RESEARCH ARTICLE

The relationship between minute ventilation and end tidal CO$_2$ in intubated and spontaneously breathing patients undergoing procedural sedation

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Abstract

Background

Monitoring respiratory status using end tidal CO$_2$ (EtCO$_2$), which reliably reflects arterial PaCO$_2$ in intubated patients under general anesthesia, has often proven both inaccurate and inadequate when monitoring non-intubated and spontaneously breathing patients. This is particularly important in patients undergoing procedural sedation (e.g., endoscopy, colonoscopy). This can be undertaken in the operating theater, but is also often delivered outside the operating room by non-anesthesia providers. In this study we evaluated the ability for conventional EtCO$_2$ monitoring to reflect changes in ventilation in non-intubated surgical patients undergoing monitored anesthesia care and compared and contrasted these findings to both intubated patients under general anesthesia and spontaneously breathing volunteers.

Methods

Minute Ventilation (MV), tidal volume (TV), and respiratory rate (RR) were continuously collected from an impedance-based Respiratory Volume Monitor (RVM) simultaneously with capnography data in 160 patients from three patient groups: non-intubated surgical patients managed using spinal anesthesia and Procedural Sedation (n = 58); intubated surgical patients under General Anesthesia (n = 54); and spontaneously breathing Awake Volunteers (n = 48). EtCO$_2$ instrument sensitivity was calculated for each patient as the slope of a Deming regression between corresponding measurements of EtCO$_2$ and MV and expressed as angle from the x-axis ($\theta$). All data are presented as mean ± SD unless otherwise indicated.
Results
While, as expected, EtCO\textsubscript{2} and MV measurements were negatively correlated in most patients, we found gross systematic differences across the three cohorts. In the General Anesthesia patients, small changes in MV resulted in large changes in EtCO\textsubscript{2} (high sensitivity, $\theta = -83.6 \pm 9.9^\circ$). In contrast, in the Awake Volunteers patients, large changes in MV resulted in insignificant changes in EtCO\textsubscript{2} (low sensitivity, $\theta = -24.7 \pm 19.7^\circ$, $p < 0.0001$ vs General Anesthesia). In the Procedural Sedation patients, EtCO\textsubscript{2} sensitivity showed a bimodal distribution, with an approximately even split between patients showing high EtCO\textsubscript{2} instrument sensitivity, similar to those under General Anesthesia, and patients with low EtCO\textsubscript{2} instrument sensitivity, similar to the Awake Volunteers.

Conclusions
When monitoring non-intubated patients undergoing procedural sedation, EtCO\textsubscript{2} often provides inadequate instrument sensitivity when detecting changes in ventilation. This suggests that augmenting standard patient care with EtCO\textsubscript{2} monitoring is a less than optimal solution for detecting changes in respiratory status in non-intubated patients. Instead, adding direct monitoring of MV with an RVM may be preferable for continuous assessment of adequacy of ventilation in non-intubated patients.

Introduction
Whereas it is standard practice to both control and monitor ventilation during general anesthesia, it is equally important to monitor ventilation in non-intubated patients undergoing procedural sedation. End tidal CO\textsubscript{2} (EtCO\textsubscript{2}) monitoring with capnography has become the standard of care in intubated patients for both confirming endotracheal tube placement and monitoring adequacy of ventilation [1,2]. Capnography with an endotracheal tube in place is considered a reliable method to non-invasively reflect arterial PaCO\textsubscript{2} [3,4], however, measuring EtCO\textsubscript{2} in spontaneously breathing patients can be inaccurate in certain settings, particularly during procedural sedation [5] and post-operatively in the post-anesthesia care unit [6–8]. Variables such as sensor positioning, changes in respiratory patterns, and changes in oxygen supplementation often distort EtCO\textsubscript{2} measurements in non-intubated patients, rendering them unreliable. As a result, it is common for healthcare providers to overlook or discount information obtained from the capnography waveform [9].

Furthermore, since EtCO\textsubscript{2} is an indirect indicator of respiratory status, it reflects ventilatory changes later than a direct measurement of ventilation, like minute ventilation (MV). This difference is especially important in spontaneously breathing subjects [10]. In current clinical applications, non-invasive measurements of EtCO\textsubscript{2} do not allow health care practitioner to identify subtle changes in ventilation over a background of confounding factors such as ventilation/perfusion mismatch, partial airway obstruction, or metabolic derangement. For these reasons, capnography has never achieved wide clinical adoption in non-intubated patients [11].

Given the limitations of EtCO\textsubscript{2} monitoring in precisely reflecting the respiratory status of patients, more emphasis may need to be placed on methods of volumetrically monitoring ventilation in non-intubated patients. With the introduction of a non-invasive Respiratory Volume Monitor (RVM) that can provide accurate measurements of MV, tidal volume (TV), and
respiratory rate (RR) in non-intubated patients [12,13], direct monitoring of ventilation in non-intubated patients has become available both inside and out of the operating room. Here we studied the ability for conventional EtCO\textsubscript{2} monitoring to reflect changes in ventilation in non-intubated surgical patients undergoing spinal anesthesia and procedural sedation. We computed the instrument sensitivity of a EtCO\textsubscript{2} monitor when detecting changes in MV in these non-intubated surgical patients and compared and contrasted this sensitivity to both intubated patients under general anesthesia and spontaneously breathing volunteers.

