

## Detecting Adverse Respiratory Effects of Anesthetics and Opioid Analgesics in the Postoperative Period

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**Abstract:** The underlying problem for two of the three most common patterns of unexpected hospital deaths (PUHD) is hypoventilation<sup>1</sup>. Current methods of post-operative respiratory monitoring give delayed signals and have a high false positive rate leading nurses to ignore alarms. We hypothesize there exists a combination of low cost sensors which are capable of providing real time feedback and alarms regarding obstructive sleep apnea and ventilatory depression. Such a monitor would be useful during space travel when monitoring personnel are limited following an injury or if astronauts were to be sedated during extended travel. **Methods:** Twenty-six subjects will be recruited to participate in a study of the effects of Propofol and Remifentanyl. Throughout the day, these patients will be exposed to varying levels of both drugs simultaneously via target controlled infusions. These patients will be attached to breathing and oxygen monitors including chest bands, pulse oximeters, nasal pressure sensors, CO<sub>2</sub> capnography, breathing microphones, and thermistors. The patients are then observed for types of apnea or ventilatory depression. **Results:** The study is currently ongoing however preliminary analyses of the data indicate multiple low cost sensors are capable of detecting breathing as well as obstructive events and apnea. **Conclusion:** Using only a combination of low cost sensors, we can provide real time respiratory event data to nurses and practitioners.

### INTRODUCTION & BACKGROUND

The underlying problem for two of the three most common patterns of unexpected hospital deaths (PUHD) is hypoventilation<sup>1</sup>. Type II PUHD (CO<sub>2</sub> narcosis) involves a reduction in respiratory rate and/or tidal volume, and if supplemental oxygen is being provided, a pulse oximeter will not detect the problem until the hypercarbia is significantly advanced and the patient is near respiratory arrest. Type III PUHD is induced by obstructive sleep apnea in the presence of arousal failure, and is recognized as a repetitive sequence of cyclic apneas and self-arousals which precede the final apnea. A pulse oximeter alarms with each apneic period and will likely be interpreted as generating many false positive alarms.<sup>1</sup> The risk of opioid-induced respiratory depression in postoperative patients is greatest in the first 24 hours after initiation of opioids<sup>2</sup>, and opioids are the most commonly used drug for treating pain in the postoperative period.<sup>3</sup>

These problems would be especially apparent in space travel where monitoring personnel are limited due to either sedation of crew members or an injury rendering the crew short-handed.

Respiratory depression is caused by drug-induced inhibition of the breathing control center of the brain stem. Partial to full airway obstruction is an anatomic problem

involving the soft palate, tongue base, and/or epiglottis, caused by drug-induced decreases in airway patency and muscle tone. Sedatives and opioids depress the response to elevated CO<sub>2</sub> (reduced drive to breathe), worsen arousal, cause airway obstruction, and change sleep patterns<sup>4-8</sup>

In the postoperative period, most adverse respiratory events occur during the first 24 hours of opioid administration.<sup>2</sup> During this period, pulse oximeter monitoring, supplemental oxygen, incentive spirometry, and intermittent nursing observation are the primary interventions used to fend off adverse respiratory events. For inpatient monitoring, pulse oximetry is often inadequate. On a busy hospital floor, it is difficult to respond to multiple remote advisory pulse oximetry alarms. Pulse oximeter alarms are ignored because they have a high false-positive alarm rate due to movement artifact and displacement.<sup>9,10</sup> Pulse oximetry primarily monitors oxygenation instead of ventilation; the SpO<sub>2</sub> signal is a delayed indicator for apnea or hypopnea, particularly when supplemental oxygen is given. By the time the pulse oximeter alarms, an apneic patient is already in danger of hypoxia, brain injury and death.

