End-tidal carbon dioxide monitoring using a naso-buccal sensor is not appropriate to monitor capnia during non-invasive ventilation

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Abstract

Background: In acute respiratory failure, arterial blood gas analysis (ABG) is used to diagnose hypercapnia. Once non-invasive ventilation (NIV) is initiated, ABG should at least be repeated within 1 h to assess PaCO2 response to treatment in order to detect NIV failure. The main aim of this study was to assess whether measuring end-tidal CO2 (EtCO2) with a dedicated naso-buccal sensor during NIV could predict PaCO2 variation and/or PaCO2 absolute values. The additional aim was to assess whether active or passive prolonged expiratory maneuvers could improve the agreement between expiratory CO2 and PaCO2.

Methods: This is a prospective study in adult patients suffering from acute hypercapnic respiratory failure (PaCO2 ≥ 45 mmHg) treated with NIV. EtCO2 and expiratory CO2 values during active and passive expiratory maneuvers were measured using a dedicated naso-buccal sensor and compared to concomitant PaCO2 values. The agreement between two consecutive values of EtCO2 (delta EtCO2) and two consecutive values of PaCO2 (delta PaCO2) and between PaCO2 and concomitant expiratory CO2 values was assessed using the Bland and Altman method adjusted for the effects of repeated measurements.

Results: Fifty-four datasets from a population of 11 patients (8 COPD and 3 non-COPD patients), were included in the analysis. PaCO2 values ranged from 39 to 80 mmHg, and EtCO2 from 12 to 68 mmHg. In the observed agreement between delta EtCO2 and deltaPaCO2, bias was −0.3 mmHg, and limits of agreement were −17.8 and 17.2 mmHg. In agreement between PaCO2 and EtCO2, bias was 14.7 mmHg, and limits of agreement were −6.6 and 36.1 mmHg. Adding active and passive expiration maneuvers did not improve PaCO2 prediction.

Conclusions: During NIV delivered for acute hypercapnic respiratory failure, measuring EtCO2 using a dedicating naso-buccal sensor was inaccurate to predict both PaCO2 and PaCO2 variations over time. Active and passive expiration maneuvers did not improve PaCO2 prediction.

Trial registration: ClinicalTrials.gov: NCT01489150.

Keywords: Respiratory monitoring; Non-invasive ventilation; End-tidal CO2; Hypercapnic respiratory failure

Background

Non-invasive ventilation (NIV) is widely used [1] in emergency rooms, in intensive and intermediate care units, and in recovery rooms to treat de novo and, even if it is more debatable [2,3], postextubation hypercapnic respiratory failure. Arterial blood gas analysis (ABG) is usually performed to diagnose hypercapnia and should at least be repeated within 1 h after NIV initiation to assess PaCO2 response to treatment [1]. However, as follow-up ABG requires a new arterial puncture in patients not previously equipped with an arterial line, this exam is often postponed with the risk of delaying NIV failure diagnosis and intubation, a condition previously associated with poor outcome [4]. Only a reliable non-invasive monitoring of the course of PaCO2 during NIV could avoid such a delay and help optimizing ventilator settings. End-tidal CO2 (EtCO2) monitoring is easy to perform and widely used during anesthesia to assess the adequacy of delivered
minute ventilation without performing repetitive ABG [5,6]. Using capnometry to monitor capnia in non-intubated patients during NIV is much more challenging. Indeed, during NIV, gas leak occurs in the respiratory ‘circuit’ and conceivably, in this situation, only gas sampling directly at the level of the patient’s airways can reflect true expiratory gas.

As new specialized naso-buccal EtCO$_2$ sensors have recently been developed to collect expired gas directly at the airway opening, there is now an opportunity to use capnometry to monitor capnia during NIV. The main aim of this study was to assess the ability of a dedicated EtCO$_2$ naso-buccal sensor to predict PaCO$_2$ variations and/or PaCO$_2$ absolute values in hypercapnic patients during NIV. The second aim of the study was to assess whether active or passive prolonged expiratory maneuvers could improve the agreement between expiratory CO$_2$ and PaCO$_2$.

