HHS Public Access

Author manuscript

Anesth Analg. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Anesth Analg. 2020 August ; 131(2): 555–563. doi:10.1213/ANE.0000000000004553.

HYPOXEMIA Within The First Three Postoperative Days Is Associated With Increased One-Year Postoperative Mortality After Adjusting For Perioperative Opioids And Other Confounders

Karsten Bartels, M.D., Ph.D. [Associate Professor],
Departments of Anesthesiology, Medicine, and Surgery, University of Colorado School of Medicine

Alexander Kaizer, Ph.D. [Assistant Professor],
Department of Biostatistics, University of Colorado School of Medicine

Leslie Jameson, M.D. [Associate Professor],
Department of Anesthesiology, University of Colorado School of Medicine

Kenneth Bullard, B.S. [Information Systems Manager],
Department of Anesthesiology, University of Colorado School of Medicine

Colleen Dingman, R.N., Ph.D. [Assistant Professor of Anesthesiology],
Department of Anesthesiology, University of Colorado School of Medicine

Ana Fernandez-Bustamante, M.D., Ph.D. [Associate Professor]
Department of Anesthesiology, University of Colorado School of Medicine

Corresponding author: Ana Fernandez-Bustamante, M.D., Ph.D., Associate Professor, University of Colorado School of Medicine, Department of Anesthesiology, 12631 E 17th Ave, AO-1, R2012, MS 8202, Aurora, CO, 80045, Ph: 303-724-2935 (office) / Fax: 303-724-1761, Ana.Fernandez-Bustamante@cuanschutz.edu.

• Contribution: Karsten Bartels contributed to study design, conduct of the study, data analysis, interpretation of the data and writing of the manuscript.
• Attestation: Karsten Bartels approved the final manuscript.
• Contribution: Alex Kaizer contributed to the study design, data analysis, interpretation of the data, and helped critically revise the manuscript.
• Attestation: Alex Kaizer approved the final manuscript. Alex Kaizer attests to the integrity of the data analysis reported in this manuscript.
• Contribution: Leslie Jameson contributed to study design, data collection, interpretation of the data, and helped critically revise the manuscript.
• Attestation: Leslie Jameson approved the final manuscript.
• Contribution: Kenneth Bullard contributed to acquisition of the data and helped critically revise the manuscript.
• Attestation: Kenneth Bullard approved the final manuscript.
• Contribution: Colleen Dingman contributed to study design, IRB compliance and helped critically revise the manuscript.
• Attestation: Colleen Dingman approved the final manuscript.
• Contribution: Ana Fernandez-Bustamante contributed to study design, conduct of the study, data collection, data analysis, interpretation of the data, and writing of the manuscript.
• Attestation: Ana Fernandez-Bustamante approved the final manuscript. Ana Fernandez-Bustamante attests to the integrity of the original data and the analysis reported in this manuscript. Ana Fernandez-Bustamante is the archival author.
Authors' contributions. KB contributed to the study design, data collection, analysis, interpretation and manuscript writing; AK contributed to the study design, data analysis, interpretation and manuscript writing; LJ contributed to study design, data collection, interpretation, and manuscript revision; KB contributed to the data collection and manuscript revision; CD contributed to the study design, IRB compliance and manuscript revision; AFB contributed to the study design, data collection, analysis, interpretation and manuscript writing, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest: None

Clinical trial number: Not applicable.

Abstract

Background—Postoperative hypoxemia (POH) is common and primarily treated with temporary oxygen supplementation. Because the clinical impact of postoperative hypoxemia is sometimes presumed as minor, efforts to better understand and minimize it have been limited. Here, we hypothesized that, after adjusting for opioids received perioperatively and other confounders, the frequency of POH events reported within the first 3 postoperative days (POD) is associated with increased postoperative 1-year mortality.

Methods—With prior IRB approval, the Epic Clarity database was queried for all adult inpatient anesthesia encounters performed at our health system (1 academic and 2 community hospitals) from 1/1/2012 to 3/31/2016. Patients with multiple hospitalizations or subsequent surgeries within the same hospitalization were excluded. We classified patients based on the presence (POH) or not (No-POH) of ≥1 documented peripheral saturation of oxyhemoglobin (SpO_2) ≤85% event of any duration occurring between the discharge from the post-anesthesia care unit until POD 3. Demographics, comorbidities, surgery duration, morphine milligram equivalents administered perioperatively, respiratory therapies, intensive care unit (ICU) admission and hospital length of stay were also collected. Logistic regression was used to characterize the association between POH and 1-year postoperative mortality after adjusting for perioperatively administered opioids and other confounding factors.

Results—A total of 43,011 patients met study criteria. At least one POH event was reported in 10,727 (24.9%) patients. Of these, 7,179 (66.9%) had ≥1 hypoxemic event on POD1, 5,340 (49.8%) on POD2 and 3,455 (32.3%) on POD3. Patients with ≥1 POH event, compared to No-POH patients, were older, had more respiratory and other comorbidities, underwent longer surgeries, received greater opioid doses on the day of surgery and POD1 and received more continuous pulse oximetry monitoring. POH patients required more frequent postoperative oxygen therapy, noninvasive ventilation, reintubation, and ICU admission. One-year postoperative mortality occurred in 4.4% of patients with ≥1 POH and 3.0% of No-POH patients ($p<0.001$). After adjusting for confounding factors, for every 10% increase in the frequency of SpO_2≤85% readings, the odds of postoperative 1- year mortality were 1.20 (95%CI: 1.11–1.29, $p<0.001$). Perioperative opioids were not independently associated with increased 1-year mortality.

Conclusions—After adjusting for perioperative opioids and other confounders, moderate/severe POH within the first 3 postoperative days was independently associated with increased 1-year postoperative mortality. Increased efforts should be directed to understand if efforts to detect and reduce postoperative hypoxemia lead to improved patient outcomes.

