# Hypoventilation in the PACU is Associated with Hypoventilation in the Surgical Ward:

## Post-hoc Analysis of a Randomized Clinical Trial

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**Running Head Title:** Hypoventilation in the PACU and in the surgical ward

**Funding:** Respiratory Motion Inc. provided funding for this study but was not involved in data analysis, writing the manuscript, or the decision to publish**.**

**Declarations of interest:** None

## Abstract

**Objective -** to evaluate the association between early postoperative hypoventilation in the last hour of the post-anesthesia care unit (PACU) stay and hypoventilation during the rest of the first 48 postoperative hours in the surgical ward.

**Design -** sub-analysis of a clinical trial

**Setting –** PACU and surgical wards of a single medical center

**Patients -** adults having abdominal surgery under general anesthesia

**Interventions -** monitoring with a respiratory volume monitor (ExSpiron®, Respiratory Motion Inc., Watertown, MA, USA) from admission to PACU until the earlier of 48 hours after surgery or discharge

**Measurements -** The exposure was having at least one low minute-ventilation (MV) event during the last hour of PACU stay, defined as MV lower than 40% the predicted value lasting at least 1 minute. The primary outcome was low MV events lasting at least 2 minutes during the rest of the first 48 postoperative hours, while in the surgical ward. The secondary outcome the rate of low MV events, during the first 48 postoperative hours while in the surgical ward,

**Main results -** Data of 292 patients were analyzed, of which 20 (6.8%) patients had a low MV event in PACU. Low MV events in the surgical ward were found in 81 (28%) patients. All patients who had low MV events in PACU had events again in the ward, while 61/272 (22%) had an event in the ward but not in PACU. The incidence rate of low MV events per hour was 24 (95% CI: 13, 46) among patients having an event in the

PACU, and 2 (1, 4) among those who did not, after weighting.~~Using PACU low MV events as a predictor, the sensitivity was 0.25 (95% CI: 0.16, 0.36), and the specificity was 1.00 (0.98, 1.00). The positive and negative predictive values were 100% and 78%, respectively.~~

**Conclusions -** In adults recovering from abdominal surgery, events of hypoventilation during the first postoperative hour are associated with similar events during the rest of the first 48 postoperative hours, with positive predictive value approaching 100%. ~~About one fifth~~Sixty-one ~~of~~ patients had ward hypoventilation that was not preceded by hypoventilation in PACU.

**Keywords:** Hypoventilation, postoperative, surgical ward, opioids

## Introduction

Worldwide, about 312 million surgeries take place every year.[1] Postoperative complications are the main determinants of survival after major surgery[2,3] and are associated with increase in hospital costs.[4] After surgical wound infection, pulmonary complications are the most common postoperative complications.[5] The incidence of postoperative respiratory depression when we use continuous monitoring is as high as ~~37~~46% with capnography [6] and 37% with pulse oximeter,[6,7]~~[6].~~ ~~and according to some~~ To monitor and prevent respiratory depression events is important because ~~reports, it~~ they might result~~s~~ in critical events such as death or severe brain injury in ~~as many as~~ 7~~5~~% of cases.[8] Moreover, the majority of these events happened within 24 h of surgery, and were classified as preventable with better monitoring and response. Specially, this respiratory postoperative monitoring seems important in patients on opioid postoperative analgesia. ~~One of the major reason of postoperative respiratory depression is opioid administration as part of postoperative analgesia.~~[8,9] because it might result in ~~Moreover, the recent introduction of adequate pain control as a quality measure[10]~~ resulted in an increase in opioid ~~administration and consequently to~~ higher incidence of opioid-related adverse events, such as over-sedation, respiratory depression and neurological damage.[10] Therefore, the American Society of Anesthesiologists now recommends ~~that all patients receiving opioids should be~~to continuous monitor ~~monitored~~ for respiratory depression using capnography during the postoperative period.[11]

However, universal monitoring of all postoperative patients in the surgical wards is challenging and expensive. It is therefore valuable to identify the patients at greater risk, and to decide when and how to monitor them during the postoperative period. ~~A~~

