CME Continuous Oximetry/Capnometry Monitoring Reveals Frequent Desaturation and Bradypnea During Patient-Controlled Analgesia

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BACKGROUND: The most serious complication of patient-controlled analgesia (PCA) is respiratory depression (RD). The incidence of RD in the literature is derived from intermittent sampling of pulse oximetry (Spo_2) and respiratory rate and defined as a deviation below an arbitrary threshold.
METHODS: We monitored postsurgical patients in a hospital ward receiving morphine or meperidine PCA with continuous oximetry and capnography. Nurses responding to audible monitor bedside alarms documented respiratory status and interventions.
RESULTS: A total of 178 patients were included in the analysis, 12% and 41% of whom had episodes of desaturation (Spo_2 <90%) and bradypnea (respiratory rate <10) lasting 3 min or more. One patient required "rescue" with positive pressure ventilation, and none required naloxone. Patients over 65 years of age and the morbidly obese were at greater risk for desaturation. Patients over 65 years of age were also more likely to have bradypnea, whereas the morbidly obese and patients receiving continuous infusions were less likely to have bradypnea.
CONCLUSIONS: Our incidence of RD by bradypnea is significantly higher than the 1%–2% incidence in the literature, using the same threshold criteria but more stringent duration criteria, while our incidence of RD based on desaturation is consistent with previous estimates. We conclude that continuous respiratory monitoring is optimal for the safe administration of PCA, because any RD event can progress to respiratory arrest if undetected. Better alarm algorithms must be implemented to reduce the frequent alarms triggered by threshold criteria for RD.
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Opioid-induced respiratory depression (RD) is a potentially catastrophic complication of opioid therapy for postoperative pain control (1). Although there is much ambiguity in the definition of RD, it is typically defined using two classes of criteria (2). The first class defines RD as a deviation of respiratory rate (RR), pulse oximetry value, or arterial carbon dioxide (CO_2) tension from an arbitrary threshold. Most studies investigating the incidence of RD using these criteria, which we term "threshold criteria," derive their data from a retrospective review of patient records. The second class of criteria defining RD uses indirect evidence of RD, such as the use of an opioid or sedative reversal drug, positive pressure ventilation, or a documented respiratory arrest. These interventions, which we term "rescue criteria," are sensitive yet non-specific markers for opioid-induced RD and occur less frequently than events meeting threshold criteria.

This study monitored patients using patient-controlled analgesia (PCA) with pulse oximetry and side stream capnography, providing a continuous record of heart rate (HR), oxygen saturation by pulse oximetry (Spo_2), RR, and end-tidal CO_2 ($ETco_2$), from which we measured the incidence of RD using threshold criteria. In addition, nurses collected data on RD by rescue criteria and verified proper placement of the transducers in response to audible monitor alarms. We hypothesized that continuous monitoring would reveal a much greater incidence of RD by threshold criteria than that reported in previous studies. We also sought to identify characteristics in the monitor data from patient subgroups previously identified as being at higher

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risk for RD, such as the elderly and patients with sleep apnea, the morbidly obese, and patients with continuous background infusions (CBI) (3–7).

METHODS

After IRB approval with waiver of individual patient consent, this observational study was conducted at St. Joseph's/Candler Health System in Savannah, GA. Postoperative patients selected by their surgeons to receive morphine or meperidine PCA were evaluated for participation in the study. Exclusion criteria were ASA physical status IV or higher, age less than 18 yr, a history of liver or kidney disease, ethanol or drug abuse, preoperative opiate use, intrathoracic surgery, or regional anesthesia during or after their procedure.

Patients received PCA using an Alaris™ Cardinal Health PCA (Model #8120) with integrated Spo_2 (Model #8210) and $ETco_2$ (Model #8300) modules; PCA was started in the postanesthesia care unit. The Oridion Smart CapnoLine™ Plus or Capnoline™ H cannulas sampled exhaled CO_2 and provided supplemental oxygen if needed. Demographic and pertinent medical histories were collected in an electronic database. The record was stripped of personal health information and indexed by study number.

Initial PCA pump settings were as follows: for morphine, 1 mg bolus, 6 min lockout interval and 30 mg, 4-h maximum; for meperidine, 10 mg bolus, 6 min lockout interval and 300 mg, 4-h maximum. Patients chosen to receive a CBI received 1 mg of morphine per hour or 10 mg of meperidine per hour. The nurses adjusted PCA settings according to the patients' needs and physicians' orders. No initial loading doses were prescribed.

