Review of Postoperative Respiratory Depression: From Recovery Room to General Care Unit

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Postoperative respiratory failure secondary to opioid-induced respiratory depression (hereafter termed *respiratory depression*) can result in permanent morbidity, such as anoxic brain injury, or even death.[1,2] In many cases, the respiratory failure seems to develop acutely and without warning, often shortly after seemingly reassuring nursing assessments.[2] Severe respiratory depression on general care units, however, is rare (3.7 to 53.3 opioid naloxone reversals per 10,000 general anesthetics),[3] and this infrequency of events has presented a barrier for healthcare organizations to invest in the equipment and personnel required for universal continuous monitoring.

To address the dual concerns that these events can be catastrophic but are rare, medical societies have published several guidelines. These guidelines, however, are primarily focused on perioperative management in patients who have obstructive sleep apnea (OSA) or are at risk for undiagnosed OSA.[4–6] In general, these guidelines focus on preoperative assessment of OSA in several ways: (1) obtaining a sleep-disordered breathing history; (2) using a validated OSA screening tool (*e.g.*, STOP-Bang [*S*nore loudly; daytime *T*iredness; *O*bserved apneas; high blood *P*ressure; *B*ody mass index greater than 35; *A*ge more than 50 yr; *N*eck circumference more than 40 cm; *G*, male sex]; table 1)[7]; (3) continuation of perioperative OSA therapy (*e.g.*, using positive airway pressure devices); and (4) tailoring perioperative care to reduce the risk of respiratory depression by choosing appropriate anesthetic management and introducing heightened surveillance for respiratory depressive episodes. Although useful, these guidelines focus on OSA and do not provide guidance for other patients who may be at increased risk for respiratory depression.

Emerging evidence regarding the phenotypic presentation and temporal course of postoperative respiratory depression has provided new insights that may help anesthesiologists to identify patients with increased risk of respiratory depression and intervene more effectively. One important aspect of these developments is a better understanding of the relationship between early respiratory depression, in the postanesthesia care unit (PACU), as a warning sign for risk of respiratory failure in general care units. Major themes of this review are summarized in box 1.

Table 1. STOP-Bang Score for Obstructive Sleep Apnea*

Characteristic	Points
Snore loudly	1
Daytime tiredness	1
Observed apneas	1
High blood pressure	1
Body mass index > 35 kg/m^2	1
Age > 50 yr	1
Neck circumference > 40 cm	1
Male sex	1
Total STOP-Bang score	

Data from Chung *et al.*[7]

*A STOP-Bang score or greater is considered *high*.

STOP-Bang, *S*nore loudly; daytime *T*iredness; *O*bserved apneas; high blood *P*ressure; *B*ody mass index greater than 35; *A*ge more than 50 yr; *N*eck circumference more than 40 cm; *G*, male sex.

Phenotypic Presentation of Respiratory Depression in General Care Units

Respiratory drive is strongly influenced by the ventilatory response to differing concentrations of arterial carbon dioxide and/or oxygen *via* peripheral and central chemoreceptors. Administration of opioids blunts these responses, which results in slowing of the respiratory rate.[24] Thus, clinical respiratory depression would be expected to manifest primarily as a slowed respiratory rate. However, patient assessment notes before critical respiratory events frequently do not document bradypnea.[2,4–7,25] One study that implemented continuous monitoring in the postoperative period showed that isolated slow respiratory rate (bradypnea) was only a rare presentation of respiratory depression.[8] Furthermore, a closed claims analysis of postoperative respiratory depression reported that the last nursing assessment before a critical event rarely documented signs of respiratory depression ("heavy snoring" was documented in only 15% of cases), with the most predominant notes preceding the critical events being somnolence (62% of cases).[2]

Studies using continuous electronic monitoring provide evidence that routine clinical monitoring with intermittent

This article is featured in "This Month in Anesthesiology," page A1.

Submitted for publication July 5, 2022. Accepted for publication September 23, 2022.

