



Muscular tissue oxygen saturation during robotic hysterectomy and postoperative nausea and vomiting: exploring the potential therapeutic thresholds

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Abstract

The relationship between muscular tissue oxygen saturation (SmtO₂) during surgery and postoperative nausea and vomiting (PONV) remains to be determined. Patients undergoing robotic hysterectomy participated in this prospective cohort study. SmtO₂ of the brachioradialis muscle in the forearm was continuously monitored during surgery. Thresholds based on relative changes or absolute values were systematically assigned. The relationship between thresholds and PONV was investigated based on threshold analysis (i.e., exceeding or not exceeding a threshold), area under the curve analysis (i.e., the size of the area enclosed by the SmtO₂ trace and threshold), and multivariable analysis by accounting for recognized PONV risk factors. PONV occurred in 35 of 106 patients (33%). Based on the multivariable analysis, the SmtO₂ threshold of 20% above baseline correlated with less PONV (OR 0.39; 95% CI 0.16–0.93; $p=0.034$), and the following values correlated with more PONV: 5% below baseline (OR 2.37; 95% CI 1.26–4.45; $p=0.007$), 20% below baseline (OR 16.08; 95% CI 3.05–84.73; $p=0.001$), < 70% (OR 2.86; 95% CI 1.17–6.99; $p=0.021$) and < 60% (OR 6.55; 95% CI 1.11–38.53; $p=0.038$). Our study suggests that a potential therapeutic goal for PONV prophylaxis may be to maintain SmtO₂ at > 70% and above baseline.

Keywords Muscular tissue oxygen saturation · Postoperative nausea and vomiting · Robotic hysterectomy · Therapeutic thresholds

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1 Introduction

Postoperative nausea and vomiting (PONV) remains prevalent despite the utilization of various prophylactic measures [1]. The incidence of PONV in female patients undergoing laparoscopic gynecological surgery can be up to 50 and 70% with and without the administration of antiemetics, respectively [2, 3]. The consequences of PONV included patient discomfort, postoperative complications, prolonged hospitalization, and increased health care costs [4]. Among the multiple risk factors, suboptimal gastrointestinal (GI) perfusion or oxygenation may be responsible for some cases of PONV; however, this speculation remains to be confirmed [5].

Optimal tissue oxygenation, which represents a balance between tissue oxygen consumption and supply, is essential for the integrity of any metabolically active tissue bed. However, GI oxygenation cannot be directly and continuously monitored in patients at this time. Whether there is an organ that can be used as a surrogate for the GI system, meaning that the tissue oxygenation of this organ not only can be

monitored but also correlates with that of the GI system, is an intriguing question. Currently, tissue oxygenation can be noninvasively measured using near-infrared spectroscopy (NIRS) in patients [6, 7]. The recent advancement in this technology enables the measurement of the oxygenation of many different tissue beds depending on oximetry probe placement [8, 9].

In this study, we hypothesize that muscular tissue oxygen saturation (SmtO₂) monitored on the forearm during surgery correlates with PONV in patients undergoing robotic hysterectomy. The aim of this study was to explore the SmtO₂ thresholds that correlate with a reduced risk of PONV and therefore have the potential to be used as therapeutic targets in the future.

2 Methods

This prospective observational cohort study was approved by the Institutional Review Board at Yale University. Consent for study participation was obtained from all patients before surgery.

2.1 Patient selection

Patients who underwent elective robotic hysterectomy from October 2016 to February 2017 at Yale New Haven Hospital participated in this study. Patients were excluded from this study if (1) they were < 18 years old; (2) they had a skin condition incompatible with the adhesive oximetry probe; (3) they had an American Society of Anesthesiologists (ASA) physical status score > III; (4) their surgeries were converted from laparoscopic to open procedures, and (5) they remained intubated and admitted to the intensive care unit instead of the post-anesthesia care unit after surgery. We did not specifically study relatively sick patients who had major organ system co-morbidities or an ASA physical status score > III based on the assumption that, even for relatively healthy patients, there is room for improvement in tissue oxygenation and hemodynamic management.