Introduction

Periods of postoperative hypoxemia (POH) are common after surgery, with a frequency ranging from 5% to 65.5%[1–6] depending on the surgical population involved, definition of hypoxemia (severity and duration) and monitoring methods (intermittent or manual *vs.* continuous or automated pulse oximetry). Accurate characterization of the frequency, duration and severity of POH requires continuous pulse oximetry[7], but routine postoperative care relies primarily on intermittent visual assessments of ventilation and manual checks of peripheral saturation of oxyhemoglobin (SpO_2). Due to practical challenges in accurate

characterization and reporting, most POH events are underdiagnosed in frequency but also severity and duration[2,8]. In a study with simultaneous monitoring methods, sporadic SpO_2 manual assessments missed 90% of episodes of SpO_2 <90% for >1h detected with continuous pulse oximetry[2]. The clinical impact of POH may also be underappreciated. Although it has been associated with increased risk of postoperative cardiac ischemia[9] and cognitive dysfunction[10], most POH episodes are resolved with temporary oxygen supplementation. However, the use of prolonged (>1 day) postoperative oxygen therapy has been associated with prolonged hospital stay, admission to the intensive care unit (ICU) and increased need of resources during and after hospital discharge[1,11,12]. The relationship of POH to 1-year postoperative mortality is unknown, but this information would reinforce the need to better characterize the etiology and reduce POH.

Episodes of POH are multifactorial, but are often related to perioperatively administered opioids[6,13,14]. Interestingly, a recent study found no significant increase in opioid-induced hypoxemia in patients using long-acting opioids *versus* short-acting opioids for patient-controlled-analgesia[14]. Nonetheless, there are ongoing efforts to limit opioid administration perioperatively, also with the goal of reducing chronification of opioid use[15]. Enhanced-Recovery After Surgery (ERAS) protocols, usually build on opioid-minimizing strategies aimed at reducing adverse opioid-related side effects[16]. However, the relationship between perioperative opioid use, POH events, and their relationship with postoperative mortality remains poorly understood.[17]

Here, we hypothesized that independently of opioids received perioperatively and other confounding factors, moderate/severe POH ($SpO_2 \leq 85\%$) documented after discharge from the PACU and within the first 3 postoperative days (POD 1–3) would be associated with increased 1-year postoperative mortality. Such an association would justify increased efforts to understand, prevent and reduce POH events that currently are often viewed as having little relevance. We tested our hypothesis in a retrospective analysis of our health system clinical data warehouse, which included one academic and two community hospitals.

Methods

We performed a retrospective database study after approval by the Colorado Multiple Institutional Review Board (COMIRB #09–0674). The requirement for informed consent was waived by the IRB.

Study design

This study was designed following the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) guideline. The primary and secondary outcomes were defined and established *a priori* at initiation of the study design. We queried the Epic Clarity electronic medical record (EMR) database at the University of Colorado Health (UCHealth) system for all adults undergoing inpatient anesthesia care in one of its hospitals between 1/1/2012 to 3/31/2016. During this period, UCHealth was composed of a large academic tertiary medical center and two community hospitals. Patients were included if they fulfilled the following criteria: ≥18 years and receiving anesthesia care for any surgical procedure. Exclusion criteria included: subsequent procedures for each patient within a year from the

first date of surgery, outpatient procedures, organ donations, missing procedure type, procedure duration <15 minutes or >24 hours, patients with Body Mass Index (BMI) <12 or >80, American Society of Anesthesiologists (ASA) physical status 5–6 or missing. Only patients with one hospitalization over the study period were included to avoid the confounding effect of patients with worse systemic health or staged procedures. Figure 1 shows the study schematic flowchart.

Data collected

We extracted demographic information, comorbid conditions, surgery duration, oral morphine milligram equivalents (OMME) administered on the date of surgery and daily on postoperative days 1–3 (POD1–3). The OMME dose on the date of surgery was chosen as a covariate as it likely also reflects the degree of procedure complexity and surgical trauma inflicted. We noted the documentation of any POH event, defined as any episode of $SpO_2 \leq 85\%$ of any duration and cause obtained with continuous or intermittent pulse oximetry from discharge from the post-anesthesia care unit (PACU) until POD 3. All postoperative SpO_2 values in our electronic medical record system are either automatically transferred to the medical chart (continuous pulse oximetry) or entered and validated by the patient's nursing staff (for intermittent pulse oximetry). The specific method of SpO_2 monitoring is not recorded in the EMR. Therefore, we assumed pulse oximetry was intermittent if SpO_2 measurements documented in the EMR daily were ≤8 *versus* continuous if >8. We expressed the frequency of POH events (POH%) as follows:

POH% = (Number of $SpO_2 \leq 85\%$ measurements POD 1–3) / (Total number of SpO_2 measurements POD 1–3)

We also collected the presence postoperatively of the following respiratory interventions: supplemental oxygen therapy, noninvasive ventilation (NIV, including auto-titrated, bi-level or continuous positive airway pressure) and reintubation with mechanical ventilation. Postoperative transfer to the ICU, either planned (if occurring immediately after surgery) or unplanned (if happening ≥12h after discharge from PACU) and the hospital length of stay were also recorded. Mortality was extracted from the EMR.

Patient classification

Patients were classified into 2 groups as presenting ≥1 POH event, defined as the presence in the patient's chart of $SpO_2 \leq 85\%$ of any duration after discharge from the PACU until POD 3 (POH) or not presenting any POH (No-POH). This classification occurred independently of cause, any concurrent oxygen supplementation or other respiratory therapies.

Endpoints

The primary outcome was mortality within 1 year after the date of surgery.

Statistical analysis

Data were inspected for outliers, missing data, and data entry errors using graphical and univariate analyses. Missing data and outlier data values were individually revised for

completion, correction or left as missing data points. Cases with insufficient data for Body Mass Index (BMI) calculation, BMI values <12 or >80, and surgery durations >24h or <15min were excluded. Values of SpO_2<50% were assumed unreliable and considered missing and values >100% were coded as 100%. The analyses were restricted to patients with only one record, excluding those with multiple records due to convergence issues with statistical models that account for correlated observations (e.g., mixed effects models and generalized estimates equations).

