

# Special REPORT

## Postoperative Opioid-Induced Respiratory Depression

### *Current Challenges and New Developments In Patient Monitoring*

**A**lthough commonly used to manage postoperative pain, opioids are associated with an increased risk for adverse events (AEs), with the most serious being respiratory depression, which can potentially lead to subsequent respiratory failure and death.<sup>1</sup> Most patients experience a balance between factors that stimulate respiration and factors that depress

respiration without complications. However, a number of factors influence respiration rate and drive, including opioid analgesics and supplemental oxygen,<sup>1</sup> that can overwhelm the body's compensatory mechanisms causing respiratory depression (Figure). In fact, 50% of postoperative respiratory failure events involved patients receiving opioids.<sup>2</sup>

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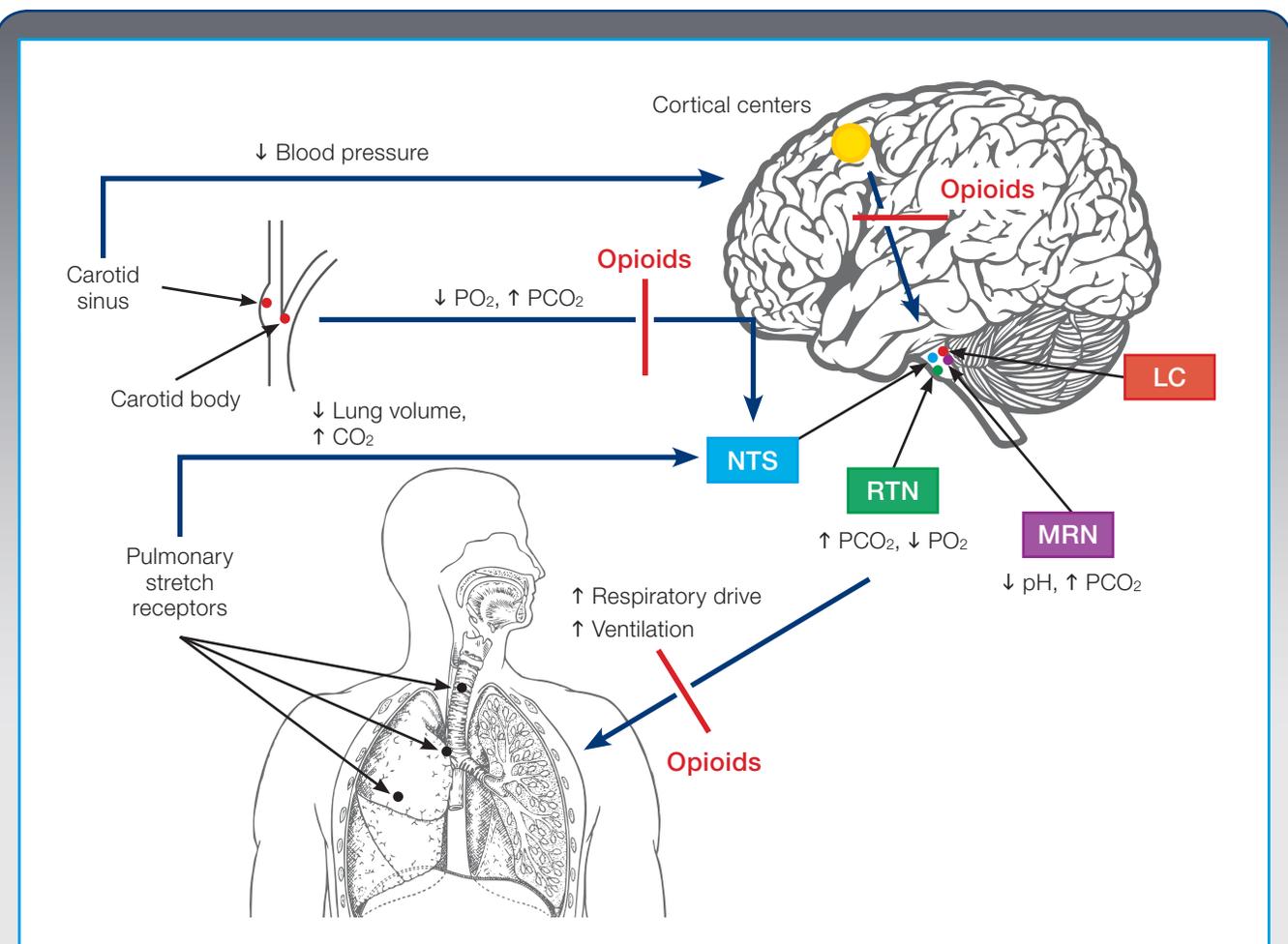
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**Figure.** Effects of opioids on respiratory physiology.