The monitors measure HR, Spo_2, $ETco_2$, and RR continually and transmit maximum, minimum, and average values, as well as alarm conditions and infusion rates to a data server every minute via a secure, wireless protocol. PCA pumps were initially programmed to sound an audible alarm at the bedside when the following thresholds were reached: Spo_2 <90%, RR <8 breaths per minute (bpm), $ETco_2$ >50 mm Hg or $ETco_2$ <30 mm Hg, HR >100 bpm or HR <50 bpm; however, thresholds could be modified by the caregiver. The audible alarm ceased when the threshold condition that triggered the alarm resolved or when a nurse disabled the alarm for 2 min. A nurse responding to an audible alarm verified proper placement of the oximetry probe and nasal cannula. The nurse also recorded the patient's level of sedation (Pasero-McCafferey Scale), a perceived numerical pain score from 1 (no pain) to 10 (maximum pain) and any of the following interventions: physical stimulation of the patient, naloxone administration, positive pressure ventilation, and assistance from a respiratory therapist, a physician, or the "code blue" team (8). Supplemental oxygen administered via the Oridion™ nasal cannula was given to patients whose saturation remained below 94% despite a RR more than 10 bpm. Medications with sedative or analgesic effects, such as sleeping aids and opioid- and non–opioid-containing analgesics given during the course of PCA treatment, were recorded in the clinical database.

Before the start of this study, a small pilot study was conducted to estimate the incidence of oxygen desaturation and bradypnea using continuous monitoring. This pilot study estimated the rate of desaturation to be 25%, a value twofold higher than previously reported from pooled data in the literature (9). The effect size for the incidence of bradypnea was found to be larger, so sample size calculations were based on oxygen desaturation. A total of 120 patients gave 90% power to reject the null hypothesis of a previously established oxygen desaturation rate of 11.5%, in favor of an incidence of 25%, using the exact binomial test at an $\alpha = 0.05$ level of significance. The sample size was inflated to a minimum of 170 patients in order to capture more RD events by rescue criteria, yet stay within the desired data acquisition time of 6 mo.

The monitor data were entered into MatLab™ and filtered for artifact as follows. Built-in artifact rejection from the monitors resulted in "null" data elements in the data stream, which were removed before analysis. Furthermore, data preceding the time at which the transducer was noted as misplaced in the clinical record was removed. To quantify only clinically relevant and discrete episodes of RD by desaturation (RDeSat) or bradypnea (RDLowRR), the desaturation or bradypnea had to be sustained below threshold for more than or equal to 3 min. A less conservative definition of two consecutive minutes with the mean Spo_2 <90% or RR <10 bpm was also considered to be consistent with the sample size estimation and allowed for comparisons with previous literature. We established an additional condition for a discrete RD event; namely that a variable that vacillates around the threshold not be credited with multiple events, because this is clinically a single event. Specifically, this condition required a RD event to be separated from the next by 3 or more minutes of Spo_2 more than 90% or RR more than 10 bpm. To explore the temporal relationship between hypoventilation, bradypnea, and desaturation, we counted the number of RDeSat events that occurred within 5 min of the start of an RDLowRR event.

In addition, the following subgroups of patients who had previously been identified as at a higher risk for RD were analyzed for differences in the incidence of RD: patients more than 65 years of age, morbidly obese (Body MA Index ≥40) and obese (Body MA Index ≥30) patients, patients with a preoperative diagnosis of sleep apnea, and patients receiving a CBI.

Standard descriptive statistics were used for this study. The incidence of RD was estimated using the exact confidence interval for a binomial proportion. Comparisons of the incidence rates across subgroups were facilitated by Fisher's exact test. *P* values ranging from 0.1 to 0.05 were considered statistical trends. *P* values less than 0.05 were considered statistically significant. The SAS System was used for all statistical analyses.

RESULTS

A total of 205 patients were enrolled in the study over the course of 3 mo, and 27 patients were excluded. Nine patients were excluded because their monitor data were incomplete because of equipment malfunction. One patient receiving hydromorphone PCA and one patient on dialysis were inadvertently enrolled and subsequently dropped from the analysis. Other (n = 16) patients had unexplained gaps in their data streams, so the analysis was limited to the n = 178 subjects who had complete, synchronized oximetry and capnography data streams and whose demographics are shown in Table 1.