Existing technologies may improve monitoring of adverse respiratory events in this setting, but are either costly or difficult to implement. For example, monitoring ventilation with capnography is expensive and it can be problematic to sample the exhaled gas with a face mask or nasal cannula in non-intubated patients.<sup>11</sup> Acoustic respiratory rate monitoring may be able to detect airway obstruction, but it is costly and may not have sufficient sensitivity to reliably detect apnea events.<sup>12</sup> We suggest that there is an urgent need for a

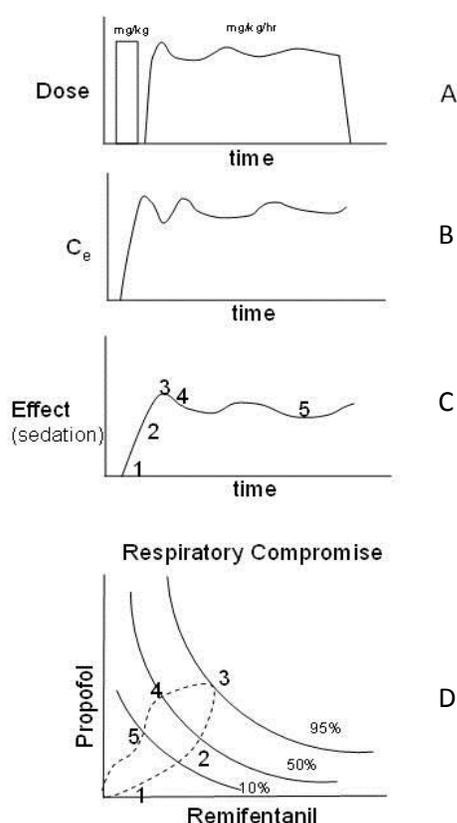
low cost, reliable respiratory depression monitoring technique that can be integrated with the signals from the pulse oximeter to give additional physiologic information about a patient's sufficiency of both ventilation and oxygenation.

Currently, we are exploring the value of integrating the information from a set of low-cost physiologic monitors that can be adapted to monitoring patients. In addition to the red and infrared component signals that comprise the pulse oximeter plethysmography waveform, we intend to integrate information from motion sensors on the finger, head, abdomen, chest wall and bed, temperature, pressure and carbon dioxide sensors embedded in a nasal cannula and acoustic respiratory rate via a microphone on the throat. We will determine from the tested set the fewest number and least costly types of sensors that can be used to accurately identify and quantify ventilatory depression and airway obstruction, provide reliable measures of oxygenation AND ventilation, provide specific alarms, and avoid artifact. We will evaluate this multi-sensor set for volunteers who receive medications to produce ventilatory depression and/or partial to complete airway obstruction.

Our team previously characterized various effects of sedatives combined with opioids using drug interaction models. Specifically, we characterized the interaction of Propofol and Remifentanyl on metrics of airway obstruction and intolerable ventilatory depression in volunteers.<sup>8</sup> We defined intolerable ventilatory depression as a respiratory rate less than 4 breaths per minute and airway compromise as either partial (tidal volume less than 3 mL/kg in the presence of a respiratory effort) or complete obstruction. Respiratory compromise was

defined as either intolerable ventilatory depression or airway obstruction or both.

Using this model, predictions of respiratory compromise (0 to 100%) can be made for various dosing schemes of Propofol and remifentanil.<sup>8</sup> (Figure 1). In general, dosing schemes that led to high concentration of Propofol were more likely to produce airway obstruction and higher doses of Remifentanil were more likely to produce intolerable ventilatory depression.



**Figure 1:** A: Dose of a drug, first as a bolus, then as a continuous infusion. B: effect site concentration ( $C_e$ ) Corresponding to the given dose and C: Observed effect (sedation) for a single administered drug. Time points 1-5 correspond to a likelihood of effect in D: Effect and corresponding drug concentrations resulting in stated probabilities for respiratory compromise.

