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"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY IN BUCHAREST
GRADUATE SCHOOL OF MEDICINE STUDIES
MEDICINE

SUMMARY

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UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
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THE ROLE OF ERECTOR SPINAE PLANE BLOCK AS A REGIONAL ANALGESIC TECHNIQUE IN CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS

SUMMARY OF THE PhD THESIS

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CONTENTS

INTRODUCTION

Multimodal analgesia is a fundamental intervention in enhanced recovery after surgery (ERAS) protocols. In non-cardiac surgery, neuraxial regional anaesthesia (RA) represents an attractive adjuvant analgesic with minimal risks, capable of significantly reducing perioperative opioid consumption. However, in cardiac surgery with cardiopulmonary bypass, its use is contraindicated due to the risk of spinal hematoma[1]–[3].

The use of ultrasound has rekindled interest in using regional anaesthesia for cardiac surgery with therapeutic anticoagulation. Ultrasound guidance has allowed for targeted administration of local anaesthetics (LA) in various muscular interfascial planes where the nerves of interest have their trajectory.

In cardiac surgery with cardiopulmonary bypass, special attention has been given to the erector spinae plane block (ESPB)[4], [5]. Its incorporation into the perioperative anaesthetic regimen has brought benefits such as reducing opioid consumption and the need for mechanical ventilation, improving analgesia, reducing the incidence of chronic pain at 6 months, and shortening hospitalization time[6].

Unlike classical regional anaesthesia techniques, ESPB exhibits a variable antinociceptive effect, dependent on the technique used, the substances utilized (i.e., type of local anaesthetic, adjuvants such as dexamethasone, dexmedetomidine), and the specific interfascial anatomy of each patient. Furthermore, its instantaneous intraoperative efficacy is inadequately predicted by traditional sensory skin testing[7]. The direct implication of these considerations is the need for real-time monitoring of intraoperative nociception. The PMD-200^{TM} monitor (Medasense Biometrics Ltd., Ramat Gan, Israel) derives the NOL index (i.e., nociception level index) by integrating photoplethysmographic, thermal, inertial, and electric resistive signals[8]. Regardless of the type of anaesthesia (i.e., general, regional, or mixed), the NOL index reflects the nociception-antinociception balance specific to each patient at every moment during surgery. As a result, based on this continuously updated and real-time index, opioid administration can be individualized and synchronized according to intraoperative nociceptive stimuli.[9].

The research described in this thesis aimed to explore for the first time the role of BPMES in cardiac surgery with sternotomy as part of an antinociceptive anaesthetic strategy that included the NOL index.

I. GENERAL PART

1. Enhanced recovery after cardiac surgery

1.1. General principles

Starting in 1995, early postoperative rehabilitation (ERAS) protocols have changed the way the perioperative period is managed. In colorectal surgery, Bardram et al. successfully introduced a multidisciplinary and multimodal approach aimed at optimizing patient physiological parameters before, during, and after surgery[10]. Since then, ERAS techniques have evolved and diversified, expanding from general surgical specialties to cardiothoracic surgery[11].

1.2. Principles of perioperative analgesia

The main goal of all ERAS strategies is to ensure adequate pain therapy and control of intraoperative nociception, regardless of the surgical specialty. In cardiac surgery with cardiopulmonary bypass, opioid analgesics remain the main drugs for pain management[12]. However, they have several drawbacks, such as nausea, vomiting, itching, respiratory depression and apnoea, delirium, sedation and drowsiness, prolonged mechanical ventilation, hyperalgesia, dependence, and ileus, which can delay postoperative recovery and increase medical costs. Thus, the current paradigm is focused on multimodal management of analgesia and nociception, with an emphasis on reducing opioid consumption and associated side effects.[13].

Median sternotomy remains the most common surgical approach in cardiac surgery, due to its ability to provide adequate exposure of the heart and intrathoracic vessels[14]. However, this technique also has disadvantages, such as postoperative pain and discomfort, often aggravated by the use of thoracic or mediastinal drains.

RA techniques represent a very useful complementary method, being able to offer efficient analgesia while contributing to the reduction of opioid use. Regarding cardiac surgery with sternotomy, RA techniques must first ensure adequate analgesia of the anterior and lateral chest wall, and secondly, of the posterior chest wall.

2. Regional anaesthesia and analgesia techniques in cardiac surgery with sternotomy

2.1. Classic techniques

Traditional sensory and motor block techniques of the thoracic wall include epidural anaesthesia (EA) and anatomical surface landmark-based paravertebral block (PVBana). Although both techniques are known for their excellent nerve blockade quality, EA and PVBana have not been widely implemented in cardiac surgery with cardiopulmonary bypass due to the increased risk of serious complications. Among these, epidural spinal hematoma (ESH) has been reported with an incidence of 1:1500.[2].

In cardiac surgery, minimizing the risks associated with (over)therapeutic anticoagulation during cardiopulmonary bypass (CPB) is more important than maximizing analgesia. Therefore, classical RA techniques remain formally contraindicated in this context.[15].

2.2. Modern techniques

Ultrasound has allowed the reinvention of ALR techniques. Due to an exceptional real-time anatomical resolution, ultrasound guidance has shifted peripheral nerve blocks from the perineuraxial space to the muscular interfascial planes, allowing the development of chest-wall interfascial plane blocks (CWFPB). CWFPB can be distributed along a common postero-anterior arc that starts from the spinal line and ends at the sternal line. The extent of the sensory block is inversely proportional to the distance between the puncture site and the spinal line, and the sympatholytic effects are characteristic only of those BTPF located in the immediate vicinity of the paravertebral space (PVS).

CWFPB come in three types 1) anteromedial, such as the pectointercostal block and the thoracic transverse muscle plane block, provide ipsilateral somatic anaesthesia of the parasternal region; 2) anterolateral, such as the pectoral muscle plane blocks and the serratus muscle plane block (SPB), produce ipsilateral somatic anaesthesia of the anterolateral thorax; 3) posterior, such as the retrolaminar block, mid-point transverse process to pleura block, intercostal/paraspinal block, rhomboid/sub-serratus block and ESPB, produce a variable combination of autonomous block and ipsilateral hemianesthesia[5].

The common denominator of posterior CWFPB is represented by the posterior administration of LA below the costotransverse ligament (CTL). Due to the permeability of

CTL to LA, posterior CWFPB penetrate into the PBS and exhibit a similar action to PVB, which is why they have been called "paraspinal blocks" or "PVB by proxy"[16], [17].

Among the posterior CWFPB, ESPB has been the most intensely studied experimentally and clinically. The target for LA deposition is the plane located between the erector spinae muscle and the tip of the T5 thoracic transverse process[5]**.** In cardiac surgery with sternotomy, this block has been attributed with a series of benefits, such as reducing perioperative opioid consumption, shortening the length of stay in the intensive care unit (ICU), and improving postoperative analgesia[18]–[21].