A total of 10,378 audible alarms were triggered during the patient monitoring, with 4893 (47%) and 2347 (23%) of these alarms being associated with low RR and desaturation. The remaining 3217 alarms were distributed as 1938 high RR, 820 high $ETco_2$, 272 low $ETco_2$ alarms, or they represented more than one alarm condition. The median duration of the alarms was 12 s, and 8572 (83%) were less than 30 s in duration. The nursing database recorded 647 bedside responses. The nasal cannula or oximetry probe was noted as misplaced on 59 occasions, and pain and sedation scores were recorded 339 times.

Using the RD criteria described above, 73 (41%; 95% CI: [34%, 49%]) patients had at least 1, 3 min or longer RDLowRR event, and 21 (12%; 95% CI: [8%, 18%]) patients had at least 1, 3 min or longer RDeSat event (Table 2). As expected, the respective incidences using the more liberal 2 min or longer definition were higher (RDLowRR = 58%, RDeSat = 21%). The incidence of bradypnea and desaturation over a range of thresholds and durations is shown in Figure 1.

Patients averaged 7.6 RDLowRR events with an average duration of 9.8 min (SD = 5.6). For desaturation events, the average number of events was 1.5, and the average duration was 6.3 min (SD = 3.7). Only one patient in the 178 studied met rescue criteria on the basis of requiring positive pressure ventilation yielding an estimated rate of RD based on rescue criteria of 0.56% (95% CI: [0.0%, 3.1%]). This patient's oximetry and capnometry alarms were triggered by persistent desaturation and tachypnea that progressed over 30 min. His symptoms were initially attributed to a pulmonary embolus, but he was subsequently diagnosed with aspiration pneumonia.

Table 1. Demographic and Clinical Characteristics of Sample (N = 178)

Variable level	N	Percent
Gender		
Female	167	93.8
Age, 65 yr or more	27	15.2
Mean (SD)	49.6 (12.8)	
BMI classification		
Obese (BMI ≥30)	83	46.6
Morbidly obese (BMI ≥40)	16	9.0
Sleep apnea	7	3.9
Supplemental O_2	15	8.4
Opioid		
Meperdine	102	57.3
Morphine	74	41.6
Both during hospital stay	2	1.1
PCA configuration		
Continuous background infusion	103	57.9
Bolus only	50	28.1
Background infusion for some period of time	25	14.0
PCA duration, mean (SD) h	23.6 (22.4)	
Surgical summary		
Abdominal	151	84.8
Laparoscopic	102	67.5
Open	49	32.5
Orthopedic	20	11.2
Other	7	3.9

Among subgroups of patients, the rates of RDLowRR and RDeSat tended to be higher in patients aged 65 yr or older and lower in those with CBI (Table 2).

Patients with CBI had lower rates of RDLowRR (32% vs 53%, $P < 0.01$) condition and tended to have lower rates of RD based on RDeSat (8% vs 17%, P = 0.06). These findings were then examined in the context of medication and dosage. The mean doses of meperidine were 19.9 (SD = 9.0) mg/h for CBI patients and 9.91 (SD = 7.2) mg/h for patients receiving bolus only ($P < 0.01$). For morphine PCA, the mean doses were 2.2 (SD = 1.0) and 1.2 (SD = 0.93) mg/h for patients receiving CBI versus bolus only, respectively ($P < 0.01$). Patients receiving meperidine PCA (n = 82) received 1.12 (SD = 0.94) boluses/h and 1.09 (SD = 0.71) boluses/h for CBI and bolus only mode, respectively (P = 0.87). Similarly, there was no difference in boluses per hour for patients on morphine PCA, namely, 1.20 (SD = 0.99) and 1.11 (SD = 0.93) boluses/h were delivered in patients with CBI and bolus only mode, respectively (P = 0.73).

Fifteen patients had supplemental oxygen added during their therapy; however, those subjects administered supplemental oxygen tended to have more RDeSat events (27% vs 10%, P = 0.08) and RDLowRR events (73% vs 38%, P = 0.01). There were six instances in which the onset of a RDeSat event followed the onset of a RDLowRR event within 5 min, three of which occurred in patients receiving supplemental oxygen.

