Comparison of ventilator-integrated end-tidal CO₂ and transcutaneous CO₂ monitoring in home-ventilated neuromuscular patients

David Orlikowski a, b, Helene Prigent c, Xavier Ambrosi a, Isabelle Vaugier b, Sandra Pottie r b, Djillali Annane a, Frederic Lofaso c, Adam Ogna a, b, *

a AP-HP, Hôpital Raymond Poincaré, Service de Réanimation médicale et unité de ventilation à domicile, 92380, Garches, France
b AP-HP, Hôpital Raymond Poincaré, INSERM CIC 14.29, 92380, Garches, France
c AP-HP, Hôpital Raymond Poincaré, Service de Physiologie-Explorations Fonctionnelles, 92380, Garches, France

* Corresponding author. Service de Réanimation médicale et unité de ventilation à domicile, AP-HP, Hôpital Raymond Poincaré, 104, Boulevard Raymond Poincaré, 92380, Garches, France.
E-mail address: adam.ogna@aphp.fr (A. Ogna).

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A B S T R A C T

Background: Non-invasive transcutaneous capnometry (TcCO₂) is used to assess the home ventilation’s efficiency. Recently, end-tidal CO₂ (ETCO₂) sensors have been integrated in life-support home ventilators. The purpose of this study was to compare the ventilator-integrated ETCO₂ with TcCO₂, in home-ventilated neuromuscular disease patients.

Methods: ETCO₂ and TcCO₂ were simultaneously measured during one night in 28 patients. Daytime blood gases were drawn on the following morning to measure arterial PCO₂ (PaCO₂).

Results: Compared to PaCO₂ values, both ETCO₂ and TcCO₂ showed a small bias (−0.1 mmHg and 0.6 mmHg, respectively) and a similar critical difference (6.8 mmHg and 7.3 mmHg, respectively). We found a good correlation between ETCO₂ and TcCO₂, both considering the mean nocturnal PCO₂ (r = 0.897, p < 0.001; bias = −1.1 [−9.0; 6.9] mmHg) and the maximal PCO₂ value over the night (r = 0.905, p < 0.001; bias = 3.1 [−4.5; 10.8] mmHg). The concordance of the two techniques in detecting overnight PCO₂ fluctuations was high, with r = 0.919 (p < 0.001) for the time spent with PCO₂ >45 mmHg and r = 0.943 (p < 0.001) for the time with PCO₂ >50 mmHg.

Conclusions: The ventilator-integrated end-tidal CO₂ monitoring is as reliable as the currently used transcutaneous measurement, resulting to be a valuable proxy of the overnight PCO₂ evolution. This result opens the possibility of a simplification in the monitoring of home ventilated patients, since ETCO₂ measurement can be performed directly at home, with a low additional cost. However, the accuracy of both these measurement techniques is not sufficient to replace blood gases, which remain the reference examination.

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1. Introduction

The development of a restrictive respiratory failure represents one of the leading causes of morbidity and mortality in neuromuscular disease (NMD) patients [1–5]. Its management by long term home mechanical ventilation (HMV) is currently one of the few available treatments improving the clinical course of these patients [3–8].

Monitoring of the ventilation’s efficiency requires regular assessment of the partial pressure of carbon dioxide (PCO₂) to confirm the correction of alveolar hypoventilation [9,10]. The reference technique is PCO₂ measurement in blood gases obtained by arterial puncture [9–11], but it has some limitations, being an invasive method which may disrupt sleep, and reflecting only a snapshot of the variable alveolar ventilation during sleep [12–14]. In recent years, two non-invasive continuous PCO₂ monitoring tools were developed allowing the assessment of arterial PCO₂ either with a transcutaneous sensor (transcutaneous capnometry,
2.2. End-tidal CO2

Expired CO2 was measured on the gas expired by the patient using infrared spectrophotometry with mainstream sensor (IRMA ETCO2, Phasein AB, Stockholm, Sweden) and recorded with a sampling rate of 10 Hz. The analysis was conducted in accordance with the declaration of Helsinki and was approved by the local ethic committee (Comité de Protection des Personnes Ile de France XI; approval N. 2013-A01629-36); written informed consent was obtained from all patients. ClinicalTrials.gov registration number: NCT02068911.