**CO<sub>2</sub>**, carbon dioxide; **LC**, locus coeruleus; **MRN**, medullary raphe nucleus; **NTS**, nucleus tractus solitarius; **RTN**, retrotrapezoid nucleus; **PO<sub>2</sub>**, partial pressure of oxygen; **PCO<sub>2</sub>**, partial pressure of carbon dioxide

Image used with permission and adapted from reference 1.

Postoperative opioid-induced respiratory depression (POIRD) is a critical, albeit potentially preventable, complication that also affects both overall hospital costs and length of stay (LOS).<sup>3</sup> The risk for opioid-associated AEs often is seen within the first hours to days in the postoperative period. A high prevalence of patients who experienced a non-cardiopulmonary resuscitation event, which was precipitated by factors including respiratory depression, received at least 1 opioid within 24 hours of the event.<sup>2</sup>

In response to the alarming incidence of suboptimal pain control in postoperative patients, the Joint Commission recommended that health care organizations recognize “pain as

the fifth vital sign.”<sup>14</sup> Given the considerable rate of respiratory compromise in the postoperative period, the Anesthesia Patient Safety Foundation (APSF) recommended that continuous electronic monitoring should be used for all inpatients receiving opioid analgesics.<sup>5</sup> Although current available technologies may have limitations, they still might be able to prevent a significant amount of patient harm.<sup>5</sup> Continuous monitoring strategies that incorporate multiple physiologic parameters—especially respiration rate, a significant indicator of a patient’s condition—can help clinicians detect respiratory deterioration early on, in order to provide effective interventions while maintaining patient safety.

## Epidemiology and Health Care Costs

Although the incidence of POIRD could be considered relatively low by the casual observer, the fact that roughly 48 million inpatient procedures are performed in the United States annually<sup>6</sup> translates into a significant absolute number of POIRD cases. The result of undetected, critical, POIRD is respiratory failure and cardiopulmonary arrest, which lead to hypoxic brain injury or death in almost 80% of cases,<sup>7</sup> and exert a disproportionate toll on overall hospital costs and LOS.<sup>3</sup> POIRD also may occur unexpectedly, even in the healthiest of patients.<sup>5</sup>

Soaring health care costs for respiratory-related conditions have also been reported by the Agency for Healthcare Research and Quality's statistical brief. In 2005, there were 20 conditions associated with the largest national hospital charges—"respiratory failure, insufficiency, and arrest" was listed as the 11th most expensive condition treated in US hospitals, and was ranked as the sixth most expensive condition billed to Medicaid, and the eighth most expensive condition billed to Medicare.<sup>8</sup>

In a published letter in the journal, *Anesthesiology*, in 2010, one expert professed that postoperative respiratory failure is the third most common patient safety-related AE affecting the Medicare population in US hospitals, accounting for 113 events per 1,000 at-risk patient admissions, and that 50% of postoperative respiratory failure events involved patients receiving opioid analgesia.<sup>2,9,10</sup> The article also noted that POIRD resulted in death or anoxic brain injury in a significant proportion of cases.<sup>7,10</sup> Finally, the expert reported that when compared with patients in the intensive care unit (ICU) who received more intensive monitoring, the worst outcomes often occurred on the general care floor (GCF) where patients received only intermittent monitoring for respiratory depression, at best.<sup>10-12</sup>

