

Official Title: Association Between Intraoperative Mean Arterial Pressure Variability and Postoperative Fatigue in Patients Undergoing Laparoscopic Abdominal Surgery

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Confidentiality Statement:

This document is intended solely for research purposes. It does not contain any personally identifiable information of study participants.

## **1. Background**

With the global demand for surgical procedures increasing significantly<sup>1</sup>, laparoscopic surgery has become the preferred technique for major abdominal operations due to its minimally invasive nature, lower complication rates, and faster postoperative recovery<sup>2,3</sup>.

Postoperative fatigue syndrome (POFS) is one of the common complications after abdominal surgery. Clinical manifestations include fatigue, muscle weakness, sleep disturbances, and impaired attention<sup>4</sup>, which can significantly hinder the implementation of enhanced recovery after surgery (ERAS) protocols<sup>5,6</sup>. POFS can prolong postoperative bed rest and delay early functional exercises. Most evidence on postoperative outcomes is collected within the first 7 days after surgery, but without early interventions, POFS may persist longer, sometimes up to 12 months postoperatively. Additionally, POFS may lead to secondary complications, extended hospital stay, and impaired social function<sup>6,7</sup>. Therefore, with the increasing adoption of ERAS, the prevention and management of POFS warrant greater attention.

The pathophysiology of POFS is complex. While some mechanisms have been elucidated, no single therapy has been proven to significantly improve POFS<sup>8</sup>. Studies suggest that esketamine may reduce POFS by increasing cerebral blood flow and facilitating the clearance of metabolic waste. Other research has shown that acupoint massage promoting blood

circulation can also reduce POFS incidence<sup>9</sup>. These findings indicate that hemodynamic stability may be closely associated with POFS improvement.

Blood pressure variability (BPV) is an important indicator of hemodynamic stability<sup>10</sup>. In healthy individuals, the compensatory mechanisms of the sympathetic and parasympathetic nervous systems ensure that blood pressure and cerebral perfusion respond adequately to environmental, physical, and emotional stimuli. The magnitude and pattern of these BP changes constitute BPV<sup>11</sup>.

Perioperative BPV is similarly important. Increased BPV has been linked to adverse postoperative outcomes, including myocardial injury, renal injury, stroke, and delirium<sup>12,13</sup>. Recent studies on cardiac and non-cardiac surgeries indicate a significant association between postoperative adverse events and both reduced mean arterial pressure (MAP) and increased MAP fluctuations<sup>14-16</sup>.

BPV partly reflects autonomic nervous system function. Moderate fluctuations are physiologically normal and indicate dynamic cardiovascular balance. However, persistently abnormal BP—either too high or too low—may signal potential perfusion issues, fluid imbalance, or other pathological conditions, requiring attention and further assessment.

Currently, BPV assessment lacks standardized methods. Standard

deviation (SD) is commonly used<sup>17,18</sup>. Hansen et al. proposed Average Real Variability (ARV)<sup>19</sup> to evaluate short-term BP fluctuations, calculated as the sum of absolute BP differences between consecutive readings multiplied by the measurement intervals and divided by total time. ARV is more reliable than SD for time-series variability but only applies to equally spaced measurements; unequal intervals may overestimate sharp fluctuations<sup>20</sup>. To address this, Mascha et al. introduced Generalized ARV (G-ARV), which does not require equally spaced data, providing more accurate representation of dynamic changes<sup>20</sup>.

In summary, we hypothesize that intraoperative BPV is associated with POFS. This study aims to explore the relationship between hemodynamic stability and postoperative fatigue in elderly patients undergoing laparoscopic abdominal surgery, providing scientific guidance for optimal intraoperative blood pressure management.

## **2. Study Objectives**

To record intraoperative blood pressure data and postoperative Christensen fatigue scores, analyze the relationship between intraoperative BPV and postoperative fatigue, and investigate the predictive value of intraoperative MAP variability for POFS. The study aims to guide clinical management of intraoperative BP and postoperative fatigue, improving anesthesia care and recovery for patients.

## **3. Study Type**

Prospective cohort study: preplanned and real-time collection of exposure (MAP variability) and outcome (POFS) data, with follow-up to track occurrence of POFS.

## **4. Research Personnel**

Preoperative Team: Screening and baseline data collection.

Intraoperative Team: Distribution of study drugs, data collection during surgery, coordination of procedures. Anesthesiologists administer drugs according to protocol.

Postoperative Team: Outcome assessment and data collection.

All personnel are trained independently and do not share patient-specific information.

Data analysis will be conducted independently by a designated statistician.