To examine the association between POH and the primary (1-year postoperative mortality) and secondary outcomes, two-sample t-tests or Chi square tests were used to estimate the unadjusted association for continuous or categorical outcomes, respectively. Multiple logistic regression was used to evaluate the adjusted association of POH and 1-year postoperative mortality, adjusting for OMME received and other variables selected *a priori* based on clinical relevance.

All analyses were performed using R v3.5.0[18]. Due to the large sample size a conservative level of significance of p<0.010 was used for all statistical tests.

Results

Characteristics

A total of 43,011 patients met study criteria (see Consort study diagram in Figure 1). At least one POH event was observed in 10,727 (24.9%) patients and 32,284 (75.1%) of patients had no POH events reported (No-POH). Table 1 shows that patients in the POH group were older than No-POH patients and had a greater systemic comorbidity load with the exception of similar smoking history and neurological disease, underwent longer surgeries performed more likely at the academic center, required higher OMMEs on date of surgery and POD1, and received more often continuous SpO_2 monitoring. Opioids received on POD2 and POD3 should be interpreted cautiously due to the high presence of missing data and variability in daily doses on those days. Several of these differences (e.g. age, BMI, asthma) were statistically significant despite a small difference between the groups due to the large sample size.

Postoperative hypoxemia, 1-year postoperative mortality and other clinical outcomes, unadjusted

The POH event(s) occurred primarily on POD1 (in 7,179 (66.9%) of POH patients), progressively decreasing on POD2 (5,340 (49.8%) of POH patients) and POD3 (3,455 (32.2%) of POH patients) (Table 2). As expected, patients with ≥1 POH event on POD1–3 required significantly more respiratory interventions, including oxygen supplementation, NIV, reintubation, as well as greater admission to ICU and longer hospital length of stay (Table 1). Mortality within 1 year of surgery was greater in patients with ≥1 POH event compared to No-POH patients (4.4% *vs.* 3.0%, respectively) (Table 2). Figure 2 describes the distribution of POH% at each POD 1–3 for both SpO_2 monitoring methods.

Factors associated with 1-year postoperative mortality, logistic regression results

Mortality within 1 year from date of surgery was significantly associated with the frequency of POH events (POH%) after adjusting for confounders (Table 3). After adjusting for other confounding factors, for every 10% increase in the frequency of $SpO_2 \leq 85\%$ measurements, the odds of 1-year postoperative mortality were 1.20 (95%CI: 1.11–1.29) ($p<0.001$). The variables with the strongest association with 1-year postoperative mortality were the ASA physical status 4 and 3, and reintubation (Table 3). Other variables independently associated with mortality were, in decreasing order of their OR: unplanned ICU admission, postoperative continuous SpO_2 monitoring, liver disease, renal disease, other respiratory diseases, diabetes, POH%, male gender, and older age (Table 3). Pre-existing hypertension and the BMI were inversely associated with 1-year postoperative mortality. Interestingly, OMME on date of surgery or POD1, cardiac disease or hospital length of stay were not significantly associated with postoperative mortality. Results of alternative logistic regression models using different definitions of POH (including mild hypoxemia with POH defined as $SpO_2<90\%$, and severe hypoxemia only with POH defined as $SpO_2<80\%$), as well the effect of accumulated POD on which POH events occurred are shown in the Supplement.

Discussion

This system-wide retrospective study evaluated if moderate/severe POH is associated with increased 1-year postoperative mortality independently of perioperatively-administered opioids and other confounders. After inpatient surgeries performed at one large academic and two community centers, the frequency of $SpO_2 \leq 85\%$ measurements of any duration and cause observed within the first 3 postoperative days was associated with increased 1-year postoperative mortality. Although perioperative opioid equivalents were higher in patients with ≥1 POH event, they were not independently associated with 1-year postoperative mortality.

We observed ≥1 POH event in approximately 25% of patients. The POH frequency described in the literature varies widely[1–6]: from 5% with intermittent SpO_2 measurements after non-cardiac surgery[2] to 65.5% when arterial blood gas analyses were used after cardiac surgery[5]. Within our health system and including both intermittent and continuous pulse oximetry, we have previously reported that 27–40% of all surgical (cardiac and non-cardiac) inpatients presenting ≥1 $SpO_2 \leq 85\%$ event after discharge from PACU[4]. Patients with multiple hospitalizations were included in that study and POH events throughout the whole hospital stay were included, which may explain the greater POH incidence observed. To minimize potential selection bias of patients with more complex health conditions or surgical interventions associated with a greater risk for mortality, we excluded patients with multiple hospitalizations in this study. We used routine postoperative SpO_2 monitoring and a threshold of moderate/severe hypoxemia ($SpO_2 \leq 85\%$). The incidence of POH at the academic center was greater than the observed at community centers, which could be related, in part, to the greater complexity of surgeries performed as reflected by longer duration and higher opioid doses administered on the date of surgery (data not shown).

Hypoxemia of different degrees and at diverse time points after surgery has been associated with increased risk of cardiopulmonary complications, confusion, prolonged hospital LOS, and discharge to a nursing facility and healthcare costs[1,9,10,12]. In our study, for every 10% increase in the frequency of $SpO_2 \leq 85\%$ measurements of any duration and cause observed within the first 3 postoperative days, the odds of 1-year postoperative mortality increased by 20%. To our knowledge, the association between POH and 1-year postoperative mortality has not been evaluated. The retrospective study design precludes any causal conclusions on the nature of this association. However, several pathophysiologic mechanisms triggered by intermittent hypoxia could contribute: activation of the sympathetic system, oxidative stress and inflammation, impaired immune responses, altered glucose and lipid metabolism[19–21] and other biological processes[22–25].