Materials and methods

Experimental design

Continuous respiratory data (MV, TV, and RR) were collected from an impedance-based RVM (ExSpiron, Respiratory Motion, Inc., Waltham, MA) simultaneously with capnography data (EtCO\textsubscript{2}) in patients in three groups: patients under Procedural Sedation (1), patients under General Anesthesia (2), and Awake Volunteers (3). The Procedural Sedation group was of primary interest in this manuscript and the other two groups were used effectively as “control” groups providing limiting conditions based on the level of sedation ranging from “none” in the Awake Volunteers to “deep” in the intubated and mechanically-ventilated patients in the General Anesthesia group.

Procedural Sedation cohort. In this group, patients underwent elective joint replacement surgery with spinal anesthesia and procedural sedation. EtCO\textsubscript{2} data were collected from a sampling nasal cannula with oral scoop sampling port (Covidien Smart CapnoLine Plus Oral/Nasal, Boulder, CO) using a ventilator (Dräger Apollo, Andover, MA). Anesthesia was initiated immediately prior to surgery, typically with an intrathecal dose of bupivacaine 0.5% (1.5–4.0 ml) and supplemented with midazolam, propofol, and fentanyl for sedation. Additional intraoperative opioids such as hydromorphone were rarely used in Spinal Anaesthesia cases. Typically, patients undergoing knee surgery also received a femoral nerve block, consisting of either 20 ml ropivacaine 0.2% or 20 ml bupivacaine 0.25%, administered in preoperative holding.

General Anesthesia cohort. In this group, patients underwent elective joint replacement surgery under general anesthesia. MV and EtCO\textsubscript{2} data were collected from the endotracheal tube using a ventilator (Dräger Apollo, Andover, MA). Anesthesia was initiated immediately prior to surgery, with various doses of a muscle relaxant (rocuronium, vecuronium, or cisatracurium), in conjunction with sedatives (midazolam, propofol, and ketamine), and opioids (fentanyl, hydromorphone, meperidine, remifentanil, and morphine). Typically, patients undergoing knee surgery also received a femoral nerve block, consisting of either 20 ml ropivacaine 0.2% or 20 ml bupivacaine 0.25%, administered in preoperative holding. A detailed summary of relevant medications used intra-operatively in the Procedural Sedation and General Anaesthesia cohorts, with frequency and dosage, can be found in Table 1.

Awake Volunteers cohort. In this group, spontaneously breathing subjects performed a total of six breathing trials at varying prescribed respiratory rates for a total of 13 min. In the first and last trials, subjects were instructed to breathe normally, while in the middle four trials, subjects alternated between fast (25 bpm) and slow (5 bpm) as set by a metronome. EtCO\textsubscript{2} data were collected from a sampling nasal cannula with oral scoop sampling port (Covidien Smart CapnoLine Plus Oral/Nasal, Boulder, CO) using a dedicated capnograph (Capnostream 20, Covidien, Boulder, CO). All subjects responded to an Institutional Review Board-approved advertisement.

Equipment. In all three cohorts, the RVM collected bio-impedance traces via an electrode padset placed in the recommended positions: sternal notch, xiphoid, and right mid-axillary
line at the level of the xiphoid. The skin was prepped and the padset applied in a fashion similar to that used in standard ECG electrode placement. At the beginning of the study, the RVM was calibrated against a ventilator in the General Anesthesia group, a Wright spirometer (Mark 14, nSpire Health, Inc., Longmont, CO) in the Procedural Sedation group, and a heated pneumoatchometer (Heated FVL, Morgan Scientific, Haverhill, MA) in the Awake Volunteers group.

Institutional review board and consent. Inclusion criteria for all three cohorts were English-speaking men and women aged 18 years to 99 years. Exclusion criteria for the Procedural Sedation and General Anesthesia groups were pregnant females, patients with an electronic implantable device, and surgery positions other than supine or lateral. Exclusion criteria for the Awake Volunteers group were hospitalization within 30 days before the study and pregnant females.