2.3. Complications of modern techniques

Ultrasound guidance has dramatically reduced the number of complications. Significant autonomic block and hypotension have been reported sporadically, especially in the case of posterior CWFPB[22]. Therapeutic anticoagulation and antiplatelet treatment are no longer an absolute contraindication for CWFPB[23], [24]. Pneumothorax is only a theoretical complication of CWFPB. In a retrospective observational study including 308 patients and 479 ESPB procedures, Tulgar et al. recorded a zero incidence of pneumothorax[25]. On the other hand, motor block was observed in one case, and four other patients developed minimal neurological symptoms suggestive of systemic LA toxicity. According to current research, it can be concluded that CWFPB and particularly ESPB are a safe and effective option for multimodal analgesia.

2.4. Principles and practice of regional block monitoring

Traditionally, nerve block assessment is performed before general anaesthesia induction through cutaneous sensory tests. However, paradoxically, intraoperative nociception and pain can coexist with a completely successful preoperative sensory block, or conversely, they can be absent despite a moderately successful preoperative sensory block[7], [26]. Therefore, cutaneous sensory tests cannot accurately predict intraoperative nociception levels. Monitoring intraoperative nociception in real-time can overcome the shortcomings of cutaneous sensory tests.

The use of a nociception monitor has the following advantages: 1) real-time evaluation of nerve block efficacy during periods of significant intraoperative nociceptive load (e.g., skin incision, sternotomy); 2) individualization and synchronization of opioid administration according to the specific needs of each patient, at every moment of the surgical intervention.

ORIGINAL PART

3. General hypotheses and objectives

General hypotheses

The perioperative benefits of ESPB in cardiac surgery with sternotomy are variable and may include: 1) reduced intraoperative and postoperative opioid consumption; 2) improvement of pain scores; 3) decreased number of days requiring mechanical ventilation; 4) accelerated recovery and reduced length of hospital stay[18], [27]–[29].

General objectives

The aim is to evaluate the perioperative clinical impact of preemptive ESPB as an adjuvant to standard general anaesthesia in cardiac surgery with sternotomy and cardiopulmonary bypass. This objective will be achieved by comparing standard general anaesthesia with the combination of preemptive ESPB and standard general anaesthesia, using a modern method to objectify the intraoperative nociception-antinociception balance.

The perioperative clinical impact of BPMES could be of interest in the following areas:

1) intraoperative and postoperative opioid consumption.
2) duration of mechanical ventilation.
3) intraoperative and postoperative consumption of inotropic and vasopressor drugs.
4) quality of postoperative analgesia.
5) postoperative mobilization.
6) adverse effects of opioid medication use.
7) length of hospital stay.
8) cardiovascular and respiratory complications.

Other objectives of interest would be:

9) evaluation of the side effects and complications associated with the use of ESPB as an adjuvant to standard general anaesthesia.
10) quality of intraoperative nociception control.
11) predictive value of traditional vital signs (e.g., heart rate, blood pressure) for identifying a nociception-antinociception imbalance.

4. The role of the erector spinae plane block with nociceptive control in open cardiac surgery (Study I)

4.1. Working hypothesis and specific objectives

In this randomized clinical study, the author hypothesized that within an objective antinociceptive strategy based on the NOL index, the addition of bilateral BPMES to standard general anaesthesia will reduce perioperative opioid consumption, improve the quality of postoperative analgesia, accelerate postoperative rehabilitation, and have a favourable impact on perioperative vasoactive medication use, without significant clinically adverse effects[30].

The primary objective was the total intraoperative consumption of fentanyl.

The secondary objectives were as follows: **1)** pre-CPB intraoperative fentanyl consumption (i.e., recorded from induction to CPB initiation); **2)** cumulative morphine consumption at 24 and 48 hours after admission to the ICU; **3)** number of patients who did not require morphine at 48 hours after admission to the ICU; **4)** time to first dose of morphine; **5)** postoperative analgesia quality recorded as a Numeric Rating Scale (NRS) at 0, 6, 12, 24, and 48 hours after extubation and at 1 hour after chest tube removal, respectively; **6)** time to extubation; **7)** number of patients extubated at 2 hours after admission to the ICU; **8)** intraoperative and postoperative norepinephrine consumption at 12 hours after admission to the ICU; **9)** time to complete norepinephrine weaning; **10)** number of patients weaned off norepinephrine at 2 and 12 hours after admission to the ICU; **11)** intraoperative and postoperative dobutamine consumption at 12 hours after admission to the ICU; **12)** time to complete dobutamine weaning; **13)** number of patients weaned off dobutamine at 2 and 12 hours after admission to the ICU; **14)** serum lactate at 2 hours after admission to the ICU; **15)** echocardiographically measured cardiac output at 2 hours after admission to the ICU; **16)** total hospitalization duration; **17)** ICU length of stay; **18)** incidence of opioid-specific adverse effects (i.e., pruritus, respiratory depression, postoperative nausea and vomiting) recorded either until discharge from the ICU or until 72 hours after ICU admission, whichever comes first; **19)** incidence of postoperative atrial fibrillation either until discharge from the ICU or until 72 hours after ICU admission, whichever comes first; **20)** incidence of postoperative delirium either until discharge from the ICU or until 72 hours after ICU admission, whichever comes first.

4.2. Material and method

4.2.1. Study design and patient enrolment

This prospective, randomized (1:1), single-centre, open-label clinical study was conducted from December 2019 to May 2021 and included adult patients who required open heart surgery with cardiopulmonary bypass (***Figure 4.1.***). The research was in accordance with the Declaration of Helsinki[31] and approved by the Ethics and Study/Grant Review Committee at the Emergency Institute for Cardiovascular Diseases "Prof. Dr. C.C. Iliescu" in Bucharest, Romania (2019.07.26/18750). The study was registered on ClinicalTrials.gov with the identification number NCT04338984, and the original study protocol is available online[32].

