ORIGINAL RESEARCH

Low minute ventilation episodes during anesthesia recovery following intraperitoneal surgery as detected by a non-invasive respiratory volume monitor

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Abstract

An electrical impedance-based noninvasive respiratory volume monitor (RVM) accurately reports minute volume, tidal volume and respiratory rate. Here we used the RVM to quantify the occurrence of and evaluate the ability of clinical factors to predict respiratory depression in the post-anesthesia care unit (PACU). RVM generated respiratory data were collected from spontaneously breathing patients following intraperitoneal surgeries under general anesthesia admitted to the PACU. Respiratory depression was defined as low minute ventilation episode (LMVe, $< 40\%$ predicted minute ventilation for at least 2 min). We evaluated for associations between clinical variables including minute ventilation prior to opioid administration and LMVe following the first PACU administration of opioid. Also assessed was a low respiratory rate (< 8 breaths per minute) as a proxy for LMVe. Of 107 patients, 38 (36%) had LMVe. Affected patients had greater intraoperative opioid dose, $P = 0.05$. PACU opioids were administered to 45 (42.1%) subjects, of which 27 (25.2%) had LMVe ($P = 0.42$) within 30 min following opioid. Pre-opioid minute ventilation $< 70\%$ of predicted normal value was associated with LMVe, $P < 0.01$, (sensitivity = 100%, specificity = 81%).Low respiratory rate was a poor predictor of LMVe (sensitivity = 11.8%). Other clinical variables (e.g., obstructive sleep apnea) were not found to be predictors of LMVe. Using RVM we identified that mild, clinically nondetectable, respiratory depression prior to opioid administration in the PACU was associated with the development of substantial subsequent respiratory depression during the PACU stay.

Keywords Noninvasive respiratory volume monitor · Opioid induced respiratory depression · General anesthesia · Postanesthesia recovery

1 Introduction

Postoperative opioid induced respiratory failure is a serious complication, which can lead to permanent disability or mortality [1]. Routine postoperative monitoring with reliance on intermittent vital sign checks can miss early warning signs for this complication, leading to "failure to rescue" events [1]. This is tragic, because like many other complications, opioid-induced respiratory failure is often preceded by easily identifiable vital sign abnormalities [2]. At our institution we have identified that nursing-diagnosed episodes of respiratory depression during Phase I anesthesia recovery in the postanesthesia care unit (PACU) are strongly associated with subsequent postoperative pulmonary complications [3, 4]. For example, patients who have respiratory depression episodes (primarily nursing-witnessed apneic spells) are at fivefold higher risk of requiring emergent administration of naloxone to reverse over-narcotization while on the postoperative ward [5].

However, reliance on human-diagnosed vital signs abnormalities, even in highly monitored settings in the PACU, is problematic because it requires the health-care provider to continuously observe the patient and does not account for potential bias between observers. Thus, automated continuous monitors of respiratory function are attractive in that they may increase the ability of nurses to detect respiratory depression. One approach is measuring cyclical changes in

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chest electrical bioimpedance that occur during breathing to determine respiratory activity. The ExSpiron 1Xi (Respiratory Motion Inc., Waltham, MA) is a commercially available, noninvasive respiratory volume monitor (RVM) that uses this approach to continuously monitor minute ventilation (MV), tidal volume (TV) and respiratory rate (RR). Monitoring the MV is the primary mode this RVM uses to detect episodes of decreased respiratory effort in nonintubated patients vis-à-vis the detection of Low Minute Ventilation events (LMVe), defined as < 40% of predicted MV (MV_{PRED}) based on a body surface area formula [6]. Detecting these LMVe episodes could be a useful tool in helping nursing staff detect episodes during Phase I recovery. In this study we examined patients who underwent a general anesthetic for intraperitoneal surgery to determine the rate of LMVe episodes and perioperative variables associated with LMVe during Phase I recovery. As a secondary aim we assess a subset of patients who were administered opioids during Phase I recovery to assess for perioperative factors associated with LMVe episodes (as a marker for opioid induced respiratory depression, [OIRD]).

