the monitor was maintained in respiratory-stable mode (with the patient's spontaneous breathing rate verified to be within the manufacturer-recommended 9-24 breaths/min range) throughout the data-collection window. No ANI segments required exclusion due to artifacts during the analyzed periods.

Anaesthesia Protocol

All procedures were performed by the same experienced anaesthesiologist using a standardized technique, thereby minimizing operator-related variability. A standard set of monitoring parameters, comprising electrocardiography, pulse oximetry, and non-invasive blood pressure, was applied during the study. No premedication (anxiolytics, sedatives, or opioids) was administered to avoid pharmacological modulation of autonomic tone. The CSEA procedure was performed at the L2-3 or L3-4 interspace, using a standard needle-through-needle technique. Local anaesthesia with 2% lidocaine was administered prior to epidural needle insertion. No patient required intra-procedural rescue analgesia or sedation during the data-collection window (T1-T4); therefore, the autonomic signals analyzed were unconfounded by any pharmacological intervention beyond the local anaesthetic itself.



Statistical Analysis

Sample size estimation was based on the correlation reported between anxiety and pain ($r=0.62$) in prior research,⁹ because at the time of study design no reliable prior estimate of the ANI-pain or ANI-anxiety correlation in conscious patients undergoing regional anaesthesia was available. Assuming a correlation coefficient of 0.6, 80% power, and $\alpha=0.05$ (two-sided), we estimated a minimum sample size of 20 patients; we enrolled 24 to allow for a 20% potential dropout rate. We acknowledge that this calculation was a pragmatic proxy and was not directly aligned with the primary ANI-related hypotheses. The study is therefore framed throughout as exploratory and hypothesis-generating, and post-hoc power estimates are reported separately for the within-patient (well-powered) and patient-level (underpowered) analyses.

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate. Differences across procedural stages were examined using the Friedman test, followed by post-hoc analysis with Dunn's multiple comparisons test.

Because each patient contributed multiple observations, simple Spearman correlations on pooled observations would violate the independence assumption and could yield biased estimates. We therefore conducted analyses at three complementary levels:

- Within-patient (within-subject) decomposition correlation [primary analysis]: for each variable, we computed within-patient centred values (raw value minus that patient's mean across T2-T4) and correlated these residuals using Spearman's method. This approach isolates covariation across procedural stages, free from between-patient confounding, and is conceptually equivalent to the within-subject component of a random-intercept mixed-effects model.
- Patient-level correlation was assessed by correlating mean values per patient (across T2-T4) using Spearman's method ($n = 24$). This examines whether patients who are, on average, more anxious or experiencing more pain also show systematically lower ANI.
- Observation-level correlation [descriptive only]: spearman correlations on pooled observations are also reported for descriptive comparison with the existing literature, with explicit acknowledgement that they do not adjust for clustering.

To formally compare the strengths of the two within-patient correlations involving ANI (ANI-VAS-A versus ANI-VAS), which share a common variable, we used the Hotelling-Williams t-test for dependent overlapping correlations (Steiger, 1980). This addresses Reviewer feedback that the central claim of a differential association of ANI with anxiety versus pain requires a formal statistical comparison.

Because no procedural nociceptive stimulus was applied at T1 and pain scores were uniformly zero, correlation analyses involving VAS were restricted to T2–T4 (72 observations). 95% confidence intervals (CIs) for Spearman coefficients were estimated via Fisher's z-transformation. A two-sided P value <0.05 was considered statistically significant.

Exploratory post-hoc analyses examined whether age, body mass index (BMI), or ASA status classification moderated the observed associations. A post-hoc power analysis was performed for the primary within-patient ANI-VAS correlation. Statistical analyses were performed using GraphPad Prism v9.0 (GraphPad Software Inc., San Diego, CA), R v4.3 (R Core Team, Vienna, Austria), and Python 3.11 with SciPy.

Results

Participants

Twenty-eight patients were screened for eligibility all of whom were male, reflecting characteristics of patients undergoing hernia repair under CSEA at our institution. Four patients were excluded because they were receiving medications known to affect autonomic function, resulting in a final analytic sample of 24 patients (Figure 2). These patients

contributed 96 observations across four predefined procedural stages, and 72 observations at T2–T4 for analyses involving VAS.

Baseline demographic and clinical characteristics are summarized in Table 1. The mean age was 60 ± 9.8 years, and the mean body mass index was 23.5 ± 3.0 kg/m². Fourteen patients (58.3%) were classified as ASA I, and ten (41.7%) were classified as ASA II.

