Detection of hypoventilation during deep sedation in patients undergoing ambulatory gynaecological hysteroscopy: a comparison between transcutaneous and nasal end-tidal carbon dioxide measurements

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Background. Transcutaneous measurement of carbon dioxide (TcCO2) provides a non-invasive estimation of arterial carbon dioxide (PaCO2). Nasal capnography (PECO2) is used to assess ventilation during monitored anaesthesia care (MAC) with sedation since it can readily detect apnoea. We compared the agreement between TcCO2 and PECO2 with PaCO2 and the ability to detect hypercarbia in patients under deep sedation.

Methods. Forty healthy female subjects receiving deep sedation for hysteroscopy were studied. A TcCO2 (TOSCA 500, Radiometer, Inc., Westlake, OH, USA) electrode was applied to the earlobe and PECO2 capnography was monitored using nasal side-stream sampling. All subjects received oxygen (3 litre min⁻¹). Subjects were evaluated at intervals using a modified Ramsay sedation score until they reached a score ≥5. Arterial blood gas values were compared with TcCO2 and PECO2 values. Bland–Altman, linear regression, and receiver operator characteristics analysis were performed.

Results. The mean (sd) absolute difference between the TcCO2, PECO2, and the PaCO2 were 0.43 (0.35) and 1.06 (0.8) kPa, respectively (P=0.002). TcCO2 demonstrated a mean bias (2SD) of 0.23 (0.07–0.4) kPa with PaCO2 compared with −0.93 (−1.24 to −0.63) kPa for PECO2. One minute before blood sampling, the sensitivity of the TcCO2 monitor for detecting PaCO2 >6.65 kPa was greater than for PECO2 (66.7% vs 33.3%, P<0.01).

Conclusions. TcCO2 demonstrated better agreement with PaCO2 than PECO2 for patients under MAC with deep sedation. TcCO2 monitoring was more sensitive for detection of PaCO2 >6.65 kPa than PECO2.

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The partial pressure of carbon dioxide in the arterial blood (PaCO2) is the most accurate assessment of the adequacy of ventilation. Non-invasive monitoring techniques have been developed to provide nearly continuous intraoperative estimation of PaCO2 without the need for arterial blood sampling. The most commonly used non-invasive technique to monitor ventilation during monitored anaesthesia care (MAC) is the measurement of end-tidal carbon dioxide (PECO2). Nasal capnography and waveform analysis allow for rapid detection of apnoea, airway obstruction, and tachypnoea and have been shown to improve safety during sedation and postoperative recovery,¹ but its ability to predict hypoventilation associated with deep sedation has not been established.

Transcutaneous measurement of carbon dioxide (TcCO2) is a non-invasive method of estimating PaCO2, and has been shown to have good agreement with PaCO2 in adult volunteers, subjects during general anaesthesia and during
recovery from anaesthesia. A limitation of the use of this device intraoperatively is the delay in detection of rapid changes in ventilation such as apnoea, because the rate of increase in $P_{\text{aCO}_2}$ in the first minute of apnoea is only 0.13 kPa. Conversely, because of the good agreement between $Tc_{\text{CO}_2}$ and $P_{\text{aCO}_2}$, this method may be advantageous for the detection of hyperventilation.

We hypothesized that transcutaneous carbon dioxide monitoring ($Tc_{\text{CO}_2}$) would produce better agreement with arterial carbon dioxide ($P_{\text{aCO}_2}$) than nasal end-tidal carbon dioxide ($P_{\text{ETCO}_2}$) monitoring in patients under deep sedation. We also hypothesized that $Tc_{\text{CO}_2}$ would be a more sensitive test of hyperventilation ($P_{\text{aCO}_2} > 6.65$ kPa) than $P_{\text{ETCO}_2}$.