~~recent~~The analysis of the Closed Claim database found that 13% of postoperative respiratory depression events occurred during the initial 2 hours after discharge from the post-anesthesia care unit (PACU), and nearly 90% of these events occur during the initial 24 postoperative hours.[8] The early postoperative period in PACU is characterized by rapid and extreme changes in organ function, and by high incidence of pulmonary complications[12–14] which are associated with a 5-fold greater risk of respiratory depression in the surgical ward.[12,15]

There are currently no accepted guidelines for monitoring opioid-related sedation and respiratory depression. Pulse oximetry is widely used but it is a measure of gas exchange and therefore it only detects late respiratory depression. Capnography provides additional information on ventilation that can detect respiratory depression prior to oxygen desaturation, especially if supplemental oxygen is administered~~, but it is often ill-tolerated by patients~~.[16] Impedance-based non-invasive respiratory volume monitors continuously evaluate respiratory rate and minute ventilation with up to 90% accuracy.[17,18] A small observational study demonstrated that ~~patients who~~patients who experienced a low minute ventilation event during the PACU stay as detected by a respiratory volume monitor had higher incidence of respiratory depression during the ~~rest of hospitalization~~first 12 postoperative hours in the surgical ward compared to patients without low minute ventilation events.[19]

We therefore aimed to evaluate in la larger nonobese population under major abdominal surgery the association between early postoperative hypoventilation in the last hour of PACU stay and hypoventilation during the rest of the first 48 postoperative hours in the surgical ward. Specifically, we tested the hypothesis that adult patients recovering

from major abdominal surgery who experience at least one low minute-ventilation event within the last hour of stay in PACU have higher incidence of hypoventilation events during the first 48 postoperative hours in the surgical ward compared to patients without such events in PACU. Secondarily, we hypothesized that patients with at least one low minute ventilation event in PACU have a higher rate of hypoventilation events per monitoring hour during the first 48 postoperative hours in the surgical ward.

## Methods

This is a sub-analysis of prospectively collected data from patients enrolled in the FACTOR Trial (Cleveland Clinic IRB #14-241, NCT #02156154), that evaluated the effect of intravenous acetaminophen *versus* placebo on the incidence of postoperative desaturation.[20] Participants were monitored with a respiratory volume monitor (ExSpiron®, Respiratory Motion Inc., Watertown, MA, USA) from admission to PACU until the earlier of 48 hours after surgery or discharge. This sub-analysis was approved by the Cleveland Clinic Institutional Review Board with waived individual consent (Cleveland Clinic IRB # 18-384). Adults undergoing abdominal surgery under general anesthesia and enrolled in the FACTOR trial were considered eligible. Patients with poor-quality or limited respiratory monitoring data, defined as less than 1 hour recording in PACU or less than 6 hours recording on the surgical ward, were excluded.

The exposure of interest was having at least one low minute-ventilation (MV) event during the last hour of PACU stay. A low MV event was defined as having a minute-

ventilation measurement lower than 40% the predicted value based on body surface area and sex,[21,22] lasting at least 1 minute. The primary outcome was the occurrence of at least one low MV event lasting at least 2 minutes during the rest of the first 48 postoperative hours, while in the surgical ward.[23,24] The secondary outcome was the rate of low MV events, defined as the number of events lasting at least 2 minutes during the first 48 postoperative hours while in the surgical ward, divided by the number of monitored hours. Gaps in monitoring were excluded from the total monitoring time.

*Data analysis*

We preliminarily assessed the association between baseline variables (prior to last hour of PACU stay) and the exposure, low MV events in PACU, using standard statistical tests, i.e., t-tests for continuous variables, chi-square or Fisher's exact test for categorical variables, as appropriate, and Wilcoxon-Mann-Whitney or another non-parametric test for ordinal or non-normal continuous data. Pre-exposure variables included age, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status score, relevant medical conditions (*i.e.*, pulmonary disease, smoking status, asthma and obstructive sleep apnea) type and length of surgery, PACU length of stay, morphine equivalents administered~~, and relevant medical conditions (*i.e.*, pulmonary disease, smoking status, asthma, obstructive sleep apnea, and obesity~~).