We pre-selected covariates for the logistic regression that are known to contribute directly or indirectly to POH and/or postoperative mortality, including the perioperatively-administered opioid doses. Perioperative opioids have received attention for their contribution to POH[6,12,13]. However, the relationship between the type and dose of perioperative opioids on POH is still not completely understood[14,26]. In this study, POH patients received greater opioid daily doses than No-POH patients (Table 1). The incidence of POH was greater on POD1 (~67% of POH patients, Table 2), which is similar to the timing observed in other studies. In a case-control study in adults after major inpatient surgery, approximately 77.4% of opioid-induced respiratory depression episodes requiring reversal with naloxone occurred during the first 24h after surgery[27]. Nonetheless, opioid doses on the date of surgery or POD1 were not associated with increased 1-year postoperative mortality (Table 3). Interestingly, attempts to limit perioperative opioids have reduced respiratory failure yet failed to decrease mortality[28].

Our logistic regression results highlight other variables that are associated with increased 1-year postoperative mortality (Table 3). However, most are non-modifiable variables: older age, male gender, respiratory comorbidities and/or overall systemic disease burden. Continuous SpO_2 monitoring, more often implemented in patients at high risk for POH, was the only modifiable variable independently associated with 1-year postoperative mortality. As expected, reintubation and unplanned ICU admission were associated with increased mortality. POH will often precede reintubation and unplanned ICU admission. However, our logistic model suggests that POH is associated with 1-year mortality even after adjusting for the presence of continuous SpO_2 monitoring, reintubation and/or unplanned ICU admission.

This study presents several limitations to the generalizability of our results, primarily related to its database retrospective nature and the challenge of the accurate assessment of hypoxemia. First and foremost, the accurate characterization of POH is limited in a retrospective study. Continuous pulse oximetry or blood gas analyses would be required to provide details of duration and severity of POH. Even POH events from patients receiving intermittent SpO_2 measurements were possibly underestimated. A study in 16 ICU patients at high risk for hypoxemia found that the reported manual SpO_2 values were an average 6.5% (95% CI, 4.0–9.0%) greater than simultaneously automated ones[8]. Similarly, our postoperative mortality was restricted to deaths reported to the EMR and may also be underestimated[29]. To increase the likelihood of detecting reported deaths after discharge, we

obtained the mortality data from the data warehouse >3 years after the last surgical procedure. Other limitations to the generalizability of our results may arise from our exclusion criteria: We excluded events of mild hypoxemia (SpO_2=86–89%), with less likely negative impact, particularly if brief. In fact, when mild POH events were included in the analyses, POH was no longer associated with 1-year mortality (Supplement). In addition, we excluded patients with multiple surgical procedures and/or hospitalizations, which likely constitute patients with more severe systemic disease and/or more complex procedures, and thus may be at increased risk of both POH events and postoperative mortality. Previous studies have suggested risk factors for POH (e.g. age >50 years, BMI >30 kg/m^2, respiratory comorbidities, SpO_2≤96% before or immediately after surgery, but not the type or duration of surgery)[26]. The purpose of this study was to determine if POH, once occurred, is independently associated with postoperative mortality without establishing any cause-effect relationships.

In conclusion, in this large database study we found that moderate/severe POH of any duration within the first 3 postoperative days is independently associated with increased 1-year postoperative mortality. Perioperative opioid doses were not independently associated with 1-year postoperative mortality. Increased efforts should be directed to understand the etiology and ultimately reduce episodes of postoperative hypoxemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure of Funding: This study was supported by a Seed Grant by the University of Colorado School of Medicine, Department of Anesthesiology (AFB) and the National Institutes of Health / National Institute on Drug Abuse, Award Number K23DA040923 (KB). The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Glossary of Terms

ASA physical status	American Society of Anesthesiologists physical status
BMI	Body Mass Index
EMR	electronic medical record
ERAS	Enhanced-Recovery After Surgery
ICU	intensive care unit
LOS	length of stay
NIV	noninvasive ventilation
OR	odds ratio
OMME	oral morphine milligram equivalents

PACU	post-anesthesia care unit
POD	postoperative day
POH	postoperative hypoxemia
SpO_2	peripheral saturation of oxyhemoglobin
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UCHealth	University of Colorado Health

References

1. Ramachandran SK, Thompson A, Pandit JJ, Devine S, Shanks AM. Retrospective observational evaluation of postoperative oxygen saturation levels and associated postoperative respiratory complications and hospital resource utilization. PloS one. 2017;12(5):e0175408. [PubMed: 28520718]
2. Sun Z, Sessler DI, Dalton JE, et al. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. Anesth Analg. 2015;121(3):709–715. [PubMed: 26287299]
3. Ge H, Jiang Y, Jin Q, Wan L, Qian X, Zhang Z. Nomogram for the prediction of postoperative hypoxemia in patients with acute aortic dissection. BMC Anesthesiology. 2018;18(1).
4. Fernandez-Bustamante A, Bartels K, Clavijo C, et al. Preoperatively Screened Obstructive Sleep Apnea Is Associated With Worse Postoperative Outcomes Than Previously Diagnosed Obstructive Sleep Apnea. Anesth Analg. 2017;125(2):593–602. [PubMed: 28682951]
5. Sutton AD, Bailey M, Bellomo R, Eastwood GM, Pilcher DV. The association between early arterial oxygenation in the ICU and mortality following cardiac surgery. Anaesth Intensive Care. 2014;42(6):730–735. [PubMed: 25342405]
6. Siriussawakul A, Mandee S, Thonsontia J, Vitayaburananont P, Areewatana S, Laonarinthawoot J. Obesity, epidural analgesia, and subcostal incision are risk factors for postoperative desaturation. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2010;57(5):415–422.
7. Pedersen T, Nicholson A, Hovhannisyan K, Moller AM, Smith AF, Lewis SR. Pulse oximetry for perioperative monitoring. The Cochrane database of systematic reviews. 2014(3):CD002013. [PubMed: 24638894]
8. Taenzer AH, Pyke J, Herrick MD, Dodds TM, McGrath SP. A comparison of oxygen saturation data in inpatients with low oxygen saturation using automated continuous monitoring and intermittent manual data charting. Anesth Analg. 2014;118(2):326–331. [PubMed: 24361847]
9. Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. British journal of anaesthesia. 1992;68:471–473. [PubMed: 1642934]
10. Rosenberg J, Kehlet H. Postoperative mental confusion--association with postoperative hypoxemia. Surgery. 1993;114(1):76–81. [PubMed: 8356531]
11. Fernandez-Bustamante A, Frendl G, Sprung J, et al. Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery: A Multicenter Study by the Perioperative Research Network Investigators. JAMA Surg. 2017;152(2):157–166. [PubMed: 27829093]
12. Rostin P, Teja BJ, Friedrich S, et al. The association of early postoperative desaturation in the operating theatre with hospital discharge to a skilled nursing or long-term care facility. Anaesthesia. 2019.
13. Rosenberg J, Oturai P, Erichsen CJ, Pedersen MH, Kehlet H. Effect of general anesthesia and major versus minor surgery on late postoperative episodic and constant hypoxemia. J Clin Anesth. 1994;6(3):212–216. [PubMed: 8060628]