Table 2. Estimation of Incidence of Respiratory Depression and its Relationship to Demographic and Clinical Characteristics

	Pulse oximetry (Spo_2 <90)						Respiratory rate (RR <10)					
	2 or more consecutive minutes			3 or more consecutive minutes			2 or more consecutive minutes			3 or more consecutive minutes		
Variable level	N	%	95% CI or *P*-value	N	%	95% CI or *P*-value	N	%	95% CI or *P*-value	N	%	95% CI or *P*-value
All patients (n = 178)	38	21.4	[15.6, 28.1]	21	11.8	[7.5, 17.5]	104	58.4	[50.8, 65.8]	73	41.0	[33.7, 48.6]
Age >65 (n = 27)	10	37.0	0.04	6	22.2	0.10	21	77.8	0.03	18	66.7	<0.01
Sleep apnea (n = 7)	1	14.3	>0.99	1	14.3	0.59	5	71.4	0.70	4	57.1	0.45
Obesity												
BMI ≥80 (n = 83)	17	20.5	0.86	10	12.1	>0.99	41	49.4	0.03	28	33.7	0.07
BMI ≥40 (n = 16)	7	43.8	0.05	6	37.5	<0.01	6	37.5	0.11	6	37.5	>0.99
Background infusion (n = 103)	17	16.5	0.09	8	7.8	0.06	48	46.6	<0.01	33	32.0	<0.01
Supplemental O_2 (n = 15)	6	40.0	0.09	4	26.7	0.08	12	80.0	0.10	11	73.3	0.01

95% confidence intervals reflect the estimate of the incidence of respiratory depression.

P-values are for a test of the equality of the rate of respiratory depression across clinical characteristics using Fisher's Exact Test.

DISCUSSION

The results of this study demonstrate that rates of RD derived using threshold criteria in patients receiving postoperative PCA may be higher than previously reported.

Two literature reviews evaluating the safety of PCA as it pertains to RD and its complications, agree in order of magnitude on the incidence of RD by threshold criteria (3,9,10). Cashman and Dolin's meta analysis found the incidence of RDLowRR and RDeSat to be 1.2% and 11.5%, respectively (9). Walder et al.'s earlier review of the literature found incidences of 1.6% and 15.2% using the same threshold criteria (10). The incidence of RD by rescue criteria is considerably lower, in the range of 2%, for naloxone reversal.

The data on respiratory depression in most studies are obtained from a retrospective chart review of PCA records and flow sheets (9–12), where data are collected intermittently. Current PCA monitoring protocols typically require a single RR, and less commonly a Spo_2 value, initially at 30-min intervals, but thereafter at intervals as far as 2–4 h apart. It is thus not surprising that when we monitored patients continuously and electronically, periods of desaturation and bradypnea were longer than previously reported.

Previous investigators using continuous pulse oximetry monitoring in patients on PCA have reported a higher desaturation incidence than that reported in the pooled data studies by Cashman and Dolin and Walder et al. (9,10). Stone et al. found severe desaturations in PCA patients breathing room air during the first postoperative night (13). They revised their protocol to give all patients supplemental oxygen on the first postoperative night and switched them to room air for their second night, during which they still found that half of their patients had individual Spo_2 values less than 90%. Routine addition of supplemental oxygen for patients on PCA, as done by Stone et al. on the first postoperative night, is controversial, as there is evidence in the literature that it may mask RD by delaying the onset of desaturation (14). To explore this temporal association, we chose 5 min as a reasonable window in which to expect a desaturation to occur if associated with hypoventilation secondary to bradypnea. We found that patients receiving supplemental oxygen had significantly more prolonged (3 or more minutes) episodes of bradypnea, yet only three had coincident desaturation events, which would support the contention that oximetry may be a late indicator of hypoventilation in these patients. However, we acknowledge that our thresholds defining RDeSat and RDLowRR influence this result and that this relationship may be better explored by trend analysis of the data.

Our incidence of bradypnea is many orders of magnitude more than the 1%–2% widely reported in the literature (9,10,15). This is also not surprising, because manually obtained RR have been found to be inaccurate in the conscious sedation setting (16,17) and are measured intermittently in the hospital ward. Our findings are consistent with those of Catley et al., who found "predictable and short-lived" changes in ventilatory patterns using continuous respiratory plethysmography monitoring in postsurgical patients, changes that were missed using intermittent observation (18). Unlike bedside pulse oximetry, side-stream capnography, from which we derive our RR and $ETco_2$ data, has not been validated in this setting. Because any amount of CO_2 in an exhaled breath is indicative of gas exchange, we are confident that our RR data are representative of the patient's RR, even when the nasal cannula is only partially in place. The accuracy of the $ETco_2$ reading, however, cannot be relied upon because it has been shown to correlate with alveolar $ETco_2$ only upon a full vital capacity