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 Anesthesiology 2022; 137:735–41. DOI: 10.1097/ALN.0000000000004391

<zdoi;. DOI: 10.1097/ALN.0000000000004391>

Box 1. Emerging Concepts Regarding Postoperative Opioid-induced Respiratory Depression

- Phenotypic presentation
  - Most common presentation is intermittent apneas or partial apneas[8,9]
  - Isolated bradypnea is a rare presentation[8,9]
  - Routine monitoring* fails to detect most events[2,8,10,11]
- Temporal distribution
  - Most life-threatening events† occur in the late afternoon and early evening[12–14]
  - The greatest number of overall events occur during early morning hours[8]
- PACU to general care unit relationship
  - Patients who have events in the PACU are at several-fold increased risk for critical events in general care units[13–15]
  - Depressed ventilation detected in the PACU persists for hours in general care units[16]
- Risk factors
  - Sleep-disordered breathing and obstructive sleep apnea are important risk factors[17,18]
  - Advancing age and greater disease burden are equally important risk factors[9,12,14,19]
  - PRODIGY score (see table 2) can be used to calculate risk[9]
  - General anesthesia has higher risk than regional anesthesia[20]
  - Longer-acting anesthetics increase risk[21,22]
  - Sedating nonopioid analgesics (*e.g.,* gabapentinoids) increase risk[20,23]

*Routine monitoring refers to intermittent vital sign checks. †Defined as administration of naloxone to reverse opioid toxicity.

PACU, postanesthesia care unit; PRODIGY, PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY.

vital sign checks has low sensitivity to detect respiratory depression. For example, Sun *et al.*[10] monitored 833 postoperative patients in general care units with continuous pulse oximetry, to which the healthcare team was blinded. Continuous pulse oximetry identified postoperative hypoxemia (oxygen saturation as measured by pulse oximetry [Spo_2] less than 90% for 1 h or more) in 37% of patients, whereas routine clinical monitoring by nurses identified only 5% of cases.

The PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial used bedside capnography and pulse oximetry for 1,335 hospitalized patients in general care units.[9] These technologies provided a detailed picture of how respiratory depression typically presents. The majority (more than 99%) of detected respiratory depression events were repetitive intermittent apnea and partial apnea events interspersed with normal to increased respiratory effort, whereas isolated slow respiratory rate (bradypnea) was rare.[8] Similar patterns of respiratory depression emerged in studies using blinded and continuous capnography and pulse oximetry in the PACU. Chung *et al.*,[26] applying these advanced monitors to 250 patients in the PACU, showed that 78% of patients had respiratory patterns that should have prompted immediate physician intervention (*e.g.*, two apnea events of 10 s or more in a 15-min epoch), but only 6% of these were clinically recognized. Of these episodes, 66% were apnea events.

There are several possible reasons why intermittent vital sign checks are insensitive for identifying respiratory depression. In the first theory, termed the "wake-up effect," a patient, somnolent from opioids and/or other sedatives, arouses transiently during the nursing assessment, which results in inaccurate assessment of respiratory depression. Because respiratory depression frequently manifests as intermittent apneas,[8] a patient could be awoken and appear to have a stable respiratory drive during the assessment, only for respiratory depression to develop again once the nurse leaves the room.[11] The second theory is that healthcare personnel may not be adept at assessing respiratory depression. This was demonstrated in a study by Taenzer *et al.*[11] using blinded pulse oximetry; they identified a subset of hypoxemic patients and showed that manually recorded Spo_2 during vital sign checks was an average of 6.5% higher than that measured with a blinded continuous pulse oximeter. With such discrepancies in Spo_2 recordings, an apparently satisfactory oxygenation level could be masking hypoxemia requiring intervention. The third theory is that healthcare professionals may interpret respiratory depression as somnolence. Two studies examining antecedent nursing notes of critical respiratory events showed that somnolence, but not respiratory depression, was documented in the majority of cases.[2,25] The possibility that healthcare professionals mistakenly identify respiratory depression as somnolence is intriguing and warrants further investigation. In the interim, healthcare staff should always be suspicious of excessive somnolence as a presentation of respiratory depression, and these patients would require more intense respiratory monitoring to avoid potentially adverse consequences.

Temporal Patterns of Postoperative Respiratory Depression in General Care Units

Examining temporal patterns of respiratory depression also yields important information that can help us devise strategies for better postoperative monitoring. Khanna *et al.*[27] postulated that critical respiratory depression develops during the early morning hours ("4:00 AM effect"). For patients who are continuously monitored, respiratory clinical decline is recognized promptly, which permits timely intervention, whereas the conditions of patients without continuous monitoring may deteriorate until unsalvageable.[28] Postoperative polysomnography has shown that surgical patients, regardless of the presence of OSA, have an increased propensity for apnea or hypopnea for several postoperative nights.[29] A subanalysis of the PRODIGY data showed the peak occurrence of respiratory depression detected by capnography and pulse oximetry to be between 2:00 and 6:00 AM during the first postoperative night.[8]