14. Belcher AW, Khanna AK, Leung S, et al. Long-Acting Patient-Controlled Opioids Are Not Associated With More Postoperative Hypoxemia Than Short-Acting Patient-Controlled Opioids After Noncardiac Surgery: A Cohort Analysis. Anesth Analg. 2016;123(6):1471–1479. [PubMed: 27607476]
15. Bartels K, Fernandez-Bustamante A, McWilliams SK, Hopfer CJ, Mikulich-Gilbertson SK. Long-term opioid use after inpatient surgery - A retrospective cohort study. Drug Alcohol Depend. 2018;187:61–65. [PubMed: 29627407]
16. Scott MJ, McEvoy MD, Gordon DB, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 2-From PACU to the Transition Home. Perioper Med (Lond). 2017;6:7. [PubMed: 28413628]
17. Hopf HW. Preventing Opioid-Induced Postoperative Hypoxemia: No Simple Answer? Anesth Analg. 2016;123(6):1356–1358. [PubMed: 27861444]
18. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria https://www.R-project.org/. Published 2018 Accessed.
19. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest. 2015;147(1):266–274. [PubMed: 25560865]
20. Snow JB, Kitzis V, Norton CE, et al. Differential effects of chronic hypoxia and intermittent hypocapnic and eucapnic hypoxia on pulmonary vasoreactivity. Journal of applied physiology. 2008;104(1):110–118. [PubMed: 17947499]
21. Drager LF, Jun JC, Polotsky VY. Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea. Best practice & research Clinical endocrinology & metabolism. 2010;24(5):843–851. [PubMed: 21112030]
22. Almendros I, Gozal D. Intermittent hypoxia and cancer: Undesirable bed partners? Respir Physiol Neurobiol. 2018;256:79–86. [PubMed: 28818483]
23. Nanduri J, Semenza GL, Prabhakar NR. Epigenetic changes by DNA methylation in chronic and intermittent hypoxia. Am J Physiol Lung Cell Mol Physiol. 2017;313(6):L1096–L1100. [PubMed: 28839104]
24. Kiernan EA, Smith SM, Mitchell GS, Watters JJ. Mechanisms of microglial activation in models of inflammation and hypoxia: Implications for chronic intermittent hypoxia. J Physiol. 2016;594(6):1563–1577. [PubMed: 26890698]
25. Chuang LP, Chen NH, Lin Y, Ko WS, Pang JS. Increased MCP-1 gene expression in monocytes of severe OSA patients and under intermittent hypoxia. Sleep Breath. 2015.
26. Kaushal A, Goyal P, Dhiraaj S, Agarwal A, Singh PK. Identification of Various Perioperative Risk Factors Responsible for Development of Postoperative Hypoxaemia. Turk J Anaesthesiol Reanim. 2018;46(6):416–423. [PubMed: 30505603]
27. Taylor S, Kirton OC, Staff I, Kozol RA. Postoperative day one: a high risk period for respiratory events. Am J Surg. 2005;190(5):752–756. [PubMed: 16226953]
28. Rigg JR, Jamrozik K, Myles PS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;359(9314):1276–1282. [PubMed: 11965272]
29. Jones B, Vawdrey DK. Measuring mortality information in clinical data warehouses. AMIA Jt Summits Transl Sci Proc. 2015;2015:450–455. [PubMed: 26306284]