2.3. Capn-oxymetry

Overnight continuous TcCO2 and oxygen saturation (SpO2) were recorded using a Digital Monitoring System (SenTec, Thervil, Switzerland) equipped with a combined Severinghaus-type TcCO2 electrode and SpO2 sensor (V-Sign, SenTec, Thervil, Switzerland). As recommended by the manufacturer, the electrode was calibrated in the integrated docking station before and after each measurement, using a service gas (mixture of 8% CO2, 12% O2, and 80% N2), allowing the measured TcCO2 values to be corrected for calibration drift. The electrode temperature was set at 42 °C to increase blood flow, thereby improving skin permeability to gases and arterIALIZED the capillary blood. An integrated factory algorithm estimated the arterial PCO2 from the measured PCO2, accounting for temperature and metabolic correction factors. According to the manufacturer, the measurement resolution for TcCO2 was 0.1 mm Hg, the in vitro drift <1%/hour and the response time <80 s. The TcCO2 signal sample interval was set at 4 s. All studies were visually inspected by the same investigator (AO) to exclude periods with artifacts from the results.

2.4. Statistical analysis

Statistical analysis was conducted using R 3.1.2 statistical software (R Core Team 2014, GNU General Public License). Continuous variables were described by mean and standard deviation; percentages were used to describe dichotomous or categorical variables. The ETCO2 and TcCO2 values measured in the morning at the time of the blood gases were first compared to the concomitant PaCO2 values. Subsequently, the ETCO2 and TcCO2 measurements of each patient were corrected for the difference to PaCO2 prior to the comparison of the two techniques.

The correlation between corresponding measurements was evaluated by computing the Pearson correlation coefficient and their agreement using the Bland-and-Altman method, computing bias (with 95% confidence interval) and limits of agreement. The critical difference (a marker of precision) was assessed based on the [bias - SD; bias + SD] interval, where SD was the standard deviation of the distribution of the differences. A sample size of 28 was chosen as it allowed to estimate the 95% confidence interval of the bias with a precision of 2 mmHg, which was considered as the minimal clinically significant difference.

3. Results

28 patients were included in the study. In one out of the 28 included patients, the ETCO2 recording was not exploitable because of a technical problem, and in a different patient we obtained no TcCO2 recording.

24 patients (86%) were ventilated non-invasively (using nasal interface in 21 and naso-buccal in 3) and 4 were ventilated through uncuffed tracheostomy. A volumetric ventilatory mode was used in 43% of the patients, including all 4 patients with tracheostomy. The patients presented 14 different neuromuscular diseases, the most frequent being Duchenne or Becker muscular dystrophy (N = 10), myotonic dystrophy type 1 (Steinert’s disease, N = 6), congenital muscular dystrophies (N = 3) and sarcoglycanopathies (N = 2). The characteristics of the study population are detailed in Table 1.

3.1. ETCO2 and TcCO2 vs blood gasses

The PCO2 values obtained in the morning by ETCO2 showed a good correlation (r = 0.867, p < 0.001) with the values obtained by simultaneous blood gasses. There was almost no difference between
The two values (bias -0.1 mmHg [95%CI -1.6; 1.4]), and the critical difference was 6.8 mmHg (Fig. 1). The results were similar comparing the values obtained by TcCO2 with those obtained by simultaneous blood gazes (r = 0.840, p < 0.001; bias 0.6 mmHg [95%CI -0.9; 2.1], critical difference 7.3 mmHg) (Fig. 2).

3.2. ETCO2 vs TcCO2

The results of both ETCO2 and TcCO2 displayed in a profile graph of the study night allowed a visual evaluation of the overall trend (Fig. 3). In accordance with the technical differences between the two methods, ETCO2 values were not available during periods of prolonged interface leakage, which accounted for a mean of 6% of the recordings in our population (range 0%–31%), whilst TcCO2 values were available even during these periods, being limited in their interpretation only by artifacts, which represented in mean 1% of the recording time (range 0%–4%).