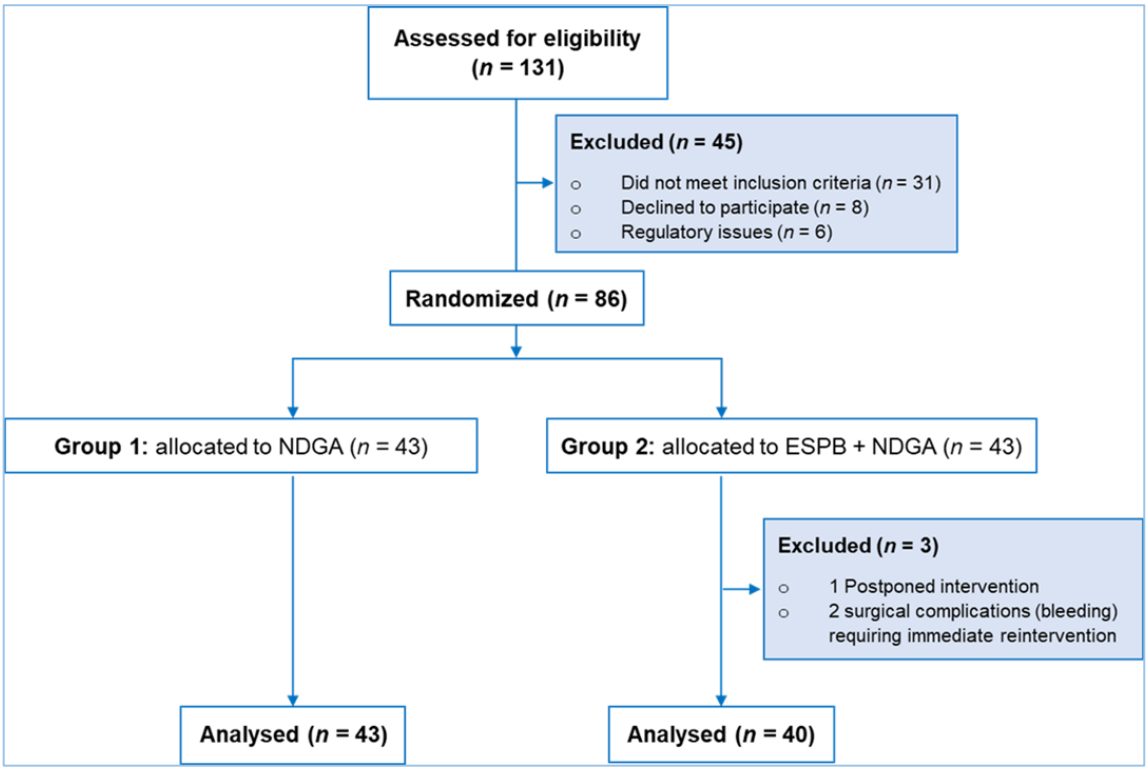

Figure 4.1. CONSORT flow diagram of enrolled patients.

Abbreviations: ESPB-NDGA, standard general anaesthesia with NOL-directed antinociceptive strategy combined with erector spinae plane block; CONSORT, Consolidated Standards of Reporting Trials; NDGA, standard general anaesthesia with NOL-directed antinociceptive strategy.

The inclusion criteria were as follows: 1) age between 18 and 75 years; 2) elective cardiac surgery with sternotomy and cardiopulmonary bypass; 3) sinus rhythm.

The exclusion criteria were as follows: 1) allergic reaction to drugs and substances used in the study; 2) body mass index greater than 35; 3) abnormal coagulation; 4) emergency or reoperation cardiac surgery; 5) American Society of Anesthesiologists (ASA) anaesthesia risk class greater than 4; 6) preoperative pharmacological or mechanical cardiocirculatory support; 7) severe left ventricular dysfunction defined as an ejection fraction less than 30%.

4.2.2. Anaesthesia management

All patients benefited from the standard monitoring package, which included 12-lead electrocardiographic monitoring and continuous analysis of the ST segment, pulse oximetry, non-invasive blood pressure cuff, central and peripheral venous cannula, arterial cannula, bispectral sensor (BIS), thermometry, urinary catheterization, and, for instantaneous monitoring of intraoperative nociception-antinociception balance, NOL sensor.

The author of this manuscript performed all the ESPB interventions. The procedure was described in detail elsewhere. [30]. The preoperative evaluation of the efficacy of ESPB using classical cutaneous sensitivity tests was not performed due to intraoperative monitoring of the NOL index. The mixture administered unilaterally was composed of 1.5 mg/kg of 0.5% ropivacaine and 8mg/20mL of dexamethasone.

After the ESPB procedure, general anaesthesia was induced and maintained with either sevoflurane outside CPB periods or with propofol during CPB periods.

During the intraoperative period, both groups were monitored using the PMD-200^{TM} monitor. The optimal nociception-antinociception balance was defined as an NOL index between 10 and 25 (i.e., $10 \leq$ NOL index ≤ 25) on a scale from 0 to 100, where 0 indicates the absence of nociception, and 100 indicates extreme nociception.[30]. Due to the fact that the NOL index is based on photoplethysmographic and electrocardiographic signals, its monitoring was only possible before the initiation of CPB. In both groups, fentanyl administration rules were based on the NOL index and were as follows: 1) after induction, initiate a continuous infusion of fentanyl 2 µg/kg/h; 2) if the NOL index > 25 for more than 60 seconds, increase the infusion rate by 0.5 µg/kg/h and administer a bolus of 1 µg/kg; 3) if the NOL index < 10 for more than 60 seconds, decrease the infusion rate by 0.5 µg/kg/h; 4) after a dose change, allow an observation period of 3 minutes before changing the dose again; 5) stop the fentanyl infusion when it decreases to 0.5 µg/kg/h and the NOL index ≤

25 for more than ten minutes. After the initiation of CPB, fentanyl administration aimed to maintain a mean arterial pressure within ±15% of the mean arterial pressure recorded under ideal nociception-antinociception balance conditions (i.e., 10 ≤ NOL index ≤ 25).

After the surgical intervention, extubation was considered based on the fulfilment of a minimum set of criteria: 1) normothermia (temperature > 36°C); 2) adequate tissue perfusion under dobutamine ≤ 5 µg/kg/minute; 3) systemic mean perfusion pressure ≥ 60 mmHg; 4) normal coagulation profile and absence of active bleeding; 5) adequate gas exchange defined as normocapnia and a partial pressure of oxygen/inspired oxygen fraction ratio greater than or equal to 250 mmHg at a positive end-expiratory pressure < 7 mbar.; 6) sustained respiratory effort (i.e., tidal volume ≥ 6 ml/kg with a respiratory rate of 10-20/minute under a support pressure ≤ 7 mbar); 7) adequate cough reflex and wakefulness.

After extubation, the quality of analgesia was quantified using the NRS (i.e., numeric rating scale). For NRS scores ≥ 4, intravenous morphine 0.03 mg/kg was administered.

4.2.3. Statistical analysis

The data collected in this study were electronically recorded and subsequently analysed using NCSS 2022 Statistical Software (NCSS, v22.0.2, LLC, Kaysville, UT, USA). Visual inspection and the Shapiro-Wilk test were applied to test the normality of quantitative variables. Quantitative variables were presented as mean ± SD (standard deviation) if normally distributed or as median and interquartile range (IQR, Q_{25}-Q_{75}) if non-normally distributed. Categorical variables were expressed as absolute values (n) and percentages [%]. For the analysis of the primary objective, the Mann-Whitney U test was applied using a superiority margin (δ) of 1.4 µg/kg/hour. For the rest of the nonparametric quantitative secondary objectives, the Mann-Whitney U test was applied as such. The chi-square test (X^2) or Fisher's exact test was applied to resolve the contingency of binary secondary objectives and adverse effects with the two study groups. The Kaplan-Meier curve was applied to analyse "time-to-event" data. Comparison of the corresponding curves of the two groups was performed with the Mantel-Cox log-rank test. For all comparisons, a bilateral probability (p) < 0.05 was used.

4.3. Results

No significant differences were found between the two groups regarding demographic data, dynamic and technical characteristics of surgical interventions, medical history,

preoperative surgical and anaesthetic risk, preoperative cardiac function, and intraoperative monitoring data, as well as preoperative laboratory analyses.[30].