A 20 gauge venous catheter is placed in an antecubital vein under local anesthesia (0.2 mL of 0.5% lidocaine) for the purpose of hydration and drug administration. The IV site is similar in all subjects. A maintenance infusion of 0.9% sodium chloride is administered at 1 ml/kg/hour throughout the study. Continuous infusions of Remifentanil and Propofol are infused into this peripheral IV.

Subjects are instrumented with a noninvasive blood pressure cuff, ECG leads, pulse oximeter(s), motion sensors, respiratory inductance plethysmography "chest bands", capnography nasal cannula, nasal gas pressure sensor, nasal thermistor and an acoustic respiratory rate sensor. These or similar monitors are placed to measure respiratory rate, tidal volume, end-tidal  $CO_2$ ,  $SpO_2$ , blood pressure, body motion and heart rate. Chest and abdominal wall excursion are measured with the attached motion sensors and the respiratory inductance plethysmography bands. Changes in respiration pattern will be displayed as real-time changes in  $CO_2$  waveforms. A processed EEG monitor and/or a cerebral oximeter are optionally placed to record data for later analysis. A motion sensor may also be placed on the bed. These devices are operational during the entire study day. Data from devices is electronically captured and recorded for later analysis. Continuous variables such as motion waveforms, pulse oximetry waveform, capnogram, and nasal airway pressure are digitized during data collection periods at 50-1000Hz during data collection periods at each target effect site concentration pair. Discrete variables are recorded every 5 seconds or as soon as data are available during data collection periods. Examples of discrete variables

include heart rate, SpO<sub>2</sub>, PetCO<sub>2</sub>, systolic blood pressure, diastolic blood pressure and respiratory rate. The tidal volume may be occasionally measured with a differential pressure flow sensor attached to an anesthesia mask or mouthpiece in order to calibrate the respiratory inductance plethysmography bands.

Each subject will receive Propofol and Remifentanil. Similar to previously collected data from our volunteer laboratory (Kern et al, 2004), each drug will be administered using a computer controlled (Stanpump<sup>14</sup>) continuous infusion pump (Pump 22; Harvard Apparatus, Limited, Holliston, MA) to achieve selected target effect site concentrations. The effect site concentration refers to the drug concentration at the pharmacologic site of action. Pharmacokinetic parameters published by Minto *et al.*<sup>15</sup> and Schnider et al.<sup>16</sup> will be used for Remifentanil and Propofol respectively.

We administer Propofol and Remifentanil pairs in a dose escalation scheme with small steps in order to creep up to the desired target effects of respiratory depression, airway obstruction and both effects while avoiding overshoot. To accomplish this, the Propofol is dosed in a range of 0.75 - 4 mcg/mL in dose escalation steps of approximately 0.5 mcg/mL. Remifentanil is dosed in a range of 0.75 to 4.0 ng/mL in escalation steps of approximately 0.25-0.5 ng/mL. If overshoot is observed for a given target effect site concentration pair, the target effect site concentrations may be lowered so assessments can be made during the target effects of respiratory depression or airway obstruction or both. Once the drug concentration pair is identified which results in the target effects for a given subject, the

steady state drug dose will be maintained for a period of data collection.

## RESULTS

While the study is currently ongoing, a preliminary analysis of the data has revealed high correlation between certain respiratory monitors and specific breathing related 'states'.