2 Methods

2.1 Study design

This is a prospective observational study. The study was approved by the Mayo Clinic Institutional Review Board (Number 15-005133, approved August 6, 2015 by Ms. Wanda Dahlgren) and all subjects provided written consent to participate. Patients were enrolled from September 23, 2015 to May 24, 2016.

2.2 Setting

The Postanesthesia Care Unit of a major academic center.

2.3 Patient population

Adult (≥ 18 years of age) patients undergoing elective intraperitoneal surgery under general endotracheal anesthesia who were admitted to the PACU following surgery were recruited. Patients with previous tracheotomies or who required postoperative mechanical ventilation were excluded.

2.4 Study equipment

A non-invasive Respiratory Volume Monitor (RVM, Respiratory Motion, Inc., Waltham, MA) was used to collect continuous measurements of respiratory status for non-intubated, spontaneously-breathing patients. The RVM provides a respiratory trace and measurements of minute ventilation (MV), tidal volume (TV), and respiratory rate (RR) in real time with data provided by a one-piece L-shaped pad-set with three electrode pads attached at the sternal notch, at the xiphoid and at the right mid-axillary line at the level of the xiphoid. Once the patient was anesthetized and placed on mechanical ventilation, the RVM was calibrated using the current MV value from the anesthesia machine. The RVM calculated the MV, TV and RR that reflected the previous 30 s of respiratory function. These 30 s measurements were updated and reported every 5 s. The output of the RVM was stored in an electronic file. Previous studies have demonstrated a high correlation between the RVM and spirometer measurements in ambulatory voluntary subjects [7] and ventilator measurements during general anesthesia under tracheal intubation [8].

2.5 Study protocol

Following induction of anesthesia and initiation of mechanical ventilation, the RVM's electrode pad-sets were applied and the device was calibrated (as described above). Using patient gender and body surface area, the monitor calculated predicted MV (MV_{PRED}) [9]. Data from the RVM were recorded from the end of surgery and extubation of the trachea, until the patient was discharged from the PACU. The RVM screen was covered so that healthcare providers were blinded to the data. Patient care was conducted as per standard protocols and not modified based on RVM data.

2.6 Data collected

Preoperative variables collected included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, burden of comorbid diseases (as determined by the Charlson Comorbidity Index) and presence of obstructive sleep apnea (OSA, all patients were queried for a history of OSA, and if a negative response was elicited, further screening was performed using the Flemons' criteria [10]). Surgical and anesthesia variables included surgical approach, duration of procedure, choice of volatile anesthetic, cumulative intraoperative dose of opioid, and intraoperative administration of midazolam, ketamine, or neuraxial opioid. Data collected during the PACU stay included administration of opioids (type, dose, and number of administrations) and the output from the RVM. Nursing diagnosed episodes of respiratory depression during the PACU stay were recorded [3, 4]. Postoperative adverse events were also recorded.

2.7 Analysis

The primary endpoint of the study was the identification of low minute ventilation events (LMVe) during Phase I anesthesia recovery. LMVe was defined as a MV < 40% of MV_{PRED}, sustained for at least 2 min. Each LMVe ended at the first time point when MV increased above 40% of MV_{PRED}. Potential associations between patient and perioperative variables and LMVe were assessed using standard univariate analysis.

Low RR measurements are often used as a proxy for low minute ventilation in diagnosing respiratory depression. In order to determine the ability of a low RR to identify periods of low minute ventilation, RR measurements were correlated to paired MV measurements. "Low RR" was defined as RR < 8 breaths per minute, while "Low MV" was again defined as MV < 40% MV_{PRED}. Sensitivity and specificity of Low RR as a proxy of Low MV were calculated.

