Identification of Respiratory Distress through Combining Modern Sensors in Patients Receiving Opioids and Anesthetics

Sean Ermer, B.S., Lara Brewer, Ph.D, and Joseph Orr, Ph.D

Department of Bioengineering in Anesthesiology, University of Utah, Utah

Abstract: The underlying problem for two of the three most common patterns of unexpected hospital deaths (PUHD) is hypoventilation[1]. Current methods of post-operative respiratory monitoring give delayed signals and have a high false positive rate leading nurses to ignore alarms. We hypothesize a combination of low cost sensors can be capable of differentially identifying obstructive sleep apnea and ventilatory depression in real-time. 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 were recruited to participate in a study of the effects of Propofol and Remifentanil. Throughout the day, these patients were exposed to varying levels of both drugs simultaneously via target controlled infusions. These patients were attached to a multitude of breathing and oxygen monitors. Adverse respiratory events were identified and recorded by clinicians. We developed breath detection algorithms and used these to identify respiratory problems in our signals which were compared against clinician input. Results: When comparing our sensors versus clinician opinions, multiple combinations of sensors successfully differentially identify adverse respiratory events. 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[1]. Type II PUHD (CO_2 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.[1] The risk of opioid-induced respiratory depression in postoperative patients is greatest in the first 24 hours after initiation of opioids[2], and opioids are the most commonly used drug for treating pain in the postoperative period.[3]

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_2 (reduced drive to breathe), worsen arousal, cause airway obstruction, and change sleep patterns[4-8]

In the postoperative period, most adverse respiratory events occur during the first 24 hours of opioid administration.[2] 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.[9,10] Pulse oximetry primarily monitors oxygenation instead of ventilation; the SpO_2 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.[11] 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.[12] 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 a hospital floor setting. 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. A monitor which correctly identifies all the different types of respiratory events individually would allow nurses and clinicians to better their care to help patients in need.

Our team previously characterized various effects of sedatives combined with opioids using drug interaction models. Specifically, we characterized the interaction of Propofol and Remifentanil on metrics of airway obstruction and intolerable ventilatory depression in volunteers.[8] We defined intolerable ventilatory depression as a respiratory rate less than 5 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.[8] (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.

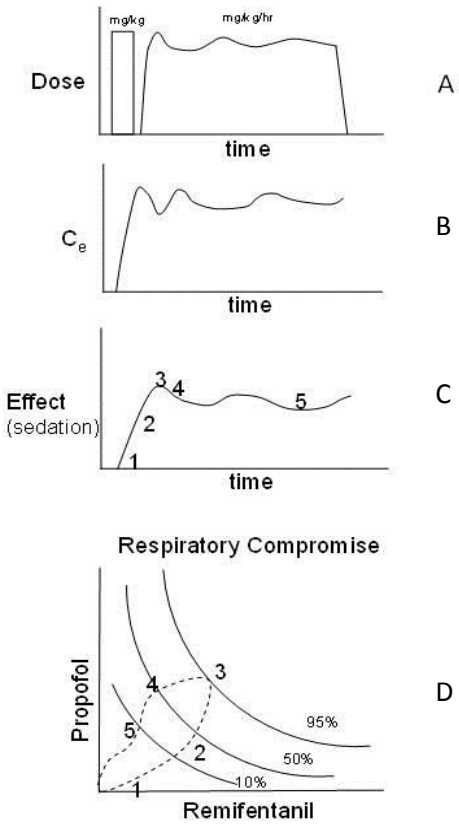

Figure 1: A: Dose of a drug, first as a bolus, then as a continuous infusion. B: effect site concentration (Ce) Corresponding to the given dose and C: Observed effect (sedation) for a single administered drug. Time points 1-5 correspond to a likelihood of effect in D: Effect and corresponding drug concentrations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

A 20 gauge venous catheter was 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 was similar in all subjects. A maintenance infusion of 0.9% sodium chloride was administered at 1 ml/kg/hour throughout the study. Continuous infusions of Remifentanil and Propofol was infused into this peripheral IV.