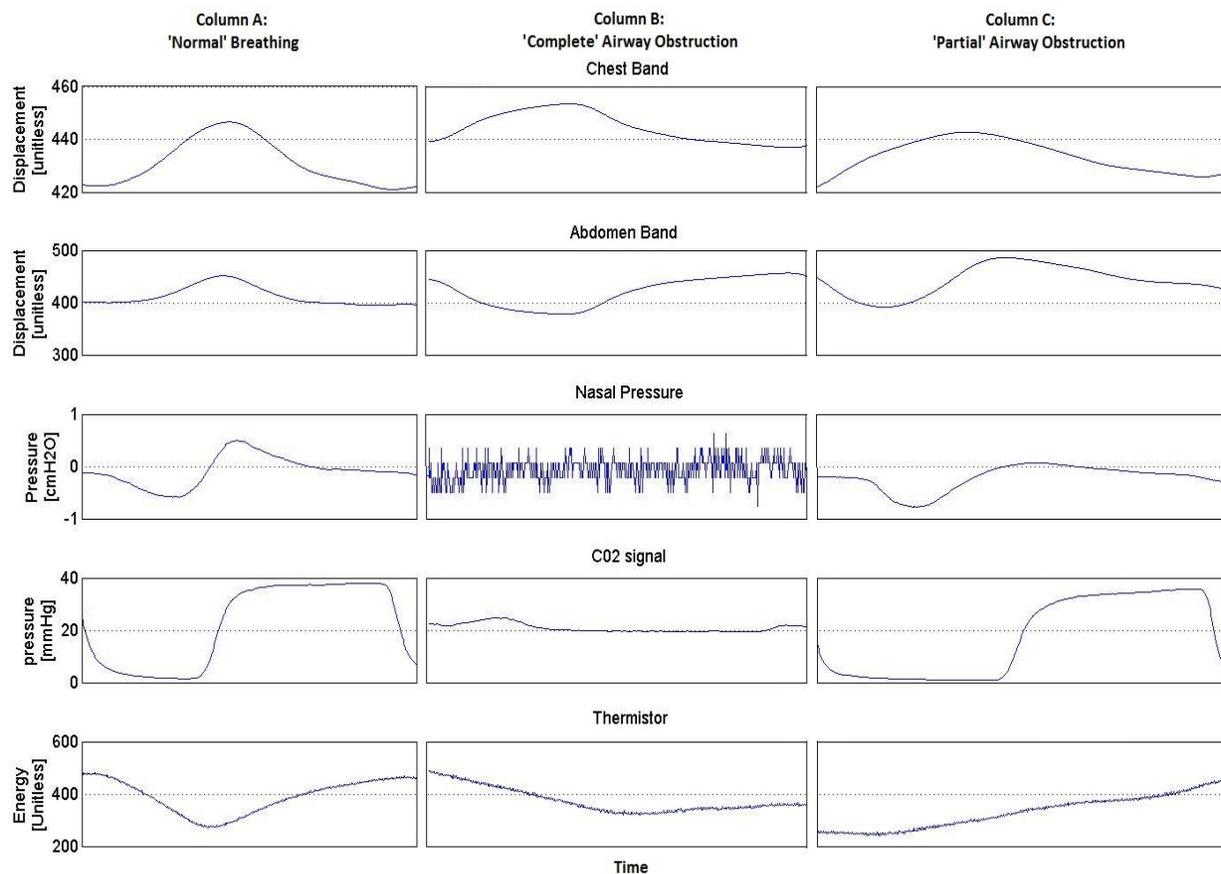
These breathing states are 'normal' breathing, complete airway obstruction (obstructive sleep apnea), partial airway obstruction (partial obstructive sleep apnea or snoring), and ventilatory depression (non-obstructive sleep apnea) characterized by a breathing rate of less than four breaths per minute. The figure below illustrates the some of the primary complex breathing patterns that we are interested in monitoring. Ventilatory depression was not included in the figure as it appears in the form of intermittent 'normal' breathing with occasionally reduced volume.