Data from a subset of patients who received opioids during Phase I recovery were further analyzed to identify those at risk for OIRD. Criteria currently used in clinical practice to identify patients at risk for this complication rely on preoperative and demographic data. Here, we use "Pre-Opioid MV", defined as the average MV over the 5-minute period before opioid administration, to classify patients as "at-risk" or "not-at-risk" for OIRD. An LMVe occurring within 30 min of opioid administration was used as an indication of OIRD. The threshold value of the Pre-Opioid MV classifier was varied from 40 to 80% of MV_{PRED} to find the optimal sensitivity and specificity and generate a receiver operating characteristic (ROC) curve. The performance of Pre-Opioid MV as a classifier was compared to clinical criteria including ASA physical status classification, OSA, BMI, age and Charlson Comorbidity Index (CCI) at predicting OIRD. Sensitivity and specificity were calculated at clinically relevant thresholds for each classifier.

Two-tailed t-tests were used to compare the "LMVe" and "No LMVe" groups in Table 1. Fisher's exact test was used to evaluate the performance of predictive criteria in Table 3 (Appendix). P value < 0.05 were considered statistically significant. Statistical analyses were performed with MATLAB version R2014b (Mathworks, Natick MA).

3 Results

One hundred and seven patients undergoing intraperitoneal surgical procedures under general anesthesia were recruited for the study. Thirty-eight (36%) of these patients were found to have an LMVe event detected by the RVM during Phase I anesthesia recovery with a median of 3 [1, 6] episodes per patient. The median duration of each event was 4.2 [3.2, 5.1] minutes. There were no nursing-diagnosed episodes

Table 1 Characteristics of patients who did and did not developed low minute ventilation episodes following intraperitoneal surgery

Variable	No LMVe (n = 69)	LMVe* (n = 38)	P
Patient factors			
Age, year	61.5 ± 15.3	57.8 ± 14.8	0.22
Male sex	43 (62.3)	22 (57.9)	0.68
Body mass index, kg/m²	29 (26.1, 34.4)	30.1 (27.3, 36.5)	0.50
Obstructive sleep apnea†	18 (26.1)	11 (29.0)	0.82
Charlson Comorbidity Index	5 (3, 7)	4.5 (2, 6)	0.65
ASA-PS ≥ III	39 (54.5)	19 (44.7)	0.31
Surgical and anesthetic factors			
Surgical approach			0.07
Laparotomy (n = 30)	15 (21.7)	15 (39.5)	
Laparoscopic (n = 77)	54 (78.3)	23 (60.5)	
Procedure duration, min	109 (62, 183)	138 (79, 193)	0.32
Opioids, mg IV ME	22.7 (16.3, 29.8)	29.2 (23.2, 35.1)	0.05
Neuraxial opioid	3 (4.4)	4 (10.5)	0.24
Midazolam	3 (4.4)	6 (15.8)	0.07
Ketamine	33 (47.8)	19 (50.0)	0.84
Desflurane	59 (85.1)	33 (86.8)	> 0.99
Phase I Anesthesia Recovery			
Length of stay, min	64 (44, 90)	74 (58, 88)	0.12
Opioid administration‡	27 (39.1)	18 (47.4)	0.42

ASA-PS American Society of Anesthesiologists physical status classification, *IV ME* intravenous morphine equivalents, *LMVe* low minute ventilation event

Data presented as number (%), mean ± standard deviation or median [25th, 75th percentile]

*LMVe: Minute Ventilation < 40% of Predicted Minute Ventilation. The median number of episodes was 3 [1, 6]. Median duration was 4.2 [3.2, 5.1] minutes per episode

†Obstructive sleep apnea was based on past medical history (N = 22) or results from a preoperative screen (N = 6)

‡For patients who received opioids in the PACU, the median dose was 9.3 (5, 12.5) mg IV ME for those who did not have LMVe and 5.2 (2.7, 13.1) mg IV ME for those who had LMVe, P = 0.21

of respiratory depression for these patients. The medical, surgical and anesthetic characteristics of patients who had an LMVe compared to those who did not are presented in Table 1, with the only difference between the groups being greater intraoperative opioid administration in those patients who had postoperative LMVe.

