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Multimodal monitoring using Analgesia Nociception Index (ANI) during catheter ablation of the heart in patients with sinus rhythm and short-term induced atrial arrhythmia: prospective observational study

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Abstract

INTRODUCTION: Catheter ablation (CA) is a painful procedure requiring an assessment of the balance between nociception associated with surgical trauma and anesthesia induced antinociception. **OBJECTIVE:** To evaluate the effectiveness of the monitoring system "ANI Monitor" for anesthesia and intensive care in patients with sinus rhythm and short-term induced (< 1 min) atrial arrhythmia (STIAA). **MATERIALS AND METHODS:** The study group of our trial consisted of 94 patients with CA and ANI Monitor. The control group consisted of 94 patients, selected using the "copy-pair" method, with standard (hemodynamic) monitoring. A Numerical Rating Scale (NRS) was used for assessment the intensity of pain. At the stage of femoral vein catheterization in all patients regional anesthesia was performed, at the CA stage, procedural sedation and/or analgesia (PSA) was titrated with the administration of propofol and fentanyl (under the control with ANI Monitor). Statistical data processing was carried out using Statistica 10.0 and SPSS programs. **RESULTS:** At the stage of CA under PSA, negative correlation was found between NRS and ANIm in patients with sinus rhythm and STIAA ($r = -0.37$). At the threshold of 56.0 the sensitivity and specificity of ANIm in detecting NRS > 3 were 60 and 100%, respectively, corresponding to ROC curve AUC of 0.81. Significant changes in hemodynamic reactivity were not registered. It was revealed the reduction of fentanyl administration in patients of the study group (0.04 ± 0.02 and 0.05 ± 0.03 μg/kg/min, respectively, $p < 0.001$) under the control of ANI

Мультимодальный мониторинг с использованием индекса анальгезии и ноцицепции (ANI) в ходе катетерной абляции сердца у пациентов с синусовым ритмом и кратковременно-индуцируемой предсердной аритмией: проспективное наблюдательное исследование

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Реферат

АКТУАЛЬНОСТЬ: Катетерная абляция (КА) является болезненной процедурой, требующей оценки баланса между ноцицепцией, ассоциированной с хирургической травмой, и антиноцицепцией, связанной с анестезией. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Оценить эффективность системы мониторинга «ANI Monitor» для анестезиологии, реанимации, интенсивной терапии у пациентов с синусовым ритмом и кратковременно-индуцируемой (< 1 мин) предсердной аритмией (КИПА). **МАТЕРИАЛЫ И МЕТОДЫ:** В исследовании основную группу составили 94 пациента с КА и ANI Monitor. Группу контроля составили 94 пациента со стандартным (гемодинамическим) мониторингом, отобранные ретроспективно по методу «копи-пара». Интенсивность боли оценивалась по цифровой рейтинговой шкале (ЦРШ). На этапе катетеризации бедренной вены у всех пациентов использована регионарная анестезия, тогда как на этапе КА процедурная седация и/или анальгезия (ПСА) поддерживалась введением пропофола и фентанила (под контролем ANI Monitor). Статистическую обработку информации проводили с использованием программ Statistica 10.0 и SPSS. **РЕЗУЛЬТАТЫ:** Отрицательная корреляция между ЦРШ и ANIm зарегистрирована на этапе КА под ПСА у пациентов с синусовым ритмом и КИПА ($r = -0,37$). Пороговое значение ANIm, равное 56,0, определило пациентов с ЦРШ > 3 баллов с чувствительностью 60 %, специфичностью 100 % и площадью под ROC-кривой AUC 0,81.

Monitor. **CONCLUSIONS:** ANI Monitor during CA in patients with sinus rhythm and STIAA was more effective in detecting harmful nociceptive stimuli compared to standard (hemodynamic) monitoring. The use of ANI Monitor to control the fentanyl administration could create conditions for opioid-sparing anesthesia.

KEYWORDS: ANI Monitor, intraoperative monitoring, catheter ablation

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Значимых изменений гемодинамической реактивности зарегистрировано не было. Введение фентанила под контролем ANI Monitor демонстрирует снижение дозы у пациентов основной группы (0,04 ± 0,02 и 0,05 ± 0,03 мкг/кг/мин соответственно, $p < 0,001$). **ВЫВОДЫ:** ANI Monitor при проведении КА пациентам с синусовым ритмом и КИПА более эффективен в выявлении ноцицептивных повреждающих стимулов в ходе КА сердца по сравнению со стандартным (гемодинамическим) мониторингом. Использование ANI Monitor для контроля введения фентанила создает условия для проведения опиоидсберегающей анестезии.