Indeed, a higher incidence of respiratory depression (ie, 29%) has been observed in clinical trials where morphine has been used as a comparator drug to morphine-6-glucuronide under close monitoring.<sup>13</sup> Another study also reported a higher incidence of respiratory depression during continuous oximetry and capnography monitoring of postoperative patients receiving patient-controlled analgesia (PCA) with opioids (POIRD=41% by respiration rate <10 breaths per minute for >3 minutes).<sup>14</sup>

Additionally, the time course of POIRD onset may be hard to predict. Shapiro and colleagues<sup>15</sup> performed a study with 1,524 patients receiving IV or neuraxial morphine on the surgical wards of a university-affiliated, 700-bed, tertiary hospital. Approximately 1.2% of patients were noted to have POIRD, based on a definition of a respiration rate of less than 10 breaths per minute.<sup>15</sup> However, the time from IV morphine initiation or last neuraxial morphine administration until the diagnosis of respiratory depression ranged widely (2-31.26 and 2-12.15 hours, respectively).<sup>15</sup> Some of the variability may be due to other medications given to the patient.<sup>15</sup> Based on the understanding of this data, the investigators concluded that respiratory depression may occur any time a patient is on opioid medication. Therefore, it can be argued that continuous monitoring of respiration rate is warranted over

intermittent monitoring of respiration rate for early detection of POIRD.<sup>15</sup>

The problem of POIRD is likely to increase due to ongoing changes in the demographics of postoperative patients. Although all patients on opioids are at risk for POIRD, certain patients, including those who are obese, those who have obstructive sleep apnea, or those who are elderly, are particularly susceptible to POIRD.<sup>16</sup> Because of trends toward increasing obesity in the general population and because advances in medicine have resulted in increased life expectancy, the proportion of hospitalized patients with risk factors for POIRD has increased over the past decade and is likely to continue to increase. Specifically, the National Hospital Bill reported a 171% increase for respiratory failure.<sup>8</sup>

## Professional Society and Accreditation Organization Recommendations

Suboptimal pain management in postoperative patients is associated with a variety of poor outcomes, including medical complications (eg, elevated blood pressure, myocardial infarction, stroke, and chronic pain syndromes), reduced time to ambulation and its related complications (eg, atelectasis and secondary pneumonia, deep vein thrombosis), increased hospital LOS, and considerable emotional suffering.<sup>17,18</sup> As a result of the Joint Commission's consideration of pain as the "fifth vital sign," pain metrics now are being used as measures of the quality of health care delivery by hospitals<sup>19</sup> and have the potential to affect hospital financials if, as expected, they are used for value-based purchasing purposes. Recently, the Joint Commission's *Sentinel Event Alert*, focused on both the safe use of opioids in the hospital setting and "actions that can be taken to avoid unintended consequences of opioid use among hospital inpatients."<sup>20</sup> Screening patients for respiratory depression was the first measure recommended to prevent accidental overuse of opioids.<sup>20</sup> Additionally, the report stated that both the APSF and the Institute for Safe Medication Practices recommend the use of continuous monitoring of oxygenation and/or ventilation of patients receiving opioids in the postoperative setting.<sup>20</sup>

In a report that examined critical respiratory event data between 2000 and 2007, Ramachandran and colleagues<sup>21</sup> described 32 cases of life-threatening critical respiratory events (as defined by the need for rescue treatment with naloxone, endotracheal intubation, or cardiopulmonary resuscitation) related to postoperative opioid administration at their institution. This information has led several medical societies to issue statements and guidelines to address this risk. One of the most prominent societies involved with the issue of POIRD is the APSF. At the 2006 APSF Workshop on the Prevention of Postoperative Respiratory Complications, the foundation first took the position that no patient should be harmed by POIRD.<sup>5</sup>