Key Points Summary

Question

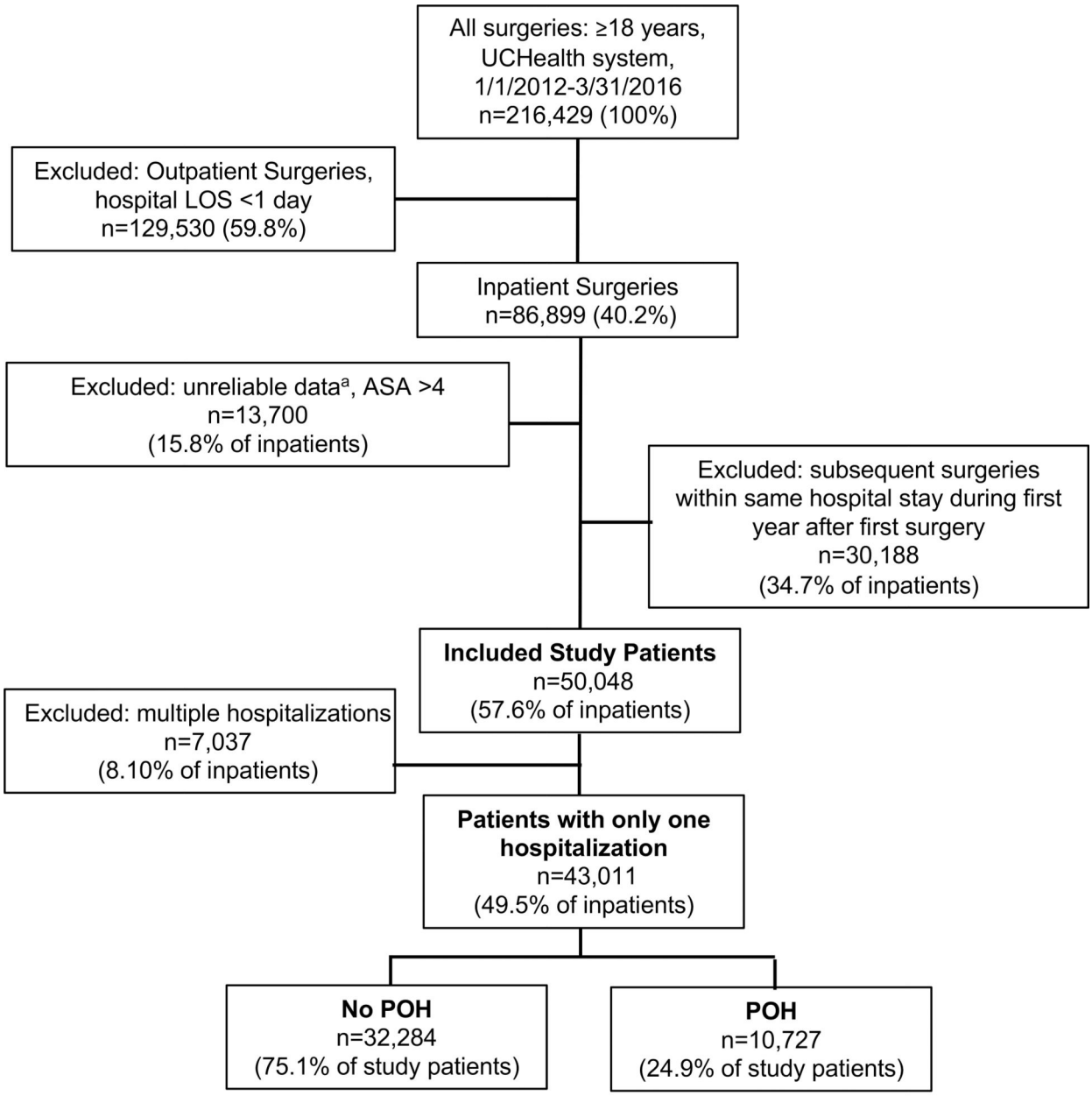
Is the frequency of moderate/severe postoperative hypoxemic events ($SpO_2 \leq 85\%$) within the first 3 postoperative days associated with increased 1-year postoperative mortality after adjusting for opioids received perioperatively and other confounding factors?

Findings

After adjusting for confounders, the OR for 1-year mortality is 1.2 (increases by 20%) with each 10% increase in the frequency of POH events.

Meaning

Future research should aim to characterize postoperative hypoxemia and to assess if interventions to minimize it can improve patient safety and reduce major morbidity and mortality after surgery.



([a] Cleaning of unreliable data: BMI <12 or >80, missing gender, surgery duration <15 minutes or >24 hours, negative survival length, records with POD 0-1 OMME ≤0 or >10,000)

Figure 1.
Study schematic flowchart.