**Methods**

A prospective pilot study was conducted in our medico-surgical ICU in Lausanne, Switzerland. The hospital ethics committee (Human Research Ethics Committee of Lausanne, Switzerland) approved the study protocol, and written informed consent was obtained before inclusion in the study. In the absence of published data reporting the use of a naso-buccal sensor to measure EtCO$_2$ in acutely ill patients undergoing NIV, no power computation could be performed.

**Patients**

Non-intubated patients suffering from hypercapnic (PaCO$_2$ ≥ 45 mmHg) acute respiratory failure, hospitalized in the ICU, equipped with an arterial line and requiring NIV could be included in the study if they had no major hemodynamic instability, no facial lesion preventing the use of the naso-buccal sensor, and no cognitive disability or psychiatric disease liable to interfere with NIV. To note, as only patients admitted in the ICU and already equipped with an arterial line could be included in the study, the NIV treatment monitored in the study was usually not the first NIV treatment delivered to the patients.

**Study protocol and measurements**

Upon inclusion, the patient was equipped with the Smart CapnoLine® naso-buccal sensor (Figure 1) designed to collect expiratory gas immediately at the airway opening both at the nose and mouth levels connected to the Capnostream 20 monitor® (Oridion Medical Ltd, Jerusalem, Israël). To perform the measurement, a sample of gas is transmitted from the patient to a micro-cell of 15 μl located in the monitor (sidestream capnography system). A sample of gas of 50 ml/min is needed for the measurement. The measurement is performed by non-dispersive infrared spectroscopy. For each respiratory cycle, the capnogram is displayed on the Capnostream 20 monitor®. For each EtCO$_2$ value recorded, the investigator checked the good quality of the capnogram displayed on the screen. The value of one respiratory cycle was recorded at each measurement time.

ABG and the corresponding EtCO$_2$ value displayed by the monitor were recorded as baseline values. NIV treatment was then initiated using an hermetic naso-buccal mask (Vygon Large®, Ecouen, France) held in place using a dedicated strap and a single-limb NIV ventilator (V60®, Respironics Philips, Amsterdam, Netherland). Calibrated intentional leakage to allow CO$_2$ expiration was created in the respiratory circuit using the dedicated whisper swivel (Whisper swivel®, Respironics Philips, Amsterdam, Netherland). A flow sensor (Hamilton, Bonaduz, Switzerland) was placed between the patient and the whisper swivel and connected to an analog-to-digital converter (MP100, Biopac, Systems, Goleta, CA, USA) to continuously record the flow-time curve. The respiratory circuit with the additional flow sensor is schematized in Figure 2. ABG and EtCO$_2$ values were recorded at 15, 30, 45, and 60 min after the initiation of NIV. At times corresponding to each PaCO$_2$ and EtCO$_2$ measurements, insufflated volumes were measured offline for ten consecutive respiratory cycles (by integration of the inspiratory flow-time curve recorded by the flow sensor placed between the patient and the whisper swivel) and the mean value was computed.
Respiratory rate and delivered minute ventilation were also computed. At 30 and 60 min after the beginning of NIV, the patient performed upon request a voluntary slow and maximal expiration. In brief, the patients were asked to slowly empty their lungs as much and for as long as possible. The expired CO$_2$ value displayed at the end of this active expiration maneuver was recorded. A passive expiratory maneuver was then performed with the help of an experienced respiratory therapist (bilateral chest compression during slow expiration), and the corresponding expired CO$_2$ value was recorded. The naso-buccal mask was not removed during the maximal expiratory maneuvers meaning that the patient expired through the nasobuccal sensor and the ventilator circuit and thus against the set PEEP. The backup safety respiratory frequency of the ventilator was set at 6 by minute to allow expiratory maneuvers of 10 s.

Calculations and statistics
To assess PaCO$_2$ variations, the differences between two consecutive PaCO$_2$ (delta PaCO$_2$) values were computed for each patient between the initial value and the 15-min value, between the 15- and 30-min values, between the 30- and 45-min values, and finally between the 45- and 60-min values. Delta EtCO$_2$ were computed to assess EtCO$_2$ variations according to the same procedure.