Changes Across Procedural Stages

Mean values for ANI, VAS-A, and VAS at each procedural stage are summarized in Table 2 and depicted in Figure 3. Significant differences across stages were observed for all three variables (Friedman test: ANI $\chi^2=60.3$, $P < 0.001$; VAS-A $\chi^2=55.7$, $P < 0.001$; VAS $\chi^2=44.2$, $P < 0.001$). VAS scores were uniformly zero at T1 per protocol, peaked at T2 (local anaesthetic infiltration), and decreased thereafter. ANI was highest at T1 and values increased at T3 and returned to their highest level at T4. VAS-A decreased monotonically progressively adapting.

Within-patient (Primary) Analysis

Within-patient decomposition correlations, after controlling for between-patient heterogeneity, confirmed strong

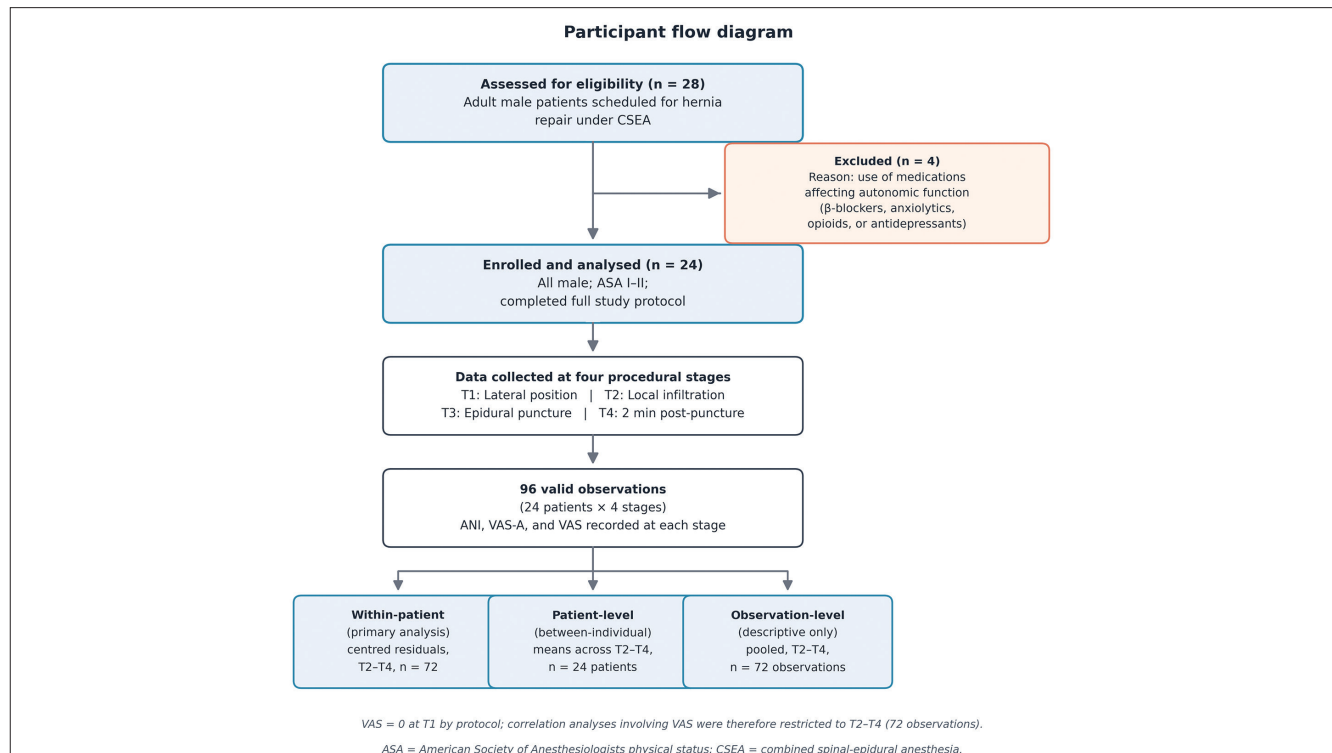


Figure 2. CONSORT-style participant flow diagram. Twenty-eight male patients were screened, four were excluded due to use of medications affecting autonomic function, and 24 patients were included in the final analysis, contributing 96 observations across four procedural stages (and 72 observations at T2–T4 for analyses involving VAS).