КЛЮЧЕВЫЕ СЛОВА: ANI Monitor, интраоперационный мониторинг, катетерная абляция

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Introduction

The global incidence of cardiac arrhythmia in 2016 was 43.6 mln people and in 2019 — 59.7 mln people [1]. The type of arrhythmia, heterogeneity and variability of traumatic and reflexogenic effects, the interventional experience of the centers and the availability of an anesthesia service as well as the age of patients and comorbid pathology determine the choice of anesthetic and the depth of sedation during catheter ablation (CA) [2]. Catheter radiofrequency (RF) ablation for cardiac arrhythmia is a painful procedure. According to Münkler et al., 7.7 % of patients reported procedural pain, and 16 % reported side effects, such as post-operative nausea and headache episodes [3]. A possible cause of procedural pain could be the increased activity of cerebral cortex areas associated with pain, presumably due to inadequate blocking of afferent nociceptors in the cardio-vascular system [4]. Intraoperative nociception is the central modulation of stimuli, due to surgical tissue damage, into behavioral, vegetative, and hormonal responses [5]. Currently there is no objective and absolute marks of nociception and pain [6] as well as «gold standard» for quantitive evaluation of nociception [7]. The specificity of somatic and vegetative reactions was insufficient to assess nociception, and the use of hemodynamic changes as markers of adequate pain relief resulted in excessive use of opioids [8]. Inappropriate administration of opioids contributes to increase of the frequency of their side effects such as nausea, vomiting, respiratory

depression, opioid tolerance [9] and opioid-induced hyperalgesia, the latter being of paramount importance as it contributes to increased post-operative pain and may initiate mechanisms responsible for chronic pain [10]. Nociception monitoring is necessary to assess the balance between nociception caused by surgical trauma and anesthesia induced antinociception.

Monitoring and modulation of intraoperative nociception is a complex problem [11]. The choice of nociception assessment method mainly depends on the clinical context and the overall purpose of monitoring [12]. The methods for nociception assessing and the limitations of the methods are presented in Appendix.

There is a tendency to integrate nociception and analgesia balance indices into multimodal anesthetic monitors. For example, CARDEAN index (cardio-vascular depth of analgesia) was integrated into monitor Philips Intellivue®, HFVI index (high frequency variability index) — into monitor MDoloris Medical Systems. HFVI uses the same calculation algorithm as ANI index [13]. ANI index is calculated based on a high frequency component of heart rate variability (HRV) [14], modulated by the influence of respiratory frequency/rhythm, and displays instantaneous (ANIi) and 2-minute moving average (ANIm) value of ANI index. In case of nociception, sympathetic tone increases and parasympathetic tone decreases, which results in a decrease in ANI values (below 50) and hemodynamic reactivity [15].

Numerous studies indicated that variations in ANI index identify and reflect vegetative reactivity to nociceptive stimulation during anesthesia with non-inhaled [16] and inhaled anesthetics [17]. Some authors have evaluated the effectiveness of ANI Monitor in detecting nociceptive stimuli in patients with procedural sedation and analgesia (PSA) [18, 19]. The painfulness of catheter ablation of cardiac arrhythmias necessitates objective monitoring of intraoperative nociception, however, most nociception monitoring methods have limitations for patients with arrhythmias (Appendix). The development of technologies and, in particular, use of 3D-mapping of arrhythmogenic zones before catheter ablation made it possible to identify arrhythmogenic zones without inducing cardiac arrhythmias or with short-term induced arrhythmia, which allowed us to assume the possibility of effective use of ANI Monitor in this category of patients.

Objective

To evaluate the effectiveness of the monitoring system "ANI Monitor" for anesthesia and intensive care in patients with sinus rhythm and short-term induced (< 1 min) atrial arrhythmia (STIAA) during CA.

In the study the hypothesis that the use of ANI Monitor when performing anesthesia during CA will improve the detection of nociceptive stimuli and reduce the dose of opioid analgesics in patients with sinus rhythm and short-term induced (< 1 min) atrial arrhythmia (STIAA) was checked.

Materials and methods

A prospective observational study was conducted between April 2022 and May 2023 (Protocol No. 4 of the meeting of the local Ethics Committee of I.I. Mechnikov North-Western State Medical University dated April 6, 2022). The study included 188 patients with Class III according to the American Society of Anesthesiologists (ASA) [20]. Elective CA was performed in an X-ray surgical operating room for the treatment of patients with complex cardiac arrhythmias. During intervention all patients were monitored using a four-lead surface electrocardiogram and intracardiac electrograms, (CARTO® 3, Biosense Webster, Johnson & Johnson MedTech, USA), respiratory rates (RR), saturation (SpO_2) and non-invasive blood pressure (NIBP), (GE B 30, General Electric Company, USA). At the time of the procedure all patients had a sinus rhythm. Then, atrial arrhythmia was provoked /induced, which was the reason for the intervention, for its mapping and subsequent treatment. The ablation index was taken into account when conducting CA in groups. The group consisted of 94 patients with sinus rhythm and STIAA during CA with monitoring of nociception/antinociception balance (ANI Monitor). The control group consisted of 94 patients selected by paired-linked selection (the "copy-pair" method according to the type of induced arrhythmia, kind and duration of intervention, gender and Charlson comorbid pathology index (Charlson Comorbidity Index, CCI). On the day of intervention antiarrhythmic therapy was performed with class II drugs (β-adrenoceptor blocking agents). ANI values were recorded at the following points: before femoral vein catheterization (FVC) (1); at the stage of FVC (2); after administration of fentanyl before CA (3); at the stage of CA (4); at the stage of hemostasis (5). At the stage of FVC using Seldinger's technique, RF ablation with lidocaine from 2.5 to 4.5 mg/kg was used under the control of an X-ray TV system. The sedation level during procedure varied from superficial to moderate (RASS −1/−2) and was achieved by intravenous fractional bolus administration of propofol. The dosage of fentanyl was carried out according to ANI (with a decrease in the index < 50). Hemodynamic parameters (Heart Rate (HR), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP)), Respiratory Rate, SpO_2, pain assessment on a Numerical Rating Scale (NRS) (Table 1) were recorded at the same time points.