The 2011 APSF conference addressed essential monitoring strategies to detect clinically significant drug-induced respiratory depression in the postoperative period. APSF conference attendees supported the use of continual electronic

monitoring for inpatients receiving postoperative opioids.<sup>22</sup> The foundation also confirmed that in the absence of supplemental oxygen, pulse oximetry was considered the most reliable and useful monitoring method currently available.<sup>22</sup> Additionally, the attendees agreed that if supplemental oxygen was added, ventilation monitoring (eg, capnography) was essential in order to detect hypoventilation.<sup>22</sup> This was proposed because the use of supplemental oxygen has been shown to mask hypoventilation, which can lead to a delay in detecting respiratory depression.<sup>16</sup> The APSF also affirmed that intermittent checks of pulse oximetry and ventilation alone were insufficient in detecting clinically significant changes.<sup>23</sup> Furthermore, overall consensus agreed that continuous electronic monitoring should supplement and not substitute traditional intermittent nursing assessments.<sup>23</sup> The APSF concluded that continuous electronic monitoring systems should incorporate multiple physiologic variables in order to recognize early signs of deterioration.<sup>23</sup>

Other recommendations for the prevention of POIRD included the increased education of health care providers on the potential risk associated with postoperative opioids, and improved assessment of sedation levels.<sup>22</sup> The APSF noted that there remained a significant rate of serious AEs related to POIRD among patients, even in those who were not thought to be at high risk.<sup>5</sup> It asserted that risk stratification was insufficient to eradicate POIRD and that continual electronic monitoring should be used for inpatients receiving postoperative opioids.<sup>22</sup>

The American Society for Pain Management Nursing (ASPMN) issued similar recommendations in 2011<sup>16</sup>; specifically, "(Continuous) technology-supported monitoring should be directed by patient risk, including preexisting conditions, response to therapy, overall clinical status, practice environment, and concurrent medication administration." The ASPMN also recommends the systematic nursing assessment of sedation level as a means of early detection of impending respiratory depression.<sup>16</sup>

## **Insights on Respiratory Depression From Emergency Response Events**

Signs of clinical deterioration, including a decrease in respiration rate, may precede POIRD, and if undetected by clinicians, can be life threatening. The formation of rapid response teams and medical emergency teams (METs) at hospitals was founded on the concept of failure to rescue, which refers to the inability to recognize early signs and symptoms of deterioration in a patient's condition or acting too late to prevent clinical decompensation.

In terms of POIRD, several types of process errors can contribute to the failure to rescue. One common problem is a detection error, which is a failure of the hospital process to detect an abnormality in the patient's clinical condition.<sup>24,25</sup> This is especially prevalent outside the postanesthesia care unit or the ICU setting, on the GCF where patients only are assessed periodically.<sup>26</sup>

This is supported by observations from a study conducted at the University of Pittsburgh Medical Center, in which the diurnal variation in MET calls was significantly higher in the non-ICU setting compared to within the ICU setting.<sup>26</sup> The authors of that study attributed this difference to the fact that patients were undergoing less-intensive monitoring and had less contact with clinical personnel in the non-ICU setting, particularly at night.<sup>26</sup>

Another problem involved in the failure to respond to POIRD is recognition errors<sup>25</sup>—failure to recognize the abnormal data or findings to trigger subsequent intervention in a patient who is undergoing intensive monitoring.<sup>24</sup> Several factors may contribute to this phenomenon, including the use of metrics that are not easily interpreted by clinical staff, lack of trending data, failure to institute criteria to trigger intervention, or understaffing.

An extensive body of research on METs has supported the importance of monitoring and detection of respiratory deterioration. For example, one study noted deficiencies in the current monitoring of vital signs in inpatients.<sup>27</sup> Specifically, there was marked variability in documentation of vital signs, with a high proportion of them missing in some hospitals. Furthermore, approximately 77% of patients suffering AEs had at least one vital sign missing from documentation immediately before the event, with respiration rate being the least commonly documented.<sup>27</sup> Another study retrospectively analyzed the medical records of patients for which MET calls were activated for respiratory distress.<sup>28</sup> Patients with respiratory distress were more likely to be postoperative (40%), and the hospital mortality for MET calls due to respiratory distress was 38%. Of note, delayed MET calls occurred in 50% of patients with respiratory distress, with a median duration of delay of 12 hours. A delay in making a MET call was associated with an increase in mortality (odds ratio, 2.10; 95% confidence interval [CI], 1.01-4.34;  $P=0.045$ ).<sup>28</sup>