CSEA, combined spinal-epidural anaesthesia; ASA, American Society of Anesthesiologists; VAS-A, visual analogue scale for anxiety; VAS, visual analogue scale (pain).

Table 1. Patient Characteristics

Characteristics	Total (n = 24)
Demographics	
Age (years)	60±9.8
Height (m)	1.72±0.07
Weight (kg)	69±7.7
BMI (kg/m ²)	23.5±3.0
ASA, n (%)	
I	14 (58.3%)
II	10 (41.7%)
Hernia type, n (%)	
Inguinal	11 (45.8%)
Umbilical	9 (37.5%)
Incisional	4 (16.7%)
CSEA vertebral level, n (%)	
L2-3	16 (66.7%)
L3-4	8 (33.3%)
Values are expressed as mean ± standard deviation or count (percentage) BMI, body mass index; ASA, American Society of Anesthesiologists; CSEA, combined spinal-epidural anaesthesia	

and statistically significant associations among the three variables: ANI vs. VAS-A: $r=-0.794$, 95% CI -0.866 to -0.689, $P < 0.001$; ANI vs. VAS: $r=-0.515$, 95% CI -0.667 to -0.322, $P < 0.001$; VAS-A vs. VAS: $r=0.591$, 95% CI 0.416 to 0.723, $P < 0.001$.

These findings indicate that within a given patient, across procedural stages, ANI are tightly coupled with concurrent increases in both pain and anxiety. Within-patient association between ANI and anxiety was substantially stronger than that between ANI and pain.

Formal Comparison of ANI-anxiety vs. ANI-pain Correlations

A Hotelling-Williams t-test for dependent overlapping correlations confirmed that the within-patient ANI-anxiety correlation was significantly stronger than the within-patient ANI-pain correlation ($t=4.10$, $df=69$, $P < 0.001$; difference in $r=0.28$). This formal test directly supports the differential association reported above and addresses the concern

that a descriptive comparison of correlation coefficients is insufficient to support the study's central claim. An analogous comparison at the observation level was also significant (Hotelling-Williams $t=3.92$, $P < 0.001$).

Patient-level (Between-patient) Analysis

Correlation analyses at the patient level, using mean values per patient across T2-T4 ($n = 24$), are summarized in Table 3 and illustrated in Supplementary Figure S1.

At the patient level, a moderate positive correlation between mean anxiety and mean pain was observed ($r=0.451$, $P=0.027$). The association between mean ANI and mean anxiety ($r=-0.405$, $P=0.050$), and the association between mean ANI and mean pain was not statistically significant ($r=-0.225$, $P=0.291$).

Observation-level (Descriptive) Analysis

For descriptive comparison with existing literature, simple observation-level Spearman correlations on pooled data from T2-T4 (72 observations) were also computed. These analyses do not account for the clustering of observations within patients and are presented reference and comparison with previous studies only (Figure 4): ANI vs. VAS-A: $r=-0.710$, 95% CI -0.809 to -0.573, $P < 0.001$; ANI vs. VAS: $r=-0.360$, 95% CI -0.546 to -0.140, $P=0.002$; VAS-A vs. VAS: $r=0.480$, 95% CI 0.279 to 0.640, $P < 0.001$.

Observation-level estimates were directionally consistent with within-patient estimates, were generally weaker, indicating that within-patient covariation across procedural stages accounts for a substantial portion of the observed associations and is partially by between-patient heterogeneity when observations are pooled. The discrepancy was most pronounced for the ANI-pain relationship, which weakened substantially when data were pooled (observation-level $r=-0.360$ vs. within-patient $r=-0.515$).

Power and Sensitivity Analyses

A post-hoc power analysis based on the within-patient ANI-VAS correlation ($r=-0.515$, 72 paired observations) yielded a statistical power of 0.997 (two-sided $\alpha=0.05$). At the patient level ($n = 24$), power for detecting an ANI-VAS correlation of $r=-0.225$ was approximately 0.18, consistent with the absence of statistical significance and reflective of exploratory nature and the limited inter-individual sample size.