2.2 Anesthesia and surgery

In the preoperative area, patients were given oral acetaminophen, gabapentin, and celecoxib per the Enhanced Recovery After Surgery protocol. Upon arrival at the operating room, patients were monitored using electrocardiography, pulse oximetry, and cuff-based non-invasive blood pressure monitoring. Following pre-oxygenation delivered via facemask, anesthesia was induced using intravenous lidocaine, fentanyl, and propofol. Endotracheal intubation was performed following the administration of rocuronium. All patients were mechanically ventilated with a tidal volume of

approximately 6 ml/kg and respiratory rate of 10–16 breaths per minute to keep the end-tidal carbon dioxide level within 30–40 mmHg. Anesthesia was maintained using sevoflurane in a 1:1 air:oxygen mixture. Intravenous propofol infusion, alone or in combination with sevoflurane, was used in some patients at the discretion of the attending anesthesiologist. All patients received intravenous ondansetron (4 mg) and dexamethasone (4 mg) for PONV prophylaxis toward the end of surgery. The procedure was performed in accordance with the published standards [10]. All patients were positioned in low dorsal lithotomy position, with their arms padded and tucked at their sides during surgery. The position of the operating table was adjusted based on the requirements of different stages of surgery.

2.3 Tissue oxygenation monitoring

SmtO₂ was monitored non-invasively using an FDA-cleared tissue oximeter (FORE-SIGHT ELITE, CASMED, Inc., Branford, CT, USA). The oximetry probe was placed over the top of the body of the brachioradialis muscle and approximately two fingers-width below the antecubital crease (i.e., on the radial side of the forearm) to monitor SmtO₂ in the arm that was not used for cuff blood pressure monitoring. Monitoring and data recording started before anesthesia induction (with the patient awake and breathing room air) and stopped at the end of surgery. The SmtO₂ data were captured every 2 s by a research computer. The median values of the measurements within each minute were used in the analysis.

We systematically assigned multiple SmtO₂ thresholds based on either relative changes or absolute values to investigate the relationship between thresholds and PONV (Table 1). The relative change is defined as the percentage change from the baseline SmtO₂ measured with the patient awake and breathing room air using the following equation: relative change = [(actual measurement – baseline measurement)/baseline measurement] × 100%. Absolute value refers to the actual measurement. In addition, we calculated the

Table 1 Thresholds of muscular tissue oxygen saturation based on relative changes and absolute values

Thresholds based on relative changes		Thresholds based on absolute values	
Lower	Upper	Lower (%)	Upper (%)
Below baseline	5% above baseline	< 75	> 75
5% below baseline	10% above baseline	< 70	> 80
10% below baseline	15% above baseline	< 65	> 85
15% below baseline	20% above baseline	< 60	> 90
20% below baseline		< 55	> 95
		< 50	
		< 45	

area under the curve (AUC) for any intraoperative measurement that exceeded pre-determined thresholds. The AUC is the area enclosed by the tissue oxygenation trace and the threshold (Fig. 1).

2.4 Postoperative nausea and vomiting

Nausea was defined as a subjective unpleasant sensation associated with the urge to vomit. Retching was defined as the labored, spastic, and rhythmic contraction of chest and abdominal muscles without expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. Patients subjected to any of the signs and symptoms of nausea, retching, or vomiting within 24 h after surgery or before hospital discharge, if they were discharged to home on the same day of surgery, were diagnosed with PONV in this study. The treatment of PONV was performed per the standard of care.

2.5 Statistical analysis

The power analysis was based on the preliminary results for the first 30 patients. The incidences of PONV in patients whose intraoperative SmtO₂ measurement exceeded or never exceeded a threshold of 15% below baseline were ~55 and 25%, respectively. With the ratio of patients dichotomized by this threshold being approximately 1:4, a total of 100 patients (i.e., 20:80) is needed in order to have a power of 80% to detect a 30% difference (i.e., 55% minus 25%) between these patients using a two-side proportion test with an alpha level of 0.05. With the anticipation of a drop-off rate of 10%, we aimed to recruit 110 patients in this study.

Categorical data are expressed as the count and percentage, while continuous data are expressed as the mean ± SD.