The literature examining the timing of critical postoperative respiratory events clearly demonstrates that most of these events occur within the first 24 postoperative hours.[2,12–14,30–32] Among such studies, three provide sufficient granularity to create a detailed temporal map of when events occur—namely, they tend to occur both early in the postoperative period and during the afternoon and evening.[12–14] Ramachandran *et al.*[13] found that 37.5% of cases occurred between 12:00 and 5:59 PM and another 25% between 6:00 and 11:59 PM, with 18.75% of events both between midnight and 5:59 AM and between 6:00 and 11:59 AM. Weingarten *et al.*[14] and Deljou *et al.*[12] examined naloxone administration within 48 postoperative hours in general care units and showed that 58% and 51% of cases occurred within the first 12 postoperative hours, and 82% and 80% of cases occurred within the first 24 h. Another study showed 70% of cases to occur between noon and midnight, whereas only 18% occurred in the early morning hours (midnight to 6:00 AM).[3]

The most plausible explanation for this peak occurrence of respiratory depression early in the postoperative period are the residual effects of anesthesia, and pain treatments with opioids being more intense in the first hours after surgery. Good evidence supports the idea that respiratory depression occurring in the afternoon results from residual postanesthesia sedation. A subanalysis of PRODIGY data among patients with respiratory depression showed that the initial respiratory depression episodes began in the late afternoon and early evening, and these initial episodes were not isolated.[8] The pattern of these events mirrored the temporal distribution of the combined data from Weingarten *et al.*[14] and Deljou *et al.*[12] of postoperative naloxone administration. Another important but not widely recognized concept associated with respiratory depression is a pain–sedation mismatch,[33] in which a sedated postoperative patient reports severe pain and receives further opioid analgesic treatment despite excessive sedation.[33]

Episodes of respiratory depression identified during the first few hours after discharge from the PACU to postoperative units could be continuations of respiratory depression events noted in the PACU. This can be demonstrated by the use of a thoracic bioimpedance respiratory monitor, which provides continuous assessment of minute ventilation, tidal volume, and respiratory rate calculated by measurement of cyclic changes in chest wall impedance that occur during breathing.[34] Schumann *et al.*[16] monitored 119 surgical patients with thoracic bioimpedance between the PACU and a general unit for the first postoperative night. The monitor was used to detect low minute ventilation episodes, defined as continuous minute ventilation less than 40% of predicted for 2 or more minutes.[16] Patients were categorized as at low or high risk for respiratory depression in the unit on the basis of 0 (low) or 1 or more (high) low minute ventilation episodes during the last 30 min of their PACU stay. The high-risk patients had higher rates of low minute ventilation episodes per hour during the PACU course (excluding the last 30 min) than low-risk patients (median [interquartile range], 0.81 [0.43 to 1.60] *vs.* 0 [0 to 0.11]; $P < 0.001$). These high-risk patients continued to have higher rates of low minute ventilation episodes per hour in the general units (median [interquartile range], 1.56 [0.31 to 2.24] *vs.* 0 [0 to 0.23]; $P < 0.001$), with 11% of monitored time in this low respiratory state, compared with 0% of monitored time in the low-risk group.[16]

Clinical Implications of Respiratory Depression in the PACU

Studies have found associations between respiratory depression in the PACU and subsequent respiratory adverse events in general care units. Gali *et al.*[33] stratified patients as those who had multiple episodes of nursing-recognized respiratory depression in the PACU *versus* those who did not. Patients without multiple episodes had low rates of postoperative pulmonary complications after PACU discharge, whereas those with multiple events went on to have higher rates of respiratory complications, especially those who had positive findings of preoperative OSA screening. Two studies of the use of postoperative naloxone in general units showed that patients with nursing-detected episodes of respiratory depression in the PACU were at a more than fivefold increased risk for naloxone administration compared with their matched controls.[12,14] Another study among patients who required naloxone in the PACU to reverse opioid toxicity and were subsequently discharged to general care units found that these patients had a more than threefold increased rate of postoperative complications compared with their matched controls.[15]

Evidence from studies of continuous respiratory monitoring from the PACU to the general unit,[16] continuous monitoring in the general unit,[8] and timing of naloxone administration[12,14] suggests that respiratory depression that develops in the PACU is likely to reoccur in postoperative areas. Therefore, respiratory depression in the PACU may be a harbinger of subsequent respiratory events in general units. Understanding this relationship provides an opportunity to better identify surgical patients at higher risk for serious postoperative respiratory complications. Seet and Chung[35] previously proposed a combination of preoperative assessment for OSA with more intense monitoring in the PACU for episodes of respiratory depression as an approach to identify high-risk patients. However, more contemporary literature suggests that other clinical variables, both intrinsic to the patient and related to the anesthetic and procedure, also can influence the risk of respiratory depression. These considerations can give the anesthesiologist a more nuanced assessment of respiratory depression risk and can provide guidance for anesthetic management that, in theory, could mitigate risk.