4.3.1. Perioperative opioid consumption and quality of analgesia

In an antinociceptive strategy based on the NOL index, BPMES significantly reduced perioperative consumption of fentanyl and morphine and the number of patients requiring morphine at 48 hours postoperatively. Additionally, BPMES improved the quality of analgesia as assessed by NRS scores at extubation, 1 hour after drain removal, and at 6, 12, 24, and 48 hours after extubation. Furthermore, BPMES prolonged the time until the first dose of morphine. (***Table 4.1.***, ***Figure 4.2.***)

Table 4.1. Perioperative opioid consumption and quality of analgesia.

Objectives		**Control** (n = 43)	**ESPB** (n = 40)	***p***
Perioperative opioid consumption				
Intraoperative Fentanil	Total, µg/kg/hour	4.5 (3.8-5.5)	1.2 (1.1-1.5)	< 0.001[#]
	Pre-CEC, µg/kg/hour	7.2 (5.7-9)	3.3 (2.7-4.5)	< 0.001
Postoperative Morphine	0-24 ore, µg/kg	46.5 (37-76.9)	0 (0-40)	< 0.001
	0-48 ore, µg/kg	60.6 (40-95.7)	22.1 (0-40.4)	< 0.001
Pts. without morphine at 48 hours		3 [7]	19 [47.5]	< 0.001
Time to first dose of morphine		345 (67.5-795)	540 (285-1110)	0.008
Quality of postoperative analgesia [§]				
NRS score at extubation		2 (2-4)	1 (0-2)	< 0.001
NRS score 6 hours after extubation		4 (3-5)	2 (1-3)	< 0.001
NRS score 12 hours after extubation		4 (3-4)	2 (1-3)	< 0.001
NRS score 24 hours after extubation		3 (2-4)	2 (0-3)	< 0.001
NRS score 48 hours after extubation		2 (1-4)	1 (1-2)	0.001
NRS score 1 hour after drain removal		2 (1-3)	2 (1-3)	0.261

The data are presented as mean ± SD, median (IQR), or n [%]

[#] The statistical significance of the primary endpoint (i.e., total intraoperative fentanyl) was determined using the Mann-Whitney U test for a superiority margin (δ) of 1.4 µg/kg/hour.

[§] NRS scores were assessed during bed mobilization.

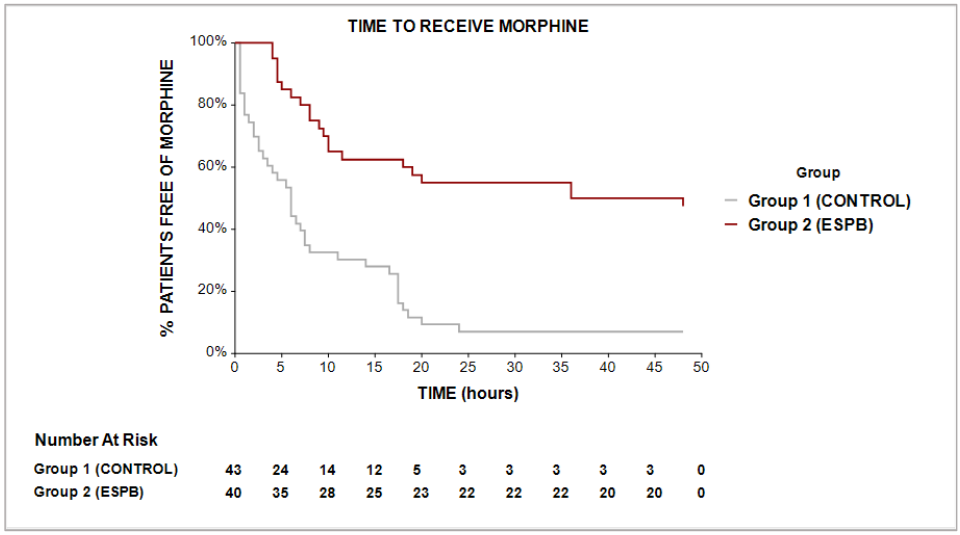

Figure 4.2. Kaplan-Meier diagram – number of patients who required morphine. Proportional Cox risk ESPB versus Control was 0.3; 95% CI: 0.18-0.50; $p < 0.001$.

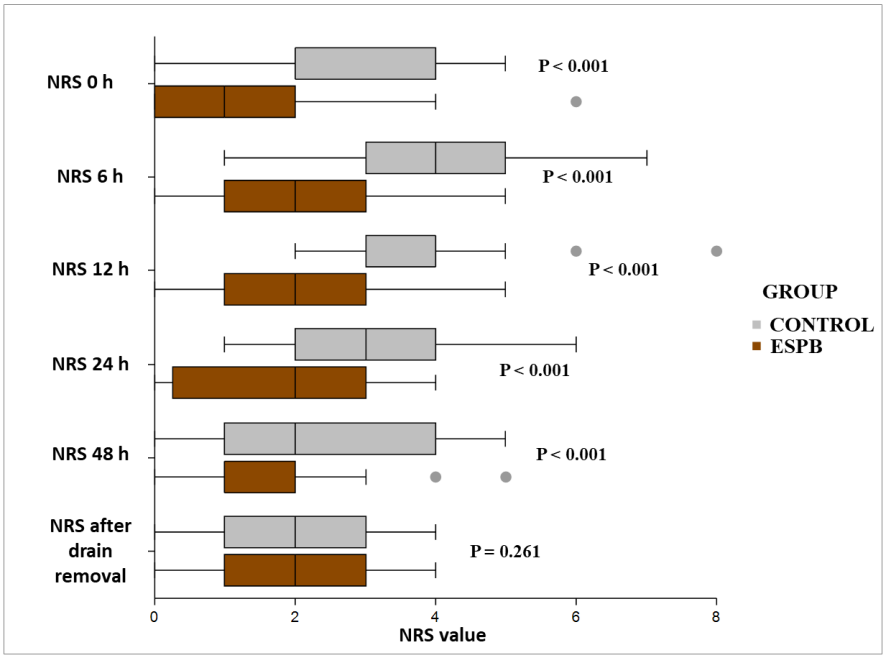

Figure 4.3. Inter-group comparison for quality of postoperative analgesia.

4.3.2. Enhanced recovery after surgery indicators

BPMES significantly improved all mechanical ventilation weaning parameters, reduced postoperative norepinephrine consumption, and accelerated norepinephrine weaning in the postoperative period (***Table 4.2***.). BPMES did not influence hospital stay durations and did not modify perioperative consumption of dobutamine or tissue perfusion indices (***Table 4.3.***).

Table 4.2. Indicators of enhanced recovery after surgery.