There were 171,913 paired MV and RR measurements, with 49,598 (28.9%) Low MV (MV < 40% MV_{PRED}) and 9,531 (5.5%) Low RR (RR < 8 breaths/min) measurements (Table 2). Using Low RR (RR < 8 breaths/min) as a proxy for Low MV (MV < 40% MV_{PRED}) had sensitivity of only

Table 2 Sensitivity and specificity of low respiratory rate as a proxy for low minute ventilation during anesthesia recovery

	Low MV measurements (MV < 40% MV$_{PRED}$)		
	Positive	Negative	
Low RR measurements (RR < 8)			
Positive	5833	3698	PPV = 61.2%
Negative	43,765	118,617	NPV = 73.0%
	Sensitivity = 11.8%	Specificity = 97.0%	

MV minute ventilation, *MV$_{PRED}$* normal minute ventilation, based on gender, age and calculated body surface area, *NPV* negative predictive value, *PPV* positive predictive value, *RR* respiratory rate

A total of 171,913 paired measurements of MV and RR were used to measure the sensitivity and specificity of low RR (RR < 8 breaths/min) as a proxy for low MV (MV < 40% MV$_{PRED}$). A low RR alarm setting of 8 breaths per minute would miss 88.2% of all low MV values due to a low sensitivity of 11.8%

11.8%, missing 43,765 (88.2%) of all Low MV measurements. Correlation between the paired MV and RR measurements was also weak ($R^2 = 0.11$) (Fig. 1). The low correlation between MV and RR measurements along with the
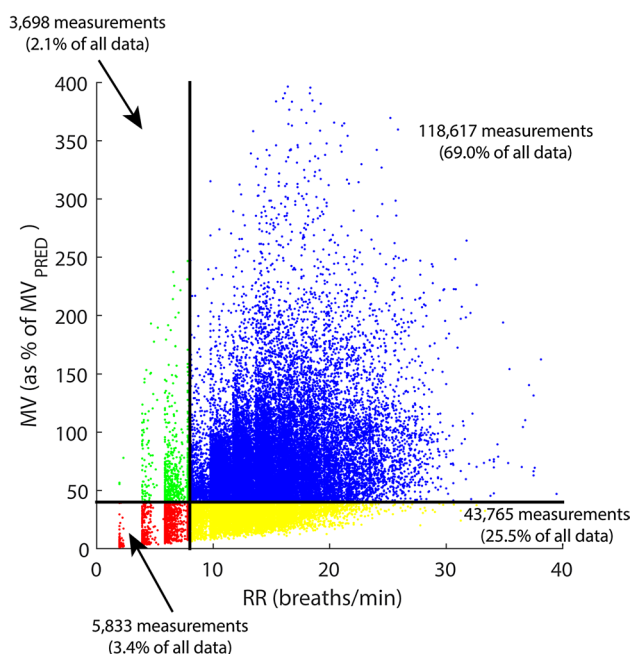

Fig. 1 A total of 171,913 paired measurements of MV and RR were acquired from all patients. There is a weak correlation between MV and RR measurements with $R^2 = 0.11$. A Low RR threshold of 8 breaths/min (vertical black line) was used to identify Low MV measurements, defined as MV < 40% MV$_{PRED}$ (horizontal black line). While 69.0% of the measurements collected had adequate MV and RR (blue dots), 25.5% of all measurements had adequate RR but Low MV measurements (yellow dots). The 8 breaths/min threshold was able to detect only 11.8% of Low MV measurements (red dots)

low sensitivity of the Low RR classifier make RR a poor proxy for MV measurements and the assessment of respiratory depression.