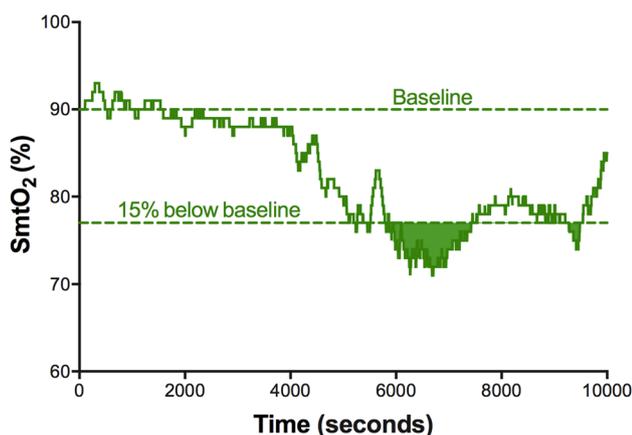


Fig. 1 Muscular tissue oxygen saturation (SmtO₂) trace from one patient. The baseline, threshold defined by 15% below baseline, and the area under curve below the threshold defined by 15% below baseline (closed green) are illustrated

The means of the continuous variables between those with PONV and those without PONV were compared using a two-sample *t* test. The proportions of the binary variables were compared using a chi-squared test.

Univariate logistic regression was used for comparisons between patients with intraoperative SmtO₂ exceeding or not exceeding the threshold to investigate if they had different risks of PONV. Univariate logistic regression was also used in patients whose AUCs were > 0 to investigate if patients with and without PONV had different AUCs. Log-transformed values of AUC were used in analysis. Multiple logistic regression was performed to investigate if the thresholds with significance based on univariate logistic regression remained significant after accounting for recognized PONV risk factors. These risk factors (i.e., age, the use of sevoflurane, anesthesia time, history of smoking, and history of PONV and motion sickness combined) were selected based on both clinical significance as well as the avoidance of collinearity, and they were always kept in the multiple regression model. The use of antiemetics or narcotics was not included because almost all patients received ondansetron and fentanyl per the standard of care.

Statistical analyses were performed using the IBM SPSS version 20.0 (Chicago, IL, USA) and MATLAB R2008b (MathWorks, Natick, MA, USA). A two-sided *p* value < 0.05 was regarded as statistically significant.

3 Results

Among 112 patients who participated in the study, six were excluded from the analysis due to incomplete SmtO₂ data (*n* = 2) or the monitor probe coming off (*n* = 4). Between patients with and without PONV, there were no differences with respect to age, anesthetic techniques, opioid usage, and intravenous fluid administered (Table 2). The baseline measurement was > 70% in 85% of patients (Fig. 2). Thirty-five of 106 patients had PONV (33%).

The results based on the threshold analysis are presented in Fig. 3 and Supplemental Table 1. Patients whose SmtO₂ exceeded the following thresholds had a significantly higher chance of having PONV: 15% below baseline (OR 2.80; 95% CI 1.05–7.43; *p* = 0.039, Fig. 3a), 20% below baseline (OR 13.80; 95% CI 2.83–67.38; *p* < 0.001, Fig. 3a), and < 60% (OR 5.75; 95% CI 1.06–31.32; *p* = 0.043, Fig. 3b).

The results based on the AUC analysis are presented in Fig. 4 and Supplemental Table 2. The AUCs for the following thresholds were significantly different between patients with and without PONV: 20% above baseline (OR 0.50; 95% CI 0.26–0.98; *p* = 0.044, Fig. 4a), 5% below baseline (OR 2.17; 95% CI 1.23–3.82; *p* = 0.008, Fig. 4a), 10% below baseline (OR 1.83; 95% CI 1.05–3.21; *p* = 0.034, Fig. 4a), <

Table 2 Demographic and clinical data in patients with and without postoperative nausea and vomiting (PONV)