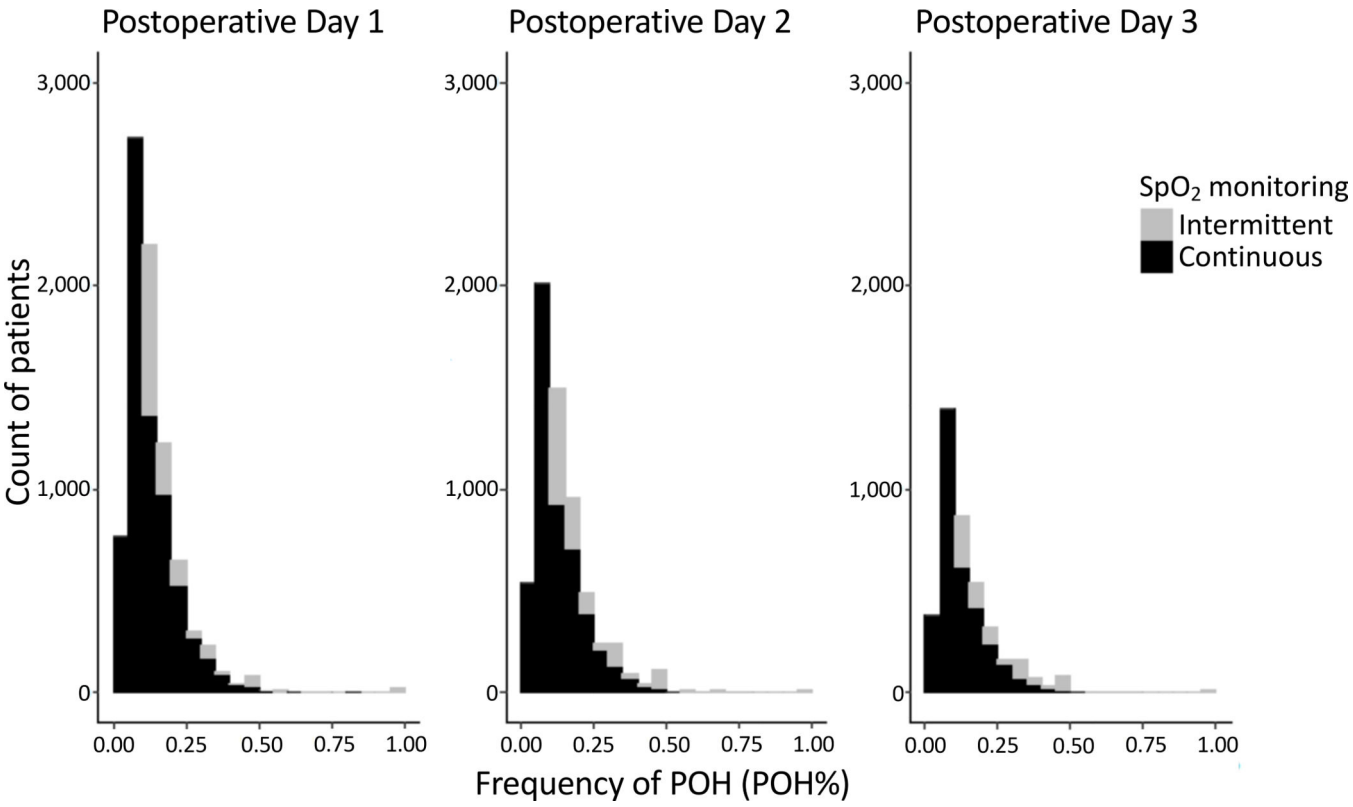


Figure 2. Histograms of frequency of postoperative hypoxemic (POH) events (POH%) for postoperative days 1–3 for both monitoring methods of peripheral saturation of oxyhemoglobin (SpO_2).

Only patients with POH included. Stacked histograms show the non-overlapping number of patients with POH events in 5% intervals as detected by continuous (black bars) and intermittent (gray bars) SpO_2 monitoring. Note, for intermittently (≤8 measurements/day) monitored patients, one hypoxemic event in 24h would correspond to POH% 12.5%, and hence not reflected in the first two columns (intervals 0.00–0.10).

Table 1.

Characteristics of patients presenting at least one or none moderate/severe postoperative hypoxemic (POH) events. Values are shown as mean (SD) or N (% of respective group) unless otherwise indicated.

	Total (N=43,011)	No POH (N=32,284)	POH (N=10,727)	P value
Demographics				
Age, years	58.0 (17.0)	57.2 (17.3)	60.5 (15.7)	<0.001
Male Gender	20,321 (47.2%)	15,531 (48.1%)	4,790 (44.7%)	<0.001
BMI, kg/m^2	28.6 (7.1)	28.3 (6.9)	29.5 (7.7)	<0.001
ASA Physical Status:				<0.001
1	1,778 (4.1%)	1,482 (4.6%)	296 (2.8%)	
2	17,243 (40.1%)	13,930 (43.1%)	3,313 (30.9%)	
3	18,820 (43.8%)	13,399 (41.5%)	5,421 (50.5%)	
4	5,170 (12.0%)	3,473 (10.8%)	1,697 (15.8%)	
Type of medical center				
Academic Center	20,228 (47.0%)	13,771 (42.7%)	6,457 (60.2%)	<0.001
Community Centers	22,783 (53.0%)	18,513 (57.3%)	4,270 (39.8%)	
Preoperative Comorbidities				
Asthma	5,004 (11.6%)	3,619 (11.2%)	1,385 (12.9%)	<0.001
COPD	3,852 (9.0%)	2,556 (7.9%)	1,296 (12.1%)	<0.001
OSA	6,707 (15.6%)	4,602 (14.3%)	2,105 (19.6%)	<0.001
Other Respiratory Diseases	5,473 (12.7%)	3,665 (11.4%)	1,808 (16.9%)	<0.001
Smoker	5,187 (12.1%)	3,937 (12.2%)	1,250 (11.7%)	0.140
Hypertension	20,715 (48.2%)	14,819 (45.9%)	5,896 (55.0%)	<0.001
Cardiac Disease (excl. hypertension)	9,725 (22.6%)	6,991 (21.7%)	2,734 (25.5%)	<0.001
Neurological Disease	9,856 (22.9%)	7,457 (23.1%)	2,399 (22.4%)	0.120
Renal Disease	6,259 (14.6%)	4,432 (13.7%)	1,827 (17.0%)	<0.001
Liver Disease	2,862 (6.7%)	2,024 (6.3%)	838 (7.8%)	<0.001
Obesity (BMI >30 kg/m^2)	14,990 (34.9%)	10,700 (33.1%)	4,290 (40.0%)	<0.001
Diabetes	7,463 (17.4%)	5,209 (16.1%)	2,254 (21.0%)	<0.001
Other Endocrine Diseases	10,688 (24.8%)	7,515 (23.3%)	3,173 (29.6%)	<0.001
Surgery Duration, minutes	181 (124.4)	168 (118.6)	220 (132.9)	<0.001
Postoperative continuous SpO_2 monitoring	22,066 (51.3%)	12,589 (39.0%)	9,477 (88.3%)	<0.001
Opioid requirements, OMME *				
Day of Surgery	181 (242.2)	173 (238.3)	203 (252.3)	<0.001
POD 1	47.7 (69.0)	45.0 (67.9)	55.8 (71.8)	<0.001
POD 2	41.7 (66.9)^{10,712}	39.2 (65.2)^{10,161}	47.2 (70.1)^{551}	<0.001
POD 3	38.4 (66.6)$^{20.837}$	36.0 (65.7)^{18,266}	42.7 (68.1)^{2,571}	<0.001

* (Opioid requirement on Day of Surgery used as surrogate for surgery complexity and related-trauma; Opioid Requirement on Postoperative Days 2 and 3 are presented but were excluded from the analysis due to high proportion of null data and variability between patients; Superscripts indicate the number of missing values for POD 2 or POD 3. These missing values are related, in part, to patients being discharged from the hospital)

(ASA=American Society of Anesthesiologists Physical Status classification; BMI=Body Mass Index; COPD=Chronic Obstructive Pulmonary Disease; CPAP=Continuous Positive Airway Pressure; DOS=Date of Service; OMME=Oral Morphine Milligram Equivalents; OSA=Obstructive Sleep Apnea, including formally diagnosed (based on existing diagnosis and/or positive airway pressure, PAP, prescription in patient's chart, independently of therapy compliance) and suspected (presence of ≥3 positive STOP-BANG risk factors on the anesthesia preoperative interview on the DOS); POD=Postoperative Day; POH= Postoperative Hypoxemia; SpO_2=peripheral saturation of oxyhemoglobin)

Table 2.