Verbal contact was used to fix the pain assessment according to NRS in patients with RASS −1/−2 at the stage of CA (the question was short and repeated three times).

A NRS score of 3 points was adopted as the threshold for comparing ANI values, since NRS > 3 indicates the presence of moderate to severe pain and is used as a startpoint

for therapeutic interventions. At the end of the intervention, a scale to assess satisfaction with anesthesiological support was used (Iowa Satisfaction with Anesthesia Scale [ISAS] in modification of E.V. Sinbukhova) [21] in the department routine practice since January 2020.

Inclusion criteria: 1) elective CA; 2) sinus rhythm; 3) III class according to the ASA classification; 4) patient consent; 5) patient age >18 or < 75 years. Exclusion criteria: 1) patients with emergency interventions; 2) patients with chronic pain or autonomic nervous system disorders; 3) patients with CCI > 3 points; 4) patients with body mass index (BMI) ≥ 30 kg/m$^{2;}$ 5) patients with a pacemaker and/or administration of atropine.

Study flowchart is shown in Figure 1.

Statistical data processing was carried out using Statistica 10.0 and SPSS programs. Patients' characteristics and comparison in groups were carried out with an assessment of the compliance of the distributions of quantitative indicators with the normal law (Kolmogorov-Smirnov criterion). For quantitative variables which distribution differed from the normal value, the data were presented in the form of median and quartiles. In the comparative analysis of two independent groups Mann-Whitney criterion was used; when comparing indicators at the stages of surgical treatment Friedman variance analysis and Wilcoxon criterion were used. A 95 % confidence interval (95 % CI) was calculated. The structure of qualitative indicators was represented by the distribution of frequencies (%), the com-

Table 1. The Numerical Rating Scale

Please rate the intensity of pain you are currently experiencing										
0	1	2	3	4	5	6	7	8	9	10
No pain					Moderate pain					Very severe pain

Note: The NRS consists of a sequential series of numbers from 0 to 10. Patients are asked to rate the intensity of pain using numbers: 0 — no pain; 5 — moderate pain and 10 — the worst pain imaginable.