We used a Fisher exact test to compare the raw incidence of low MV events in the surgical ward between patients with and without PACU low MV events. We then reported the sensitivity, specificity, predictive value and accuracy, using PACU low MV events as a predictor of low MV events in the surgical ward. Odds ratio of the unadjusted association is not reported, because all patients who experienced a low MV event in the PACU also

had events in the surgical ward.

For our primary analysis, the potential confounding effect of all baseline variables was controlled using inverse propensity score weighting (IPTW).[25] We then assessed the adjusted association between low MV events in PACU and the occurrence of low MV events during the rest of the first 48 postoperative hours using negative binomial regression, with adjustment for number of post-PACU hours of measurement after inverse propensity score weighting. We used similar methods to test the adjusted association between low MV events in PACU and the secondary outcome, defined as the number of low MV events during the rest of the first 48 postoperative hours, divided by the number of monitoring hours. We did not adjust for PACU duration, surgery duration and surgery type for the secondary analysis due to model not converging issue.

We used the absolute standardized difference (ASD) to evaluate imbalance between the groups on baseline variables. ASD is defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation. Variables were considered significantly different if ASD was greater than 0.2. The significance level for all statistical tests was set to 0.05.

Sample size was calculated based on the primary hypothesis. We estimated that 10% of patients would experience a low MV event in the last hour prior to PACU discharge. Assuming a standard deviation of 1.5 low MV events/hour across the population, a total of 270 patients would be needed to detect a difference of 1 low MV event/hour between groups (assuming 10% of patients in the exposure group) with 90% power at the 0.05 significance level.[26]

All analyses were performed with SAS Ver 9.4.

## Results

In total, 292 patients who were enrolled in the FACTOR trial were eligible for this sub-analysis (Figure 1). Baseline characteristics, opioid consumption, and monitoring duration are summarized in **Table 1**, presented according to the presence or absence of PACU low MV events. In total, 20 (6.8%) patients had a low MV event in PACU. These patients had higher body mass index than patients who did not experience low MV event in PACU. Other potential confounding variables were not different between the two groups. After propensity score weighting, the balance of all potential confounders was well controlled, with a maximum absolute standardized difference (ASD) of 0.05.

Low MV events in the surgical ward were found in 81 (28%) patients. All patients who had low MV events in PACU had low MV events again in the surgical ward, while 61/272 (22%) had an event in the surgical ward without having an event in PACU (**Table 2**). PACU low MV events were strongly associated with low MV events in the surgical ward (Fisher exact test P <0.001) before and after inverse propensity score weighting. Using PACU low MV events as a predictor, the sensitivity was 0.25 (95% CI: 0.16, 0.36), and the specificity was 1.00 (0.98, 1.00). The positive and negative predictive values were 100% and 78%.

The secondary outcome was the rate of low MV events in the surgical ward, expressed as the number of events per monitoring hour. Low MV events in PACU were significantly associated with the rate of low MV events in the surgical ward. The incidence rate of low MV events per hour was 24 (95% CI: 13, 46) among patients having an event in the PACU, and 2 (1, 4) among those who did not, after weighting. The incidence rate

odds ratio of low MV events was 12 (5, 28; P<0.001) adjusted for all confounders in **Table 1**.

## Discussion

In this sub-analysis of a clinical trial involving adults recovering from abdominal surgery, we found a strong association between low MV events during PACU stay and the risk of experiencing a hypoventilation event during the initial 48 postoperative hours while in the surgical ward. We also found that patients with low MV events in PACU have many more events of hypoventilation in the surgical floor.