Risk Factors for Postoperative Respiratory Depression

OSA is a recognized risk factor for postoperative respiratory complications[17,18] and has been the focus of specific perioperative management guidelines, with emphasis on postoperative continuation of OSA-specific noninvasive ventilatory therapies.[4–6] Preoperative screening for OSA with tools such as STOP-Bang[7] is recommended because in many patients, OSA is not diagnosed. Although OSA is an important risk factor for respiratory depression, evidence clearly suggests that other patient-specific factors also impart risk. A meta-analysis of 12 observational trials of postoperative respiratory depression found that, in addition to OSA (odds ratio, 1.4), preexisting cardiovascular diseases (odds ratio, 1.2) and pulmonary diseases (odds ratio, 2.2) also increased the risk.[19] The PRODIGY trial assessed 46 patient variables as potential risk factors for postoperative respiratory depression as detected by continuous capnography and pulse oximetry.[9] That study showed older age (60 to 70 yr: odds ratio, 2.2; greater than 70 to 80 yr: odds ratio, 3.4; greater than 80 yr: odds ratio, 4.8); male sex (odds ratio, 2.1); opioid naïvety (odds ratio, 1.3); chronic heart failure (odds ratio, 2.1); and sleep-disordered breathing (*i.e.*, OSA history, or a positive screen for OSA using STOP-Bang: odds ratio, 1.6) to be independent risk factors.[9] These variables were used to create a PRODIGY score, which is easy to calculate and categorizes patients as at low, intermediate, or high risk of postoperative respiratory depression (intermediate risk [*vs.* low]: odds ratio, 2.3; high risk [*vs.* low]: odds ratio, 6.1; table 2).[9] The score can be integrated into electronic health record systems to automatically provide a risk category for individual patients. Furthermore, studies of the use of naloxone to reverse opioid toxicity in general units have shown that impaired cognitive status (*e.g.*, dementia: odds ratio, 4.1)[14] and debility (odds ratio, 3.1) also increase risk.[12] Therefore, when assessing the risk of respiratory depression, anesthesiologists should consider the patient's overall health and should not solely focus on OSA.

Table 2. PRODIGY Score for Risk of Postoperative Opioid-induced Respiratory Depression*

Risk Factor	Points
Age, yr	
< 60	0
60–69	8
70–79	12
≥ 80	16
Male sex	8
Opioid naïve	3
Known sleep-disordered breathing or high STOP-Bang score†	5
Coexisting congestive heart failure	7
Total PRODIGY score	

Data from Khanna *et al.*[9]

*Risk level for respiratory depression is *low* with a total PRODIGY score less than 8, *intermediate* with a score of 8 to 14, and *high* with a score ≥ 15 or greater. †See table 1 for STOP-Bang score calculation.

PRODIGY, PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY; STOP-Bang, *S*nore loudly; daytime *T*iredness; *O*bserved apneas; high blood *P*ressure; *B*ody mass index greater than 35; *A*ge more than 50 yr; *N*eck circumference more than 40 cm; *G*, male sex.

Chronic (at-home) use of opioids may also influence the risk of postoperative respiratory depression. A recent review of 45,515 adult colectomy patients found that preoperative use of opioids increased the risk of postoperative pulmonary complications in a dose-dependent manner.[36] Another large, retrospective, observational trial in 163,191 hospitalized patients showed that opioid naïvety decreased the risk of oversedation.[37] A retrospective study of postoperative naloxone administration on general care units reported that chronic opioid use was associated with an almost twofold increased risk of respiratory depression.[12] These findings are in contrast to those of PRODIGY,[9] in which opioid naïvety increased the risk of respiratory depression, as detected by continuous capnography and pulse oximetry. One explanation for these disparate results is that PRODIGY was conducted in Eastern Asia, Western Europe, and North America, and the frequency of respiratory depression showed racial differences, with the highest rates among Asian patients, who were also the most likely to be opioid-naïve.[38]