From this data we can already see multiple breathing patterns once we combine signals such as chest or abdomen band excursion (ventilatory effort) and nasal pressure, expired CO<sub>2</sub>, or thermistor readings (ventilatory success). In column A, we see what we would expect for each of these signals under normal breathing conditions; The chest and abdomen are in phase with each other, the biphasic nasal pressure signal is synced with ventilatory effort, and the expired CO<sub>2</sub> increases at expiration. Column B of figure 2 illustrates how these signals change during airway obstruction; Chest and abdomen bands are out of phase with each other (paradoxical) while measures of ventilatory success are zeroed. Column C shows partial airway obstruction; the abdomen band becomes biphasic and

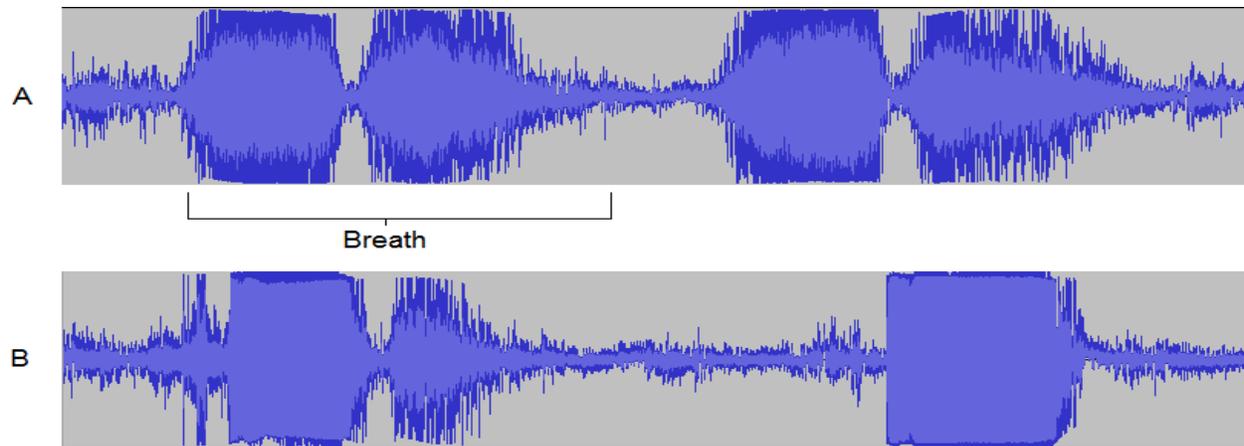
only syncs with the chest during the latter half of the breath attempt where the obstruction was partially cleared. The lower magnitude nasal pressure is one indicator of the patient's difficulty passing air.

Figure 3 shows an example of audio data recorded from a microphone attached to one side of the subject's throat. Again we see the differences between normal breathing (A) and obstructed breathing (B).

In the normal breathing case we see a generally lower magnitude, lower frequency sound as the passage of air is relatively quiet. Each breath has two distinct parts: inspiration and expiration. During obstructed breathing we see that the expiration phase is much lower in magnitude (or nonexistent in the second breath) because little or no air is passing. The first phase, however, is much higher in magnitude and frequency because the airway is restricted.



**Figure 2:** Electronic signals collected during different breathing related 'states'. The signals shown from top to bottom are: Chest band, abdomen band, nasal pressure, expired co<sub>2</sub>, and thermistor. The columns are one breath samples from the breathing states listed at the top of the figure.



**Figure 3:** Audio data from a microphone placed to the side of the subject's throat. Both samples contain two breath attempts. Row A is an example of normal, unobstructed breathing. Row B is an example of partially obstructed breathing in the first breath and completely obstructed breathing in the second.

## CONCLUSION

A low cost, accurate, and minimally sized respiratory monitor would be useful during space travel when personnel are limited following an injury/emergency procedure or if astronauts were to be sedated during extended voyages.

Overall, preliminary analysis of the signals has been successful in proving that within individual patients, low cost signals exhibit discernible patterns during obstructive apnea, partial airway obstruction, and ventilatory depression.

Unfortunately, the data set is slightly too small at the moment to draw statistically meaningful conclusions about the amount of patient to patient variation in signal shape. Potential variation in signal shape must be accounted for in any algorithm which attempts to identify breathing patterns and adverse respiratory events in a population of patients.

As we collect more data, we hope to prove that the data patterns we have thus far identified persist through patients of variable age, gender, size, weight, and any other potentially confounding factors.

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