### Table 1. Intraoperative medications in the Procedural Sedation and General Anaesthesia cohorts.

| Medication                          | PROCEDURAL SEDATION     | GENERAL ANESTHESIA   |
|-------------------------------------|-------------------------|----------------------|
|                                     | N = 58                  | N = 54               |
|                                     | Dose                    | Dose                |
|                                     | N | Mean | SD | N | Mean | SD |
| Spinal:                             |   |      |   |   |      |   |
|         Bupivacaine 0.5% (ITHEC) (ml)| 54 | 53%  | 1.8| 0 | 0%   | 0   |
|         Bupivacaine 0.75% (ITHEC) (ml)| 4  | 7%   | 2.0| 0 | 0%   | 0   |
| Paralytic:                           |   |      |   |   |      |   |
|         Rocuronium (mg)              | 0 | 0%   | 21| 39%| 68.2 | 28.8|
|         Cis atracurium (mg)          | 0 | 0%   | 14| 26%| 15.7 | 6.7 |
|         Vecuronium (mg)              | 0 | 0%   | 6 | 11%| 12.3 | 4.1 |
|         LMA Insertion (no paralytic) | 0 | 0%   | 4 | 7% |      |     |
|         Paralytic not specified      | 0 | 0%   | 1 | 2% |      |     |
| Inhalation Agent:                   |   |      |   |   |      |   |
|         Sevoflurane                  | 0 | 0%   | 43| 80%|      |     |
|         Isoflurane                   | 0 | 0%   | 8 | 15%|      |     |
| Reversal Agent:                     |   |      |   |   |      |   |
|         Neostigmine (mg)             | 0 | 0%   | 31| 57%| 2.8  | 1.1 |
| Femoral Block:                      |   |      |   |   |      |   |
|         Ropivacaine 0.2% (ml)        | 29| 50%  | 19.7| 1.3| 20  | 37% |
|         Bupivacaine 0.25% (ml)       | 8 | 14%  | 24.5| 14.4| 2 | 4%  |
| Sedatives:                          |   |      |   |   |      |   |
|         Midazolam (mg)               | 54| 93%  | 2.5| 1.1| 44  | 81% |
|         Propofol (Total) (mg)        | 48| 83%  | 331| 252.3| 54 | 100%|
|         : bolus (mg)                 | 11| 19%  | 32.1| 20.7| 54 | 100%|
|         : infusion (mg)              | 45| 78%  | 345| 245.4| 3  | 6%  |
|         Ketamine (mg)                | 1 | 2%   | 46.4|      | 3 | 6%  |
| Opioids:                            |   |      |   |   |      |   |
|         Fentanyl (mcg)               | 51| 88%  | 98.4| 51.1| 52 | 96% |
|         Hydromorphone (mg)           | 2 | 3%   | 0.5| 0.0| 44  | 81% |
|         Meperidine (mg)              | 0 | 0%   | 1 | 2% | 25.0 | 0   |
|         Remifentanil (mg)            | 0 | 0%   | 3 | 6% | 0.4 | 0.2 |
|         Morphine (mg)                | 0 | 0%   | 4 | 7% | 8.3 | 3.5 |
| Other:                              |   |      |   |   |      |   |
|         Haloperidol                  | 2 | 3%   | 1.0| 0.0| 28  | 52% |
|         Succinylcholine              | 0 | 0%   | 10| 19%| 114 | 50  |

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The study for the Procedural Sedation and General Anesthesia cohorts was approved by the Partners Institutional Review Board, Boston, MA (2011P002898). The study for the Awake Volunteers group was approved by the Schulman Associates Institutional Review Board, Cincinnati, OH (201102306). All patients gave informed written informed consent.

Data and statistical analysis

The ability of EtCO$_2$ to reflect changes in MV (instrument sensitivity) was calculated for each patient. Specifically, instrument sensitivity was defined as the slope calculated by a Deming regression between individual corresponding measurements of EtCO$_2$ and MV. The slopes of the regression were presented as angles from the x-axis ($\theta = \tan^{-1}\left(\frac{\Delta\text{EtCO}_2}{\Delta\text{MV}}\right)$). A steep correlation line (i.e., $\theta \approx -90^\circ$) corresponds to high instrument sensitivity, indicating a small change in MV leads to a large change in EtCO$_2$. A flatter correlation line (i.e., $\theta \approx 0^\circ$) corresponds to low instrument sensitivity, indicating a small change in MV results in almost no change in EtCO$_2$.

The stated EtCO$_2$ accuracies of the ventilator and capnograph used in this study were ±3.8 mm Hg [14] and ±2.0 mm Hg [15], respectively. Previous work suggests that the minimally acceptable instrument sensitivity for clinically-relevant EtCO$_2$ monitoring is -4.0 mmHg/L/min (i.e., $\theta = -76^\circ$) [10]. For each patient, MV was calculated as a percent of their individual predicted MV (MV$_{\text{PRED}}$), based on each patient’s body surface area and sex [16,17], which has been shown to be a better predictor of actually observed MV during spontaneous respiration than MV$_{\text{PRED}}$ based on Ideal Body Weight (IBW) [18]. Unbalanced one-way ANOVAs were used to compare demographics, instrument sensitivities, as well as average EtCO$_2$ and MV measurements across cohorts. All data are presented as mean ± SD unless otherwise indicated.

Results

Data were collected from 160 patients across the three cohorts (Table 2). Height and weight were not significantly different across the three cohorts (p = 0.12 and p = 0.17, respectively), however, BMI and age were significantly lower in the Awake Volunteers group compared to the Procedural Sedation and General Anesthesia groups (BMI: p < 0.02; age: p < 0.0001 for
both comparisons). Procedural Sedation and General Anesthesia patients tended to have more comorbidities than the Awake Volunteers. All patients in the Procedural Sedation and General Anesthesia groups received supplemental oxygen and both groups had a similar average FiO$_2$ delivered throughout the procedure ($p = 0.86$).

Patients in the three cohorts had similar MV$_{PRED}$ ($p = 0.25$, Table 3). During the course of the surgical procedure, General Anesthesia patients had an average MV of 80.9% MV$_{PRED}$, suggesting a decreased metabolic function resulting from the anesthesia. In contrast, the Procedural Sedation patients had a significant higher average MV of 148.4% MV$_{PRED}$, due to both an increased TV and RR ($p < 0.0001$), indicative of their lightly sedated state. In comparison, during normal breathing trials, Awake Volunteers maintained close to their predicted MV (106.3% MV$_{PRED}$).