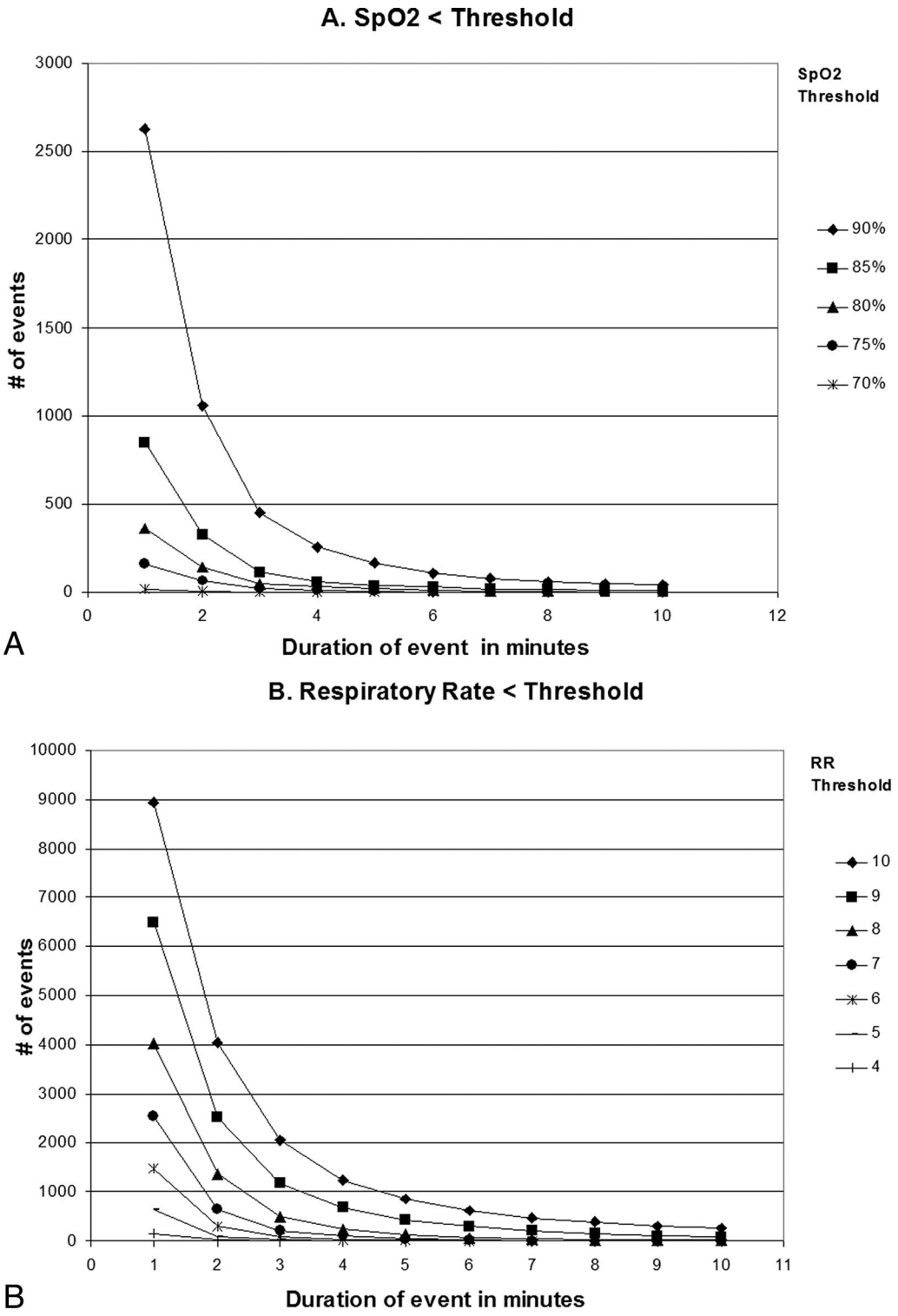

Figure 1. Distribution of RD events by threshold and duration for (A) oxygen saturation (Spo2) and (B) respiratory rate.

breath, which rarely occurs in our setting (19). Thus, its value may lie in trend analysis.

Among the subpopulations of interest, patients over age 65 yr were more likely to have RD, as determined by threshold criteria, for both desaturation and bradypnea, confirming earlier studies (3,20). The group with a pre-existing diagnosis of sleep apnea was too small to draw any conclusions. The breathing of obese patients is typically faster, more shallow, and has a decreased functional residual capacity (21), which makes these patients more susceptible to desaturation. This pattern is confirmed by our data, which show that obese patients tend to have more desaturation events and fewer low RR events.