Table 2. Mean Values of ANI, VAS-A and VAS Across Procedural Stages (n = 24)

Variable	T1 (lateral position)	T2 (local infiltration)	T3 (epidural puncture)	T4 (2 min post)
ANI	74.0±8.9	53.9±9.9	59.6±10.3	79.2±10.7
VAS-A (0-10)	6.59±1.39	5.78±0.99	4.51±1.02	2.39±0.86
VAS (0-10)	0±0	2.54±1.05	1.47±0.87	1.00±0.78
Values are mean ± standard deviation. The Friedman test was significant ($P < 0.001$) for all three variables ANI, Analgesia Nociception Index; VAS, visual analogue scale (pain); VAS-A, visual analogue scale for anxiety				

Table 3. Patient-Level Spearman Correlations (n = 24, Means Across T2-T4)

Pair	Spearman r	95% CI	P value
Mean VAS-A vs. mean VAS	+0.451	+0.058 to +0.723	0.027
Mean ANI vs. mean VAS	-0.225	-0.576 to +0.197	0.291
Mean ANI vs. mean VAS-A	-0.405	-0.695 to -0.001	0.050

VAS, visual analogue scale (pain); VAS-A, visual analogue scale for anxiety; ANI, Analgesia Nociception Index; CI, confidence interval

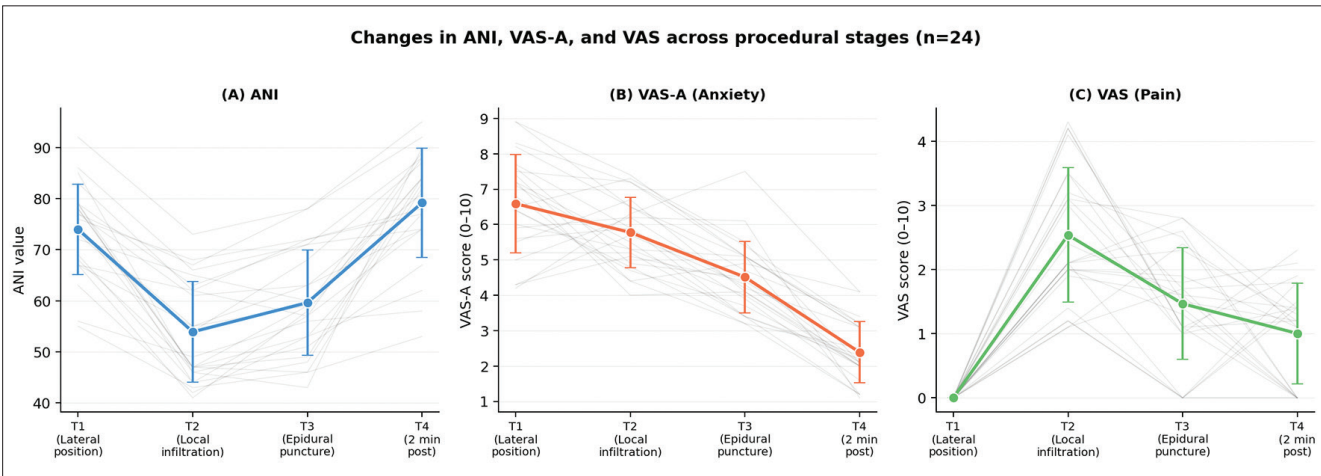


Figure 3. Changes in ANI, VAS-A, and VAS across procedural stages (n = 24). (A) ANI; (B) VAS-A (anxiety); (C) VAS (pain). Coloured points and lines represent group means at each stage; error bars represent standard deviations. Light grey lines depict individual patient trajectories. Differences across stages were significant for all three variables (Friedman test, $P < 0.001$).

VAS, visual analogue scale (pain); VAS-A, visual analogue scale for anxiety; ANI, Analgesia Nociception Index.