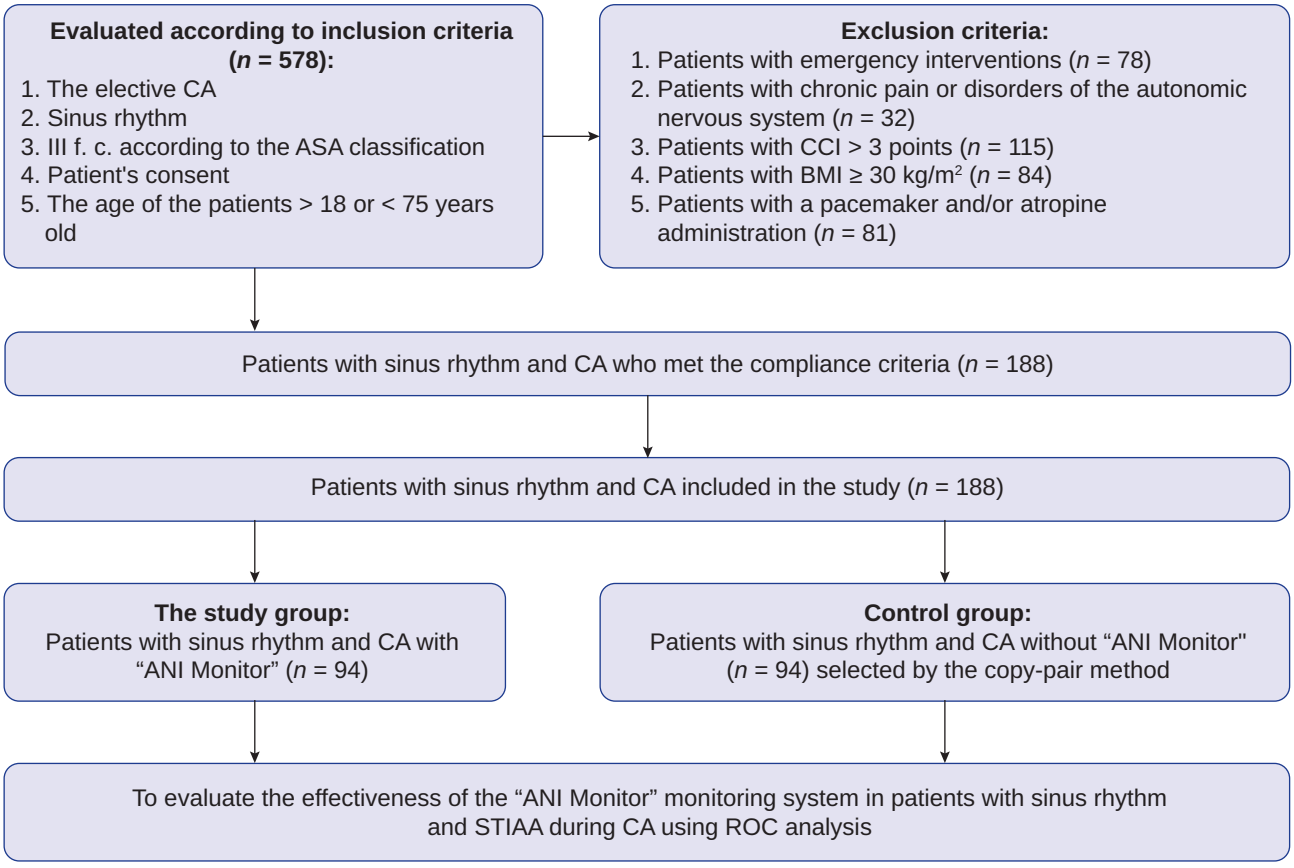

Fig. 1. Study flowchart

BMI — Body Mass Index; CA — catheter ablation; CCI — Charlson Comorbidity Index; STIAA — Short-Term Induced Atrial Arrhythmia.

parison of which in independent groups was performed by Pearson criterion c^2. Correlation of quantitative indicators was assessed by means of a correlation coefficient. The assessment of the strength of the correlation coefficients was carried out on the Cheddock scale. The analysis was carried out using Spearman's rank correlation method. Differences in measured values were recognized as significant at the level of $p < 0.05$. To calculate ANI threshold values, classifying patients into 2-q groups according to NRS level (> 3 and ≤ 3) at the stages of FVC (Femoral Vein Catheterization) and ablation, ROC-analysis was performed with the construction of a characteristic curve (Receiver Operator Characteristic curve). The diagnostic informativity of the method was assessed by determining the area under ROC-curve (AUC or Area Under Curve). The point on the ROC-curve maximizing the sum of sensitivity and specificity of classification was chosen as the optimal threshold value. The results of the diagnostic test with an area under the ROC-curve AUC equal to 0.8 were classified as good.

Results

The study and control groups were comparable in gender, CCI, ASA functional class, anesthetic support, type of surgery and its duration, heart rate before surgery and types of STIAA. Differences between the compared groups in age and body mass were revealed. The patients of the study group were older (age in the main group — 61.38 ± 11.35 years, in control group — 53.84 ± 15.10 years, $p = 0.0005$) and were overweight (BMI in the main group — 28.15 ± 4.94 kg/m^2, in control group — 25.35 ± 3.90 kg/m^2, $p < 0.0001$). The differences in ablation time in the study group were 52.36 ± 2.06 s, in control group — 50.87 ± 0.93 s, $p < 0.0001$. A comparison of the study and control groups is presented in Table 2.

ANI Monitor values were recorded during entire anesthetic support (Table 3).

At FVC stage during RF ablation, 22 (23.4 %) patients of the study group with sinus rhythm had pain syndrome with NRS > 3, which was accompanied by a decrease of ANIi in-

Table 2. Comparison of the main and control groups ($n = 188$)

Parameter	Main group ($n = 94$)	Control group ($n = 94$)	*p-value*
Age, years	61.38 ± 11.35	53.84 ± 15.10	0.0005*
Female, *n* (%)	54 (57.40 %)	57 (60.60 %)	0.6564
BMI, kg/m^2	28.15 ± 4.94	25.35 ± 3.90	< 0.0001**
CCI, points	2.11 ± 1.17	1.87 ± 1.06	0.2197
Surgical intervention, *n* (%)			
RF-isolation of the entries of the pulmonary veins	70 (74.50 %)	66 (70.20 %)	0.3064
RF-modification of AV-connection	20 (21.30 %)	23 (24.50 %)	
RFA ACP	2 (2.10 %)	0 (0 %)	
CA of cavo-tricuspid isthmus	2 (2.10 %)	5 (5.30 %)	
Heart rates at CA stage, *n* (%)			
Sinus rhythm	70 (74.50 %)	58 (61.70 %)	0.0081
SVT	23 (24.50 %)	23 (24.50 %)	
AFL	1 (1.10 %)	5 (5.30 %)	
AF	0 (0 %)	8 (8.50 %)	
Ablation time, s	52.36 ± 2.06	50.87 ± 0.93	< 0.0001**
Surgery duration, min	53.46 ± 17.67	50.95 ± 28.00	0.1528
NRS > 3 with CA, *n* (%)	25 (26.60 %)	20 (21.30 %)	0.3928
Fentanyl dose, μg /kg/min	0.04 ± 0.02	0.05 ± 0.03	< 0.0001**
Propofol dose, mg/kg/min	0.22 ± 0.06	0.27 ± 0.05	0.0609
Health complications (total), %	0 (0 %)	3 (3.30 %)	0.1551
Satisfaction with Anesthesia Scale, points	153.96 ± 3.00	152.30 ± 5.39	0.0494*