Subjects were 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 were 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 were measured with the attached motion sensors and the respiratory inductance plethysmography bands. Changes in respiration pattern were displayed as real-time changes in CO_2 waveforms. A processed EEG monitor and/or a cerebral oximeter were optionally placed to record data for later analysis. A motion sensor was also placed on the bed. These devices were operational during the entire study day. Data from devices was electronically captured and recorded for later analysis. Continuous variables such as motion waveforms, pulse oximetry waveform, capnogram, and nasal airway pressure were digitized during data collection periods at 50-1000Hz during data collection periods at each target effect site concentration pair. Discrete variables were recorded every 5 seconds or as soon as data were available during data collection periods. Examples of discrete variables

include heart rate, SpO_2, $PetCO_2$, systolic blood pressure, diastolic blood pressure and respiratory rate. The tidal volume was 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 received Propofol and Remifentanil. Similar to previously collected data from our volunteer laboratory (Kern et al, 2004), each drug was administered using a computer controlled (Stanpump[14]) 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.15 and Schnider et al.16 was used for Remifentanil and Propofol respectively.

We administered 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 was dosed in a range of 0.75 - 4 mcg/mL in dose escalation steps of approximately 0.5 mcg/mL. Remifentanil was 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 was observed for a given target effect site concentration pair, the target effect site concentrations were lowered so assessments could be made during the target effects of respiratory depression or airway obstruction or both. Once the drug concentration pair was identified which resulted in the target effects for a given subject, the steady state drug dose was maintained for a period of data collection.

From the data collected, we isolated all the ten minute periods during which there was no interaction with the patient. This provided us with 1128 minutes (18.8 hours) of continuous monitoring to be analyzed.

Breath detection for the capnogram was performed using the algorithm built in to the capnometer (LoFlo, Philips, Wallingford CT). Breath detection algorithms for the respiratory inductance plethysmography bands, nasal pressure, and thermistor was performed using an algorithm that measured signal excursion the baseline. Samples of these signals are shown in figure 2.

We then created definitions based on our study protocols to identify respiratory problems. If no breaths were detected during the last 30 seconds of monitoring by either signal, a central apnea flag was created in the data. This implies that one signal in a pair may identify a breath during a given 30 second interval and still identify a central apnea. In order to identify complete obstructions, we relied on pairing signals above and below the point of obstruction (the trachea). To this end, we grouped the chest bands, accelerometers, and impedance signals together as ‘body’ signals and we grouped the nasal pressure, thermistor, and capnometer signals together as ‘head’ signals. Whenever a breath was identified in the ‘body’ signal, the algorithm would search for a ‘matching’ breath in the ‘head’ signal. The width of the search region for matching breaths was dependent on the signals included. For example, the capnogram is the most ‘delayed’ signal in terms of identifying breaths. This is due to the side stream technology that takes time