The perioperative course also influences postoperative respiratory depression risk, with shorter-acting anesthetics associated with a decreased respiratory depression risk.[21] An analysis of a practice improvement initiative at our institution (implemented because of inadequate PACU space, resulting in operating room inefficiencies) showed that use of desflurane instead of isoflurane decreased respiratory depression in the PACU (odds ratio, 0.72; 95% CI, 0.55 to 0.93; $P = 0.01$).[21] Another study of respiratory depression in the PACU after total joint arthroplasty showed lower rates with spinal anesthesia than general anesthesia (144 *vs.* 312 per 1,000 anesthetics; $P < 0.001$).[20] Increasing doses and long-acting intraoperative opioids (morphine, hydromorphone, or preoperative sustained-release oxycodone, *vs.* fentanyl) also increase the risk of postoperative respiratory depression.[15,20,23] A retrospective study of patients undergoing laparoscopic surgery found an increased risk of respiratory depression in the PACU with the use of isoflurane compared with less soluble and shorter-acting anesthetic agents (*i.e.*, desflurane, sevoflurane, or propofol infusion; odds ratio, 1.32; 95% CI, 1.15 to 1.50; $P < 0.001$).[22] Several studies have shown associations between gabapentinoid use (both chronic or home use and as part of a multimodal analgesic pathway) and increased respiratory depression in the PACU,[20,23] increased administration of naloxone in general units,[12] increased rates of emergency response team activation for postoperative mental status changes and pulmonary decompensation,[39] and increased risk of postoperative pulmonary complications.[21,40–42]

Proposed Treatment Pathway for Postoperative Respiratory Depression

These recent advances in the understanding of postoperative respiratory depression can allow the anesthesiologist to better appreciate and take mitigating action to reduce the risk of acute postoperative respiratory depression (fig. 1). With this approach, the anesthesiologist would assess the risk of postoperative respiratory depression, incorporating not only OSA but also the overall health of the patient, with the understanding that risk increases with age, disease burden, cognitive decline, and debility. Calculation of the PRODIGY score is one practical way of calculating this risk.[9] Patients with known OSA after major operations should have continuation of their OSA therapies.[4–6] Anesthetic management could be tailored to mitigate risk, with the use of regional anesthesia when feasible, adjuvant local anesthetics (*e.g.*, field infiltration with local anesthetic for postsurgical analgesia), shorter-acting anesthetic agents (*e.g.*, desflurane, propofol) and opioids (*e.g.*, remifentanil, alfentanil), and nonsedating analgesics (*e.g.*, ketorolac, acetaminophen). During anesthesia recovery, patients should be closely monitored for signs of respiratory depression. Even self-limited episodes of respiratory depression (*e.g.*, apnea episode) should be considered clinically relevant because these are associated with subsequent respiratory decompensation.[12,14] Considering the entire perioperative course from preoperative assessment through anesthesia recovery, the anesthesiologist should formulate a postoperative care plan, which could range from standard care, to continuous monitoring of respiratory status, to escalation to an even higher level of postoperative monitoring and care (*e.g.*, intensive care unit). Even though firm thresholds have not been established, escalation of care should be strongly considered for patients deemed at high risk on preoperative assessment (*e.g.*, high PRODIGY score) and who exhibit signs of respiratory depression during anesthesia recovery (*e.g.*, apnea episodes).

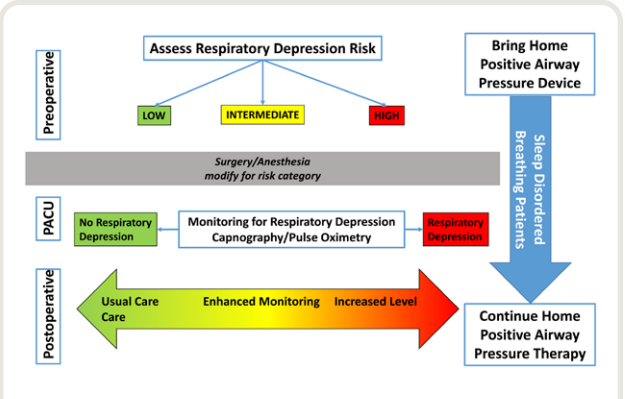

Fig. 1. Proposed clinical pathway for patients with postoperative opioid-induced respiratory depression. Clinical decisions on the postoperative level of care are complex and unique for each patient. Preoperatively, patients should have a risk assessment for respiratory depression. The surgical and anesthetic management should be tailored for this risk. During anesthesia recovery, patients' respiratory status should be monitored for various signs of respiratory depression. Postoperative management decisions regarding level of monitoring and care should be guided by preoperative status, intraoperative status, and the anesthesia recovery course. Home therapies for sleep-disordered breathing should be continued into the postoperative period. PACU, postanesthesia care unit.

Acknowledgments

Alyssa B. Quiggle, Ph.D., E.L.S., Mayo Clinic, Rochester, Minnesota, substantively edited the manuscript. The Scientific Publications staff at the Mayo Clinic provided proofreading, administrative, and clerical support.

Research Support

This work was supported by the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota.

Competing Interests

Dr. Weingarten receives consulting fees from Medtronic (Minneapolis, Minnesota) and Merck (Rahway, New Jersey). Dr. Sprung declares no competing interests.

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