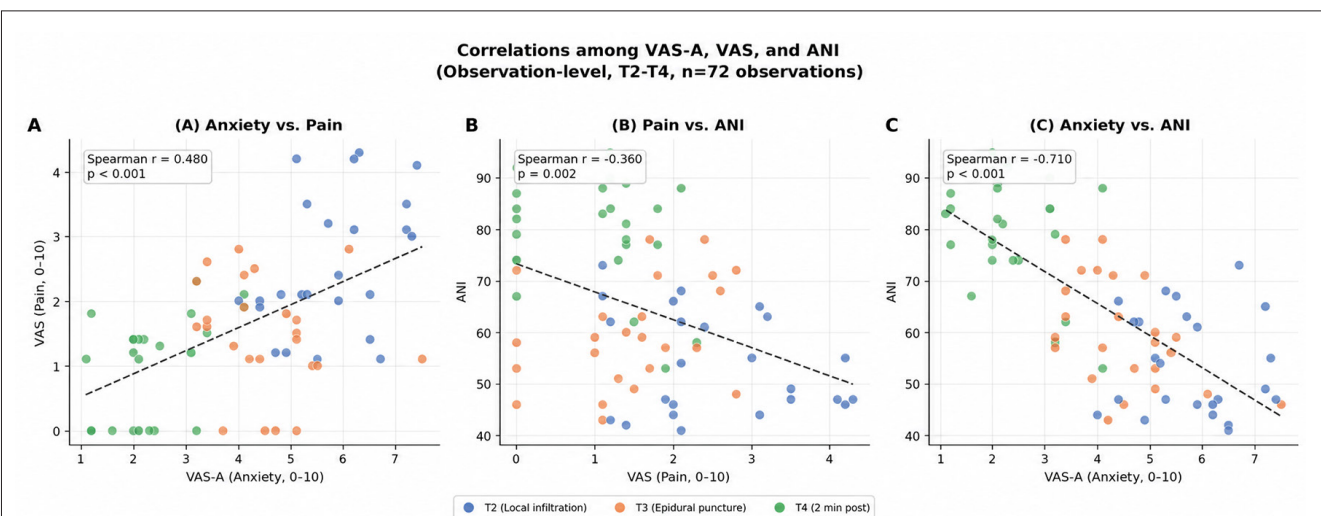


Figure 4. Observation-level Spearman correlations among VAS-A, VAS, and ANI across T2-T4 (n = 72 observations, descriptive analysis). Each dot represents a single observation; colour denotes procedural stage (T2—local infiltration, T3—epidural puncture, T4—2 min post). (A) VAS-A vs. VAS: $r = +0.480$, $P < 0.001$. (B) VAS vs. ANI: $r = -0.360$, $P = 0.002$. (C) VAS-A vs. ANI: $r = -0.710$, $P < 0.001$. Dashed lines represent fitted trendlines. Note that this descriptive analysis does not adjust for the non-independence of repeated observations within patients; the within-patient analysis presented in the results section is the primary analysis.

VAS-A, visual analogue scale for anxiety; ANI, Analgesia Nociception Index.

Exploratory analyses examining potential moderating effects of age, BMI, and ASA classification did not reveal any significant influence on the observed associations.

Discussion

In this exploratory study of male patients undergoing hernia repair with CSEA, ANI was negatively associated with both pain and anxiety at the within-patient level. Notably, the within-patient ANI—anxiety correlation ($r=-0.794$) was substantially stronger than the within-patient ANI—pain correlation ($r=-0.515$), suggesting that ANI in conscious patients may be more closely associated with emotional autonomic input than with nociceptive input. A moderate positive within-patient correlation between self-reported anxiety and pain intensity was observed, consistent with previous findings.¹⁰

The present study also highlights the importance of distinguishing within-patient from between-patient associations. The within-patient analyses confirmed that the associations are not artefacts of pooling repeated observations: when between-patient variance is removed, the ANI-anxiety correlation actually strengthens (from -0.710 at the observation level to -0.794 within-patient), as do the ANI-pain correlation (from -0.360 to -0.515) and the anxiety-pain correlation (from 0.480 to 0.591). These findings remained robust after accounting for between-patient heterogeneity.

Differential Within-patient Associations

In conscious male patients undergoing CSEA, ANI showed a significantly stronger within-patient association with anxiety than with pain. This finding suggests that ANI in awake patients may be more strongly associated with emotional autonomic activity than with nociceptive autonomic activity and should therefore not be interpreted as a pain-specific indicator.

To our knowledge this differential association has not been quantified explicitly in prior conscious-patient ANI studies, although it is consistent with the qualitative observations of Baroni et al.⁷ that ANI lacks specificity for pain in awake individuals. This is also among the first conscious-patient ANI studies to formally distinguish within-patient from between-patient autonomic associations using a decomposition-based repeated-measures framework, providing an inferential basis for the differential association reported here that is not available in analyses that pool observations across patients.