The PaCO$_2$-EtCO$_2$ gradient (Pa$_{\text{E}}$-CO$_2$) was computed for each patient with the pair of values recorded at the beginning of the NIV session and at 15, 30, 45 and 60 min after the initiation of NIV. The number of Pa$_{\text{E}}$-CO$_2$ values of more than ±10 mmHg was reported. The ratio of this number over the total number of measurements represents the proportion of clinically unacceptable EtCO$_2$ values. The treshold of 10 mmHg to consider Pa$_{\text{E}}$-CO$_2$ as clinically acceptable or not was an arbitrary choice.

All statistical analyses were performed using MedCalc Statistical Software version 12.7.2 (MedCalc Software, Ostend, Belgium). Considering the small number of included patients, non-normal distribution of the results was assumed. All results are given as median [25th and 75th percentile].

The agreement between delta PaCO$_2$ and delta EtCO$_2$ was assessed by the Bland and Altman method adjusted for the effect of repeated measurements. The differences between each deltaPaCO$_2$ and deltaEtCO$_2$ values were also computed. The percentage of differences higher than 5 mmHg was reported as they were arbitrarily considered as clinically unacceptable values.

Agreement between PaCO$_2$ and EtCO$_2$ absolute values was assessed using the Bland and Altman method adjusted for the effects of repeated measurements. Expiratory CO$_2$ to PaCO$_2$ agreement for values obtained after active and passive complete expirations was also computed with the Bland and Altman method adjusted for the effects of repeated measurements. The gradient between expiratory CO$_2$ and PaCO$_2$ was computed with the values obtained after active and passive complete expirations respectively. Clinically unacceptable values were arbitrarily defined as values above 10 mmHg. The proportions of clinically unacceptable gradients recorded were compared.
between normal expiration, active complete expiration, and passive complete expiration by chi-square test. \( p < 0.05 \) was considered as statistically significant.

**Results**

The whole 45-min protocol could be applied to ten patients. In one patient (patient number 4), the NIV treatment had to be interrupted after 45 min because of intolerance. In this patient, the second set of active and passive expiratory manoeuvers was performed after 45 min instead of 1 h, immediately before stopping NIV. Overall, 54-paired data sets of PaCO\(_2\) and EtCO\(_2\) from 11 patients (seven men/four women) could be recorded and were included in the analysis. Patients’ demographic and clinical data are given in Table 1. Among the 11 included patients, eight patients had chronic obstructive pulmonary disease (COPD) of various severity (Table 1). Median age was 68 [62 and 77] years old and median SAPS II score was 43 [34 and 44]. Initial blood gas analysis, respiratory rate, inspired fraction of oxygen (FiO\(_2\)), PaO\(_2\)/FiO\(_2\) ratio, and initial ventilator settings during NIV are mentioned in Table 2.

During the study period, PaCO\(_2\) ranged from 39 to 80 mmHg, and EtCO\(_2\) from 12 to 68 mmHg. At the time of the measurements, delivered inspiratory volume was 724 [597–896] ml and delivered minute ventilation was 18.6 [14.0-22.7] l/min. When assessing the agreement between EtCO\(_2\) and PaCO\(_2\) gradients between two consecutive measurements, 43 paired data sets could be analyzed. The bias was \(-0.3\) mmHg and the limits of agreement were \(-17.8\) and +17.2 mmHg. The Bland and Altman graphic representation is displayed in Figure 3.

Sixteen of 43 differences (37%) between delta PaCO\(_2\) and delta EtCO\(_2\) were higher than 5 mmHg. When assessing agreement between PaCO\(_2\) and EtCO\(_2\) absolute values, bias was 14.7 mmHg and the limits of agreement were \(-6.6\) and 36.1 mmHg (Figure 4). The Bland and Altman graphic representation is displayed in Figure 4 both for COPD patients and non-COPD patients. Pa\(_{E-CO_2}\) was 12.4 [8.6-20.2] mmHg in median but very high values were documented in some patients (maximal value of 42.7 mmHg) and non-physiologic slightly negative values were observed in one patient (Figure 5). The number of clinically unacceptable values for Pa\(_{E-CO_2}\) was 35/54 (65%).