Objectives		Control (n = 43)	ESPB (n = 40)	*p*
Weaning of mechanical ventilation				
Time to extubation, minutes		360 (285-510)	90 (60-105)	< 0.001
No. [%] extubated-2 h postoperatively		0[0]	35 [87.5]	< 0.001
Weaning of vasopressor support				
Noradrenaline	Intraoperative dose, µg/kg/h	1.1 (0.6-2.2)	1.9 (0.6-3.1)	0.147
	Postoperative dose-12 h, µg/kg	9 (0-32.3)	0 (0-1.3)	< 0.001
	Time to weaning, minutes	240 (0-720)	0 (0-60)	< 0.001
	No. [%] weaned-2 h postop.	20 [46.5]	35 [87.5]	< 0.001
Dobutamine	Intraoperative dose, µg/kg/h	0 (0-62.3)	27.8 (0-43.2)	0.178
	Postoperative dose-12 h, µg/kg	0 (0-9.5·10^{-12})	0 (0-818.3)	0.146
	Time to weaning, minutes	0 (0-7.2·10^{-12})	45 (0-420)	0.074
	No. [%] weaned-2 h postop.	33 [76.7]	26 [65]	0.238
Length of stay				
ICU stay, days		2 (2-3)	3 (2-4)	0.102
Hospital stay, days		7 (7-9)	8 (7-9.75)	0.598

The data are presented as mean ± SD, median (IQR), or n [%]

Table 4.3. Indicators of tissue perfusion.

Objectives	Control (n = 43)	ESPB (n = 40)	*p*
Lactate-2 h postop., mmol/L	1.6 (1.3-2.2)	1.8 (1.4-2.5)	0.344
Cardiac output-2 h postop., L/min	2.4 (2.3-2.5)	2.5 (2.2-2.6)	0.482

The data are presented as mean ± SD, median (IQR), or n [%].

4.3.3. Postoperative complications and adverse effects

The incidence of postoperative complications and adverse reactions is reported in ***Table 4.4.*** It is important to mention that in the ESPB group, no secondary adverse effects of opioids were recorded. ESPB did not lead to the occurrence of specific adverse effects or complications such as hematoma, pneumothorax, or systemic toxicity in AL.

Table 4.4. Postoperative complications and adverse effects.

Events		**Control** (n = 43)	**ESPB** (n = 40)	***p***
Opioid-related				
Pruritus		1 [2.3]	0 [0]	NS
Nausea and vomiting		3 [7]	0 [0]	NS
Respiratory depression		1 [2.3]	0 [0]	NS
Cardiovascular				
Postoperative atrial fibrillation		4 [9.3]	5 [12.5]	NS
Neurological				
Delirium	Hypoactive	3 [7]	2 [5]	NS
	Hyperactive	0 [0]	0 [0]	-
	Mixed	0 [0]	0 [0]	-
ESPB-related				
Hematoma		-	0 [0]	-
LAST		-	0 [0]	-
Pneumothorax		-	0 [0]	-

The data are presented as mean ± SD, median (IQR), or n [%].

NS, statistically non-significant; LAST, local anaesthetic systemic toxicity.

4.3.4. Indicators of block efficacity

After skin incision, two patients in the ESPB group experienced nociception with an NOL index >25 and required rescue fentanyl according to the analgesic protocol. After sternotomy and sternal retraction, one of them and two other patients with the block required rescue fentanyl according to the NOL index. Until the initiation of CPB, the three patients regained nociception control (i.e., NOL index <25). The remaining patients with ESPB had an appropriate nociception-antinociception balance from the beginning.

4.3.5. Indicators of block feasibility

The median (IQR) execution time of the ESPB was 8 (6.25-9) minutes. There were no significant technical difficulties.

4.4. Discussion

Several aspects need to be addressed before drawing conclusions. A first aspect is the analgesic efficacy of BPMES for median sternotomy. The results of our study demonstrate a circumferential analgesic effect of ESPB.[33]. Several other clinical studies have demonstrated a similar effect[18], [19], [27], [29], [34], consistent with the mechanism proposed initially by Forero et al.[33]. However, a few experimental and anatomical studies have refuted the unilateral paramedian effect of BPMES[35], [36]. Reconciliation of these contradictory observations becomes possible by appreciating that the area of the unilateral BPMES sensory block underestimates that of bilateral BPMES, as the parasternal area is redundantly innervated by the contralateral nerve fibres.[7]. The second aspect concerns the monitoring of nociception. Uniquely, this study used the NOL index from anaesthesia induction until the initiation of CPB. The pre-CPB period sums up the most important nociceptive stimuli, such as skin incision, sternotomy, and sternal retraction, becoming a dynamic nociceptive test to which patients respond individually and specifically, with or without blockade. Consequently, the use of the NOL index during this nociceptive avalanche allows for the evaluation of block efficacy and the individualization of opioid administration. The third aspect concerns the quality of postoperative analgesia and postoperative opioid consumption. The most important determining factor is the BPMES strategy, single-shot puncture versus interfascial catheter. How can we simultaneously achieve the advantages of both techniques, technical simplicity, and prolonged effect? For this purpose, the author of this study used dexamethasone 8mg/20 mL as an adjuvant to ropivacaine 0.5%.[37]–[39]. The fourth aspect is accelerated extubation, most likely the consequence of reducing intraoperative fentanyl consumption. Other studies that used fentanyl have reported similar results [18], [29]. Conversely, ESPB did not influence the duration of mechanical ventilation after sufentanil anaesthesia[27]. In a comparative study, Ahonen et al. reported that the latest extubation was achieved after fentanyl (i.e., on average 2 hours after sufentanil and 3 hours after alfentanil)[40]. In conclusion, the beneficial effects of BPMES in cardiac surgery will be significant, particularly for anaesthetic protocols that use fentanyl and less evident for those using new-generation short-acting opioids such as sufentanil, remifentanil, and alfentanil. The fifth relevant aspect of our study is the reduction in norepinephrine consumption, demonstrating that BPMES can be used as a hemodynamic tool with decatecholaminizing effects.

The main limitations of this study were the open design and the monocentric enrolment of patients.

5. Nociceptive control in cardiac anaesthesia with and without erector spinae plane block (Study II)

5.1. Working hypothesis and specific objectives

In this post-hoc analysis of the primary study, the author hypothesized that due to the preemptive antinociceptive action of ESPB, the ESPB group would have better control of intraoperative nociception compared to the Control group.[41].

The quality of intraoperative nociception control was continuously quantified in real-time based on the NOL index. For comparison purposes, NOL index measurements were taken at five different time points: pre-incision (T1), post-incision (T2), pre-sternotomy (T3), post-sternotomy (T4), and pre-CPB (T5). Pre-event NOL values were determined as the average of three equally spaced NOL values (i.e., 10-second interval) taken within a 30-second window before the event. Post-event NOL values were determined as the average of three equally spaced NOL values (i.e., 10-second interval) taken within a 30-second window that started 60 seconds after the event (***Figure 5.1.***).

The primary objective was the mean value of the NOL index across the five moments of interest.

The secondary objectives were as follows: 1) the values of the NOL index at the five moments of interest; 2) the incidence of an inadequate nociception response quantified by the number of patients in each group who exhibited an NOL index > 25 at the five moments.

5.2. Material and method

5.2.1. Study design and patient enrolment

This post-hoc analysis included all patients from the primary analysis (***Chapter 4***) and two additional patients from the ESPB group who were initially excluded due to immediate postoperative complications requiring emergency reintervention. Therefore, we analysed 43 patients in the Control group and 42 patients in the ESPB group[41].

