Original Article/*Özgün Araştırma*

doi: 10.54875/jarss.2024.78942

Pain Evaluation Using Analgesia Nociception Index (ANI) in Postoperative Cardiovascular Intensive Care Patients

Postoperatif Kardiyovasküler Yoğun Bakım Hastalarında Analjezi Nosisepsiyon İndeksi (ANI) Kullanılarak Ağrının Değerlendirilmesi

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ABSTRACT

Objective: This study evaluated the analgesia nociception index (ANI) for pain assessment in conscious, sedated, and mechanically ventilated patients in the cardiovascular intensive care unit (ICU) after elective coronary artery bypass graft (CABG) surgeries. It also explored the influence of inotropic/vasoconstrictor agents on ANI.

Methods: Conducted from January 2019 to January 2020, the study enrolled 135 participants who underwent elective isolated CABG surgeries. Participants were categorized into three groups: Group S0 received no additional cardiac support, Group S1 received inotropic support with dopamine, and Group S2 received combined inotropic and vasopressor support. Analgesia nociception index electrodes were placed at V1 and V5 leads for ANI assessment at key time points: before extubation (Eb), after extubation (Ea), before thoracic drain removal (Rb), and after thoracic drain removal (Ra).

Results: Gender distribution showed no significant differences. Intubation duration was significantly longer in Group S2 compared to Groups S0 and S1. Hemodynamic parameters varied significantly. Mean arterial pressure (MAP) and heart rate (HR) increased significantly from Eb to Ea and decreased from Rb to Ra. Specifically, MAP increased from 82.4 ± 8.1 mmHg to 89.6 ± 9.2 mmHg ($p<0.05$) and HR increased from 72.5 ± 7.4 bpm to 78.3 ± 8.6 bpm ($p<0.05$) between Eb and Ea. Conversely, MAP decreased from 90.2 ± 8.4 mmHg to 85.1 ± 8.3 mmHg ($p<0.05$) and HR decreased from 80.5 ± 7.5 bpm to 74.2 ± 7.8 bpm ($p<0.05$) between Rb and Ra. ANI values varied across groups and time points, with Group S2 showing higher ANI values post-extubation (Ea) and post-thoracic drain removal (Ra).

Conclusion: ANI is a feasible tool for continuous pain assessment in the cardiovascular ICU post-cardiac surgery. The dynamic hemodynamic responses and distinct ANI patterns highlight ANI's potential in tailoring postoperative pain management strategies.

Keywords: Analgesia nociception ındex, mechanical ventilation, cardiovascular intensive care unit, inotropic support

ÖZ

Amaç: Bu çalışmada, kardiyovasküler yoğun bakım ünitesinde (YBÜ) elektif koroner arter bypass grefti (KABG) ameliyatlarından sonra bilinci açık, sedasyonlu ve mekanik ventilasyona bağlı hastalarda ağrının değerlendirilmesi için analjezi nosisepsiyon indeksi (ANI) değerlendirildi. Ayrıca inotropik/vazokonstriktör ajanların ANI üzerindeki etkisi de araştırıldı.

Yöntem: Ocak 2019'dan Ocak 2020'ye kadar gerçekleştirilen çalışmaya, elektif izole KABG ameliyatı geçiren 135 katılımcı dahil edildi. Katılımcılar üç gruba ayrıldı: Grup S0 ek kardiyak destek almadı, Grup S1 dopamin ile inotropik destek aldı ve Grup S2 kombine inotropik ve vazopressör desteği aldı. Analjezi nosisepsiyon indeksi elektrotları ANI değerlendirmesi için V1 ve V5 derivasyonlarına ekstübasyondan önce (Eb), ekstübasyondan sonra (Ea), torasik dren çıkarılmadan önce (Rb) ve torasik dren çıkarıldıktan sonra (Ra) yerleştirilmiştir.