When we compared agreements between PaCO\(_2\), concomitant EtCO\(_2\), and expired CO\(_2\) after active and passive expiration maneuvers, we had 22-paired data available for each comparison. The bias was respectively 15.7, 9.9, and 9.8 mmHg. Bland-Altman plots for active and passive expiration maneuvers are displayed in Figure 6A,B respectively. The number of clinically unacceptable gradient values was not different between the three measurements (respectively, 13 (60%), 9 (41%), and 9 (41%), \( p = 0.37 \)).

**Discussion**

Our results show that, in patients suffering from hypercapnic acute respiratory failure, measuring EtCO\(_2\) by a dedicated naso-buccal sensor during NIV was inaccurate to predict either PaCO\(_2\) variation over time or the absolute PaCO\(_2\) value. Adding complete passive or active expiratory maneuvers to expiratory CO\(_2\) measurements did not significantly improve the reliability of PaCO\(_2\) prediction.

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Table 1 Patient’s characteristics and clinical information.

| Patient number | Sex | Age [years] | BMI [kg/m\(^2\)] | SAPS 2 score | Cause of acute respiratory failure | Respiratory comorbidity | FEV1 (% of predicted value) | GOLD classification |
|----------------|-----|-------------|------------------|--------------|-----------------------------------|------------------------|------------------------|-------------------|
| 1              | F   | 52          | 25.3             | 24           | COPD exacerbation                 | COPD                   | 36                     | III               |
| 2              | M   | 80          | 22.9             | 43           | Chest trauma with multiple rib fractures | None                   |                        |                   |
| 3              | M   | 68          | 24.5             | 58           | Pneumonia                         | COPD                   | 43                     | III               |
| 4              | M   | 59          | 42.6             | 44           | Acute lung injury (bacterial peritonitis) | COPD                   | 57                     | II                |
| 5              | M   | 77          | 29.3             | 43           | Pneumonia                         | COPD                   | 32                     | III               |
| 6              | M   | 77          | 29.4             | 43           | Acute lung injury (pancreatitis)   | None                   |                        |                   |
| 7              | M   | 63          | 29.4             | 31           | COPD exacerbation                 | COPD                   | 33                     | III               |
| 8              | M   | 77          | 26.1             | 36           | Acute lung injury (peritonitis)    | None                   |                        |                   |
| 9              | F   | 71          | 22.0             | 45           | COPD exacerbation                 | COPD                   | Not available           | Not available     |
| 10             | F   | 61          | 17.2             | 42           | COPD exacerbation                 | COPD                   | 28                     | IV                |
| 11             | F   | 62          | 21.5             | 32           | Central hypoventilation (analgesia-sedation) | COPD                   | 54                     | II                |

Median 68, 25.3, 43
Centile 25 62, 22.5, 34
Centile 75 77, 29.4, 44

F, female; M, male; FEV1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; BMI, body mass index.
Before discussing the results in more details, we must acknowledge the following limitations of our study. First, only a small number of patients were included. However, a high number of paired EtCO$_2$ and PaCO$_2$ could be analyzed. As the correlation was poor with very high limits of agreements, it is unlikely that increasing the number of patients would have significantly modified the results. Second, this study used a specific system to measure EtCO$_2$ and we cannot exclude that using another device could have yielded different results. Third, only one EtCO$_2$ value was recorded at each time. Even if the quality of the corresponding capnogram was carefully checked, we cannot exclude that averaging the values of several respiratory cycles could have provided slightly different results. However, as airway resistance usually not varies between one breath and the following, this effect, if present, should be