Preoperative risk factors such as age, sex, BMI, hypertension, American Society of Anesthesiologists (ASA) physical status score, as well as type and length of surgery were previously reported as risk factors for PACU[27] and postoperative respiratory depression.[28,29] We only observed large difference in BMI, with absolute standardized difference of 66% between patients with and without hypoventilation in PACU, but not in other factors.

In general, the reported incidence of respiratory depression is highly variable, depending on the outcome definition. We only found 6.8% of patients to have a low MV event in PACU, which is significantly lower than the 15-24% incidence described in previous retrospective cohort studies,[13,14] and the 11% reported in previous studies using similar ~~definition of~~cutoff of low MV events.[19] This difference might be explained because in Schumann et al,[19] the average BMI was 37±10 kg/m$^2$, with 20% incidence of OSA and almost half of patients under bariatric surgery. While in our study,the average

BMI was around 27±10 kg/m$^2$, with and OSA incidence of 5% and no patients under bariatric surgery. Our incidence of low MV events in the surgical ward was 30%, which is within the range previously reported, depending on the method used to detect respiratory depression. For example, respiratory depression occurred in 44% of patients in the recently published PRODIGY study,[29] in which hypoventilation was defined by a composite of respiratory rate, oxygen saturation, and capnography. However, respiratory depression was only found in 4.2% of participants in the PERISCOPE study[28] where it was defined as new onset of hypoxemia ($PaO_2$ <8 kPa or SpO2 <90%) within 5 postoperative days. This large variability surely originates from the difference in definitions, and in monitoring technologies. ~~presumably from different clinical practices (e.g., opioid sparing pathways).~~

The rate of low MV events per hour was 12 times higher OR 12 (95%CI: 5, 28; P<0.001) in patient who had low MV at PACU compared to those who did not. These results are consistent with Schumann et al.[19] results that forum 1.5 more events in the patients classifies as at risk in PACU. Moreover, Broens et al.[30] found a correlation between the incidence of respiratory events (bradypnea and apnea) in PACU and during the first 6 postoperative hours on the ward, in patients over 60 year old having elective surgery. [30]

The positive predictive value of hypoventilation during the last hour of PACU stay reached 100%, suggesting that patients suffering even one hypoventilation event during that period will almost certainly continue to have such events during the rest of their postoperative recovery. This rate of detection was superior to the values previously reported by others.[28,29] The test's negative predictive value was 78%, suggesting that

about 20% of patients not detected to have hypoventilation in PACU will still suffer such event in the hospital ward. Notably, the incidence rate of low MV events per hour was only 2 among patients not suffering a hypoventilation event in PACU (compared to 24 among patients having an event in PACU). Such a low incidence rate may explain why some of the 81 patients with ward hypoventilation events were not detected during the last hour in PACU.

Our findings are of special interest since postoperative respiratory complications are common and are associated with deleterious outcomes that might impact overall recovery.[8,31] However, there are no accepted guidelines for routine respiratory monitoring of spontaneously breathing surgical patients, so that patients at risk are neither identified, diagnosed, monitored, nor treated appropriately.[11] The most commonly used modality is oxygen saturation, but desaturation is often a late sign of respiratory failure.[16] Capnography is a much earlier and more sensitive sign of hypoventilation but is rarely utilized in clinical practice ~~due to patient discomfort and low compliance with the nasal canula that mandates accurate and stable placement~~.[29] The respiratory volume monitor reliably detects respiratory depression in the surgical ward.

The main limitations of our study are the limited sample size and the low baseline incidence of the exposure. We were therefore underpowered to detect an association between hypoventilation events and the incidence of clinically important outcomes such as respiratory failure, cardiac arrest, or death. Two notable strengths are the prospective data collection and the previously demonstrated reliability of the monitor in measuring respiratory volumes.[17,18]

In summary, we found a strong association between low MV events during PACU stay and the risk of hypoventilation during the initial 48 postoperative hours in adults recovering from abdominal surgery. These results should encourage clinicians to closely monitor patients who demonstrate hypoventilation during the immediate postoperative recovery phase to improve earlier detection of postoperative respiratory depression.

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