*, ** Statistically significant difference.
AF — atrial fibrillation; AFL — atrial flutter; BMI — body mass index; CA — catheter ablation; CCI — Charlson comorbidity index; NRS — The Numerical Rating Scale; RF — radio frequency; RFA ACP — RF ablation of accessory conduction pathway; SVT — supraventricular tachycardia.

dicators. The revealed moderate negative correlation was statistically significant ($r = -0.44$; $p < 0.0001$). ANIi threshold value equal 51.0 divided patients with NRS > 3 and NRS ≤ 3 with sensitivity 68.18 % and specificity 92.96 %. Area under ROC-curve AUC 0.78 (95 % CI 0.71–0.85; $p < 0.001$) for ANIi in patients at the stage of FVC with RA, which indicates good quality of information content of the predictive model. In parallel, ANIm indicators were recorded. Negative correlation between ANIm and NRS was statistically significant ($r = -0.39$; $p < 0.0001$). ANIm threshold value equal to 47.0 divided patients with NRS > 3 and NRS ≤ 3 with sensitivity 54.55 % and specificity 100.00 %. Area under ROC-curve AUC 0.75 (95 % CI 0.68– 0.82; $p < 0,001$) for ANIm in patients at the stage of FVC with RA, which indicates good quality of information content of the predictive model. A retrospective analysis of the control group did not reveal any signs of pain syndrome in anesthesia and intervention protocols at the stage of FVC. At the stage of CA in patients of the study group, pain syndrome with NRS > 3 was detected in 25 (26.60 %) patients, whereas in the control group — in 20 (21.30 %) patients respectively, $p = 0.3928$. When comparing hemodynamic reactivity within groups by NRS ≤ 3 and NRS > 3 the following changes were registered as shown in Table 4.

Differences in heart rate were registered in the study group between patients with NRS > 3 and patients with NRS ≤ 3 (77.76 ± 17.69 and 68.81 ± 14.46 bpm respectively, $p = 0.0175$). An analysis of HR dynamics at the stages after administration of fentanyl before and during CA in the study group showed a decrease in HR from 80.72 ± 23.84 bpm to 77.76 ± 17.69 bpm which amounted to 3.62 %. Comparisons in the control group revealed differences in DBP between patients with NRS > 3 and patients with NRS ≤ 3 (72.35 ± 6.14 и 75.61 ± 5.15 mm Hg respectively, $p = 0.0338$).

ANI difference was significant between patients with NRS ≤ 3 and NRS > 3. ANIi indicator in 69 (73.4 %) pa-

Table 3. Number of ANI Monitor measurements at the stages of surgery and ANI and NRS values ($n = 94$)

Stages	Number of measurements, M ± SD		Values, Me (Q1–Q3)		NRS, M ± SD
	ANIi	ANIm	ANIi	ANIm	
Before FVC (background)	5.5 ± 1.3	1.5 ± 0.7	75.00 (65.25–79.00)	69.00 (60.00–76.00)	0
FVC	11.0 ± 1.0	3.5 ± 0.7	69.50 (52.00–80.00)	68.00 (59.00–79.00)	0.6 ± 1.8
After fentanyl before CA	4.0 ± 1.0	1.0 ± 0.0	72.00 (61.00–82.00)	67.00 (54.25–80.00)	0
CA	53.0 ± 17.0	13.0 ± 3.0	70.00 (58.50–78.00)	64.50 (58.00–76.00)	1.5 ± 2.4
Hemostasis	12.5 ± 1.9	2.5 ± 0.7	72.00 (60.50–80.00)	68.00 (60.00–80.00)	0

ANI — analgesia and nociception index; CA — catheter ablation; FVC — femoral vein catheterization; NRS — The Numerical Rating Scale.

Table 4. Hemodynamic reactivity in the study groups with pain rating on the NRS ≤ 3 and NRS > 3 ($n = 188$)