Forty-five patients (42.1%) were administered opioids during Phase I recovery, with 27 (25.2%) having LMVe and 18 (16.8%) not having LMVe, $P = 0.42$. All 27 patients with LMVe received an opioid within 30 min of the LMVe episode. Figure 2 shows the receiver operating characteristic (ROC) curve for a classifier based on opioid administration during Phase I recovery when stratifying patients "at risk" for LMVe. Mild respiratory depression prior to opioid administration was found to be associated with LMVe. Using a threshold value of 70% MV$_{PRED}$, sensitivity could be maximized at a value of 1, while maintaining a specificity of 0.81 (Fig. 3). The corresponding negative predictive value is 1 with a corresponding positive predictive value of 0.68. Similar analysis assessing the performance of ASA physical status classification, OSA, BMI, age, sex and CCI score yielded predictors with ROC curves similar to the performance of a random classifier [Fig. 2, (Table 3—Appendix)].

This study was not designed to assess outcomes following completion of Phase I recovery. However, 4 patients were discharged to the intensive care unit from the PACU. Three of these cases (1 LMVe patient) were for respiratory causes (2 needed unplanned noninvasive positive pressure ventilation and one had high supplemental oxygen requirements) and one for hypotension refractory to fluid administration. Three other patients needed subsequent transfer to the intensive care unit later during their hospitalization because of hemodynamic instability. One patient on the day following
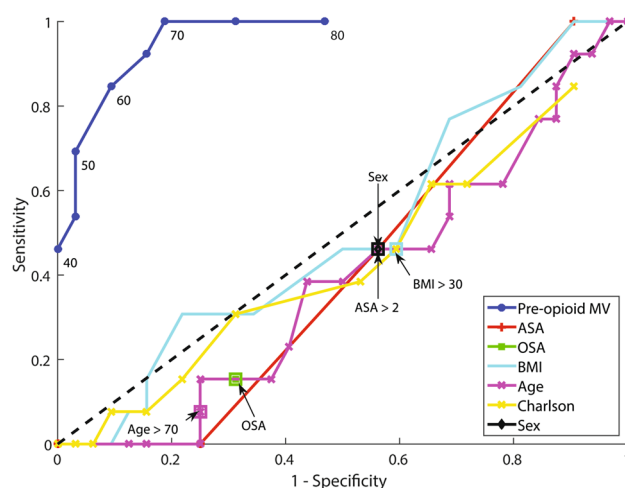
Fig. 2 Receiver operating characteristic (ROC) curves of 7 different classifiers (predictors) based on: Pre-opiod MV measurements (blue), ASA PS Classification (red), OSA history (green), BMI (cyan), age (magenta), Charlson Comorbidity Index (yellow), and sex (black) used to stratify patients into "At-Risk" and "Not-At-Risk" for OIRD. Dashed black line indicates the performance of a random chance classifier
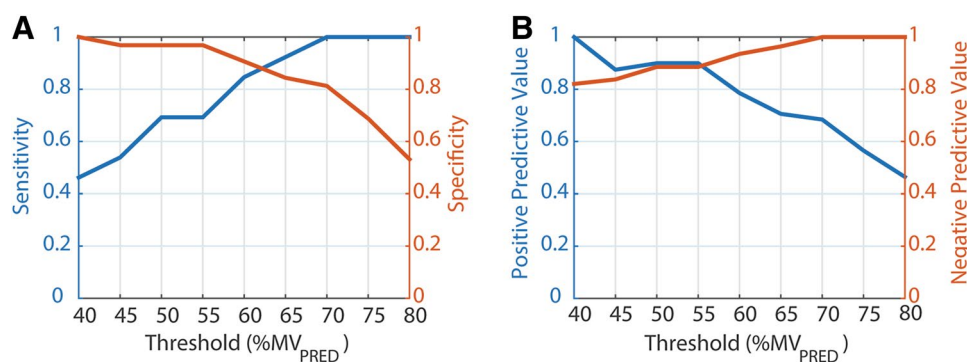
Fig. 3 **a** By varying the threshold of Pre-Opioid MV the classifier can be tuned to achieve desired sensitivity (blue) and specificity (red) values. Sensitivity is maximized at thresholds greater than 70% of MV_{PRED}, while specificity is greatest below 55% of MV_{PRED}. **b** A negative predictive value (red) of 1 can be achieved as a tradeoff for a lower positive predictive value (blue) of 68.4% at a threshold value of 70% MV_{PRED}