In a given patient, a plot of EtCO$_2$ measurements against corresponding MV measurements produced a negatively correlated distribution: as MV increased, EtCO$_2$ generally decreased (Fig 1). In a representative intubated patient under General Anesthesia (blue), small changes in MV (from 5.3 to 6.7 L/min) triggered large changes in EtCO$_2$ (from 43.7 to 34.1 mmHg). Specifically, a 1 L/min increase in MV resulted in a 13.2 mmHg decrease in EtCO$_2$, yielding a high EtCO$_2$ instrument sensitivity of 13.2 mmHg/L/min, equivalent to $\theta_{GA} = -85.7^\circ$ (nearly vertical line, as shown in Fig 1). In contrast, in an Awake Volunteer (green), a ten times larger change in MV (from 4.3 to 25.2 L/min) was required to trigger a similar change in EtCO$_2$ (from 26.1 to 36.0 mmHg). For this patient, a 1 L/min increase in MV resulted in a 0.27 mmHg decrease in EtCO$_2$, yielding an instrument sensitivity of 0.27 mmHg/L/min, equivalent to $\theta_{AV} = -14.9^\circ$ (nearly horizontal line, as shown in Fig 1). Interestingly, patients under Procedural Sedation (red), fell between the General Anesthesia and Awake Volunteer patients. Specifically, in the example patient, a 1 L/min increase in MV led to a 2.0 mmHg decrease in EtCO$_2$, yielding an instrument sensitivity of 2.0 mmHg/L/min, equivalent to $\theta_{PS} = -63.5^\circ$.

EtCO$_2$ instrument sensitivity was calculated for each patient and the distributions of the instrument sensitivity for each of the three groups were analyzed (Fig 2). The median EtCO$_2$ instrument sensitivities were -85.1’, -38.1’, and -20.2’ for the General Anesthesia, Procedural Sedation, and Awake Volunteer cohorts, respectively. The General Anesthesia and Awake Volunteers cohorts had unimodal distributions of EtCO$_2$ instrument sensitivity, well described by single Gaussian functions fit to these data. EtCO$_2$ instrument sensitivities were significantly higher in the intubated patients under General Anesthesia ($\theta = -83.6 \pm 9.9^\circ$) compared to non-intubated Awake Volunteers ($\theta = -24.7 \pm 19.7^\circ$, $p < 0.0001$). Interestingly, the distribution of EtCO$_2$ instrument sensitivity for the Procedural Sedation cohort was clearly bimodal, illustrating a lack of uniformity in this group. A mixed-model of two Gaussian was therefore fit to these data, showing that 47% (27/54) of the patients experienced high EtCO$_2$ instrument sensitivity ($\theta = -96.6 \pm 15.0^\circ$), similar to the General Anesthesia patients, while the remaining patients had low instrument sensitivity ($\theta = -1.2 \pm 22.4^\circ$), similar to the Awake Volunteers.

Table 3. Subject cohort respiratory metrics.

| Respiratory Metric                      | Procedural Sedation | General Anesthesia | Awake Volunteers |
|-----------------------------------------|---------------------|--------------------|------------------|
| Predicted Minute Ventilation, MV$_{PRED}$ (SEM), L/min | 7.0 (0.1)           | 6.9 (0.1)          | 6.8 (0.1)        |
| Minute Ventilation (SEM), L/min         | 10.3 (0.7)          | 5.6 (0.2)          | 7.1 (0.4)        |
| Minute Ventilation (SEM), % MV$_{PRED}$ | 148.4 (8.5)         | 80.9 (2.3)         | 106.3 (6.1)      |
| Tidal Volume (SEM), mL                  | 673 (39)            | 481 (13)           | 623 (39)         |
| Respiratory Rate (SEM), bpm             | 15.2 (0.3)          | 11.6 (0.3)         | 12.4 (0.6)       |

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Importantly, while the majority of patients in the General Anesthesia group (43/54, 80%) had EtCO₂ instrument sensitivity which showed changes in EtCO₂ in the clinically-relevant range (shaded gray area), less than half of Procedural Sedation patients (24/58, 41%) and no patients in the Awake Volunteers cohort had clinically-relevant EtCO₂ instrument sensitivity of -76˚ corresponding to -4 mmHg/L/min.

Fig 1. Representative correlations between MV and EtCO₂. Data from three individual patients are included, one from each group: Procedural Sedation (red), General Anesthesia (blue) and Awake Volunteer (green). Each data point corresponds to a single 30 sec measurement pair (MV and EtCO₂). The lines (Deming regressions) and confidence ellipses (±1 SD) show the best-fits to the data. In a representative patient from the General Anesthesia cohort, a 1 L/min increase in MV resulted in a 13.2 mmHg decrease in EtCO₂ (EtCO₂ instrument sensitivity (i.e., slope) = 13.2 mmHg/L/min = θ₉GA = -85.7˚). In a patient from the Awake Volunteers group, across a range of breathing patterns, a 1 L/min increase in MV resulted in a 0.27 mmHg decrease in EtCO₂ (EtCO₂ instrument sensitivity = 0.27 mmHg/L/min = θ₀AV = -14.9˚). The patient from the Procedural Sedation group falls between the patients from General Anesthesia and Awake Volunteers groups. Specifically, a 1 L/min increase in MV led to 2.0 mmHg decrease in EtCO₂ (EtCO₂ instrument sensitivity = 2.0 mmHg/L/min, corresponding with θ₀PS = -63.5˚).