Bulgular: Cinsiyet dağılımında anlamlı bir farklılık görülmedi. Entübasyon süresi Grup S2'de Grup S0 ve S1'e göre anlamlı olarak daha uzundu. Hemodinamik parametreler önemli ölçüde değişti. Ortalama arter basıncı (MAP) ve kalp atış hızı (HR), Eb'den Ea'ya önemli ölçüde arttı ve Rb'den Ra'ya düştü. Spesifik olarak, Eb ve Ea arasında MAP 82,4 ± 8,1 mmHg'den 89,6 ± 9,2 mmHg'ye ($p<0,05$) ve HR ise 72,5 ± 7,4 bpm'den 78,3 ± 8,6 bpm'ye ($p<0,05$) yükseldi. Tersine, Rb ve Ra arasında MAP 90,2 ± 8,4 mmHg'den 85,1 ± 8,3 mmHg'ye ($p<0,05$) ve HR ise 80,5 ± 7,5 bpm'den 74,2 ± 7,8 bpm'ye ($p<0,05$) düştü. ANI değerleri gruplara ve zaman noktalarına göre değişiklik gösterdi; Grup S2, ekstübasyon sonrası (Ea) ve torasik drenaj sonrası (Ra) daha yüksek ANI değerleri gösterdi.

Sonuç: Analjezi nosisepsiyon indeksi, kalp cerrahisi sonrası kardiyovasküler yoğun bakım ünitesinde sürekli ağrı değerlendirmesi için uygun bir araçtır. Dinamik hemodinamik tepkiler ve farklı ANI modelleri, ANI'nin postoperatif ağrı yönetimi stratejilerini uyarlamadaki potansiyelini vurgulamaktadır.

Anahtar sözcükler: Analjezi nosisepsiyon indeksi, mekanik ventilasyon, kardiyovasküler yoğun bakım ünitesi, inotropik destek

Received/Geliş tarihi : 14.02.2024
Accepted/Kabul tarihi : 11.07.2024
Publication date : 29.07.2024

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Cite as: Tanrikulu N, Polat F, Haspolat A, Koprulu AS. Pain evaluation using analgesia nociception index (ANI) in postoperative cardiovascular intensive care patients. JARSS 2024;32(3):167-173.

INTRODUCTION

Pain, as defined by the International Association for the Study of Pain (IASP), is an intricate blend of unpleasant sensory and emotional sensations originating from various bodily regions. These sensations are intricately tied to the potential or actual tissue damage and are influenced by the complex interplay of past experiences (1). In the context of cardiovascular surgery, postoperative pain is a multifaceted challenge, arising from diverse sources such as sternotomy, pericardiotomy, blood vessel harvesting, and manipulations of delicate structures like the parietal pleura. The intricate nature of these procedures can lead to musculoskeletal traumas and an array of potential discomforts (2). Poorly managed pain following cardiac surgery can have far reaching implications, contributing to respiratory complications like atelectasis and pneumonia due to hampered respiratory function, thromboembolic risks due to limited patient mobilization, and an augmented burden on the cardiovascular system. The latter manifests as heightened systemic vascular resistance increased cardiac workload and escalated myocardial oxygen consumption due to an overactive sympathetic response and the release of catecholamines. These interconnected effects can disrupt the delicate hemodynamic equilibrium, resulting in elevated morbidity and mortality rates (3).

While conventional approaches to pain management in the aftermath of cardiac surgery often rely on narcotic analgesics, the inherent subjectivity of pain perception, and the considerable individual variability in responses underscore the need for more refined strategies (1). Achieving effective pain control requires not only adherence to standardized administration protocols but also accurate and thorough assessment and documentation (4). Ideally, patients' self-reporting of pain would serve as the gold standard, but practical constraints within the cardiovascular intensive care unit (ICU), particularly during the immediate postoperative period, limit its feasibility.

The pursuit of quantitative and objective pain assessment methods has led to the exploration of innovative approaches, such as skin conductance and pupillary reflex measurement, both of which offer potential benefits in enhancing pain evaluation (5,6). Among these novel techniques, the analgesia nociception index (ANI) stands out. Developed by MetroDolaris Medical Systems in Lille, France, ANI aims to delineate the delicate balance between nociception and analgesia by meticulously evaluating the parasympathetic nervous system's involvement (7). Rooted in heart rate variability (HRV), ANI leverages the temporal interval between successive R waves, effectively isolating these intervals from respiratory cycle-related fluctuations. This enables ANI to provide a nuanced quantification of parasympathetic tone (p∑), which spans a scale from 0 to 100. The interpretive framework designates ANI values ≥50 as indicative of effective analgesia, values ranging between 30–50 as reflective of moderate pain, and values below 30 as indicative of severe pain (8). Although preoperative applications of ANI have garnered research attention, its potential utility within the realm of cardiovascular surgery and specifically within the cardiovascular ICU remains an unexplored territory.