5.2.2. Anaesthesia management

The detailed methodology of the anaesthetic procedures was previously described (***Subchapter 4.2.2.***). ***Figure 5.1.*** shows the schema of the NOL-oriented analgesic protocol. Monitoring of the NOL index started with induction and ended at the initiation of CPB.

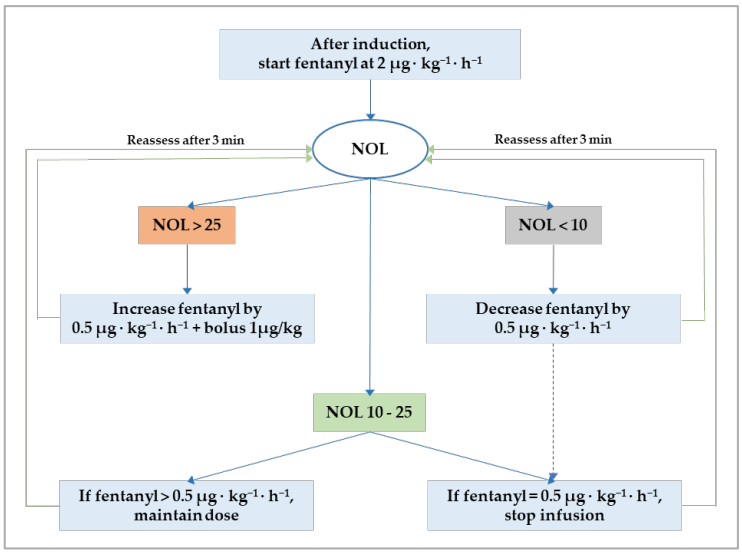

Figure 5.1. Decisional tree for fentanyl administration.

5.2.3. Statistical analysis

In a manner analogous to the primary study[30], all statistical analyses of this secondary study were performed using NCSS 2022 Statistical Software (NCSS, v22.0.2, LLC, Kaysville, UT, USA)[41]. The dynamic course of NOL index values over the 5 moments of interest was studied using a mixed model for repeated measures (MMRM) with random intercepts for patients. The fixed effects of the MMRM were the study group (i.e., Control versus ESPB), the moment of interest, and the interaction between study group and moment of interest. The intra-group variance-covariance matrix was set to a random diagonal pattern. The MMRM test produces mean values ± SE (standard error) adjusted by the least squares adjustment (LSA) method. For non-MMRM tests, the bilateral critical probability was set to 0.05. For the MMRM test, *the adjusted-Bonferroni p-value* was reported in the thesis text. It was calculated by multiplying *the observed p-value* by the number of observations made. Therefore, for a number of observations equal to 10, statistical significance was reached either if *the adjusted p-value* was less than 0.05 or if *the observed p-value* was less than 0.005.

5.3. Results

This post-hoc analysis included 43 patients in the Control group and 42 patients in the ESPB group[41]. Demographic data, surgical technical characteristics, blood group distribution, chronic medication treatment, and preoperative risk remained balanced[41]. The MMMR test allowed: 1) an inter-group comparative analysis, i.e., a comparison between the Control group and the BPMES group for each of the 5 moments of interest, as well as

for the average of the 5 moments of interest; 2) an intra-group comparative analysis (i.e., T1 versus T2/T3/T4/T5, T2 versus T3, T3 versus T4, T4 versus T5).

5.3.1. NOL objectives

The MMMR analysis of the temporal profile of the NOL index revealed significant fixed effects for group, time, and the interaction between group and time ($p < 0.001$).

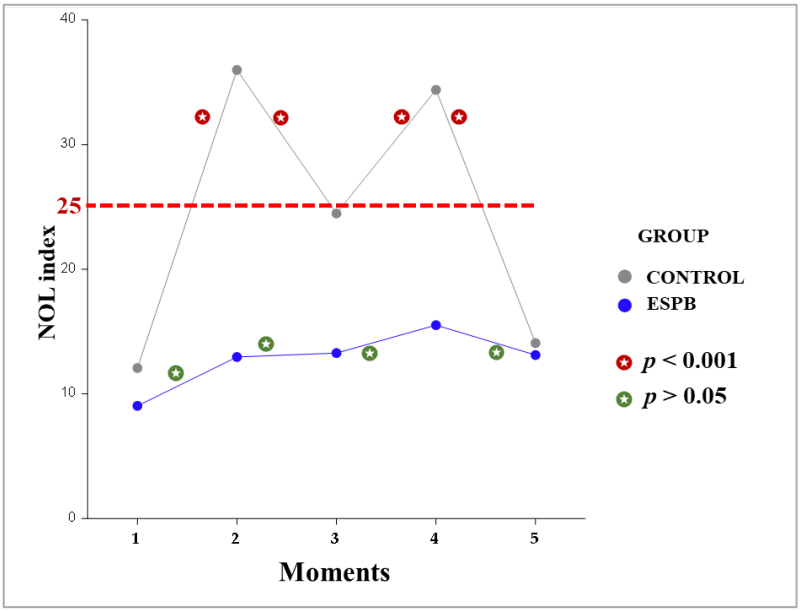

Figure 5.2. NOL index temporal profile

Table 5.1. Values of the NOL index by group and moment.

Group, Moment	LSA mean	SE	95% CI Inf. limit	95% CI Sup. limit	Degrees of freedom
Control, 1	12.07	1.47	9.18	14.97	394.8
Control, 2	35.97	1.47	33.08	38.87	394.8
Control, 3	24.44	1.47	21.54	27.33	394.8
Control, 4	34.39	1.47	31.50	37.29	394.8
Control, 5	14.04	1.47	11.15	16.94	394.8
ESPB, 1	9.07	1.49	6.14	12.00	394.8
ESPB, 2	12.95	1.49	10.02	15.88	394.8
ESPB, 3	13.28	1.49	10.35	16.21	394.8
ESPB, 4	15.52	1.49	12.59	18.45	394.8
ESPB, 5	13.09	1.49	10.16	16.02	394.8

Table 5.2. NOL index values – inter-group Control versus ESPB comparison.

Moment	LSA Mean Difference	F value	Degrees of freedom numerator	Degrees of freedom denom.	*p* observed	*p*§ Bonferroni	No. observ.
1	3.00	2.06	1	394.8	0.151	0.759	5
2	23.02	120.77	1	394.8	< 0.001	< 0.001	5
3	11.15	28.35	1	394.8	< 0.001	< 0.001	5
4	18.87	81.13	1	394.8	< 0.001	< 0.001	5
5	0.95	0.20	1	394.8	0.650	1.000	5

Table 5.3. NOL index values – intra-group comparison.