This pattern is mechanistically biologically plausible. ANI is derived from the high-frequency component of HRV and primarily reflects rapid fluctuations in parasympathetic tone. Anxiety in conscious patients is a sustained autonomic state mediated by central amygdala-brainstem projections that withdraw parasympathetic outflow and activate sympathetic

drive;^{11,12} in our cohort this tonic state was highest at T1 (anticipatory anxiety before any procedural stimulation), when VAS-A averaged 6.6/10 while VAS was 0, and ANI was already well below its post-procedural rebound value at T4 (74.0 vs. 79.2). As the procedure progressed and the patient adapted, VAS-A decreased monotonically (T1 → T4: 6.6 → 5.8 → 4.5 → 2.4), and ANI broadly tracked this once the acute nociceptive perturbation at T2 had passed. Procedural pain, by contrast, was relatively brief (peaking at T2 with a mean VAS of 2.5/10) and was blunted by the regional block during the most invasive step (epidural puncture, T3). The autonomic signal generated by anxiety may therefore have been larger and than that generated by transient mild-to-moderate which provides a plausible mechanistic account for the differential association we inputs.

Interpretation of Within- vs. Between-patient Findings

A second central observation is the dissociation between within-patient and findings. Within a given patient, decreases in ANI tracked closely with concurrent increases in pain and anxiety across procedural stages. In contrast, when we compared mean values across patients, the ANI-pain relationship was not statistically significant and the ANI-anxiety relationship was only borderline.

This pattern is well-known in repeated-measures research, where it is sometimes referred to as a within-between divergence. It indicates that within- and between-person processes may be governed by different mechanisms. The strong within-patient coupling is consistent with the physiology of ANI: ANI to rapid, stimulus-locked fluctuations in parasympathetic tone and is therefore well suited to capture moment-to-moment a procedure, but it is less informative about stable differences. Between-patient comparisons are confounded by stable individual factors—baseline autonomic tone, body habitus, fitness, respiratory pattern, and personality traits—that may obscure the underlying ANI—pain and ANI—anxiety relationships. Furthermore, the patient-level analysis was clearly underpowered (post-hoc power ≈ 0.18 for the observed ANI-pain correlation), so absence of statistical significance at this level should not be interpreted as absence of a true between-patient relationship. The two levels of analysis answer different questions: the within-patient analysis is most relevant to real-time intra-procedural monitoring, whereas the patient-level analysis would be more relevant to pre-procedural risk stratification, for which our sample is underpowered.

Autonomic Mechanisms

The underlying autonomic mechanism provides a plausible explanation for the observed associations. Both nociceptive stimulation and psychological stress reduce parasympathetic

tone while increasing sympathetic activation.¹³ Consequently, reductions in ANI may represent a global autonomic response rather than a pure indicator of nociceptive input.¹⁴ This may explain the strong within-patient coupling between ANI, pain, and anxiety observed in our study, and is in keeping with prior reports that emotional factors can substantially influence ANI in awake individuals.¹⁵

Nonetheless, anxiety and pain covaried moderately within patients in our cohort ($r=0.591$). The stronger within-patient correlation of ANI with anxiety than with pain therefore does not establish that ANI tracks anxiety independently of nociception; anxiety and procedural pain may instead behave as parallel components of a shared autonomic stress response that ANI primarily indexes.¹⁶ Disentangling the relative contributions of these two inputs-and any potential mediating pathways-will require larger studies with sufficient power for partial-correlation or mediation analyses, ideally with experimentally dissociable nociceptive and affective stimuli.

A further caveat is that anxiety, pain, and ANI all changed systematically across T2-T4, so that part of the within-patient covariation that we report inevitably reflects shared procedural-stage and order effects rather than stimulus-specific autonomic coupling. The within-patient design controls for stable between-patient characteristics, but does not separate stimulus-locked from stage-locked variance. Designs that randomise the order of stimuli or include multiple within-stage replicates would be needed to dissociate these contributions more clearly in future studies.

Sex-related Considerations

As all participants were male, the generalizability of these results to female patients cannot be assumed. Sex-related differences in autonomic regulation are well documented: oestrogen modulates HRV and parasympathetic tone, and women generally show higher baseline HRV than men of comparable age.¹⁷ Whether these differences translate into systematically different ANI responses to nociceptive or affective stimuli remains unclear. Future studies should include both sexes and adopt sex-stratified analyses to address this important question.