Therefore, the primary objective of this study is to investigate the feasibility of implementing ANI in the assessment of pain for conscious, sedated, and mechanically ventilated patients within our cardiovascular ICU who face communication challenges. Moreover, as a secondary objective, we seek to elucidate any potential influence of (+) inotropic agents and/or vasoconstrictors on ANI values. By delving into this uncharted area, we aspire to uncover new insights and potentially clinically relevant information that could contribute to refining postoperative pain management strategies and optimizing patient outcomes.

MATERIAL and METHODS

This prospective observational study was conducted from January 2019 to January 2020 at a single center, involving cardiology, cardiovascular surgery, anesthesia, and reanimation departments. Ethical approval was received from the University Institutional Ethics Committee (Approval Date: April 13, 2018, Approval No: 2018/04-2). Informed consent was directly obtained from eligible patients, ensuring their autonomy and confidentiality.

Eligible participants, aged 18 to 75 years, were scheduled for elective isolated coronary artery bypass graft (CABG) surgeries addressing 2–4-vessel disease. We included patients without perioperative complications, who were postoperatively monitored within the Cardiovascular ICU using the ANI. Exclusions comprised patients needing emergency surgery, those with preoperative chronic pain, autonomic nervous system anomalies, or rhythms differing from preoperative and postoperative spontaneous sinus rhythm.

Given the observational nature of our study, randomization was not performed. Participants were assigned to groups based on clinical decisions and the need for specific interventions. Three study groups were identified: Group S0 received no additional cardiac support, Group S1 received inotropic support through dopamine, and Group S2 received combined inotropic (dopamine) and vasopressor (noradrenaline) support.

Tailored pain management and anesthetic protocols, aligned with established clinical practices, were administered by experienced anesthesiologists to ensure patients' well-being during surgery and recovery. Mild pain was managed using non-steroidal anti-inflammatory drugs (NSAIDs), with opioid treatment introduced as required for those with inadequate pain relief.

During cardiovascular ICU monitoring, we recorded vital signs, including mean arterial pressure (MAP, mmHg), heart rate (HR, beats min^{-1}), oxygen saturation (SpO_2, %), and respiratory rate (RR, breaths min^{-1}). We assessed instantaneous ANI (ANIi) using ANI electrodes placed at V1 and V5 leads, as per manufacturer recommendations. ANIi, acknowledged for capturing transient pain stimuli, was selected for analysis (7,8). Measurements were taken at specific time points: before extubation (Eb), after aspiration and extubation (Ea), before thoracic drain removal (Rb) and after thoracic drain removal (Ra).

Demographic characteristics including gender, age, height, weight, body mass index (BMI), and intubation duration (in hours) were compared across the three groups. Gender differences were evaluated using the Chi-square test, while differences in age, weight, height, BMI, and intubation duration were assessed using One-Way ANOVA.

Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Parametric tests were applied after confirming normal distribution and homogeneity of variances. Normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Levene's test.

For comparisons among the three groups (S0, S1, S2) at specific time points (Eb, Ea, Rb, Ra), one-way ANOVA was utilized for normally distributed data with homogeneity of variances. Post-hoc pairwise comparisons were conducted using the Tukey HSD test. For comparisons within groups across different time points (Eb vs Ea, Rb vs Ra), paired sample t-tests were employed if the assumptions of normality and homogeneity of variances were met. Non-parametric tests (Wilcoxon signed-rank test) were planned if these assumptions were not met.

Significance levels were set at p<0.05, with p<0.001 considered highly significant. The sample size was determined based on practical considerations to facilitate meaningful correlations and insights in this study, acknowledging the limitations associated with the lack of randomization.

RESULTS

In this study, a total of 135 participants were included, with Group S0 (n=51), Group S1 (n=48), and Group S2 (n=36). Participants consisted of 102 males and 33 females, with a mean age of 60.68 ± 9.79 years, mean weight of 80.82 ± 10.11 kg, mean height of 168.41 ± 9.77 cm, and mean BMI of 28.53 ± 2.93 kg m^{-2}.

Gender distribution among the groups showed that S0 had 39 males (76.5%) and 12 females (23.5%), S1 had 36 males (75.0%) and 12 females (25.0%), and S2 included 27 males (75.0%) and 9 females (25.0%). A Chi-square analysis indicated no significant gender distribution differences between the groups (p=0.9). When age, weight, height, BMI, clamp time, LIMA usage, total revascularized vessel number, and intubation duration were compared, no significant difference was observed except for the intubation duration, which was significantly longer in Group S2 patients (S2:17.58 ± 5.11 hours; S0:11.94 ± 3.68 hours; S1: 11.94 ± 3.68 hours) (Table I).