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Fig 2. Distributions of EtCO$_2$ instrument sensitivity to changes in MV. For each patient group (General Anesthesia (top, blue), Procedural Sedation (middle, red), and Awake Volunteers (bottom, green)), the distribution of EtCO$_2$ instrument sensitivity is presented as both a box-plot and histogram. Each box-plot shows the median EtCO$_2$ instrument sensitivity (middle vertical line), the box extends from the 25th to 75th percentile, the whiskers extend to the most extreme non-outlier data points, and statistical outliers are plotted individually (plus signs). The median EtCO$_2$ instrument sensitivities were -85.1˚, -38.1˚, and -20.2˚ for the General Anesthesia, Procedural Sedation, and Awake Volunteer cohorts, respectively. The General Anesthesia and Awake Volunteer cohorts had unimodal distributions of EtCO$_2$ instrument sensitivity and single normal distributions were fit to these data (black lines). EtCO$_2$ instrument sensitivities were significantly higher in the intubated patients under General Anesthesia ($\theta = -83.6 \pm 9.9˚$, vertical dashed blue line) compared to non-intubated Awake Volunteers over a range of prescribed breathing patterns ($\theta = -24.7 \pm 19.7˚$, vertical dashed green line, $p < 0.0001$). The distribution of EtCO$_2$ instrument sensitivity for the Procedural Sedation cohort was bimodal. Therefore, a mixture of two normal distributions was therefore fit to these data. Approximately half of the patients experienced high EtCO$_2$ instrument sensitivity ($\theta = -96.6 \pm 15.0˚$), consistent with the General Anesthesia patients, while the remaining patients had low instrument sensitivity ($\theta = -1.2 \pm 22.4˚$), consistent with...
The average EtCO$_2$ measurement over the length of monitoring was calculated for each patient and the distributions of these average measurements for the three groups were analyzed (Fig 3). Measured EtCO$_2$ values were higher in the General Anesthesia (37.2 ± 4.3 mmHg) group than the Procedural Sedation (23.3 ± 4.8 mmHg) and Awake Volunteers (31.4 ± 5.2 mmHg) groups (p < 0.0001). Interestingly, the average measured EtCO$_2$ of the Awake Volunteers across the prescribed breathing patterns was higher than the Procedural Sedation group (p<0.0001). The majority of General Anesthesia patients (37/54, 69%) had an average EtCO$_2$ measurement within the normal range of EtCO$_2$ (35–45 mmHg, shaded yellow area). In contrast, only 27% (13/48) of the Awake Volunteers and only 5% (3/58) of the Procedural Sedation patients had an average EtCO$_2$ measurement within the normal range.

**Discussion**

In this study, we assessed and quantified the ability of capnography to measure and reflect real-time changes in respiratory status, specifically ventilation (MV), in non-intubated patients undergoing procedural sedation. First, we quantified EtCO$_2$ instrument sensitivity for each patient as the slope of a Deming regression between corresponding measurements of EtCO$_2$ and MV. Next, we compared the instrument sensitivity between patients under Procedural Sedation and two control groups: General Anesthesia and Awake Volunteers. In the intubated patient under General Anesthesia, we found a strong relationship between MV and EtCO$_2$ (median EtCO$_2$ instrument sensitivity of -85.1˚). This EtCO$_2$ instrument sensitivity was better than the clinically-relevant EtCO$_2$ instrument sensitivity of -76˚, confirming EtCO$_2$ measurements in intubated patients could adequately reflect changes in MV. In contrast, in the non-intubated patients (i.e., both the Procedural Sedation and Awake Volunteer groups), the relationship between MV and EtCO$_2$ is much weaker (median EtCO$_2$ instrument sensitivities of -38.1˚ and -20.2˚, respectively) and better than the clinically-relevant instrument sensitivity of -76˚ in only 23% (24/106) of the non-intubated patients. This finding indicates that the EtCO$_2$ instrument sensitivity in non-intubated and spontaneously breathing individuals may not be adequate for detecting meaningful changes in MV in over three-fourth of patients.

We found EtCO$_2$ instrument sensitivity in Procedural Sedation patients exhibited a bimodal distribution with approximately half of the patients having high EtCO$_2$ instrument sensitivity and other half exhibiting low EtCO$_2$ instrument sensitivity. We saw very similar low EtCO$_2$ instrument sensitivity to that demonstrated in the Awake Volunteer cohort. One potential explanation for this observation is that more deeply sedated Procedural Sedation patients behaved similarly to patients under General Anesthesia and therefore showed high EtCO$_2$ instrument sensitivity, while less deeply sedated Procedural Sedation patients behaved more similarly to the Awake Volunteers and maintained their ability to modulate MV in response to changes in EtCO$_2$. Within the Procedural Sedation group, there was not a significant difference between average supplemental oxygen FiO$_2$ delivered to patients with high EtCO$_2$ instrument sensitivity compared to patients with low EtCO$_2$ instrument sensitivity (p = 0.70).