In the literature, CBIs have been implicated as a risk factor for RD (3,12,20,22), yet the ASA Practice Guidelines do not support this contention (23). Our surgeons perceive CBIs as providing better pain control and use

them frequently. Although CBI patients received almost twice as much opioid per hour as bolus patients, they had significantly fewer bradypneic episodes and tended to have fewer desaturation events. We hypothesize that, because the average plasma concentration of opioid in CBI patients was higher, a bolus dose resulted in smaller relative change in plasma concentration, which may have had a smaller effect on RR. We will perform a pharmacokinetic/dynamic analysis of our PCA dosing regimens to further examine this theory. We did not obtain sufficient pain and sedation scores per patient to allow a meaningful analysis of the relationship between RD events and analgesia and sedation.

There are some important limitations in the present study. The predominance of women in this study reflects a very active gynecologic surgical service. There are gender-based differences in pain sensitivity and respiratory depression between men and women. Thus, our analysis may not apply to men. Opiates, specifically morphine, are more potent analgesics in women than in men, and there are similar differences for the respiratory effects of opiates (20,24). Because most data are derived directly from monitors, and since only a small percentage of alarms were verified by nurses, we must discuss artifact, false positive alarms, and the low nursing response rate to audible alarms. There are three categories of false alarms, of which technical false alarms and clinical false alarms are most common (25). Technical false alarms are those in which the monitor threshold value for a variable is reached but not physiologically accurate, examples of which are a malpositioned or missing transducer, or a patient who is moving. We reduced technical false alarms by removing "null" data elements and data from witnessed, misplaced transducers from the database. We acknowledge some technical artifact resulting in false positive alarms may remain. Trend analysis and multivariate interpretation of related data, such as RR and $ETco_2$, are other techniques used to identify technical false alarms (25). We intend to apply sophisticated trend analysis and contextual algorithms to these data in a future analysis. Clinical false alarms are those in which the variable is actually below threshold but not a clinical cause for concern. A clinical false alarm scenario in the study was a Spo_2 value that hovered on either side of the 90% threshold but remained steady. The audible alarm triggered with each excursion below 90% and silenced shortly thereafter as the Spo_2 returned above 90%. This can happen as frequently as the update cycle of the monitors, which occurs every 2 and 20 s for the oximeter and capnometer, respectively. We prevented hover from artificially inflating the RD count of clinically relevant events by requiring that events be separated from one another by 3 min. However, the monitor alarms had no such filter and, as Figure 1 shows, most bradypnea and desaturation events were of short duration and generated a brief audible alarm. We speculate that the low nursing response rate to alarms can be attributed in part to the short duration of alarms. Unlike the case where bedside alarms are located in an intensive care unit or operating room and where the caregiver is in the immediate vicinity of the patient, a nurse in a hospital ward caring for multiple patients in different locations may not hear the alarm or be able to respond before the alarm is silenced. More sophisticated alarm algorithms that monitor trends in physiologic variables, combined with telemetry surveillance, may be a more effective monitoring strategy in this setting, and one less prone to false positive alarms.

While the sample size was inflated to 170 patients in order to capture additional RD events by rescue criteria, power was substantially limited for many subgroup analyses (e.g., analysis with sleep apnea and morbid obesity). The percentages have been reported to aid future power calculations so that appropriately powered subgroup comparisons can be planned. While multiple testing was conducted, a strict Bonferroni correction would be too conservative due to the correlation of the tests. Thus, unadjusted *P* values have been reported in the results to allow the reader to gauge the strength of the association.

The point estimate for the rescue incidence of one patient in 178 (0.6%) was less than the 2% in the literature, but not statistically different from 2%. We believe that the safety features of continuous monitoring, such as an audible alarm that arouses a patient and summons a nurse, contribute to the low incidence of rescue events, although this is best verified by a randomized, prospective trial of continuous monitoring versus conventional monitoring. However, it is clear that a conventional PCA monitoring protocol fails to detect frequent episodes of bradypnea and desaturation. Although most are transient, any one of these episodes can deteriorate to respiratory arrest. Further research will clarify patient characteristics and under which conditions this occurs and will improve alarm algorithms to reduce the high false positive alarm rate typical of threshold triggered alarms. Until this research is done, increased monitoring of oxygenation and ventilation of PCA patients is warranted.

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