Moment versus Moment	LSA Mean Difference	F value	Degrees of freedom numerator	Degrees of freedom denom.	*p* observed	*p*§ Bonferroni	No. observ.
Intra-group comparison* – CONTROL *group							
1 vs. 2	-23.89	148.46	1	332.0	< 0.001	< 0.001	20
2 vs. 3	11.53	34.58	1	332.0	< 0.001	< 0.001	20
3 vs. 4	-9.95	25.75	1	332.0	< 0.001	< 0.001	20
4 vs. 5	20.34	107.64	1	332.0	< 0.001	< 0.001	20
1 vs. 3	-12.36	4.50	1	332.0	< 0.001	< 0.001	20
1 vs. 4	-22.31	-6.45	1	332.0	< 0.001	< 0.001	20
1 vs. 5	-1.96	-4.02	1	332.0	0.316	1.000	20
Intra-group comparison* – ESPB *group							
1 vs. 2	-3.88	3.82	1	332.0	0.051	1.000	20
2 vs. 3	-0.33	0.02	1	332.0	0.866	1.000	20
3 vs. 4	-2.23	1.27	1	332.0	0.260	1.000	20
4 vs. 5	2.42	1.49	1	332.0	0.221	1.000	20
1 vs. 3	-4.21	4.50	1	332.0	0.034	0.688	20
1 vs. 4	-6.45	10.57	1	332.0	0.001	0.025	20
1 vs. 5	-4.02	4.11	1	332.0	0.043	0.868	20

§ Adjusted p-value Bonferroni is the observed p-value times number of observations. LSA mean is the mean calculated using the least square adjustment method. Pre-incision (T1), post-incision (T2), pre-sternotomy (T3), post-sternotomy (T4), and pre-CPB (T5).

The inter-group analysis revealed that, compared to the Control group, the ESPB group recorded lower absolute values of the NOL index at T2, T3, and T4. Before nociceptive stimuli (T1) and the initiation of CPB (T5), there were no differences between the groups (***Table 5.2.***). The intra-group analysis revealed that the NOL index had a constant trend in the ESPB group, suggesting a robust antinociceptive shield due to the block. Conversely, the Control group showed an unstable trend of the NOL index (***Figure 5.2***.) which required additional fentanyl administration according to the NOL protocol (***Figure 5.1.***). In a inter-group analysis, the incidence of an inadequate nociceptive response was significantly reduced by adding ESPB to general anaesthesia (***Table 5.4.***).

Table 5.4. Inter-group comparison for incidence of nociception (NOL index> 25).

Moment	**No. Pts. with NOL index > 25**		**Inter-group comparison Control vs. ESPB**
	Control (n = 43)	**BPMES** (n = 42)	*p*
T1	2 [4.6]	0 [0]	0.494
T2	34 [79]	2 [4.7]	< 0.001
T3	16 [37.2]	0 [0]	< 0.001
T4	34 [79]	3 [7.1]	< 0.001
T5	3 [7]	0 [0]	0.241

5.3.2. Additional explorations regarding traditional nociception indicators

The traditional indicators of nociception are represented by mean arterial pressure and heart rate. The temporal profile exploration was performed similarly to the NOL index (i.e., MMRM model). The information is presented in a concise manner.

Heart rate - inter-group analysis showed no significant differences in the 5 moments of interest ($p > 0.05$), suggesting that predicting an NOL index > 25 based on this indicator will be modest. Intra-group analysis revealed a significant difference only between T4 and T5, with an increase in heart rate resulting from large vessel instrumentation (***Figure 5.3.***). On the other hand, the NOL index remained discriminative, indicating an adequate response to nociception in both groups (Figure 5.2.). Mean arterial pressure - inter-group comparative analysis revealed significant differences between groups at T2, T3, and T4 (***Figure 5.4.***), with the substrate being represented by the incidence of nociception in the groups (***Table 5.4.***). The group analysis revealed a constant trend of mean arterial pressure in the ESPB

group until T4. In the Control group, the mean arterial pressure significantly increased at T2 and maintained its value until T4. During the T4-T5 transition, the mean arterial pressure significantly decreased in both groups due to large vessel instrumentation (***Figure 5.4.***).

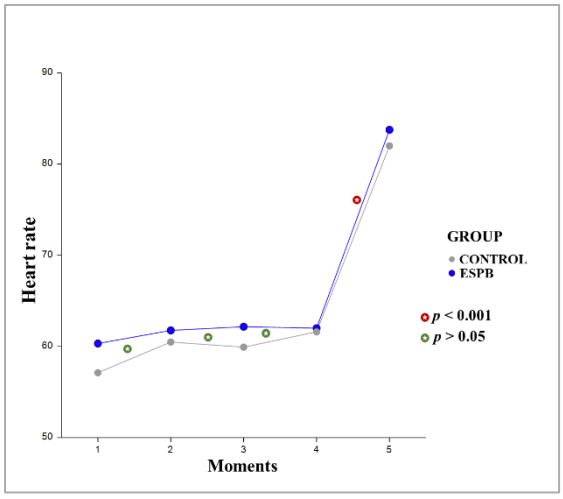

Figure 5.3. Heart rate trend.

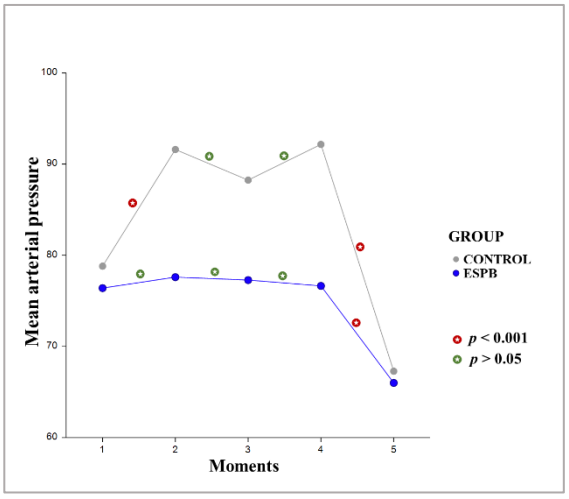

Figure 5.4. Blood pressure trend.

Figure 5.5 illustrates the predictive capacity of traditional nociception indicators for nociception, defined as an NOL index > 25. The variation in mean arterial pressure and heart rate was the difference between the values recorded after the event and those recorded before the event. The events of interest were incision and sternotomy.

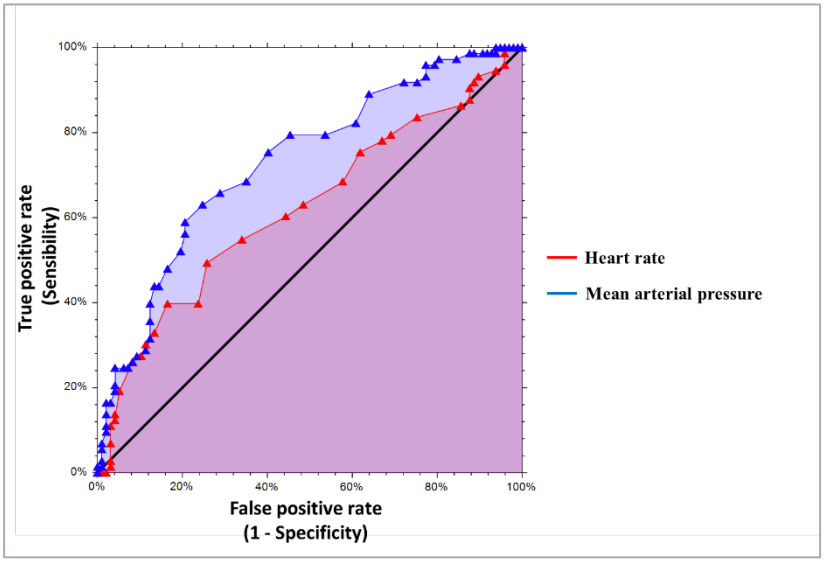

Figure 5.5. ROC curve to predict an NOL index > 25.