| Patient number | RR [cycles/min] | SaO$_2$ [%] | pH | PaCO$_2$ [mmHg] | Bicarbonates [mmol/L] | PaO$_2$ [mmHg] | FIO$_2$ | PaO$_2$/FIO$_2$ ratio [mmHg] | Initial IPAP [cmH$_2$O] | Initial EPAP [cmH$_2$O] |
|----------------|----------------|-------------|-----|-----------------|----------------------|----------------|--------|--------------------------|-----------------------|---------------------|
| 1              | 12             | 93          | 7.41| 45              | 27.7                 | 62             | 0.28   | 159                      | 15                    | 10                  |
| 2              | 17             | 92          | 7.38| 52              | 29.6                 | 64             | 0.35   | 148                      | 12                    | 7                   |
| 3              | 16             | 88          | 7.46| 45              | 31.1                 | 53             | 0.5    | 89                       | 14                    | 6                   |
| 4              | 41             | 91          | 7.41| 55              | 34.7                 | 58             | 0.35   | 158                      | 12                    | 7                   |
| 5              | 21             | 94          | 7.32| 80              | 39.8                 | 67             | 0.4    | 200                      | 20                    | 8                   |
| 6              | 30             | 99          | 7.41| 55              | 34.0                 | 112            | 0.4    | 138                      | 12                    | 7                   |
| 7              | 27             | 92          | 7.42| 61              | 38.8                 | 62             | 0.5    | 123                      | 8                     | 5                   |
| 8              | 29             | 91          | 7.40| 50              | 30.7                 | 61             | 0.5    | 101                      | 11                    | 6                   |
| 9              | 25             | 90          | 7.33| 58              | 29.4                 | 58             | 0.4    | 145                      | 15                    | 6                   |
| 10             | 28             | 95          | 7.37| 58              | 32.5                 | 75             | 0.35   | 165                      | 12                    | 6                   |
| 11             | 20             | 92          | 7.47| 51              | 36.7                 | 59             | 0.3    | 171                      | 15                    | 6                   |
| Median         | 25             | 92          | 7.41| 55.3            | 32.5                 | 62             | 0.4    | 148                      | 12                    | 6                   |
| Centile 25     | 19             | 91          | 7.37| 51              | 30.2                 | 58             | 0.35   | 131                      | 12                    | 6                   |
| Centile 75     | 29             | 93          | 7.42| 58              | 35.7                 | 65             | 0.45   | 162                      | 15                    | 7                   |

RR, respiratory rate; SaO$_2$, oxygen saturation in arterial blood; PaCO$_2$, carbon dioxide partial pressure in arterial blood; PaO$_2$, oxygen partial pressure in arterial blood gas; PaO$_2$/FIO$_2$, oxygen partial pressure in arterial blood gas over inspired fraction of oxygen ratio; IPAP, set inspiratory pressure; EPAP, set expiratory pressure.

Figure 3 Bland-Altman plot of agreement between delta PaCO$_2$ and delta EtCO$_2$. Bland-Altman plot of agreement between delta PaCO$_2$ and delta EtCO$_2$. PaCO$_2$, CO$_2$ partial pressure in arterial blood; EtCO$_2$, end-tidal CO$_2$; circle markers, COPD patients values; square markers, non-COPD patients values; COPD, chronic obstructive pulmonary disease. The horizontal lines represent the bias and the upper and lower limits of agreement.
minor. Fourth, using another patient-ventilator interface or other ventilators, e.g., ICU ventilators equipped with inspiro-expiratory circuits, might also lead to different results. Fifth, during the active and passive complete expiration maneuvers, some patients could potentially not have emptied their lungs enough to reach the residual volume because of maneuver intolerance or because they had to expire through the breathing circuit against the set PEEP. Thus, expired CO₂ values might not truly reflect expired CO₂ at residual lung volume. Finally, we cannot exclude that different results could have been found if we had measured EtCO₂ after stopping NIV treatment. However, as, in clinical practice, it can be difficult or even dangerous to interrupt NIV treatment in patients suffering from acute respiratory failure, we did not test this alternative approach.

Figure 4 Bland-Altman plot of agreement between PaCO₂ and EtCO₂. Bland-Altman plot of agreement between PaCO₂ and EtCO₂. PaCO₂, CO₂ partial pressure in arterial blood; EtCO₂, end-tidal CO₂; circle markers, COPD patients values; square markers, non-COPD patients values; COPD, chronic obstructive pulmonary disease. The horizontal lines represent the bias and the upper and lower limits of agreement.