An investigation by Taenzer and colleagues showed that increased monitoring combined with an automated alert system can result in improved outcomes.<sup>29</sup> In that study, a patient surveillance system based on pulse oximetry was implemented with nursing notification of violation of alarm limits through a wireless pager. Rescue events decreased from 3.4 to 1.2 per 1,000 patient discharges and ICU transfers from 5.6 to 2.9 per 1,000 patient-days, whereas the unmonitored units had no change.<sup>29</sup> Based on these data, the investigators concluded that patient surveillance monitoring results in a reduced need for rescues and ICU transfers.<sup>29</sup>

## **Nursing Perspectives**

Because their clinical duties place them directly at the point of care, nurses arguably play the most important role in terms of human monitoring for respiratory depression and determining the need for intervention. Typically, nurses are the first responders who play an important role in the identification and evaluation of at-risk patients, as well as the implementation of interventions to prevent serious AEs during opioid administration for pain management.<sup>16</sup>

**Table 1. Independent Predictors of Mortality**

Event	Odds Ratio (95% CI)
Bradypnea (RR <6)	14.4 (2.6-80.0)
Decrease of consciousness	6.4 (2.6-15.7)
Hypotension	2.5 (1.6-4.1)
Hypoxemia (SpO <sub>2</sub> <90)	2.4 (1.6-4.1)
Loss of consciousness	6.4 (2.9-13.6)
Tachypnea (RR >30)	7.2 (3.9-13.2)

**CI**, confidence interval; **RR**, respiration rate; **SpO<sub>2</sub>**, saturation of peripheral oxygen

A prospective study of 6,303 patients on the general hospital ward showed that extremes of RR could be a strong predictor of in-hospital mortality.

Adapted from reference 31.

Although nurses play a critical role in patient care, Jarzyna and colleagues noted that the previous lack of universal guidelines on monitoring for POIRD has caused disparities in monitoring practices.<sup>16</sup> Despite the APSF declaration that continuous monitoring should be used for all inpatients receiving postoperative opioids, a small qualitative study by Hogan and colleagues showed a general lack of patient monitoring by nursing staff.<sup>30</sup> The study also showed that respiration rate was one monitoring parameter that the nursing staff recorded less than 50% of the time.<sup>30</sup> Jarzyna and colleagues recommended that all nurses who care for patients receiving opioid therapy should be educated on potential patient and pharmacologic factors that contribute to an increased risk for inadvertent advancing sedation and respiratory depression, as well as parameters and criteria for recognizing sedation and respiratory issues.<sup>16</sup> This recommendation underscores the importance of regularly monitoring both sedation levels and trends to ensure that deeper levels of sedation are detected early and managed appropriately.<sup>21</sup>

Respiration rate is a significant clinical indicator of a patient's condition. In a prospective study of 6,303 patients on the GCF, 6 clinical events (bradypnea, tachypnea, loss of consciousness, decrease of consciousness, hypotension, and hypoxemia) were independently associated with a high risk for subsequent death (Table 1).<sup>31</sup> Furthermore, a univariate analysis in the same study showed that a decrease in respiration rate (<6 minutes<sup>-1</sup>) was associated with a 13.7-fold (95% CI, 2.9-64.0) increase in the risk for death after release from the hospital.<sup>31</sup>

A concern regarding the identification of POIRD using continuous mechanical monitoring is clinical alarm fatigue in nurses. Displaced monitoring sensors as well as threshold alarms, which are sometimes adjusted to reduce the incidence of false-negative alarms, can cause false-positive alarms. For example, while investigating patient surveillance monitoring, Taenzer and colleagues lowered their SpO<sub>2</sub> alarm threshold significantly (from <93% to <80%) after 1 month of data collection because of excessive false alarms,<sup>29</sup> and found that a repeatedly unreliable monitor often results in delayed response or no response from nurses. At the 2011 APSF conference on electronic monitoring strategies, discussion turned to the need for multimodal monitors that could detect specific patterns from multiple vital signs preceding an abnormal clinical event.<sup>22</sup>