In spontaneously breathing patients, an increase in partial pressure of carbon dioxide in the arterial blood (PaCO$_2$) triggers an increase in ventilation in order to maintain a relatively constant level of PaCO$_2$ within the physiological range. In spontaneously breathing patients under...
Fig 3. Distributions of average EtCO\(_2\) measurements. For each patient group (General Anesthesia (top, blue), Procedural Sedation (middle, red), and Awake Volunteers (bottom, green)), the distribution of average EtCO\(_2\) is presented as both a histogram and box-plot. Each box-plot shows the median EtCO\(_2\) instrument.
anesthesia, this respiratory drive to increase ventilation in response to hypercapnia is blunted through depressed drive from both central and peripheral muscular chemoreceptors [19]. These decreases in MV results in a buildup of PaCO$_2$, and in turn EtCO$_2$, without a compensatory increase in ventilation.

In mechanically ventilated patients, measurements of EtCO$_2$ provide a clinically useful surrogate for the PaCO$_2$, and capnography is the standard of care in this setting [3,4]. Recently, capnography was proposed as a tool to detect respiratory depression in non-intubated patients earlier than pulse oximetry [20–23]. However, despite the initial enthusiasm, capnography has not achieved wide clinical adoption in hospital settings such as the post-anesthesia care unit and general hospital floor [6,11]. Even in the more controlled setting of the procedure room, capnography has proved to be less reliable than anticipated due to cannula dislodgement, patient noncompliance, and complexity in interpreting CO$_2$ waveforms [9,11,24]. Other factors which decrease the accuracy and utility of capnography in non-intubated patients include mouth versus nose breathing, changes in flow of oxygen, procedures requiring oral intervention or lack of access to the head of the bed to ensure proper cannula placement [25]. Furthermore, EtCO$_2$ does not consistently reflect PaCO$_2$, particularly in patients with cardiac and respiratory failure and in patients with a high ventilation-perfusion ratio [6–8,26–29]. Even when reliable EtCO$_2$ measurements are obtained, they provide a lagging indicator of respiratory performance rather than direct measure of changes in respiratory volumes [30].

Recent work has shown that capnography has poor instrument sensitivity to changes in MV in a cohort of spontaneously breathing volunteers [10]. Here we evaluated the capability of capnography to detect changes in respiratory status in a group of patients undergoing procedural sedation for a surgical procedure and demonstrated the surprisingly variable instrument sensitivity of capnography, often outside of the clinically-relevant range. The data suggest that the RVM can provide more clinically useful information than capnography during procedural sedation. These results are in-line with the findings that the RVM provides an indication of respiratory depression in advance of changes in pulse oximetry in patients following orthopedic procedures [31] and can also be used to identify and quantify respiratory depression following the administration of midazolam peri-operatively [32]. Furthermore, Holley et al. demonstrated the superiority of MV monitoring over monitoring RR alone during procedural sedation for upper endoscopic procedures [33]. During these procedures, the RVM detected decreases in MV in response to sedatives and also identified increases in MV following airway maneuvers such as chin lifts and jaw thrusts [34,35]. In addition to changes in MV, the RVM is also able to detect periods of airway obstruction [12]. Combining our findings with these previous reports supports the conclusion that monitoring respiratory volumes directly in non-intubated patients under procedural sedation delivers earlier and more reliable assessment of respiratory status than capnography or pulse oximetry, providing a better alternative for use in adjusting sedation to maintain both patient safety and comfort.
The most challenging aspect of this study was the establishment of clinically-relevant instrument sensitivity in the Awake Volunteers control group. Whereas the General Anesthesia cohort was very similar to the Procedural Sedation cohort, the Awake Volunteers were in some ways out of place in this study. In both Procedural Sedation and General Anesthesia groups all measurements of EtCO\textsubscript{2} and MV were done in a purely observational manner, the Awake Volunteers had to be instructed to breathe over a range of breathing patterns in order to provide a wide measurement range over which EtCO\textsubscript{2} instrument sensitivity could be accurately estimated. The Awake Volunteers were also younger, had lower BMIs, and fewer comorbidities than the General Anesthesia and Procedural Sedation patients. Therefore, the combination of these factors suggest that the capacity for exhalation of CO\textsubscript{2} is likely less in the General Anesthesia and Procedural Sedation cohorts compared to the Awake Volunteers group. Nonetheless, the addition of this cohort provided us with data from non-anesthetized patients to help bracket and better understand the group of lightly sedated Procedural Sedation patients. Interestingly, it also helped to profile the fact that in general, the Procedural Sedation group was hyperventilating, with an average MV of 148\% MV\textsubscript{PRED}.