Figure 5 Evolution over time of PaCO₂-EtCO₂ gradient for all the patients. This figure shows the evolution over time of PaCO₂-EtCO₂ gradient for all the patients. PaCO₂, CO₂ partial pressure in arterial blood; EtCO₂, end-tidal CO₂. Patient numbers 1, 3, 4, 5, 7, 9, 10, and 11 are COPD patients.
EtCO₂ has been efficiently used for decades in intubated anesthetized patients [7] to monitor PaCO₂ and ventilation, although many limitations have been recognized, particularly for patients suffering from chronic respiratory diseases (increased VD/VT ratio [8], airflow limitation) or hemodynamic instability leading to ventilation-perfusion mismatches [7,9]. Nasal EtCO₂ has been successfully used to monitor normocapnic patients with almost healthy lungs undergoing regional anesthesia or recovering from general anesthesia [10]. In line with the results of the present study, two studies performed in spontaneously breathing patients suffering from acute respiratory failure found poor agreement between EtCO₂ and PaCO₂ values [11,12]. Oppositely, in more stable and tracheotomized patients, EtCO₂ values were closer to PaCO₂ values [13].

In contrast to our results (see Figure 4), in this last study [13], the agreement between EtCO₂ and PaCO₂ was better in non-COPD patients than in those suffering from COPD. This last point suggests that during NIV, physiopathological reasons probably do not explain by themselves the poor performances of EtCO₂ measurement. A possible explanation for the poor agreement we observed between EtCO₂ and PaCO₂ during NIV could be the presence of a high airflow and of significant and often variable leaks during NIV that may have caused sampled expiratory gas dilution.

To try to overcome the expected limitation of EtCO₂ measurement to assess PaCO₂ absolute values and based on the assumption that, in the absence of major haemodynamic instability and of bronchodilatator administration, Pa-E-CO₂, even if often unpredictable, might be sufficiently constant over an hour in a given patient to enable the tracking of PaCO₂ evolution, we assessed the time evolution of EtCO₂ and PaCO₂. This approach clearly reduced the bias, but the wide limits of agreement preclude its clinical use. Of course, we cannot exclude that physiological reasons, as alveolar recruitment occurring during NIV, could have decreased the VD/VT ratio and contributed to the poor performance of EtCO₂ variations to assess PaCO₂ variations during NIV. However in this situation, EtCO₂ values would have been closer to PaCO₂ values at the end of the 1-h NIV treatment, which was not the case.

To try to better assess PaCO₂, we also attempted to sample gas closer to the alveolar compartment by measuring expiratory CO₂ at the end of a ‘complete’ expiration (either active or passive) [14] but this approach was also disappointing. Again, this observation contrasts with a study on stable tracheostomized patients [13] and underlines that performing reliable complete expiration maneuvers in acutely ill patients is very difficult.

The present study suggests that other technologies should be considered to non-invasively assess PaCO₂ and PaCO₂ over time during NIV. Even if the reliability of using transcutaneous CO₂ monitoring to assess PaCO₂ in case of acute respiratory failure is still controversial [15,16], recent technological improvements in the transcutaneous CO₂ monitoring technology suggest that this technique could be of interest to monitor PaCO₂ during NIV. This hypothesis, however, should be formally explored prospectively.

**Conclusions**

When a naso-buccal sensor is used, major variations of Pa-E-CO₂ along time and poor limits of agreements between EtCO₂ and PaCO₂ preclude the use of EtCO₂ measurement to predict PaCO₂ or its variation over time during NIV delivered for acute hypercapnic respiratory failure. Adding complete expiration maneuvers, whether
passive or active did not improve PaCO\textsubscript{2} prediction using EtCO\textsubscript{2} during NIV. The optimal approach to non-invasively monitor PaCO\textsubscript{2} during NIV in patients with acute hypercapnic respiratory failure remains to be determined.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
LP participated in the design of the study, conducted the study, contributed to statistical analysis, and drafted the manuscript. DT participated in the design of the study, collected the data, and helped with the data analysis and presentation. PJ participated in the design of the study and extensively revised the manuscript. JPR participated in the design of the study, performed the statistical analysis, and extensively revised the manuscript. All authors read and approved the final manuscript.

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