**Methods**

This prospective, blinded study was approved by the Institutional Review Board of Northwestern University. Clinical trial registration for this study can be found at Clinicaltrials.gov; url: http://www.clinicaltrials.gov; and registration identifier: NCT00954733. Forty healthy women, scheduled for hysteroscopy under MAC with sedation, provided written informed consent for study participation. $P_{\text{ETCO}_2}$ was measured using a calibrated infrared analyzer attached (Capnomac Ultima, Datex-Ohmeda, Madison, WI, USA) to a nasal cannula with side-stream sampling. A transcutaneous carbon dioxide electrode (TOSCA 500, Radiometer America Inc., Westlake, OH, USA) was attached to the patient’s earlobe. Before placement, the electrode was cleaned, and a new membrane was applied and device calibrated. The working temperature of the $Tc_{\text{CO}_2}$ monitor electrode was set at 42°C. At least 10 min before the start of the surgery, the electrode was applied to the earlobe skin that was swabbed with alcohol before placement to facilitate adherence of the disc.

Subjects received supplemental oxygen at 3 litre min$^{-1}$ via nasal cannula, to maintain oxygen saturation >90%. The oxygen flow was not increased during the period of the study. The anaesthetic management was left to the discretion of the anaesthesia personnel, who were blinded to the $Tc_{\text{CO}_2}$ monitor. In order to standardize the timing for the arterial sampling, subjects were evaluated every 5 min until they achieved a modified Ramsay sedation score $\geq 5$ (1, anxious/agitated/restless; 2, cooperative/oriented/tranquil; 3, drowsy/responds to commands only; 4, brisk response to shaking/loud sound; 5, sluggish response to shaking/loud sound; 6, no response). Ventilatory frequency, bispectral index, $P_{\text{ETCO}_2}$, and $Tc_{\text{CO}_2}$ values were recorded at the time the subject first reached a Ramsay score $\geq 5$, the time of needle insertion for arterial blood sampling, and end time of blood sampling by an independent observer. Blood gas analysis was performed at 37°C. Patient characteristic data collected included the subject’s age, height, and weight.

The number of subjects ($n=40$) was determined to achieve an 80% power to detect a difference of 1.06 kPa (with $\alpha=0.05$) between the two methods with an estimated standard deviation of 2 kPa using a paired $t$-test or the Wilcoxon signed-rank test. This difference was determined based on clinical experience using the device (data not shown). This estimation assumed that the actual distribution was uniform. The sample size calculation was made using PASS 2008 (NCSS, LLC, Kaysville, UT, USA).

The absolute difference between the non-invasive monitor ($P_{\text{ETCO}_2}$ or $Tc_{\text{CO}_2}$) and the $P_{\text{aCO}_2}$ was calculated and compared between groups using a paired $t$-test. The relationship between differences in non-invasive values and $P_{\text{aCO}_2}$ was evaluated by the examination of Bland–Altman plots and bias and precision [95% confidence level (CI) of the bias] between the methods was determined. Linear regression analysis was used to determine the slope of the relationship between the non-invasive monitors and the $P_{\text{aCO}_2}$. Respiratory parameters and the bispectral index were compared across time intervals using repeated-measures analysis of variance and paired $t$-tests.

Hyperventilation was defined as a value of $P_{\text{aCO}_2} > 6.65$ kPa because values above this number were associated with the development of respiratory acidosis in our sample. The overall predictive power of $P_{\text{ETCO}_2}$ and $Tc_{\text{CO}_2}$ at each measurement interval was determined by constructing a receiver-operating characteristic (ROC) curve of the sensitivity vs 1-specificity and calculating the area under the curve (AUC). To assess the predictive utility of the monitors in detecting $P_{\text{aCO}_2} > 6.65$ kPa, $P_{\text{ETCO}_2}$ and $Tc_{\text{CO}_2}$ were dichotomized at $Tc_{\text{CO}_2} > 6.65$ kPa mm Hg and $P_{\text{ETCO}_2} > 6.0$ kPa (to compensate for possible dead space). Sensitivity was compared between methods by constructing 95% CIs of the difference between methods using Yates’ corrected $\chi^2$ method. A value of $P<0.05$ was required to reject the null hypothesis. Data were analyzed using STATA 11 (StataCorp, College Station, TX, USA) and NCSS version 7.1.19, release date November 29, 2009 (NCSS2007, NCSS, LLC).