There are several other limitations to this study. First, the anesthetic and sedation regimens were chosen by the anesthesiologist and individualized for each patient. The level of sedation in the Procedural Sedation cohort was not standardized. Since individual patients respond significantly differently to similar levels of opioids and sedatives, even with a standardized sedation protocol, sedation levels still might vary greatly from patient to patient. Depth of anesthesia was not monitored with a bispectral monitor or with sedation scores as part of the standard of care. Future studies where depth of anaesthesia is also monitored are needed to test if the bimodal distribution of EtCO\textsubscript{2} instrument sensitivities is explained by sedation level.

**Conclusions**

While EtCO\textsubscript{2} is a useful indicator of respiratory status in patients under General Anesthesia, its sensitivity to changes in ventilation is greatly reduced in non-intubated patients. Therefore, augmenting standard patient care with EtCO\textsubscript{2} monitoring is a suboptimal solution for monitoring respiratory status in non-intubated patients undergoing Procedural Sedation. The addition of direct monitoring of MV with an RVM may be preferable for primary continuous assessment of adequate ventilation of non-intubated patients undergoing procedural sedation.

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References

1. American Society of Anesthesiologists. Standards for basic anesthetic monitoring. 2010.

2. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7.1: Adjuncts for Airway Control and Ventilation. Circulation. 2005;112: IV-51 LP-IV-57.

3. Kodali B-S, Moseley H, Kumar AY, Delph Y, Bhavani-Shankar K, Moseley H, et al. Capnometry and anaesthesia. Can J Anaesth. Springer-Verlag; 1992; 39: 617–32. https://doi.org/10.1007/BF03008330 PMID: 1643689

4. Razi E, Moosavi GA, Omidi K, Khakpour Saebi A, Razi A. Correlation of end-tidal carbon dioxide with arterial carbon dioxide in mechanically ventilated patients. Arch trauma Res. Kowsar Medical Institute; 2012; 1: 58–62. https://doi.org/10.5812/atr.6444 PMID: 24396744

5. Mehta PP, Kochhar G, Albealdawi M, Kirsh B, Rizk M, Putka B, et al. Capnographic Monitoring in Routine EGD and Colonoscopy With Moderate Sedation: A Prospective, Randomized, Controlled Trial. Am J Gastroenterol. 2016; 111: 395–404. https://doi.org/10.1038/ajg.2015.437 PMID: 26902229

6. Jabre P, Jacob L, Auger H, Jaulin C, Monribot M, Aurore A, et al. Capnography monitoring in nonintubated patients with respiratory distress. Am J Emerg Med. 2009; 27: 1056–1059. https://doi.org/10.1016/j.ajem.2008.08.017 PMID: 19931750

7. Wahba RW, Tessler MJ. Misleading end-tidal CO2 tensions. Can J Anaesth. 1996; 43: 862–866. https://doi.org/10.1007/BF03013040 PMID: 8840067

8. Belenky S, Ivey KM, Batchinsky AI, Langer T, Ncsouc I, Baker W, et al. Noninvasive carbon dioxide monitoring in a porcine model of acute lung injury due to smoke inhalation and burns. Shock. 2013; 39: 495–500. https://doi.org/10.1097/SHK.0b013e318292c331 PMID: 23572088

9. Ortega R, Connor C, Kim S, Djang R, Patel K. Monitoring ventilation with capnography. N Engl J Med. 2012; 367: e27. https://doi.org/10.1056/NEJMvcm1105237 PMID: 23134404

10. Williams GW, George CA, Harvey BC, Freeman JE. A Comparison of Measurements of Change in Respiratory Status in Spontaneously Breathing Volunteers by the ExSpiron Noninvasive Respiratory Volume Monitor Versus the Capnostream Capnometer. Anesth Analg. 2017; 124: 120–126. https://doi.org/10.1213/ANE.0000000000001395 PMID: 27384980

11. Deiorio NM. Continuous end-tidal carbon dioxide monitoring for confirmation of endotracheal tube placement is neither widely available nor consistently applied by emergency physicians. Emerg Med J. 2005; 22: 490–493. https://doi.org/10.1136/emj.2004.015818 PMID: 15983084

12. Voscopoulos C, Brayanov J, Ladd D, Lalli M, Panasyuk A, Freeman J. Special article: evaluation of a novel noninvasive respiration monitor providing continuous measurement of minute ventilation in ambulatory subjects in a variety of clinical scenarios. Anesth Analg. 2013; 117: 91–100. https://doi.org/10.1213/ANE.0b013e3182918098 PMID: 23733842

13. Voscopoulos CJ, MacNabb CM, Brayanov J, Qin L, Freeman J, Mullen GJ, et al. The evaluation of a non-invasive respiratory volume monitor in surgical patients undergoing elective surgery with general anaesthesia. J Clin Monit Comput. 2015; 29: 223–30. https://doi.org/10.1007/s10877-014-9596-0 PMID: 25037938

14. Medical D. Apollo Operator’s Instruction Manual. 2005.

15. Covidien. Capnostream 20 Portable Bedside Capnograph/Pulse Oximeter: Operator’s Manual. 2014.

16. Du Bois D, Du Bois E. Clinical Calorimetry Tenth Paper: A Formula to Estimate The Approximate Surface Area if Height and Weight be Known. Arch Intern Med. American Medical Association.; 1916; XVII: 863–871. https://doi.org/10.1001/archinte.1916.00080130010002

17. American Academy of Respiratory Care Protocol Committee: Subcommittee Adult Critical Care. Adult Mechanical Ventilator Protocols. 2003.