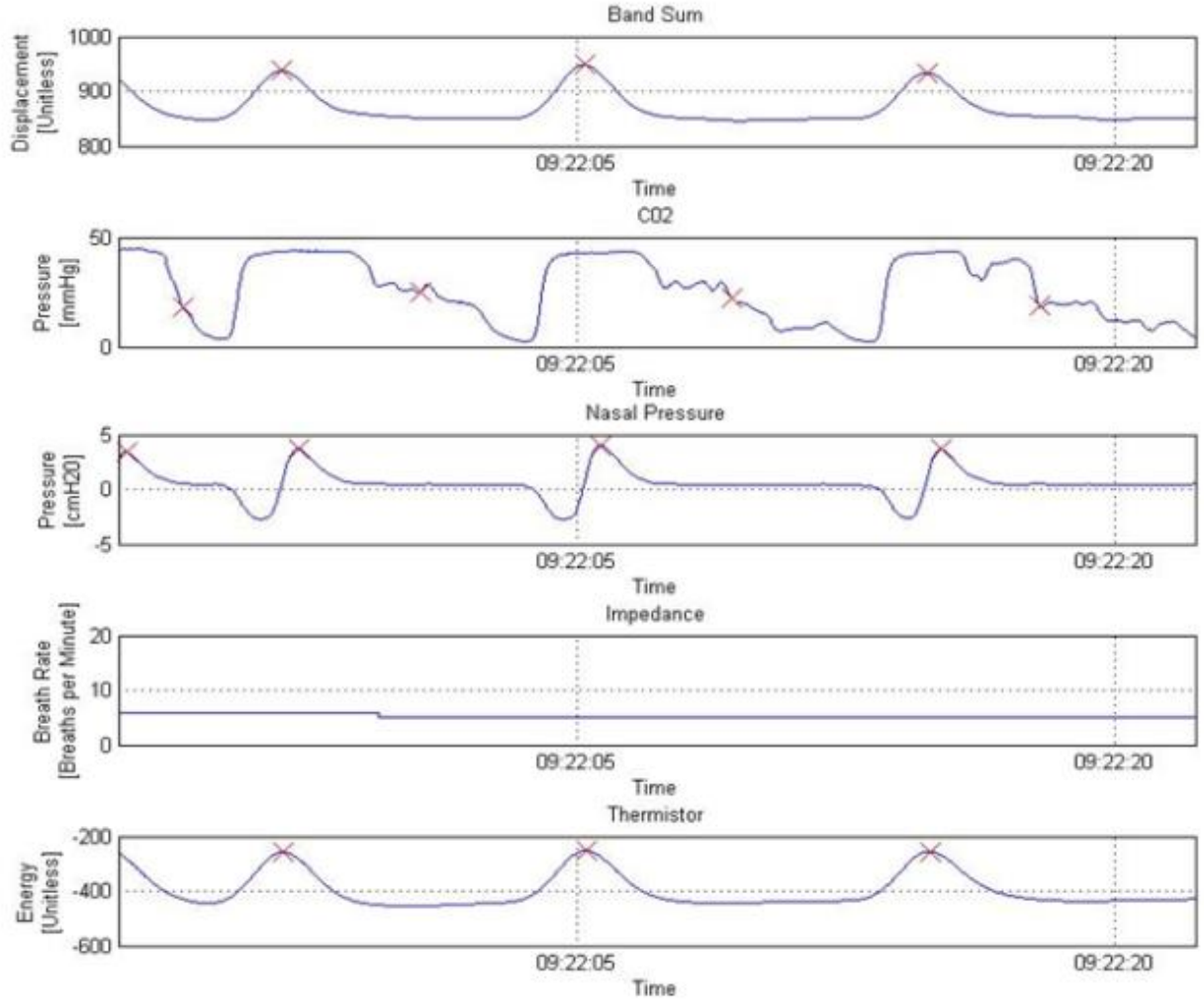

Figure 2: Sample waveforms from some of the signals applied during our study. In order of top to bottom, these are respiratory inductance plethysmography bands, capnography, nasal pressure sensor, chest impedance, and nasal-oral thermistor. Red x's denote breaths identified through our algorithms except in the case of impedance which is recorded directly as a breath rate from the equipment.

to sample air from the circuit and the underlying breath detection mode that identifies the end of expiration. If no matching breath was found in the 'head' signal, then the breath was marked as 'obstructed'. Any period of two or more obstructed breaths in a row was marked as an obstructive apnea. A simple summary of these definitions are presented in figure 3.

To begin our analysis, we isolated respiratory events that were confirmed by the clinicians. These periods were specifically identified as containing either central or obstructive apnea. Thirty nine obstructive apnea events and thirty central apnea events were identified in this manner. We also identified thirty periods of 'normal' breathing (when the drug level was low), to use as a negative control. To analyze hypopnea, we relied solely on the hypopnea flags created by the Phillips capnogram in leiu of clinician input because the clinicians were relying on the capnogram to identify