**Results**

Forty-one subjects were approached and 40 gave informed consent for study participation, one subject declined participation. In one other subject, the arterial blood gas was not able to be processed and that subject’s data were excluded from the analysis. Subjects were healthy women between 27 and 65 yr of age. The mean (sd) age was 42 (9) yr. The mean (sd) BMI was 25 (5) kg m$^{-2}$ (range 17–34 kg m$^{-2}$).

The mean (sd) absolute difference between $Tc_{\text{CO}_2}$ and $P_{\text{aCO}_2}$ at deep sedation was 0.43 (0.35) kPa compared with a mean (sd) absolute difference between $P_{\text{ETCO}_2}$ and $P_{\text{aCO}_2}$ of 1.06 (0.8) kPa ($P=0.002$). The agreement between the methods is shown in Figure 1. The Bland–Altman analysis revealed a positive bias (2 sd) between $Tc_{\text{CO}_2}$ and $P_{\text{aCO}_2}$ of 0.23 (0.07–0.4) kPa. $P_{\text{ETCO}_2}$ demonstrated a negative bias (95% CI) of $-0.93$ ($-1.24$ to $-0.63$) kPa.
The linear association between paired $T_c\text{CO}_2$, $P_{\text{tc}}\text{CO}_2$, and $P_{a\text{CO}_2}$ values is shown in Figure 2. The slope (95% CI) of the $T_c\text{CO}_2/P_{a\text{CO}_2}$ line 0.83 (0.10) ($P<0.0001$), but not $P_{\text{tc}}\text{CO}_2/P_{a\text{CO}_2}$ line 0.26 (0.16) ($P=0.11$), was different from a slope of zero. The slope of the $T_c\text{CO}_2/P_{a\text{CO}_2}$ regression line was different from the $P_{\text{tc}}\text{CO}_2/P_{a\text{CO}_2}$ regression slope ($P=0.003$). The goodness of fit for $T_c\text{CO}_2/P_{a\text{CO}_2}$ was $r^2=0.64$ compared with $r^2=0.07$ for $P_{\text{tc}}\text{CO}_2/P_{a\text{CO}_2}$.

Ventilatory frequency, arterial saturation, and $P_{\text{tc}}\text{CO}_2$, were not different from the time a Ramsay sedation level of $\geq 5$ was reached through the time of arterial blood collection (Table 1). The mean difference and 95% CI of the difference in the bispectral index between the time a Ramsay sedation level of $\geq 5$ until needle insertion was 5 (1–9) ($P=0.02$). The difference in mean $T_c\text{CO}_2$ was 0.7 (0.5–0.9) kPa during this same interval ($P<0.005$) (Fig. 3). The median slope [inter-quartile range (IQR)] of the $T_c\text{CO}_2$ per minute vector during this period was 1.3 (1–2) kPa min$^{-1}$.

Twelve subjects demonstrated $P_{a\text{CO}_2}$ values $>6.65$ kPa. The $T_c\text{CO}_2$ monitor recorded a value $>6.65$ kPa in eight of the 12 subjects, whereas only one of the 12 had a $P_{\text{tc}}\text{CO}_2$ value $>6.0$ kPa ($P=0.09$). The area under the ROC curve, AUC (95% CI), of the $T_c\text{CO}_2$ for detecting $P_{a\text{CO}_2}$ values $>6.65$ kPa at the time the subject first reached a Ramsay score $\geq 5$, the time of needle insertion for arterial blood sampling, and end time of blood sampling were 0.79 (0.64–0.94), 0.84 (0.70–0.99), and 0.87 (0.75–0.99), respectively. The AUC at each time was $>0.5$ ($P<0.05$), but the areas were not different from each other. The AUC for the $P_{\text{tc}}\text{CO}_2$ were 0.67 (0.48–0.86), 0.67 (0.47–0.86), and 0.69 (0.51–0.88) at the three sampling points. The AUCs for the $P_{\text{tc}}\text{CO}_2$ were not $>0.5$ or different from each other. At the predefined cut-off values of $T_c\text{CO}_2$ $>6.65$ kPa and $P_{\text{tc}}\text{CO}_2$ $>6.0$, the sensitivity of the monitors for detecting $P_{a\text{CO}_2}$ $>6.65$ at the time the subject first reached a Ramsay score $\geq 5$ was 33.3% and 25.0%, respectively ($P=4.2$). At the time of needle insertion, the sensitivity (95% CI) of the $T_c\text{CO}_2$ monitor was 66.7 (39.1–86.1)% compared with 33.3 (13.8–60.9)% for $P_{\text{tc}}\text{CO}_2$ ($P=0.01$).