Clinical outcomes of patients presenting moderate/severe postoperative hypoxemic (POH) events. Values are shown as mean (SD) or N (% of group) unless otherwise indicated.

	Total (N=43,011)	No POH (N=32,284)	POH (N=10,727)	P value
Postoperative In-hospital Course				
Patients With At Least One Hypoxemic Event (SpO_2 ≤85%, any duration):				
PACU (not considered POH)	1,585 (3.7%)	1,018 (3.2%)	567 (5.3%)	<0.001
POD 1	7,179 (16.7%)	0 (0.0%)	7,179 (66.9%)	<0.001
POD 2	5,340 (12.4%)	0 (0.0%)	5,340 (49.8%)	<0.001
POD 3	3,455 (8.0%)	0 (0.0%)	3,455 (32.2%)	<0.001
Any POH event on POD 1, 2, or 3	10,727 (24.9%)	0 (0.0%)	10,727 (100.0%)	
% of Hypoxemic Events (POH%) *				
POD 1	2.4 (6.7)	0 (0.0)	9.5 (10.6)	<0.001
POD 2	1.9 (6.3)	0 (0.0)	7.5 (10.8)	<0.001
POD 3	1.2 (5.3)	0 (0.0)	4.9 (9.8)	<0.001
Postoperative O_2 Therapy Duration, days	3.7 (5.4)	3.1 (5.3)	5.3 (5.5)	<0.001
Postoperative NIV (CPAP, BiPAP, APAP)	5,905 (13.7%)	3,783 (11.7%)	2,122 (19.8%)	<0.001
Postoperative Reintubation	1,535 (3.6%)	1,025 (3.2%)	510 (4.8%)	<0.001
ICU Admission:				
Planned (direct transfer after surgery)	4,447 (10.3%)	2,849 (8.8%)	1,598 (14.9%)	<0.001
Unplanned (>12h after PACU discharge)	926 (2.2%)	500 (1.5%)	426 (4.0%)	<0.001
Hospital Length of Stay, days	4.9 (5.8)	4.5 (5.7)	6.1 (5.9)	<0.001
Death within 1 year from DOS	1,426 (3.3%)	958 (3.0%)	468 (4.4%)	<0.001

* The frequency of POH events is expressed as percentage of hypoxemia events out of the total SpO_2 measurements per day for POD 1–3.

(APAP=Auto-titrating Positive Airway Pressure; BiPAP= Bi-level Positive Airway Pressure; CPAP=Continuous Positive Airway Pressure; DOS=Date of Service; ICU=Intensive Care Unit; NIV=Non-Invasive Ventilation, including CPAP, APAP or BiPAP; PACU=Post-Anesthesia Care Unit; POD=Postoperative Day; POH= Postoperative Hypoxemia, SpO_2=Peripheral Saturation of Oxyhemoglobin by pulse oximetry)

Table 3.

Logistic regression model results including the frequency of postoperative hypoxemic (POH) events obtained during POD 1–3 and death within 1 year from day of surgery as the outcome.

Covariate	OR	95% CI	p-value
% of POH (in 10% increments) *	**1.20**	**(1.11,1.29)**	**<0.001**
Age, years	1.02	(1.02,1.03)	<0.001
Male Gender	1.20	(1.07,1.35)	0.002
BMI	0.96	(0.95,0.97)	<0.001
ASA 2 (*vs.* 1)	3.14	(1.00,9.91)	0.051
ASA 3 (*vs.* 1)	12.51	(4.00,39.17)	<0.001
ASA 4 (*vs.* 1)	24.59	(7.81,77.43)	<0.001
Academic Center (*vs.* Community Centers)	1.21	(1.07,1.38)	0.003
Asthma	0.77	(0.63,0.95)	0.016
COPD	0.97	(0.82,1.15)	0.722
OSA	0.78	(0.64,0.95)	0.014
Other Respiratory Diseases	1.48	(1.28,1.71)	<0.001
Hypertension	0.75	(0.66,0.86)	<0.001
Cardiac Disease (excl. hypertension)	1.05	(0.92,1.19)	0.455
Renal Disease	1.71	(1.51,1.95)	<0.001
Liver Disease	1.86	(1.57,2.19)	<0.001
Diabetes	1.31	(1.14,1.49)	<0.001
Other Endocrine Disease	0.95	(0.82,1.10)	0.518
Surgery Duration, mins	0.998	(0.997,0.998)	<0.001
DOS OMME	1.00	(1.00,1.00)	0.731
POD 1 OMME	0.999	(0.9975,0.99996)	0.006
Postoperative continuous SpO_2 monitoring	1.33	(1.16,1.53)	<0.001
Postoperative NIV (CPAP, BiPAP, APAP)	0.92	(0.77,1.09)	0.328
Postoperative Reintubation	3.62	(2.96,4.41)	<0.001
Planned ICU admission	0.91	(0.77,1.08)	0.297
Unplanned ICU admission	2.75	(2.22,3.41)	<0.001
Hospital Length of Stay, days	1.01	(1.01,1.02)	<0.001

* Interpretation: For each 10% increase in POH events out of the total measured, the OR for 1-year mortality is 1.2 (increases by 20%)

(APAP=Auto-titrating Positive Airway Pressure; ASA=American Society of Anesthesiologists Physical Status classification; BiPAP= Bi-level Positive Airway Pressure; BMI=Body Mass Index; COPD=Chronic Obstructive Pulmonary Disease; CPAP=Continuous Positive Airway Pressure; DOS=Date of Service; ICU=Intensive Care Unit; NIV=Non-Invasive Ventilation, including CPAP, APAP or BiPAP; OMME=Oral Morphine Milligram Equivalents; OSA=Obstructive Sleep Apnea; PACU=Post-Anesthesia Care Unit; POD=Postoperative Day; POH= Postoperative Hypoxemia; SpO_2=Peripheral Saturation of Oxyhemoglobin by pulse oximetry)