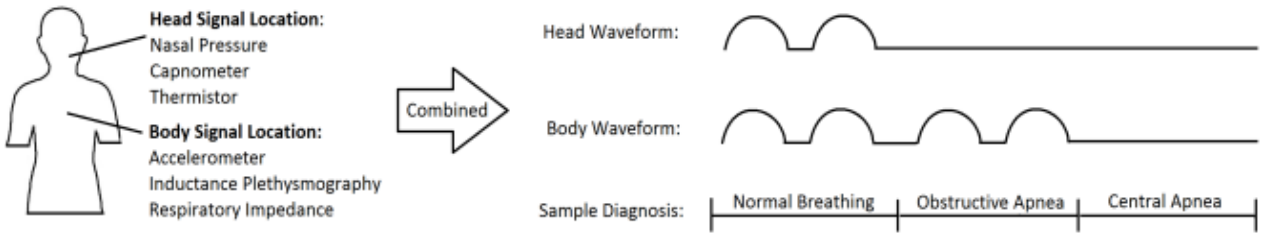

Figure 3: Method for combining head and body signals in a way that differentially identifies central and obstructive apnea. When there are no breaths in either signal, central apnea is marked. If there are breaths in the body waveform and no breaths in the head waveform, obstructive apnea is marked.

hypopneas. That is, whenever the capnogram identified 5 or fewer breaths in the past 60 seconds, a hypopnea flag was created. Thus there were significantly more hypopnea events included in our comparison.

With these definitions in place, alarm flags were created for each signal and pair of signals. If more than fifty percent of the period denoted by the clinician was matched by the signal alarm algorithm, then the period was denoted a 'true positive'. If any alarm was created during our negative control periods, no matter the length, then the period was denoted as a 'false positive'. False negatives occurred if there was less than fifty percent overlap between our signal-based alarm and the clinician judgement. True negatives occurred when no alarm was created during our negative control periods. Sensitivity and specificity was calculated based on this data

RESULTS

Thus far, we have applied these methods to combinations of the signals displayed in figure 5. The results are displayed in table 1. The best signals for detecting central apnea were the respiratory inductance plethysmography bands, the capnometer, and the nasal pressure sensors (and any combination of these). The best signal combination for identifying obstructive apneas was respiratory inductance plethysmography in combination with a nasal pressure sensor. For detecting hypopnea, the most effective individual signal was the nasal pressure sensor. The most effective pair was nasal pressure and respiratory inductance plethysmography bands.

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.

Preliminary analysis of the signals has been successful in proving that low cost signals can match clinician opinion with sufficient accuracy.

While this knowledge gives hope for moving forward, there is still much work to be done in creating an affordable respiratory monitor. We plan to add even more signals to our analysis in the future. Having a wider array of tested signals will better allow us to compare and contrast the strengths and weaknesses of each. We also plan to expand the capability of our monitors to detect partial airway obstructions which have thus far been left out. We also hope to

Table 1: Results of combining different signals and comparing their output to clinician opinion (in the case of central and obstructive apnea) or capnography (in the case of hypopnea).

Signal 1	Signal 2	Central Apnea Sensitivity	Central Apnea Specificity	Obstructive Apnea Sensitivity	Obstructive Apnea Specificity	Hypopnea Sensitivity	Hypopnea Specificity
Chest (RIP) Bands	N/A	1	1	N/A	N/A	.83	.88
Impedance Sensor	N/A	.53	.8	N/A	N/A	.60	.81
Capnometer	N/A	1	1	N/A	N/A	N/A	N/A
Nasal Pressure	N/A	1	1	N/A	N/A	.88	.88
Thermistor	N/A	.7	.96	N/A	N/A	.78	.87
Chest (RIP) Bands	Capnometer	1	1	.82	1	N/A	N/A
Chest (RIP) Bands	Nasal Pressure	1	1	.89	1	.97	.83
Chest (RIP) Bands	Thermistor	1	.97	.53	1	.91	.80
Impedance Sensor	Capnometer	.97	.8	.09	1	N/A	N/A
Impedance Sensor	Nasal Pressure	.97	.8	.13	1	.91	.76
Impedance Sensor	Thermistor	.8	.8	.02	1	.88	.67

identify patterns in single signals that will allow us to identify airway obstructions with sufficient accuracy. The ability to identify airway obstructions using only one signal would reduce both the cost of the device and the clutter on the patient.

Overall, we are confident these goals will be reached and provide invaluable insight that will allow us to save patient lives.

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