Hemodynamic parameters showed significant variations between specific time. Mean arterial pressure and HR exhibited significant differences between Eb and Ea, and Rb and Ra, reflecting responses to extubation and thoracic drain removal. Oxygen saturation remained consistent within each group across all time points (Eb-Ea, Rb-Ra). However RR displayed significant differences at various time points. ANIi varied consistently across different groups and at different time points (Table II).

Table I: Demographic and Procedure-Related Characteristics of Patients according to Inotropic and Vasopressor Support Groups n (%), Mean±SD

Patient Characteristics	Group S0 (n=51)	Group S1 (n=48)	Group S2 (n=36)	p-value
Gender (Male)	39 (76.5%)	36 (75.0%)	27 (75.0%)	0.994
Age (year)	60.65 ± 10.3	59.38 ± 8.36	62.5 ± 11.7	0.720
Weight (kg)	83.06 ± 9.72	80.88 ± 9.05	77.58 ± 12.26	0.373
Height (cm)	170.88 ± 9.38	168.5 ± 9.87	164.75 ± 10.3	0.263
Body Surface Index	28.53 ± 3.32	28.54 ± 2.72	28.52 ± 3.01	0.997
Cross clamp time (min)	46.78 ± 5.64	44.45 ± 4.92	45.62 ± 5.05	0.791
Left internal mammary artery use (%)	82.19 ± 6.61	80.26 ± 4.91	83.23 ± 6.17	0.410
Total revascularized vessel number	2.95 ± 0.75	3.01 ± 0.85	2.92 ± 0.78	0.216
Intubation time (hour)	11.94 ± 3.68	12.19 ± 5.14	17.58 ± 5.11	0.004

Table II: Intra-Group Analysis of Mean Arterial Pressure, Heart Rate, Oxygen Saturation, Respiratory Rate and Instantaneous Analgesia Nociception Index Measurements at Different Time Intervals

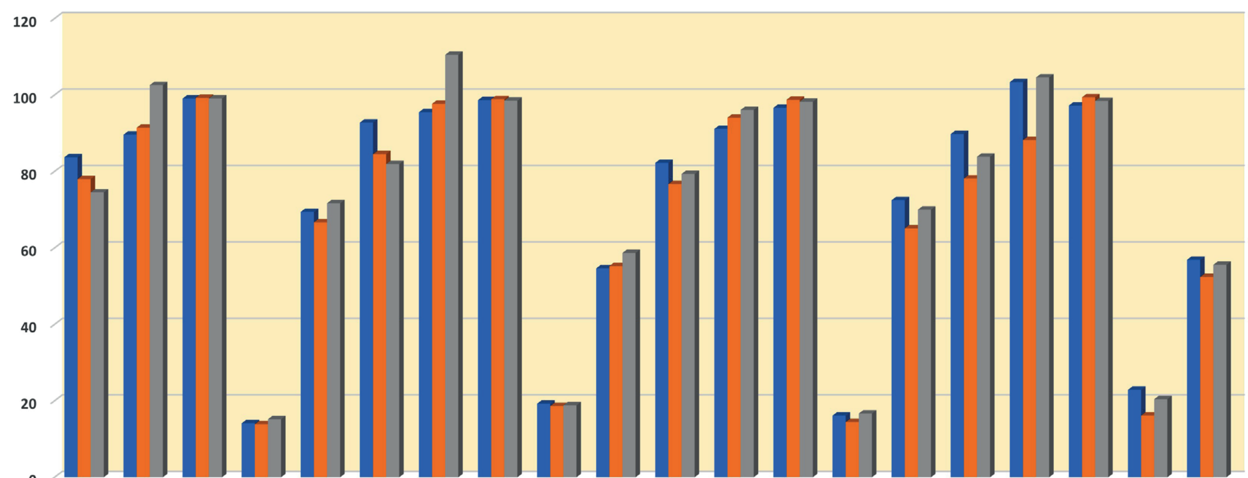
	Parameters	Before extubation (Eb)	After extubation (Ea)	p-value
Group S0	MAP	83.71±11.69	92.76±10.81	<0.001
	HR	89.59±11.57	95.47±13.39	0.015
	SpO_2	99.06±1.48	98.65±1.97	0.203
	RR	14.12±4.9	19.24±3.6	0.002
	ANI i	69.41±17.19	54.65±20.81	0.025
Group S1	MAP	78±12.21	84.5±10.06	0.014
	HR	91.44±16.26	97.69±14.49	<0.001
	SpO_2	99.25±1.13	98.88±2.13	0.440
	RR	13.88±1.36	18.63±4.08	0.001
	ANI i	66.69±12.03	55.25±11.11	0.001
Group S2	MAP	74.5±12.55	81.92±14.61	0.012
	HR	102.58±16.14	110.5±16.5	0.001
	SpO_2	99.08±1.51	98.5±2.11	0.027
	RR	15.17±3.19	18.83±3.64	<0.001
	ANI i	71.67±12.27	58.67±12.42	0.001
	Parameters	**Before thoracic drain removal (Rb)**	**After thoracic drain removal (Rb)**	**p-value**
Group S0	MAP	82.24±9.53	89.76±9.11	0.034
	HR	91.12±13.57	103.35±12.95	0.003
	SpO_2	96.65±2.18	97.24±2.39	0.507
	RR	16.12±3.46	22.88±3.22	0.000
	ANI i	72.47±15.59	56.88±19.39	0.004
Group S1	MAP	76.69±10.52	78.13±12.82	0.581
	HR	94.06±16.13	88.19±18.93	0.227
	SpO_2	98.75±1.00	99.38±0.96	0.055
	RR	14.44±1.55	16.13±4.13	0.143
	ANI i	65.13±14.81	52.38±12.45	0.003
Group S2	MAP	79.33±12.55	83.83±12.61	0.002
	HR	96.08±9.73	104.58±12.87	<0.001
	SpO_2	98.25±1.6	98.42±1.78	0.658
	RR	16.67±4.38	20.42±3.58	0.006
	ANI i	70.00±9.27	55.58±13.19	0.002