	All patients (n = 106)*	PONV		p value**
		Yes (n = 35)	No (n = 71)	
Age (years)	56 ± 11	54 ± 10	57 ± 12	0.17
Weight (kg)	83 ± 22	84 ± 25	82 ± 20	0.67
Height (cm)	162 ± 7	164 ± 7	162 ± 8	0.20
BMI	32 ± 8	32 ± 9	32 ± 8	0.96
ASA = I/II/III [n (%)]	0/62/44 (0/58/42%)	0/25/10 (0/71/29%)	0/37/34 (0/52/48%)	0.058
Hypertension [n (%)]	44 (42%)	12 (34%)	32 (45%)	0.29
Diabetes mellitus [n (%)]	13 (12%)	3 (9%)	10 (14%)	0.62
Cardiac disease [n (%)]	13 (12%)	5 (14%)	8 (11%)	0.90
Pulmonary disease [n (%)]	28 (26%)	12 (34%)	16 (23%)	0.20
Anemia [n (%)]	10 (9%)	1 (3%)	9 (13%)	0.20
History of smoking [n (%)]	38 (36%)	12 (34%)	26 (37%)	0.81
History of PONV and/or motion sickness [n (%)]	20 (19%)	10 (29%)	10 (14%)	0.07
Inhalational/intravenous/combined anesthesia [n (%)]	63/11/32 (60/10/30%)	19/3/13 (54/9/37%)	44/8/19 (62/11/27%)	0.56
Anesthetic time (min)	203 ± 60	209 ± 61	199 ± 60	0.42
Surgical time (min)	174 ± 62	178 ± 67	172 ± 60	0.60
Crystalloid (ml)	1416 ± 478	1394 ± 425	1427 ± 504	0.34
Intraoperative neostigmine (mg)	3 ± 1 (n = 31)	4 ± 0.8 (n = 9)	3 ± 1 (n = 22)	0.91
Intraoperative Sugammadex (mcg)	201 ± 79 (n = 65)	198 ± 78 (n = 22)	202 ± 81 (n = 43)	0.83
Intraoperative fentanyl (mcg)	206 ± 80 (n = 104)	217 ± 72 (n = 33)	201 ± 83 (n = 71)	0.35
Intraoperative hydromorphone (mg)	1.0 ± 0.5 (n = 64)	1.1 ± 0.5 (n = 24)	1.0 ± 0.5 (n = 40)	0.67
Postoperative fentanyl (mcg)	74 ± 43 (n = 59)	75 ± 51 (n = 21)	74 ± 38 (n = 38)	0.91
Postoperative hydromorphone (mg)	0.9 ± 0.7 (n = 53)	1.1 ± 0.8 (n = 21)	0.9 ± 0.6 (n = 32)	0.26
Postoperative oxycodone (mg)	16 ± 13 (n = 60)	16 ± 8 (n = 19)	16 ± 14 (n = 41)	0.95
Length of hospital stay (hours)	24 ± 17	27 ± 11	23 ± 20	0.27

ASA American Society of Anesthesiologists, BMI body mass index

*Data are expressed as mean ± SD for continuous variable and count (percentage) for binary variable

**Unpaired *t* test was used for continuous variables and Chi-Squared test for binary variables

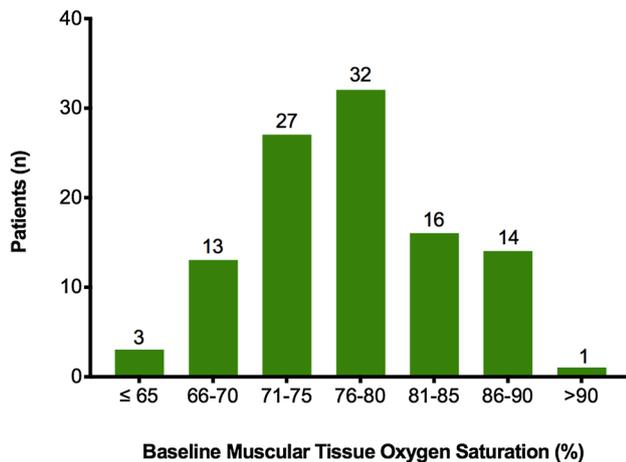


Fig. 2 Distribution of the baseline muscular tissue oxygen saturation measurements in the study population

70% (OR 2.02; 95% CI 1.06–3.86; $p = 0.033$, Fig. 4b), and < 65% (OR 4.60; 95% CI 1.18–17.84; $p = 0.028$, Fig. 4b).