18. Mehta JH, Cattano D, Brayanov JB, George EE. Assessment of perioperative minute ventilation in obese versus non-obese patients with a non-invasive respiratory volume monitor. BMC Anesthesiol. 2017; 17: 61. https://doi.org/10.1186/s12871-017-0352-0 PMID: 28446134

19. Pavlin EG, Hombein TF. Anesthesia and the Control of Ventilation. Comprehensive Physiology. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2011. https://doi.org/10.1002/cphy.cp030225
20. Vargo JJ, Zuccaro G, Dumot JA, Conwell DL, Morrow JB, Shay SS. Automated graphic assessment of respiratory activity is superior to pulse oximetry and visual assessment for the detection of early respiratory depression during therapeutic upper endoscopy. Gastrointest Endosc. 2002; 55: 826–831. PMID: 12024135

21. Lightdale JR, Goldmann DA, Feldman HA, Newburg AR, DiNardo JA, Fox VL. Microstream capnography improves patient monitoring during moderate sedation: a randomized, controlled trial. Pediatrics. 2006; 117: e1170—8. https://doi.org/10.1542/peds.2005-1709 PMID: 16702250

22. Miner JR, Heegaard W, Plummer D. End-tidal carbon dioxide monitoring during procedural sedation. Acad Emerg Med. 2002; 9: 275–280. PMID: 11927449

23. Waugh JB, Epps CA, Khodneva YA. Capnography enhances surveillance of respiratory events during deep sedation with propofol by anesthesiologists: a randomized controlled trial. Anesth Analg. 2014; 119: 49–55. https://doi.org/10.1213/ANE.0b013e3182a1f0a2 PMID: 24836471

24. van Loon K, van Rheineck Leyssius AT, van Zaane B, Denteneer M, Kalkman CJ. Capnography during deep sedation with propofol by nonanesthesiologists: a randomized controlled trial. Anesth Analg. 2014; 119: 49–55. https://doi.org/10.1213/ANE.0b013e3182a1f0a2 PMID: 24836471

25. ECRI Institute. Top 10 Health Technology Hazards for 2017. Health Devices. 2016.

26. Poirier MP, Gonzalez Del-Rey JA, McAneney CM, DiGiulio GA. Utility of monitoring capnography, pulse oximetry, and vital signs in the detection of airway mishaps: a hyperoxic animal model. Am J Emerg Med. 1998; 16: 350–352. PMID: 9672448

27. Heines SJ, Strauch U, Roekaerts PM, Winkens B, Bergmans DC. Accuracy of end-tidal CO2 capnometers in post-cardiac surgery patients during controlled mechanical ventilation. J Emerg Med. 2013; 45: 130–5. https://doi.org/10.1016/j.jemermed.2012.11.019 PMID: 23375221

28. Parrillo JE, Dellinger RP. Critical Care Medicine—Principles of Diagnosis and Management in the Adult. 4th ed. Philadelphia: Mosby; 2014.

29. Kerr ME, Zempsky J, Sereika S, Orndoff P, Rudy EB. Relationship between arterial carbon dioxide and end-tidal carbon dioxide in mechanically ventilated adults with severe head trauma. Crit Care Med. 1996; 24: 785–90. PMID: 8706454

30. Lumb AB. Nunn’s Applied Respiratory Physiology. 8th ed. 2017. 10.2307/20024538

31. Galvagno SM, Duke PG, Eversole DS, George EE. Evaluation of Respiratory Volume Monitoring (RVM) to Detect Respiratory Compromise in Advance of Pulse Oximetry and Help Eliminate False Desaturation Alarms. J Trauma Acute Care Surg. 2016; https://doi.org/10.1097/TA.0000000000001152 PMID: 27270857

32. Gonzalez Castro LN, Mehta JH, Brayanov JB, Mullen GJ, Limjucor M, Shade r R. Quantification of respiratory depression during pre-operative administration of midazolam using a non-invasive respiratory volume monitor. Rosenberg er P, editor. PLoS One. Public Library of Science; 2017; 12: e0172750. https://doi.org/10.1371/journal.pone.0172750 PMID: 28235069

33. Holley K, MacNabb CM, Georgiadi s P, Minasyan H, Shukla A, Mathews D. Monitoring minute ventilation versus respiratory rate to measure the adequacy of ventilation in patients undergoing upper endoscopic procedures. J Clin Monit Comput. 2016; 30: 33–39. https://doi.org/10.1007/s10877-015-9674-y PMID: 25735263

34. Holley K, Mathews D, Ladd D, Campa na L, Schapiro H. Respiratory Volume Monitoring to Assess the Effect of Airway Maneuvers on Ventilation during Upper Endoscopy. Open J Anesthesiol. Scientific Research Publishing; 2014; 4: 281–290. https://doi.org/10.4236/ojanes.2014.411041

35. Ebert TJ, Middleton AH, Makhija N. Ventilation monitoring during moderate sedation in GI patients. J Clin Monit Comput. 2017; 31: 53–57. https://doi.org/10.1007/s10877-015-9809-1 PMID: 26628270