Hemodynamic reactivity	NRS > 3 ($n = 45$)	NRS ≤ 3 ($n = 143$)	*p-value*
SBP, mm Hg	126.51 ± 22.75	125.02 ± 14.39	0.6539
DBP, mm Hg	75.24 ± 9.68	75.55 ± 7.52	0.4746
HR, bpm	75.02 ± 14.42	71.08 ± 12.84	0.1701
Main group ($n = 94$)			
Hemodynamic reactivity	**NRS > 3 ($n = 25$)**	**NRS ≤ 3($n = 69$)**	***p-value***
SBP, mm Hg	134.00 ± 27.22	130.78 ± 18.21	0.8438
DBP, mm Hg	77.56 ± 11.38	75.49 ± 9.48	0.4652
HR, bpm	77.76 ± 17.69	68.81 ± 14.46	0.0175*
Control group ($n = 94$)			
Hemodynamic reactivity	**NRS > 3 ($n = 20$)**	**NRS ≤ 3 ($n = 74$)**	***p-value***
SBP, mm Hg	117.15 ± 9.84	119.65 ± 5.78	0.4919
DBP, mm Hg	72.35 ± 6.14	75.61 ± 5.15	0.0338*
HR, bpm	71.60 ± 7.99	73.20 ± 10.80	0.4759

* Statistically significant difference.
DBP — diastolic blood pressure; HR — heart rate; NRS — The Numerical Rating Scale; SBP — systolic blood pressure.

tients of the study group with NRS ≤ 3 amounted to 72.88 ± 10.11, whereas in 25 (26.6 %) patients with NRS > 3 amounted to 54.40 ± 16.09, respectively, p <0.0001. ANIm in 69 patients of the study group with NRS ≤ 3 amounted to 68.30 ± 11.39, whereas in 25 patients with NRS > 3 amounted to 60.64 ± 12.80, respectively, $p = 0.0084$. At CA stage in patients with sinus rhythm and STIAA under superficial/moderate sedation (RASS −1/−2) a statistically insignificant negative correlation was revealed between NRS and ANIi ($r = -0.15$; $p = 0.1370$). ANIi threshold value equal to 56.0 divided patients with NRS > 3 and NRS ≤ 3 with sensitivity 48.00 % and specificity 88.41 %. Area under ROC-curve AUC 0.68 (95 % CI 0.64–0.71; $p < 0.001$) for ANIi in patients with sinus rhythm and STIAA at CA stage under moderate/superficial sedation, which indicates the average quality of information content of the predictive model.

Significant negative moderate correlation between the intensity of pain with NRS and ANI m ($r = -0.37$; $p = 0.0003$) revealed at the stage of ablation in the study group in 94 patients is shown in Figure 2.

ANIm threshold value equal to 56.0 divided patients with NRS > 3 and NRS ≤ 3 with sensitivity 60.00 % and specificity 100.00 %. Area under ROC-curve AUC 0.81 (95 % CI 0.74 — 0.88; $p < 0.001$) for ANIm in patients with sinus rhythm and STIAA at the stage of CA under moderate/superficial sedation, which indicates a very good quality of information content of the predictive model.

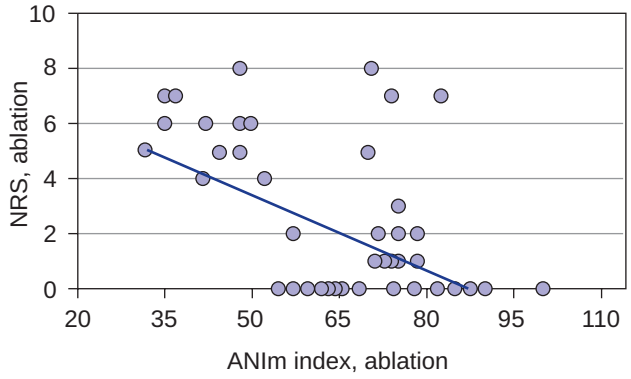

Fig. 2. Correlation between NRS and ANIm at the CA stage ($n = 94$)

* Equal registered ANIm values (points) are displayed as one.

NRS — The Numerical Rating Scale.

The resulting Table 5 shows the thresholds and diagnostic information value of ANI in the detection of pain/nociception in patients at the stages of FVC and CA.

The total dose of fentanyl in the study group was 0.04 ± 0.02 μg/kg/min, whereas in the control group it was 0.05 ± 0.03 μg/kg/min, respectively, $p < 0.001$.

A comparison of the overall satisfaction of patients on Satisfaction with Anesthesia Scale in the study and control groups showed a statistically significant difference between investigated groups (see Table 1). Satisfaction with Anesthesia Scale score in patients of the study group was higher than in patients of the control group (153.96 ± 3.00 and 152.30 ± 5.39 respectively, $p = 0.0494$).

Discussion

Multimodal approaches aimed at maintaining an optimal balance of nociception and analgesia provide a reduction in postoperative nausea and vomiting, residual postoperative sedation and post-operative pain and are crucial for reducing the duration of hospitalization unrelated to the procedure [22]. The choice of using a particular monitoring mainly depends on the clinical context and the overall purpose of monitoring (Appendix).