After multivariable analysis, the following values remained significant in the threshold analysis: 20% below baseline (OR 16.08; 95% CI 3.05–84.73; $p = 0.001$) and < 60% (OR 6.55; 95% CI 1.11–38.53; $p = 0.038$). The following threshold values remained significant in the AUC analysis: 20% above baseline (OR 0.39; 95% CI 0.16–0.93; $p = 0.034$), 5% below baseline (OR 2.37; 95% CI 1.26–4.45; $p = 0.007$), and < 70% (OR 2.86; 95% CI 1.17–6.99; $p = 0.021$).

4 Discussion

Our study demonstrated that there is a close relationship between intraoperative SmtO₂ and PONV in patients receiving robotic hysterectomy. Multiple threshold values based on the threshold, AUC, and multivariable analyses were able to delineate the risk of PONV. An SmtO₂

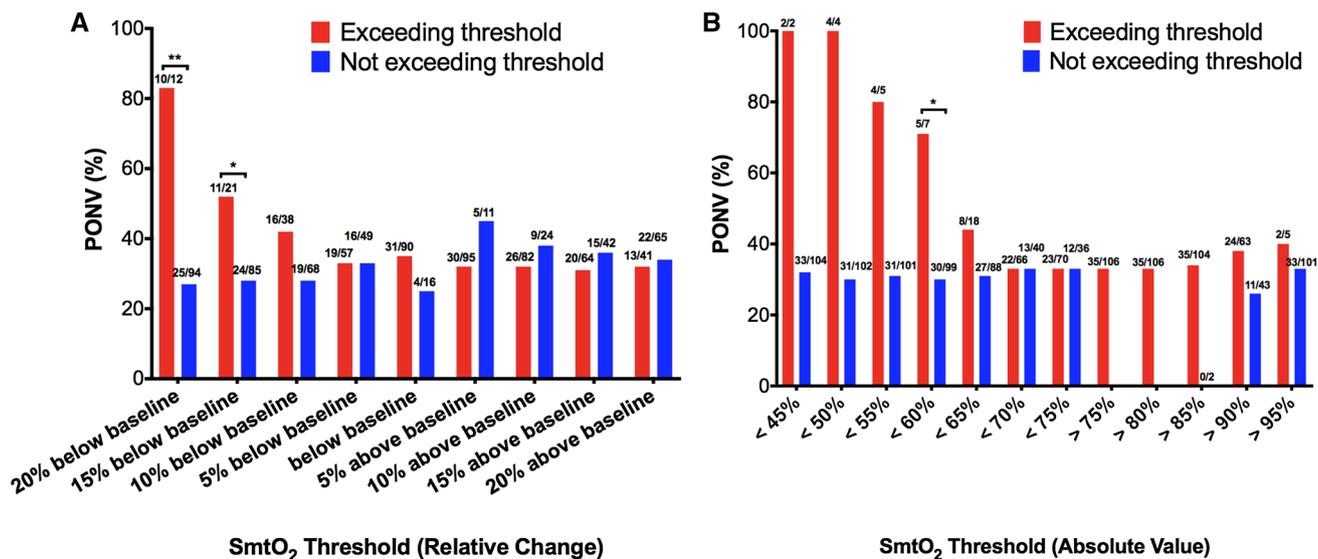


Fig. 3 Percentage of postoperative nausea and vomiting (PONV) in patients whose intraoperative muscular tissue oxygen saturation (SmtO₂) levels exceeded (red bars) and did not exceed (blue bars) the systematically assigned thresholds as defined by relative changes (a)

and absolute values (b). The denominator is the number of patients who exceeded or did not exceed the threshold, while the numerator is the number of patients with PONV. *p < 0.05; **p < 0.01