We found a good correlation between ETCO2 and TcCO2 both considering the mean and the maximal PCO2 value over the night (r = 0.897, p < 0.001 and r = 0.905, p < 0.001, respectively). The Bland and Altman analysis showed a difference between ETCO2 and TcCO2 of -1.1 mmHg [95%CI -2.8; 0.6] for the nocturnal mean value (limits of agreement -9.0 to 6.9 mmHg), and 3.1 mmHg [95%CI 1.6; 4.7] for the maximal value (limits of agreement -4.5–10.8 mmHg) (Figs. 4 and 5). The concordance of the two techniques in detecting overnight PCO2 fluctuations was high, with an r = 0.919 (p < 0.001) for the time spent with PCO2 >45 mmHg and r = 0.943 (p < 0.001) for the time with PCO2 >50 mmHg (Fig. 6).

### Table 1
Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (N, %)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37.6 (12.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.2 (28.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 (10.0)</td>
</tr>
</tbody>
</table>

### Respiratory parameters

| VC sitting (%pred) | 30 (23) |
| MIP (cmH2O)       | 26 (17) |
| SNIP (cmH2O)      | 28 (14) |
| MEP (cmH2O)       | 26 (18) |

### Morning blood gases

| pH               | 7.39 (0.03) |
| PaCO2 (mmHg)     | 43.4 (6.7)  |
| PaO2 (mmHg)      | 77.3 (30.8) |
| Total CO2 (mmol/l) | 27.4 (3.9) |

### Ventilation

| Volumetric mode (N, %) | 12 (43%) |
| Interface (N, %)       | 4 (14%)  |
| Tracheostomy           | 21 (75%) |
| Nasal                  | 3 (11%)  |
| HMV duration (y)       | 7.5 (5.8) |

### Nocturnal Oximetry

| Duration of the recording (min) | 546 (124) |
| Mean Oxygen Saturation (%)      | 95.1 (3.0) |
| Time with SpO2<90% (%)          | 4.8 (13.2) |

BMI: body mass index; VC: vital capacity; %pred: percentage of the predicted value; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PaCO2: arterial partial pressure of CO2; PaO2: arterial partial pressure of O2; TcCO2: transcutaneous measure of CO2; HMV: home mechanical ventilation.

4. Discussion

Our data show that ventilator-integrated End-Tidal CO2 monitoring represents a valuable alternative to transcutaneous PCO2 recording for the monitoring of home-ventilated patients with neuromuscular diseases. The results obtained with the two techniques were well correlated and showed a good accuracy and a small bias. Furthermore, both techniques showed a similar accuracy when compared with arterial PCO2 assessment.

TcCO2 has been increasingly used for follow-up monitoring of home ventilated patients, allowing to detect episodes of transient hypoventilation, that are not detected by punctual blood gazes [9]. Contrary to older devices, which showed a poor agreement with arterial PCO2 because of a calibration drift occurring during extended recording times [17], the TcCO2 monitor used in our study (SenTec Digital Monitoring System) was calibrated at the beginning and at the end of the recording period, allowing the measured TcCO2 values to be corrected for calibration drift. As a consequence, we found a very small bias between the TcCO2 value in the morning and the PCO2 value obtained by concomitant arterial blood gases. Our results are in accordance with two recent studies performed with the same device, showing a bias of 0.8 mmHg and a limit of agreement of -4.9 to 6.5 in the first [12] and a bias of -0.8 mmHg and a critical difference of ±6.8 mmHg in the second [14]. However, the use of this monitoring tool is limited in the outpatient setting as it is quite expensive and fragile.