MAP: Mean arterial pressure, **HR:** Heart rate, **SpO_2:** Oxygen saturation, **RR:** Respiratory rate, **ANIi:** Instantaneous analgesia nociception index.

No statistically significant differences in MAP, HR, SpO_2, RR, or ANIi between any group comparisons at Eb and Rb. At Ea and Ra, no significant differences were observed in SpO2, RR, or ANIi. However, significant differences in MAP were identified between S0 and S1, and S0 and S2, at Ea. Additionally, significant differences in HR were noted between S0 and S2, and S1 and S2, at Ea. Similar observations were made at Ra, with MAP and HR differences (Figure 1).

DISCUSSION

The comprehensive analysis of participant characteristics, hemodynamic, respiratory, and ANI responses provides valuable insights into the complex dynamics of cardiovascular surgery and hemodynamic support. The observed stability in SpO_2 suggests effective respiratory management, while significant hemodynamic variations underscore the intricate interplay between procedural interventions and physiological responses. Furthermore, the variable trends in RR underscore



	Before extubation (Eb)					After extubation (Ea)					Before thoracic drain removal (Rb)					After thoracic drain removal (Rb)				
	MAP	HR	SpO2	RR	ANI i	MAP	HR	SpO2	RR	ANI i	MAP	HR	SpO2	RR	ANI i	MAP	HR	SpO2	RR	ANI i
S0	83.71	89.59	99.06	14.12	69.41	92.76	95.47	98.65	19.24	54.65	82.24	91.12	96.65	16.12	72.47	89.76	103.35	97.24	22.88	56.88
S1	78	91.44	99.25	13.88	66.69	84.5	97.69	98.88	18.63	55.25	76.69	94.06	98.75	14.44	65.13	78.13	88.19	99.38	16.13	52.38
S2	74.5	102.58	99.08	15.17	71.67	81.92	110.5	98.5	18.83	58.67	79.33	96.08	98.25	16.67	70	83.83	104.58	98.42	20.42	55.58

Figure 1: Comparison of mean arterial pressure, heart rate, oxygen saturation, respiratory rate and instantaneous analgesia nociception index measurements between groups.

the multifaceted nature of respiratory patterns in the context of postoperative interventions. The consistent ANI responses reinforce its potential as a reliable indicator for pain assessment and modulation of autonomic activity.

Pain perception significantly impacts ICU patients' physiological systems (9). Sources of pain, ranging from medical interventions to catheters, are pervasive even during rest, affecting approximately 30% of ICU patients (10). Addressing pain, particularly post open-heart surgery in the cardiovascular ICU, is challenging, notably due to inadequate pain assessment in mechanically ventilated patients (5,11).