**Discussion**

The important finding of this study is that in patients under deep sedation, non-invasive carbon dioxide monitoring by using $T_c\text{CO}_2$ was more sensitive and accurate for detecting hypercarbia ($P_{a\text{CO}_2}$ $>6.65$ kPa) than standard nasal $P_{\text{tc}}\text{CO}_2$ in patients who were hypoventilating. $T_c\text{CO}_2$ monitoring during MAC and deep sedation had a better agreement with $P_{a\text{CO}_2}$ than $P_{\text{tc}}\text{CO}_2$.

Our findings in patients under MAC with deep sedation support previous studies evaluating $T_c\text{CO}_2$ monitoring in adults and children during surgery under general anaesthesia. Reid and colleagues demonstrated an absolute difference of 0.93 kPa between $P_{\text{tc}}\text{CO}_2$ and $P_{a\text{CO}_2}$, but only 0.31 kPa between $T_c\text{CO}_2$ and $P_{a\text{CO}_2}$ in 22 patients during general anaesthesia. Similarly, Phan and colleagues reported a bias of $-1.04$ kPa between $P_{\text{tc}}\text{CO}_2$ and $P_{a\text{CO}_2}$ and $-0.21$ kPa between $T_c\text{CO}_2$ and $P_{a\text{CO}_2}$ in adults receiving general anaesthesia. In severely obese patients receiving general anaesthesia, Griffin and colleagues concluded that the transcutaneous carbon monoxide monitoring provides a better estimate of $P_{a\text{CO}_2}$ than $P_{\text{tc}}\text{CO}_2$.

Most similar to the current study, Stein and colleagues reported a positive bias (2 sd) of 0.74 (0.45) kPa between $T_c\text{CO}_2$ and $P_{a\text{CO}_2}$ and a negative bias (2 sd) of $-1.9$ (1.0)
between $P_{\text{tc}}^{\text{CO}_2}$ and $P_{\text{a}}^{\text{CO}_2}$, in spontaneously breathing patients recovering from general anaesthesia. The study used similar methodology to the present study with agreement between methods based on a single arterial $P_{\text{a}}^{\text{CO}_2}$ determination, although the direction of the $T_c^{\text{CO}_2}$ with $P_{\text{a}}^{\text{CO}_2}$ time relationship before the arterial sampling was not determined. In addition, Stein and colleagues did not independently assess the level of sedation or ventilatory frequency; however, this study demonstrated no better agreement between the use of a facemask and oral/nasal cannula for collecting $P_{\text{tc}}^{\text{CO}_2}$ values.

Our data suggest that hypercarbia may frequently be undetected during deep sedation when only $P_{\text{tc}}^{\text{CO}_2}$ monitoring is used, since the slope of the $P_{\text{tc}}^{\text{CO}_2}$ to $P_{\text{a}}^{\text{CO}_2}$ relationship was not different from zero and much less than between $T_c^{\text{CO}_2}$ and $P_{\text{a}}^{\text{CO}_2}$. However, since $P_{\text{tc}}^{\text{CO}_2}$ is often displayed as a capnograph from which respiration can be determined, it is an ideal monitor for detection of airway obstruction and apnoea. Soto and colleagues\textsuperscript{12} found the $P_{\text{tc}}^{\text{CO}_2}$ to be crucial in early detection of airway obstruction and apnoea. $T_c^{\text{CO}_2}$ would be less sensitive to detect acute airway events due to the lag in time between the event and the increase in $P_{\text{a}}^{\text{CO}_2}$. Therefore, we believe that our findings suggest that the two monitors can complement each other during deep sedation.