surgery developed postoperative somnolence requiring opioid reversal with naloxone. This patient was a 56-year-old man with chronic pancreatitis and opioid tolerance, who also had two LMVe episodes. His postoperative pain was controlled with an aggressive regimen of intravenous hydromorphone and oral oxycodone and tramadol as well as zolpidem for sleep. The median [interquartile range] hospital length of stay among patients who had an LMVe was 2 [1, 5] days and 1 [1, 3] days among those who did not such event, $P = 0.23$.

4 Discussion

The main finding in this study was that LMVe following opioid administration in the PACU was associated with pre-existing mild respiratory depression (MV < 70% of MV_{PRED}) as detected by the RVM. However, there were no nursing-diagnosed episodes of respiratory depression during Phase I recovery. Therefore, continuous monitoring of MV using RVM can aid in the accurate assessment of respiratory status, as well as provides an opportunity for individualized opioid dispensation which may lead to reduction of opioid-induced respiratory depression. Risk classification schemes based on variables such as ASA physical status class, OSA diagnosis, BMI and age have failed to produce classifiers that are simultaneously sensitive and specific, regardless of threshold values. In addition, while RR is routinely monitored in PACU, with the low rate considered to be a marker of respiratory depression [3, 4] we demonstrated that low RR (RR < 8 breaths per minute) missed 88.2% of all low MV (< 40% of MV_{PRED}) events. This suggests that monitoring RR alone in our surgical population was a poor parameter for detection of respiratory depression. This observation is similar to the study by Voscopoulos et al. [6] that used the RVM to detect episodes of OIRD during Phase I recovery among patients undergoing elective joint replacement. They

found that decreases in MV following opioid administration were primarily due to reductions in TV (20.9 ± 3.5%) rather than RR (11.1 ± 3.0%). Similarly, Holley et al. [11] reported among patients undergoing endoscopic procedures that monitoring of RR was inadequate to detect LMVe episodes. For example, a cut off 8 breaths per minute missed greater than 70% of LMVe episodes [11]. Gonzales Castro et al. [12] used RVM to assess respiratory depression after midazolam administration and recorded that reductions in MV were largely due to reductions in TV, and that in younger patients there was a compensatory increase in RR which mitigated the midazolam-induced MV reduction.

In our study mild respiratory depression prior to opioid administration in recovery room was associated with LMVe after opioid dosing. In this cohort, 70% of MV_{PRED} was found to be the optimal threshold (high sensitivity and specificity) for classifying patients as "at risk" for OIRD. Two previous studies that assessed the same monitoring technique during Phase I anesthesia recovery after elective joint replacement surgeries, under general or spinal anesthesia, found similar results with 80% of MV_{PRED} as the optimal threshold, yielding sensitivities and specificities of 93 and 86% [6] and 92 and 80% [13], respectively. In the context of detection of patients at increased risk for development of OIRD, a gain in sensitivity is preferable over a minor loss in specificity, since the potential measures this classification will occasionally warrant, such as additional postoperative monitoring and changes in the analgesic regimen (e.g. adjustment in the opioid dosing, start of a multimodal or an opioid-free approach), have limited potential for harm.