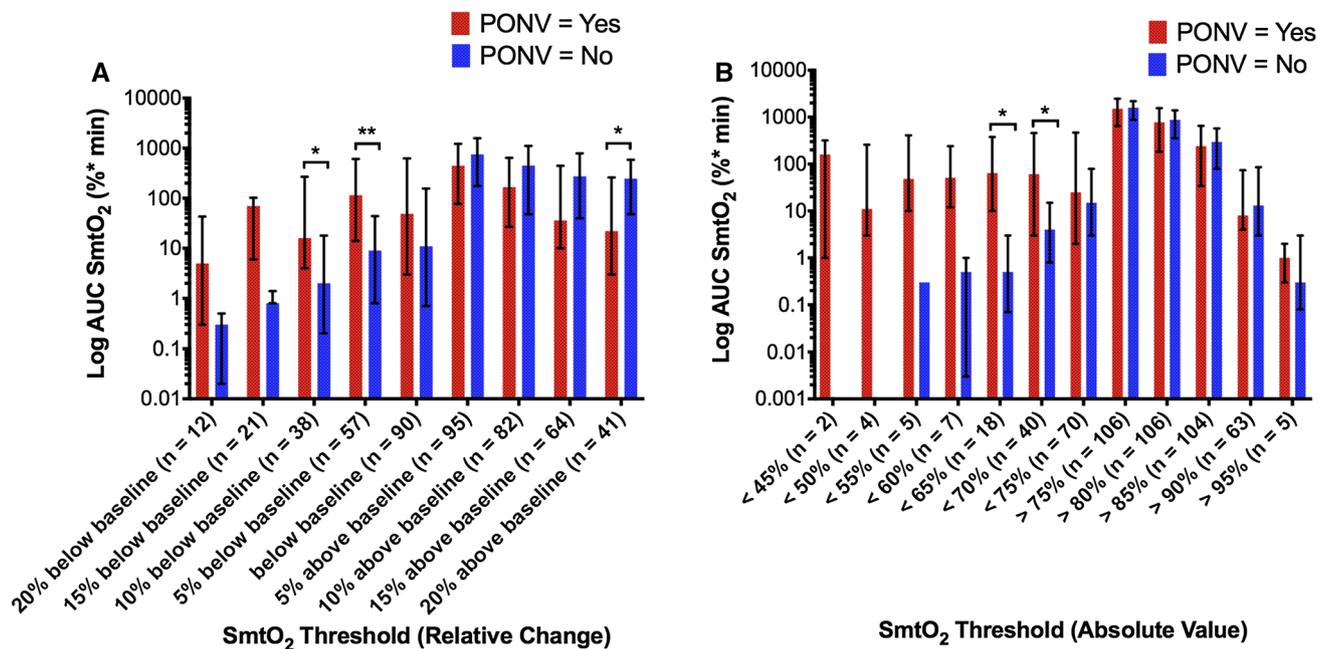


Fig. 4 Log-transformed size of the area under the curve (AUC) for patients with (red bars) and without (blue bars) postoperative nausea and vomiting (PONV). Only patients who exceeded thresholds (and

AUC > 0) were included in the analysis. AUCs were calculated as the size of the area enclosed by the trace and the threshold defined by the relative change (a) or absolute value (b). *p < 0.05; **p < 0.01

threshold 20% above baseline correlated with a reduced risk of PONV, while the following thresholds correlated with an increased risk of PONV: 5% below baseline, 20% below baseline, < 70%, and < 60%. Taken together, our study suggests that maintaining SmtO₂ at > 70% and above

baseline have the potential to be used as a therapeutic prophylaxis for PONV.

PONV is a big “little problem”. The etiology of PONV is multifactorial [4]. Hypovolemia [11] and hypotension [12] have been linked with PONV. A previous study

showed that patients who had a normal intramucosal pH had a reduced incidence of PONV [13]. Increased inspired oxygen concentration during surgery was associated with a decreased incidence of PONV [14, 15]; however, this finding was refuted by a different study [16]. Overall, the evidence suggests that GI ischemia and hypoxia may be responsible for some cases of PONV. The tissue bed of the GI tract is metabolically active [17]; however, it has minimal [18] to no [19, 20] autoregulatory capacity and is notoriously intolerant of even a brief period of ischemia and hypoxia [21]. In our study population, there were risk factors for GI ischemia and hypoxia, including general anesthesia [22], fasting [23], body tilting [22], pneumoperitoneum [22], the use of vasopressors [24], and the impact of direct surgical maneuvers [25].