Patient factors may affect the accuracy of $T_c^{\text{CO}_2}$ monitoring including variations in skin thickness, the presence of oedema, tissue hypoperfusion, or the use of vasoconstrictor drugs. Technical factors related to transtracheal $CO_2$ monitoring include the following: air bubbles trapped under the membrane, improper electrode placement, damaged membranes, and inappropriate calibration. The TOSCA monitor used in this study heats the area under the electrode to 42°C to enhance blood flow. This limits the duration that the electrode may be used on a single site to avoid thermal injury. There is an intrinsic calibration factor used to correct for sampling temperature and the use of the Severinghaus correction to improve the accuracy of the estimation of $P_{\text{a}}^{\text{CO}_2}$ from $T_c^{\text{CO}_2}$. Overcompensation of the measured $CO_2$ tension may be the reason for the positive bias between $T_c^{\text{CO}_2}$ and $P_{\text{a}}^{\text{CO}_2}$ seen in this and other studies.\textsuperscript{3} There are also logistic factors associated with the TOSCA 500 monitor used in this study. The manufacturer recommends a 5 min calibration period before placement of the monitor and an additional 10 min equilibration period after the placement on the patient for stabilization of the measurement. Advantages of this monitor are the use of a low pressure earlobe clip or an alternative skin stick on the holder and the inclusion of pulse oximetry in the same sensor.

There are limitations to our study. We included only healthy female subjects without significant co-morbidities, which limits our ability to generalize our findings to elderly and sicker patients who might benefit the most from this monitor. Our major limitation was that we obtained only one measurement of arterial blood gas per patient at a constant level of sedation which limits the assessment of reliability of the method during rapidly changing values of $P_{\text{a}}^{\text{CO}_2}$. We believed that patient discomfort during multiple sticks, especially at superficial levels of sedation, would make the study unethical. An alternative would be placing an arterial line; however, this invasive procedure carries risk and is rarely indicated in sedation cases and would be difficult to justify. Additional studies using multiple arterial blood samples are needed to evaluate the response time of the monitor during varying levels of sedation and rates of $P_{\text{a}}^{\text{CO}_2}$ increases.

In conclusion, $T_c^{\text{CO}_2}$ monitoring was more sensitive for detection of a $P_{\text{a}}^{\text{CO}_2} > 6.65$ kPa than $P_{\text{tc}}^{\text{CO}_2}$ and may provide better assessment of hypoventilation for patients receiving MAC and deep sedation.

### Table 1

Bispectral index and respiratory parameters. Data presented as mean (SD) or median (IQR). $^1$P<0.05 compared with time first reached a Ramsay score $\geq 5$

<table>
<thead>
<tr>
<th></th>
<th>Time first reached a Ramsay score $\geq 5$</th>
<th>Time of needle insertion for arterial blood sampling</th>
<th>End time of blood sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time difference (min)</td>
<td>$-3$ (−5 to −2)</td>
<td>$-1$ (−1 to −1)</td>
<td>−</td>
</tr>
<tr>
<td>BIS Vista index</td>
<td>72 (61–77)</td>
<td>67 (60–75)</td>
<td>68 (57–76)$^1$</td>
</tr>
<tr>
<td>Ventilatory frequency (bpm)</td>
<td>13 (4)</td>
<td>12 (3)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>$\Delta a_o$ (%)</td>
<td>99 (2)</td>
<td>99 (2)</td>
<td>98 (5)</td>
</tr>
<tr>
<td>$P_{\text{tc}}^{\text{CO}_2}$ (kPa)</td>
<td>5.1 (1.0)</td>
<td>5.1 (0.9)</td>
<td>5.2 (0.8)</td>
</tr>
<tr>
<td>$T_c^{\text{CO}_2}$ (kPa)</td>
<td>5.6 (1.0)</td>
<td>6.3 (0.8)$^1$</td>
<td>6.4 (0.8)$^1$</td>
</tr>
</tbody>
</table>

**Fig 3** Vector plot of $T_c^{\text{CO}_2}$ values vs time before arterial blood sampling. (A) The time first reaching a Ramsay sedation level of $\geq 5$ until time of needle insertion for arterial blood sampling. (B) The time of needle insertion until completion of arterial blood sampling.
Acknowledgement
The authors were responsible for study design and data analysis, and controlled all data.

Conflict of interest
The TOSCA devices and disposables used in this study were supplied by TOSCA 500, Radiometer America Inc., Westlake, OH, USA.

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