## **5. Inclusion Criteria**

Age  $\geq$  18 years;

ASA physical status I–III;

Scheduled for elective laparoscopic abdominal surgery under general anesthesia

## **6. Exclusion Criteria**

Severe cardiac, hepatic, or renal insufficiency, or major neurological/psychiatric disorders;

Known drug allergies during the study period;

Participation in other clinical trials within the past 3 months;

Unable to complete required questionnaires or assessments;

Surgery duration  $<$  60 minutes

## **7. Withdrawal Criteria**

Severe perioperative complications;

Insufficient BP readings (artifacts lasting >5 minutes<sup>1</sup> or readings spaced >5 minutes)<sup>20</sup>;

Patient or proxy requests withdrawal

## **8. Study Procedures**

Preoperative visit: 16:00–20:00 on the day before surgery; collect basic information, baseline BP, medications, and history; informed consent signed

Monitoring & Anesthesia: Noninvasive BP, radial artery catheter for invasive BP, ECG, SpO<sub>2</sub>, temperature, BIS

Induction: Sufentanil, propofol, rocuronium IV

Maintenance: Remifentanyl 0.1–0.5 µg/kg/min, rocuronium as needed, sevoflurane 1–3%, propofol infusion, BIS 40–60

Postoperative analgesia: PCIA with sufentanil citrate; rescue doses allowed as per protocol

Follow-up: Pre- and postoperative data collection per appendices

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<sup>1</sup> Artifact Removal Criteria: Recorded artifacts; Out-of-range readings: SBP  $\geq$  300 mmHg or  $\leq$  20 mmHg; SBP  $\leq$  DBP + 5 mmHg; DBP  $\leq$  5 mmHg or  $\geq$  225 mmHg; Sudden changes: SBP change  $\geq$  80 mmHg in any direction within 1 minute, or  $\geq$  40 mmHg in both directions within 1 minute

## **9. Exposure Variable**

This study plans to enroll patients at Lianyungang First People's Hospital who meet the inclusion criteria.

Based on a pilot study including 90 subjects, with an effect size of  $f=0.25$ , a significance level of  $\alpha=0.01$ , and a statistical power of 0.90, it was calculated that 94 subjects are required per group. Considering a 20% dropout rate, the total sample size is at least 353 subjects.

## **10. Outcomes**

Primary Outcome:

Postoperative fatigue (Christensen score, postoperative days 1, 3, 7)

Secondary Outcomes:

Intraoperative vasoactive drug use

Postoperative recovery quality (QoR-15, days 1, 3, 7)

Postoperative opioid consumption

## **11. Adverse Events**

Tachycardia, bradycardia, hypotension, hypertension, intraoperative awareness

Serious events: death, life-threatening, prolonged hospitalization, permanent disability

All events recorded, treated, and reported per protocol

## 12. Statistical Analysis

Continuous variables will be presented as mean  $\pm$  standard deviation (SD) or median (minimum, maximum; or interquartile range), and categorical variables will be expressed as number (percentage).

All statistical analyses will be two-sided, and a p-value  $< 0.05$  will be considered statistically significant.

The generalized average real variability (G-ARV) of intraoperative blood pressure (BP) will be calculated using the following formula:

$$\text{Generalized ARV} = \frac{1}{T} \sum_{k=1}^{N-1} |\text{BP}_{k+1} - \text{BP}_k| \text{mmHg/min}$$

where T is the total time from the first to the last BP measurement, and N is the total number of BP readings.

The G-ARV values will be ranked in ascending order, and P33 (33rd percentile) and P67 (67th percentile) will be calculated. Postoperative fatigue data will be categorized into three groups:

Low Variability (LV):  $\text{G-ARV} \leq \text{P33}$

Medium Variability (MV):  $\text{P33} < \text{G-ARV} \leq \text{P67}$

High Variability (HV):  $\text{G-ARV} > \text{P67}$

Bonferroni tests will be used to compare postoperative fatigue among groups. Analysis of covariance (ANCOVA) will be applied to adjust for covariates and to account for imbalanced confounding factors between groups (e.g., baseline fatigue score, age, surgery duration, and anesthesia

time).

## **10. Quality Control**

Research Personnel: Training, accurate data recording, calibration of monitors, rigorous statistical analysis.

Patients: Clear explanation, informed consent, right to withdraw, trial halted if study-related deaths occur.

## **11. Ethics**

The study protocol must be approved by the ethics committee before the research can commence.

For each potential participant, the investigator is responsible for fully explaining the purpose of the study, procedures, and possible risks in writing.

Each participant must be informed that he or she has the right to withdraw consent and discontinue participation at any time during the study.

A written informed consent form must be provided to each participant.

Each participant or authorized proxy must sign the consent form prior to participation, and the written informed consent will be kept as part of the clinical trial documentation.

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