The comparative ROC analysis confirmed that the predictive value of mean arterial pressure for an NOL index > 25, although modest (area under the curve, AUC = 0.73; 95%

CI: 0.64-0.79; cut-off: 6 mmHg), is significantly better than the predictive value of heart rate (AUC = 0.62; 95% CI: 0.52-0.70; cut-off: 4 beats/minute; p = 0.03).

5.4. Discussions

Several aspects need to be addressed before drawing conclusions. One primary aspect is the choice of NOL index as a method of monitoring nociception. In the absence of a gold standard, selecting the method with the highest accuracy is a challenging task. Compared to other methods available for clinical use, the NOL index has the theoretical advantage of integrating multiple signals, such as heart rate and heart rate variability, photoplethysmographic wave amplitude and its variation, skin conductance response amplitude and its variation, peripheral temperature, and movement[8]. Additionally, an artificial intelligence algorithm capable of distinguishing nociceptive patterns from non-nociceptive patterns, as well as the ability to identify a specific pattern for each patient, is also an advantage[42]. These characteristics explain the results of comparative clinical studies that have shown that the NOL index provided the best ratio between opioid consumption and endogenous stress response[43]. A second aspect is the influence of nociception monitoring on current medical practice and patient prognosis. Some studies have shown that, despite similar intraoperative opioid doses, monitoring the NOL index allowed for the adjustment of opioid administration based on nociceptive stimuli, leading to better control of postoperative pain quality[44], [45]. The third aspect concerns the utility of the NOL index in the context of mixed anaesthesia techniques (i.e., general anaesthesia in combination with regional anaesthesia techniques). So far, special attention has been given to integrating this index into general anaesthesia, but its experience in the field of regional anaesthesia is very limited. However, it should be noted that traditional sensory tests do not adequately measure the antinociceptive dimension of the block, regardless of the type of block performed[7]. Additionally, their use is limited, as they can only be performed when the patient is awake. In contrast, as demonstrated previously, the NOL index is capable of distinguishing nociceptive signals from non-nociceptive signals, both in simple general anaesthesia and in general anaesthesia combined with regional anaesthesia techniques. The interest in adopting nociception monitors in regional anaesthesia is increasing. A pilot study by Bolag et al. showed that the epidural block did not reduce the ability to predict the nociceptive activity of the PMD-200^{TM} monitor in patients receiving combined thoracic general and epidural anaesthesia [46]. The main limitations of this study were the post-hoc design and sequential analysis of the NOL index.

6. General conclusions

In an intraoperative antinociceptive algorithm based on the NOL index, the addition of single-shot BPMES to standard general anaesthesia had the following benefits:

1) reduced intraoperative fentanyl consumption and postoperative morphine consumption.
2) improved postoperative analgesia quality.
3) accelerated weaning from mechanical ventilation and vasopressor support.
4) improved intraoperative nociception control quality.
5) although statistically insignificant, reduced the incidence of opioid-related adverse effects.

The results of this study confirm that the risk-benefit ratio of ESPB is excellent. This analysis differs from other studies in that it found that the use of ESPB did not reduce the length of stay in the ICU or the total hospital stay. These findings suggest that achieving ERAS goals requires a unified and multidisciplinary approach involving efforts from all healthcare professionals involved in patient care, including anaesthesiologists and surgeons, as well as the entire medical institution.

ESPB did not modify tissue perfusion indicators or perioperative dobutamine consumption. These results are not surprising, as the study included patients with stable preoperative hemodynamic status and no need for pharmacological or mechanical cardio-circulatory support. This research suggests that the selective inclusion of patients with poor hemodynamic status could be particularly advantageous. Theoretically, these patients will benefit most from reducing perioperative opioid consumption and accelerating the process of weaning from mechanical ventilation.

Mean arterial pressure had modest predictive power for nociception (i.e., NOL index > 25) but was more precise than heart rate. It is noteworthy that most patients had chronic treatment with beta-blockers (79% in the Control group versus 85.7% in the ESPB group, $p = 0.421$). In this context, if used alone, heart rate interpretation could lead to erroneous decisions. In the absence of objective nociception monitoring, mean arterial pressure remains the best predictor. In this case, continuous invasive arterial pressure monitoring is necessary.

7. Personal contributions

1) The study aimed to evaluate the role of BPMES in cardiac surgery with cardiopulmonary bypass within an antinociceptive strategy based on the NOL index. The implementation of the NOL index is an innovative contribution for two reasons: 1) intraoperative nociception using the NOL index has not been documented before in cardiac surgery; 2) the effectiveness of BPMES has not been previously evaluated with the NOL index.

2) The research confirmed the conclusions of other studies regarding the role of BPMES in reducing opioid consumption during the perioperative period, accelerating extubation, and improving postoperative analgesia quality. In addition, this study made an important contribution by highlighting that ESPB can be used as an analgesic tool with hemodynamic benefits. Adding ESPB to standard general anaesthesia led to a reduction in postoperative norepinephrine consumption and facilitated norepinephrine weaning.

3) This research examined for the first time the temporal profile of the nociception-antinociception balance in adult patients undergoing cardiac surgery with cardiopulmonary bypass. In this context, adding BPMES to standard general anaesthesia not only reduced perioperative opioid consumption but also improved intraoperative nociception control.

4) In a secondary analysis of the data, a modest predictive capacity was found for hemodynamic indicators of nociception (i.e., mean arterial pressure and heart rate) for a critical NOL index > 25. In the absence of a nociception monitor, this study suggests that only continuous monitoring of mean arterial pressure could be used to make decisions regarding opioid administration.

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LIST OF PUBLICATIONS

1. **C. Balan**, S.-I. Bubenek-Turconi, D. R. Tomescu, and L. Valeanu, **Ultrasound-Guided Regional Anesthesia–Current Strategies for Enhanced Recovery after Cardiac Surgery**, *Medicina* , vol. 57, no. 4. 2021, doi: 10.3390/medicina57040312.
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2. **Balan, C.;** Tomescu, D.R.; Valeanu, L.; Morosanu, B.; Stanculea, I.; Coman, A.; Stoian, A.; Bubenek-Turconi, S.I., **Nociception Level Index-Directed Erector Spinae Plane Block in Open Heart Surgery: A Randomized Controlled Clinical Trial**, *Medicina (B. Aires).*, vol. 58, no. 10, p. 1462, Oct. 2022, doi: 10.3390/medicina58101462.
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3. **Balan, C.**; Tomescu, D.R.; Bubenek-Turconi, S.I., **Nociception Control of Bilateral Single-Shot Erector Spinae Plane Block Compared to No Block in Open Heart Surgery—A Post Hoc Analysis of the NESP Randomized Controlled Clinical Trial**. Medicina 2023, 59, 265. https://doi.org/10.3390/medicina59020265.
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