ANI Monitor allows to identify nociceptive stimuli in conscious patients. In our study a negative moderate correlation between ANI and NRS was found, which meant lower ANI scores with higher NRS values (pain) at the stage of FVC in patients who are conscious under RA. Registration of ANI index at FVC stage under RF ablation showed the presence of pain syndrome with pain intensity according to NRS > 3 in 22 (23.4 %) patients with sinus rhythm. A statistically significant moderate negative correlation was revealed ($r = -0.44$; $p < 0.0001$) between NRS and ANIi index as well as between NRS and ANIm ($r = -0.39$; $p < 0.0001$). With ANI threshold value 51 and 47 in patients with NRS > 3 with area under curve AUC 0.78 and 0.75, which indicates good information content of the predictive model. Similar data were obtained by Boselli et al. in investigation of 200 post-operative patients with ANI threshold values 57 and 48

Table 5. Thresholds and information value of ANI monitor in the detection of pain/nociception ($n = 94$)

Parameters	FVC stage		CA stage under PSA	
	ANIi	ANIm	ANIi	ANIm
ANI threshold values	51	47	56	56
Area under curve ROC-curve AUC	0.78 (0.71–0.85)	0.75 (0.68–0.82)	0.68 (0.64–0.71)	0.81 (0.74–0.88)
Sensitivity, %	68.18	54.55	48.00	60.00
Specificity, %	92.96	100.00	88.41	100.00

CA — catheter ablation; FVC — femoral vein catheterization; PSA — procedural sedation and/or analgesia.

to separate patients with NRS > 3 and > 7 with area under ROC-curve (AUC) 0.86 and 0.91 respectively [23]. However, the data obtained by the researchers vary. Baroni et al. defined correlation between ANI and Numerical Rating Scale (NRS) in patients, who are conscious, as weak [19].

Nociception monitors reflect physiological and pathophysiological responses to surgical stimuli, and therefore can be used to evaluate additional aspects of surgical stress responses [24]. Pain with NRS > 3 at CA stage is registered in 25 (26.5 %) patients. Analysis of hemodynamic reactivity (HR, SBP, DBP) in case of pain in patients with NRS ≤ 3 and NRS > 3 during procedure did not show significant differences, whereas the difference in ANI indicators was significant. These results are consistent with previous studies and confirm the fact that hemodynamic variables are insufficient as a tool for detecting nociceptive stimuli. [25]. The group under investigation was characterized by the presence of STIAA during CA. That was ANIm or 2-minute moving average what made it possible to neutralize STIAA effects (< 1 min). Threshold value for ANIi and ANIm was identical and equal 56 in case of pain with NRS > 3 in patients at the stage of CA under PSA with RASS from −1 to −2, whereas specificity and sensitivity were different. Threshold value 56 for division of patients with NRS ≤ 3 and NRS > 3 at CA stage was obtained as for ANIi as for ANIm but good quality of the predictive model was achieved only for ANIm with AUC 0.81.

The issue of the effectiveness of using ANI index to control the administration of opioids is debatable. In our study titration of the dose of the opioid analgesic fentanyl under ANI control made it possible to significantly reduce opioid consumption in patients of the study group. A meta-analysis of six studies revealed no differences in intraoperative administration of opioids using analgesia under ANI control, whereas a gender analysis of subgroups showed the effectiveness of ANI for reducing opioid doses in female patients [26]. A meta-analysis by Ma et al. showed that intraoperative opioid administration was significantly lower in patients with NOL (Nociception Level index) and PPI (Pupillary Pain Index) monitoring than in patients with standard monitoring; however, no significant differences were found between patients with ANI and SPI (Surgical Pleth Index) control and patients with standard monitoring [25].

The key point of patient satisfaction with anesthesiological support was the absence of pain at all stages of surgery as well as nausea and vomiting and other negative consequences. Satisfaction with Anesthesia Scale Score in patients of the study group with ANI Monitor was higher.

Conclusion

ANI Monitor during CA in patients with sinus rhythm and STIAA was more effective in detecting harmful nociceptive stimuli compared to standard (hemodynamic) monitoring. The use of ANI Monitor to control the fentanyl administration could create conditions for opioid-sparing anesthesia.

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Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. This study was approved by the local Ethical Committee of North-Western State Medical University named after I.I. Mechnikov (reference number: 4-06.04.2022).