Insufficient pain management triggers physiological responses, contributing to neurovegetative and neuroendocrine dysregulation (12,13). This stress response adversely affects myocardial function, patient-ventilator synchronization, and cognitive well-being. Prolonged mechanical ventilation results in unfavorable outcomes, such as extended stays and potential mortality increase (5,11).

Persistent pain fosters lasting stress, leading to adrenal insufficiency, immune alterations, and disruptions in glucose metabolism. The challenge of inadvertent analgesic and sedative overdosing presents further concerns, including prolonged ventilation and withdrawal syndromes (5,13). Insights from opioid-induced hyperalgesia underscore the risk of lingering pain post-discharge due to excessive opioid use in the ICU (13). Addressing pain comprehensively within ICU care is essential for better patient outcomes.

Traditional pain assessment methods, relying on patient self-expression via scales like visual analogue scale, verbal rating scale, and numeric rating scale, encounter limitations in ICU patients, especially when sedated or intubated (11,14). While physiological indicators such as MAP, HR, RR, and SpO_2 have been explored, their role in ICU pain assessment is debated, influenced by drug effects and individual variations (15). The American Society for Pain Management Nursing highlights the limited sensitivity of physiological indicators in distinguishing pain from other stressors (16).

Prior studies offer inconsistent findings on the utility of vital signs for pain assessment, with their applicability best suited for mechanically ventilated or unconscious patients (17). Our study further explores this by revealing diverse vital parameter responses during painful stimuli and the ANI, underscoring the complexities of pain assessment in critical care.

Various tools have emerged to address pain assessment challenges in patients with communication limitations. Examples include "CPOT," "BPS," and "CPOT + BPS" (2,10,18) Combined usage has demonstrated improved validity in mechanically ventilated ICU patients (19). Additionally, the reliability and validity of BPS and CPOT have been affirmed in cardiac surgery patients (15).

Emerging methods such as the ANI provide novel approaches for objective pain assessment (7,8). Our study contributes to this area by demonstrating ANI's efficacy in cardiovascular ICU settings, where painful stimuli induced rapid ANI reductions, promptly returning to baseline.

While our study supports ANI's potential in specialized patient groups, the application of ANI across diverse ICU contexts remains underexplored. Our study, the first in the cardiovascular ICU, aimed to assess ANI's pain detection efficacy in this context, highlighting its utility as painful stimuli led to swift ANI reductions.

Despite the variability of ANI values, responses to painful stimuli remained consistent, likely influenced by individual controls. Our findings align with limited research, emphasizing ANI's effectiveness in detecting pain (20-24).

ANI emerges as an effective tool for pain assessment in deeply sedated critically ill patients, potentially extending to patient subgroups receiving dopamine and norepinephrine. Our study's application of ANI in intubated postoperative cardiovascular ICU patients introduces a noninvasive, user-friendly, and compact monitoring solution, enabling continuous pain assessment. Such an approach, similar to other proven scoring systems, could improve analgesic dosage optimization, pain reduction, and overall quality of care, potentially leading to shorter intensive care and hospital stays and improved morbidity and mortality outcomes (20,24).

Limitations of this study include its observational design, which precludes establishment of causal relationships between interventions and outcomes. The modest sample size and lack of randomization may limit the generalizability of findings to broader ICU populations. Additionally, the exclusion of patients receiving preoperative analgesics and the absence of data on intraoperative and postoperative analgesic use could impact the comprehensive understanding of ANI responses in the context of pain management strategies. These factors highlight the need for larger-scale interventional studies with standardized protocols to further elucidate ANI's utility and optimize its application in diverse ICU settings.

CONCLUSION

In conclusion, this prospective observational study explored the feasibility of implementing the ANI for pain assessment in conscious, sedated, and mechanically ventilated patients within the cardiovascular ICU, addressing the communication challenges often faced in postoperative care. The comprehensive analysis of participant characteristics, hemodynamic responses, respiratory patterns, and ANI values revealed valuable insights into the complex dynamics of post-cardiac surgery recovery. Our findings support the potential of ANI as an effective and noninvasive tool for continuous pain assessment in this specialized patient population. While acknowledging the limitations inherent in an observational study with a modest sample size, this research provides a basis for further research into the utility of ANI in pain assessment in various ICU contexts.

AUTHOR CONTRIBUTIONS

Conception or design of the work: NT
Data collection: FP, NT
Data analysis and interpretation: FP, NT, AH
Drafting the article: FP, NT
Critical revision of the article: FP, NT
The author (FP, AH, NT) reviewed the results and approved the final version of the manuscript.

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