### Ideal Monitoring Modalities for the Detection of POIRD

With clinical recommendations for the use of continuous technology-supported monitoring from the APSF, questions remain regarding characteristics of the ideal monitoring system for POIRD. Monitoring modalities for the detection of POIRD vary in response time, reliability, sensitivity, and specificity.<sup>22</sup> Therefore, it is essential to consider these factors when considering the characteristics of an ideal monitoring system. Sensitivity measures the ratio of false-negatives to true-positives, and because the consequences of missing critical POIRD are catastrophic, an electronic monitoring system needs to be highly sensitive. Yet, specificity (ratio of false-positives

**Table 2. Desirable Characteristics of an Electronic Monitoring System for POIRD**

<b>Sensitive</b>
End points that result in low rate of false-negative alarms in proportion to true-positive alarms
Use of end points that enable detection of POIRD <i>early</i> in the process
Might employ multiple parameters and context-specific algorithms to best identify the patient with early POIRD
Automated notification of appropriate personnel when the system has identified a patient with early POIRD
<b>Specific</b>
Reduced false-positive alarms (in proportion to true-negative non-alarms) and avoidance of “alarm fatigue”
<b>Continuous</b>
Allows detection of events not otherwise predicted by risk assessment or detected by intermittent monitoring
Allows observations of trends in data that may improve overall sensitivity and specificity of system
<b>Convenience</b>
Cost-effective
Noninvasive
Does not interfere with patient mobility (untethered, small [body borne], wireless)
Does not interfere with sleep yet provides vigilance during sleep
<b>Evidence that such monitoring plus intervention contributes to improved outcomes</b>

**POIRD**, postoperative opioid-induced respiratory depression

to true-negatives) also is important because false-positive alarms contribute to alarm fatigue, which may result in the monitor being switched off or alarms being ignored. A multimodal approach, in which multiple parameters are used to help assess respiratory function, may allow sensitivity and specificity to be optimized (Table 2).<sup>22</sup>

In a 2011 study, an integrated monitoring system that continuously amalgamated abnormalities of single, noninvasive monitoring parameters (ie, heart rate of <40 or >140 beats per minute, respiration rate of <8 or >36 breaths per minute, systolic blood pressure of <80 or >200 mm Hg, diastolic blood pressure of >110 mm Hg, and peripheral oxygen saturation of <85%) into a context-dependent weighted instability index value (INDEX) correlated significantly with cardiorespiratory instability-concern criteria, and usually occurred before overt instability.<sup>32</sup> Furthermore, when this system was combined with a nursing alert, it allowed early intervention and a subsequent decrease in cardiorespiratory instability-concern criteria.<sup>32</sup>

Other qualities of an ideal monitor for POIRD may include the use of an assessment parameter with good sensitivity and specificity for early respiratory decompensation combined with “smart” technology designed to recognize abnormal patterns and trends in these data.<sup>22</sup> Because of the incidence of POIRD, smart technologies that reliably detect early progression of clinical abnormalities and alert caregivers in a timely manner are an important factor in improving patient outcomes.<sup>22</sup>

## Conclusion

Analgesic regimens using opioids often are required to achieve adequate pain control in the postoperative setting, but this strategy also is associated with a small but significant risk for respiratory depression and serious complications. Intermittent monitoring of respiration rate and the use of pulse oximetry monitoring alone may not be sufficient to detect POIRD in a timely manner, especially in the setting of supplemental oxygen administration.

The addition of continuously displayed metrics that demonstrate adequate oxygenation and ventilation combined with smart analysis algorithms can help clinicians detect respiratory deterioration early on, in order to provide effective interventions while maintaining patient safety.<sup>22</sup>

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