Clinical Implications

Clinically, our findings have direct implications for the interpretation of ANI at the bedside in awake or arousable patients. From a clinical perspective, these findings suggest that a low ANI value in a conscious patient should not automatically be interpreted as evidence of inadequate analgesia. Instead, ANI should be interpreted alongside patient-reported pain and anxiety, as psychological distress may contribute substantially to autonomic responses during regional anaesthesia.¹⁸

Although our within-patient ANI-pain correlation was somewhat stronger than that reported in some prior

conscious-patient studies,⁷ this may be attributable to the controlled procedural setting of CSEA, in which discrete and well-defined nociceptive stimuli are delivered at predictable time points. Future studies should explore multimodal approaches integrating autonomic and psychological parameters to improve the accuracy of nociception monitoring in conscious patients.

Study Limitations

Several limitations should be acknowledged. First, the modest sample size ($n = 24$) and single-centre design limit the precision of point estimates and the external generalizability of our findings. In addition, the patient-level analysis is clearly underpowered. Second, the inclusion of only male patients further restricts external validity, particularly given known sex-related differences in autonomic regulation; future studies should explicitly test for sex $\times$ anxiety interactions on ANI, given known differences in basal HRV and parasympathetic reactivity. Third, although our within-patient analytical strategy adequately addresses the non-independence of repeated measures, residual confounding from unmeasured physiological variables (e.g., respiratory pattern, transient blood pressure fluctuations, posture) and unmeasured psychological traits (e.g., trait anxiety, prior surgical experience) cannot be excluded; the present sample size also limits the number of covariates that can be reliably included in a multivariable model without causing overfitting. Fourth, the absence of premedication may have influenced baseline anxiety levels; this was a deliberate choice to avoid pharmacological modulation of autonomic tone, but it may also have amplified the role of anxiety in our measurements. Fifth, anxiety was assessed before pain at each time point to avoid acute nociceptive ratings from priming subsequent anxiety reports, but the inverse priming effect (anxiety reports priming pain) cannot be ruled out; future studies should consider counterbalanced or simultaneous assessment designs. Sixth, restriction of correlation analyses involving VAS to T2-T4 (because pain scores were uniformly zero at T1) excluded a time point at which anxiety was high and ANI was at its peak; this conservative choice is likely to have attenuated rather than inflated the reported ANI-anxiety association, but readers should bear it in mind when comparing with studies that include baseline measurements. Finally, the study's exploratory nature precludes strong causal or specificity claims, and findings should be regarded as hypothesis-generating. Larger, sex-balanced, multicentre studies-ideally using mixed-effects models with a richer covariate set-are recommended to confirm and extend these observations.

Conclusion

In this exploratory study of male patients undergoing hernia repair under CSEA, the within-patient correlation between ANI and anxiety ($r=-0.794$) was both substantially

and significantly stronger than that between ANI and pain ($r=-0.515$; Hotelling-Williams $P < 0.001$). Patient-level correlations were attenuated, with the ANI-pain analysis clearly underpowered. These findings suggest that, in conscious patients, ANI may be more strongly with emotional autonomic input than with nociceptive input; a low ANI in an awake patient should therefore not be interpreted as evidence of analgesic need alone, as overinterpretation administration or to misjudgment of analgesic adequacy when ANI is used in isolation. ANI should be interpreted as a composite autonomic signal and used alongside—not in place of—subjective pain and anxiety assessment. Given the small, single-centre, male-only design, these results should be regarded as hypothesis-generating, and larger, sex-balanced, multicentre studies are needed to confirm and extend these observations.

Ethics

Ethics Committee Approval: This study was approved by the Capital Medical University Beijing Chao-Yang Hospital Institutional Ethics Committee (2021-ke-490, September 2021). The study was registered at ClinicalTrials.gov (NCT05053633).

Informed Consent: Written informed consent was obtained from all enrolled participants.

Acknowledgements

The authors thank MetroDoloris Medical Systems (Lille, France) for providing the Analgesia Nociception Index monitor and electrodes. The equipment provider had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.G., H.W., L.Y.; Concept - S.G.; Design - S.G., L.Y.; Data Collection and/or Processing - S.G.; Analysis and/or Interpretation - S.G., H.W.; Literature Review - S.G., H.W.; Writing - S.G., H.W., L.Y.

Declaration of Interests: The authors declare that they have no conflicts of interest.

Funding: The author(s) reported there is no funding associated with the work featured in this article.

Supplementary Figure Link: <https://d2v96fxpocvxx.cloudfront.net/0ee09c26-769b-4fdf-b99e-2fb4a8591f00/content-images/a82147af-11f7-44cd-b608-821d1d3712cb.pdf>

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