Another important observation is that patient, surgical and anesthetic characteristics, with the exception of increasing doses of intraoperative opioids, were not associated with LMVe. In previous studies, we found that nursing-diagnosed episodes of respiratory depression during Phase I recovery were associated with patient factors such as older age, male

sex, greater comorbidity, and presence of OSA, as well as perioperative factors such as duration of surgery, choice of volatile anesthetic, and increasing doses of intraoperative opioid analgesics [14, 15]. In the present study no nursing-diagnosed episodes of respiratory depression were recorded during Phase I recovery which is likely related to our recent changes to practice protocols (e.g., choice of volatile and analgesic administration) [5] designed to reduce this type of complication [14, 15]. This same reasoning may be extended to the finding of lack of associations between patient and procedural characteristics and LMVe measured with RVM.

Previous studies of nursing diagnosed episodes of respiratory depression during Phase I recovery have observed increased rates of postoperative complications. Gali et al. [4] found that 33% patients who had both a positive screen for OSA as well as repeated episodes of respiratory depression had a postoperative respiratory complication. Another study found that a patient who had a single episode of respiratory depression during Phase I recovery [4] was at a fivefold increased risk for emergent naloxone administration to reverse OIRD on the postoperative ward [5]. In other studies, rates of ICU admissions were much greater in patients who had similarly defined respiratory depressive episodes during Phase I recovery [14, 15]. The present study was not powered to determine if LMVe as detected by the RVM were associated with increased risk for postoperative complications. However, one patient who required postoperative naloxone administration after PACU dismissal did have LMVe in the PACU. This patient was opioid tolerant and on an aggressive multimodal regimen for both pain and insomnia, and was probably at high risk for adverse events related to oversedation. A previous study demonstrated that the presence of LMVes on patients receiving opioids postoperatively was associated with 93% longer PACU stay [16]. While it is logical that patients that demonstrate a tendency toward respiratory depression as manifested by LMVe in the PACU would be more likely to suffer postoperative complications, further studies need to be performed to demonstrate this. Nonetheless, the proposed classification system, based on pre-opioid MV, is both simple and intuitive.

This prospective study is limited by its small sample size which limits our ability to detect certain patient and perioperative factors that may be associated with LMVe. Further, this smaller sample size limits our ability to determine if subclinical LMVes detected with RVM are associated with postoperative complications.

In conclusion, our observation that RVM-detected mild MV depression prior to opioid administration is associated with increased risk for LMVe suggests that this monitor could be used to provide guidance for opioid treatment and may aid in reduction of perioperative opioid-induced adverse events. Furthermore, we found respiratory rate to be a poor indicator for LMVe and hence respiratory depression. This new information may question the value of purely clinical observation for the signs of respiratory depression, especially those that rely on respiratory rate, and suggests the importance of introduction of more advanced respiratory assessments for early recognition of looming respiratory depression.

Compliance with ethical standards

Appendix

See Table 3.

Table 3 Predictors of low minute ventilation events following opioid administration during Phase I anesthesia recovery

Criteria	LMVe true positive (n = 13)	No LMVe false positive (n = 32)	P	Sensitivity (%)	Specificity (%)
Pre-opioid MV < 70% of MV$_{PRED}$	13	6	0.0001	100.0	81.2
ASA physical status 3 or 4	6	18	0.74	46.2	43.8
Obstructive sleep apnea	2	10	0.46	15.4	68.8
Body mass index > 30 kg/m^2	6	19	0.52	46.2	40.6
Age > 70 years	1	8	0.25	7.7	75.0
CCI score > 5	4	10	> 0.99	30.8	68.8
Male sex	6	18	0.74	46.2	43.8

ASA American Society of Anesthesiologists, *CCI* Charlson Comorbidity Index, *LMVe* low minute ventilation, *MV* minute ventilation, *MV$_{PRED}$* normal minute ventilation, based on gender, age and calculated body surface area

The Pre-opioid MV < 70% of MV$_{PRED}$ value was selected based on an analysis of varying Pre-opioid MV values to generate a receiver operating characteristic curve to find the optimal sensitivity and specificity as a classifier for LMVe episodes (See Fig. 3). *P* values were calculated using Fisher's exact test. Only Pre-opioid MV was a statistically significant predictor of LMVe (*P* = 0.0001)

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