NIRS-based tissue oximetry was introduced into clinical use 20+ years ago [26]. It has been primarily used for cerebral tissue oxygen saturation (SctO₂) monitoring, with the probe placed on the forehead. Studies, primarily performed in cardiac surgery, have shown that there is a close association between intraoperative *cerebral* desaturation and unfavorable postoperative outcomes, including stroke [27], cognitive decline [28, 29], and prolonged hospitalization [29]. Over time, technological innovation has enabled the application of tissue oximetry at a peripheral location to monitor *non-cerebral* tissue oxygenation, including the monitoring of SmtO₂ [8]. It has been shown, in patients undergoing major spinal surgery, that SmtO₂ has a better association with the length of hospital stay and the occurrence of composite complications than SctO₂ [9]. Together, this evidence suggests that the monitoring of tissue oxygenation of different tissue beds may have different merits in different patient populations, likely due to the different profiles of clinical priorities. This speculation is corroborated by our study, which showed a close relationship between SmtO₂ and PONV in association with robotic hysterectomy.

The purpose of most physiological monitoring is as a guide to maintain optimal physiological conditions via the timely detection and correction of unwarranted derangements [30]. To do so, therapeutic thresholds based on real-time measurements need to be first established. In this study, we investigated the association between different SmtO₂ thresholds and the occurrence of PONV in patients undergoing robotic hysterectomy, a population that has been recognized as having a high risk of PONV. Instead of arbitrarily assigning a threshold, we tested different thresholds in a systematic manner based on both relative changes and absolute values. Assessing relative change takes into account an individual patient's baseline measurement, while an absolute value does not. The results of our study showed that thresholds based on both relative changes and absolute values are able to differentiate patients with and without PONV.

Our study also highlights the value of an analysis based on the AUC in understanding the impact of a physiological derangement on outcomes. The AUC and threshold analyses are related yet distinct approaches. The question asked by a threshold analysis is, if the measurement exceeds the threshold, what is the risk of having an unwarranted outcome? In contrast, the question asked by an AUC analysis is, if the measurement exceeds the threshold (i.e., AUC > 0), would patients with different AUCs have different outcomes? Our study suggests that the results based on threshold or AUC analyses may differ and that these two methods should be used in a complementary manner to explore the therapeutic thresholds of a physiological measurement.

The therapeutic thresholds of SmtO₂ suggested by our study need to be validated by randomized controlled trials. The question of *how* to intervene based on SmtO₂ monitoring cannot be answered by this observational study, and whether the results of our study can be extrapolated to other patient populations remains to be determined. The association between arm SmtO₂ and GI tissue oxygenation could not be determined by our study, although our findings suggested that arm SmtO₂ has the potential to be used as a surrogate for GI tissue oxygenation.

There are different commercially available peripheral tissue oximeters on the market; however, measurements based on different monitors cannot be used interchangeably [31]. In practice, it is prudent to use the trend of changes in tissue oxygenation instead of absolute values as therapeutic thresholds. If using absolute values as a therapeutic threshold, different monitors should be tested to establish their own standards based on independent investigations. Results from oxygenation monitoring of different tissue beds are also not interchangeable, which is exemplified by the distinct therapeutic effects of phenylephrine on cerebral [6] vs. muscular [32] tissue oxygenation (i.e., decrease vs. increase). At this time, how to best use tissue oxygenation monitoring based on NIRS technology to improve clinical outcomes is a work in progress [33].

In summary, PONV remains prevalent in patients undergoing robotic hysterectomy despite the utilization of different antiemetics. SmtO₂ during robotic hysterectomy correlates with PONV, and maintaining SmtO₂ at > 70% and above baseline has the potential to be used as therapeutic prophylaxis for PONV. Whether interventions guided by these SmtO₂ thresholds can reduce the incidence or severity of PONV needs to be tested in randomized controlled trials.

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Author contributions GL contributed to the study design and the interpretation and acquisition of the data. LL contributed to the study design and acquisition of the data. FD contributed to analysis and

interpretation of the data. XG contributed to the interpretation of the data. LM contributed to the study design and the acquisition and interpretation of the data. All authors were involved in the writing and revising of the manuscript.

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Compliance with ethical standards

Conflict of interest LM is a consultant to CAS Medical Systems, Inc. The other authors declare no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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