![Fig. 1. Comparison of the PCO2 obtained in the morning by ETCO2 and blood gazes. ETCO2: end-tidal CO2; PaCO2: arterial partial pressure of CO2. On the right panel, dotted lines represent bias and limits of agreement.](image-url)
In our study the ventilator-integrated ETCO2 module showed a similar accuracy as TcCO2, when compared with arterial PCO2 assessment, allowing to consider it as a valid measurement according to the American Academy of Sleep Medicine (AASM) guidelines [9]. The advantage of the ventilator-integrated ETCO2 monitor lies in the low additional cost and in its continuous availability at the patient’s home. In previous studies, ETCO2 was found to be unsuitable for the monitoring of mechanical ventilation [18–20]. These results were influenced by some of the characteristics of ETCO2, specifically its inaccuracy in the presence of ventilation/perfusion inhomogeneity (depending on the presence of parenchymal lung diseases) and in case of exhaled sample dilution due to intentional or unintentional air leaks, which regularly occur in ventilated patients [9,15,16]. The first source of error is dependent of the clinical setting, and was not present in our population, since neuromuscular disease patients mostly have an intact lung parenchyma in contrast to COPD and intensive care units patients, the subjects of most of the previous studies. However, the main novelty of our protocol was the filtering of the ETCO2 values according to the instantaneous leakage measurement, since both values were recorded by the ventilator. Despite the missing information about PCO2 during the periods of prolonged leak, the results provided by the ETCO2 monitoring were equivalent to those obtained by TcCO2. We found no statistically significant correlation between magnitude of leaks and inaccuracy of ETCO2, even though the four patients having >10% leaks were amongst the participants showing the largest differences between ETCO2 and TcCO2. Interestingly, we found no apparent difference in the accuracy of ETCO2 between patients ventilated with barometric and volumetric mode, despite the differences in the expected dilution effect in case of leaks between the two modes. On the other hand, the ventilator-integrated ETCO2 monitoring gave informations about prolonged leakage during the study night, which represent one of the main problems leading to ventilation’s inefficacy, but were not available with TcCO2.

The main limitation of our study is represented by the selection
Fig. 4. Comparison of the mean nocturnal PCO₂ obtained by ETCO₂ and TcCO₂. ETCO₂: end-tidal CO₂; TcCO₂: transcutaneous measure of CO₂. On the right panel, dotted lines represent bias and limits of agreement.

Fig. 5. Comparison of the maximal nocturnal PCO₂ obtained by ETCO₂ and TcCO₂. ETCO₂: end-tidal CO₂; TcCO₂: transcutaneous measure of CO₂. On the right panel, dotted lines represent bias and limits of agreement.

Fig. 6. Time spent with PCO₂ >45 and >50 mmHg according to ETCO₂ and TcCO₂. ETCO₂: end-tidal CO₂; TcCO₂: transcutaneous measure of CO₂. Comparison of ventilator-integrated End-Tidal CO₂ and transcutaneous CO₂ monitoring in home-ventilated neuromuscular patients.
of a population without expected airways and lung parenchyma abnormalities, not allowing the extension of our results to other populations and settings. It should however be noted, that only the absolute PCO2 values and not their relative overnight variations would be affected by lung parenchyma abnormalities, when the ventilation/perfusion distribution remain stable over the assessment period. As a consequence, ETCO2 may be reliable in this setting, after correction of the absolute PCO2 value for the difference with arterial PCO2. Furthermore, the measurement of ETCO2 and the leak estimation require the use of an unvented ventilation circuit, which is usually the case when life-support ventilators are prescribed [21]. Some further limitations of the study arise from the inhomogeneous of patients population according to ventilator mode and interface, the hospital setting and the use of a ventilator different from the usual patient’s one.

Despite the good correlation and the small bias when compared to arterial PCO2, none of the tested non-invasive methods of PCO2 measurement can completely substitute the gold standard blood gases, since they both showed a similar and quite poor precision in the estimation of absolute PaCO2, with a critical difference near to 7 mmHg. Nevertheless, both transcutaneous and end-tidal analyses of gas exchange seem to be appropriate surrogates for PaCO2 for the overnight monitoring of the PCO2 variations.

5. Conclusions

The ventilator-integrated End-Tidal CO2 monitoring is as reliable as the transcutaneous measurement, resulting to be a valuable proxy of the overnight PCO2 evolution in ventilated neuromuscular patients. This result opens the possibility of a simplification in the monitoring of HMV, since ETCO2 measurement can be performed directly and repeated at home, with a low additional cost. However, the accuracy of both these measurement techniques is not sufficient to replace blood gases, which remains the reference examination to determine absolute PCO2 value.

Author contributions

DO, IV, DA and AO: designed the experiment; DO, HP, XA, SP and AO: conducted the research; DO, IV, FL and AO: analysed the data and performed the statistical analyses; DO, HP, FL and AO: wrote the manuscript; AO has primary responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all of the data (including statistical reports and tables) in the study, revised the manuscript for important intellectual content and approved the final version of the manuscript.

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