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Appendix

Table A1. Monitoring of nociception

Monitoring of nociception	Measurement procedure	Threshold values of nociceptive stimulus for anesthesia	Limitations of the technique in accordance with the instruction of the manufacturer
Multichannel functional near-infrared spectroscopy system (fNIRS) (CW7, Tech En, Massachusetts, USA)	fNIRS wave length 690 and 830 nm and frequency 25 Hz Changes in hemoglobin oxygenation depending on cerebral activity	Nociceptive stimulus changes concentration ± 0,3 mM of oxygenated hemoglobin in certain brain regions (for example, somatosensorial and frontal polar cortex)	Movement artifacts Noise pollution Hemodynamic changes unrelated to brain activity The need for multiple optical sensors
Brain Anesthesia Response Monitor (BARM, Medtech Cortical Dynamics Ltd., Australia)	Electroencephalography	Index of cortical state (CS) and cortical input (CI) and its modifications	The level of nociception during anesthesia is not defined Children's age
Spectral Entropy Monitor (Module E-Entropy to patient's monitors, GE Healthcare, Finland)	Electroencephalography Electromyography	ΔSE-RE less than 10	The level of nociception during anesthesia is not defined Children's age
Monitor for monitoring the depth of anesthesia and analgesia CONOX, QM 7000-M (Fresenius Kabi, Germany)	Electroencephalography Electromyography	qNOX Index 61–99 — a patient prone to reacting to pain stimulation 40–60 — a patient is unlikely to respond to pain stimulation 0–39 — low probability of reaction to pain stimulation	Blockers of neuromuscular transmission Use as the only parameters for the dosage of an anesthetic A history of psychiatric, neurological diseases, drug and alcohol addiction Drugs administration affecting the central nervous system Defibrillation Children's age
Nociceptive flexor reflex (NFR, Neurosoft, Russia)	Electromyography	> 31.9 mA weak nociceptive stimulus (placing laryngeal mask) > 42.9 mA strong nociceptive stimulus (skin incision)	Obesity Myopathies Blockers of neuromuscular transmission Children's age
Pupillometry of analgesia (PRD/PPI IDMED, France)	Pupil size Pupillary light reflex and reflex pupil dilation Response to pain stimulation	Amplitude of pupil dilation (PRD) < 25 % (< 30 % in children) Pupillary pain index (PPI) > 7	Ptosis Heterotropia Anisocoria Aglia Afferent and efferent pupillary defects Neostigmine Droperidol Metoclopramide Clonidine Vasoactive drugs Cholinergic drugs Opioid analgesics (high doses)
The method of measuring skin conductivity (Med-Storm Innovations, AS, Norway)	Amplitude of fluctuations SC (ASCF) and number of fluctuations SC per second (NFSC) depending on the moisture percentage of the skin	A value of 0–0.07 corresponds to WBFS 0 (No pain), within 0.13–0.21 corresponds to WBFS 1–3 (Mild pain), 0.21–0.26 — WBFS 4–5 (Moderate pain), 0.26–0.33 — WBFS 6–8 (Severe pain) and 0.40–0.7 — WBFS 8–10 (Intense pain)	Skin temperature Ambient temperature Cholinergic and anticholinergic drugs Decreased sympathetic activity during deep anesthesia Children's age

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Monitoring of nociception	Measurement procedure	Threshold values of nociceptive stimulus for anesthesia	Limitations of the technique in accordance with the instruction of the manufacturer
Surgical plethysmographic index (SPI, GE Healthcare, Finland)	SPI combines the normalized photoplethysmographic wave aplitude (PPGA) and normalized heart beat interval (HBI) into algorithm that displays the SPI values	SPI < 20 — low level of surgical stress > 50 — high level of surgical stress	Antiarrhythmics Cardiostimulator Chronotropic drugs Ephedrine Hypertension Poor signal and weak plethysmographic pulse Tachycardia Patient's position Severe hypothermia Cardiac arrhythmia Can't be used for other areas of the body except the finger Children's age
Monitor PMD-200™ with NOL index (Medasense Biometrics Ltd., Israel)	Pulse rate, pulse rate variability (0.15–0.4 Hz) Photoplethysmographic wave amplitude (PPGA) Number of fluctuations per second (NFSC) Accelerometer (movement) Peripheral temperature	NOL index > 25 may indicate a strong nociceptive reaction and the need for analgesia NOL between 0–25 assumes adequate analgesia NOL < 10 with surgical stimulation may indicate excessive analgesia	Chronotropic drugs Vasoactive drugs Children's age
Monitoring system «ANI Monitor» for anesthesiology, intensive care (Metrodoloris SAS, France)	High frequency range of HRV and respiratory arrhythmia	ANI index < 50 high probability of nociceptive stimulus > 80 low probability of nociceptive stimulus	Atrial fibrillation Cardiostimulator (some types) Heart transplantation (period of EC): Drugs affecting cardiac sinusoidal activity (atropine) Respiratory rate less than 9 cycles/min Asphyxia Variable respiratory volume during measurement, i.e. 64-x s) Interrupted respiration
CARDEAN Monitor (Alpha-2 Ltd, Lyon, France)	Heart rate Non-invasive blood pressure	CARDEAN index > 60 somatosympathetic reflex and high probability of nociceptive stimulus ≤ 60 vagus nerve baroreflex and low probability of nociceptive stimulus	Cardiac arrhythmia Inotropic drugs Chronotropic drugs Vasoactive drugs

***Note*:** ANI — analgesia and nociception index; ASCF — amplitude of fluctuations per second; BP — blood pressure; CARDEAN index — The CARdiovascular Depth of Analgesia index; CI — cortical input; CS — composite cortical state; EC — Extracorporeal circulation; HBI — normalized heart rate interval; HR — heart rate; HRV — heart rate variability; NFR — nociceptive flexor reflex; NFSC — number of fluctuations per second; NOL — nociception level; PPGA — photoplethysmographic wave amplitude; PPI — pupillary pain index; PRD — amplitude of pupil dilation; RE — reaction entropy; SE — state entropy; SPI — surgical plethysmographic index; WBFS — The Wong–Baker Faces Pain Rating Scale.