Monitoring Transcutaneously Measured Partial Pressure of CO_2 During Intubation in Critically Ill Subjects

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BACKGROUND: The risk for severe hypoxemia during endotracheal intubation is a major concern in the ICU, but little attention has been paid to CO_2 variability. The objective of this study was to assess transcutaneously measured partial pressure of CO_2 (P_{tcCO_2}) throughout intubation in subjects in the ICU who received standard oxygen therapy, high-flow nasal cannula oxygen therapy, or noninvasive ventilation for preoxygenation. We hypothesized that the 3 methods differ in terms of ventilation and CO_2 removal. METHODS: In this single-center, prospective, observational study, we recorded P_{tcCO_2} from preoxygenation to 3 h after the initiation of mechanical ventilation among subjects requiring endotracheal intubation. Subjects were sorted into 3 groups according to the preoxygenation method. We then assessed the link between P_{tcCO_2} variability and the development of postintubation hypotension. RESULTS: A total of 202 subjects were included in the study. The P_{tcCO_2} values recorded at endotracheal intubation, at the initiation of mechanical ventilation, and after 30 min and 1 h of mechanical ventilation were significantly higher than those recorded during preoxygenation ($P < .05$). P_{tcCO_2} variability differed significantly according to the preoxygenation method ($P < .001$, linear mixed model). A decrease in P_{tcCO_2} by > 5 mm Hg within 30 min after the start of mechanical ventilation was independently associated with postintubation hypotension (odds ratio = 2.14 [95% CI 1.03–4.44], $P = .039$) after adjustments for age, Simplified Acute Physiology Score II, COPD, cardiac comorbidity, the use of propofol for anesthetic induction, and minute ventilation at the start of mechanical ventilation. CONCLUSIONS: P_{tcCO_2} variability during intubation is significant and differs with the method of preoxygenation. A decrease in P_{tcCO_2} after the beginning of mechanical ventilation was associated with postintubation hypotension. (ClinicalTrials.gov registration NCT0388430.) *Key words: intubation; transcutaneous blood gas monitoring; intensive care unit; preoxygenation; mechanical ventilation; hypotension.* [Respir Care 2021;66(6):1004–1015. © 2021 Daedalus Enterprises]

Introduction

Endotracheal intubation is a frequently performed procedure in the ICU that has been shown to be associated with severe complications, including profound hypoxemia.[1] Several studies on oxygenation parameters and potential strategies to prevent this life-threatening complication have been conducted.[1-5] However, little data are available about the evolution of P_{aCO_2} during endotracheal intubation.[6-8] Nevertheless, it may be useful to estimate P_{aCO_2} throughout intubation, as its variability may play a role in the development of postintubation hypotension.[9]

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To date, the continuous monitoring of P_{aCO_2} has been performed with end-tidal CO_2 pressure (P_{ETCO_2}) assessments. This measurement is the recommended method to confirm the appropriate placement of the endotracheal tube after intubation and to detect an esophageal intubation,[10] but P_{ETCO_2} only provides data at the beginning of mechanical ventilation and not during preoxygenation and apneic oxygenation. Furthermore, it does not provide any reliable estimates of P_{aCO_2} because factors such as spirometric changes, ventilation system leaks, respiratory dead space, and cardiac output can affect the $P_{aCO_2} - P_{ETCO_2}$ gradient.[11-13] The transcutaneously measured partial pressure of CO_2 (P_{tcCO_2}) is another reliable continuous method that is available to estimate P_{aCO_2} in the ICU within a few minutes.[13-16] Because P_{tcCO_2} estimation requires a transcutaneous sensor, this technique is not disrupted by spirometric changes and enables P_{aCO_2} variability to be recorded during endotracheal intubation, including before the start of mechanical ventilation (ie, before, during, and after apnea).

Alveolar ventilation during this preoxygenation and its effect on P_{aCO_2} may differ depending on whether subjects receive standard O_2, high-flow nasal cannula oxygen therapy (HFNC), or noninvasive ventilation (NIV) during preoxygenation. NIV is associated with a high flow of oxygen and increases in the mean airway pressure and PEEP.[17] HFNC is associated with a flow of oxygen exceeding the peak inspiratory flow and a positive pressure at approximately the 2–3 cm H_2O level, and it may have an effect on CO_2 removal from anatomic dead space. Standard O_2 is associated with a lower flow than NIV and HFNC and does not create a positive pressure in the airways.[1,4,18] P_{aCO_2} has significant effects on vascular tone. Rapid variability in P_{aCO_2} throughout intubation may lead to an imbalance between the direct action of hypercapnic acidosis, which inhibits cardiac contractility and reduces vascular tone, and a counterbalanced response of the sympathoadrenal system, leading to an increase in cardiac output.[19-22] We hypothesized that P_{tcCO_2} varies widely during endotracheal intubation in critically ill subjects and that the variability of P_{tcCO_2} differs by the preoxygenation method used. We therefore conducted a single-center, prospective, observational study to assess the variability in P_{tcCO_2} during endotracheal intubation in the ICU. The secondary aims were to assess the agreement of this measure with P_{aCO_2} and to investigate the link between the variability in P_{tcCO_2} during intubation and the development of postintubation hypotension.

QUICK LOOK

Current knowledge

Endotracheal intubation is frequently performed in ICUs and is associated with complications such as hypotension. Little evidence is available about P_{CO_2} variability during this procedure. Physiological studies have shown a link between a P_{CO_2} decrease and the development of hypotension, but clinical studies have not confirmed these findings after intubation.

What this paper contributes to our knowledge

There is major variability in transcutaneously measured partial pressure of CO_2 during endotracheal intubation in the ICU. A decrease in transcutaneously measured partial pressure of CO_2 after the start of mechanical ventilation was associated with the development of hypotension postintubation, which is consistent with the results of physiological studies.

Methods

Trial Design

This prospective, observational study was conducted from May 2018 to June 2019 in a mixed 21-bed ICU in Rennes University Hospital, a teaching hospital in Rennes, France. This study was approved by the hospital's ethics committee (18.32), and the database was declared to the Commission Nationale Informatique et Libertés. The study was registered with ClinicalTrials.gov (NCT0388430). Verbal and written information was given to the subjects, as required by the French law.

Subjects > 18 y old who were hospitalized in the ICU and undergoing endotracheal intubation were eligible for the study. Patients for whom tracheal intubation was needed immediately (ie, without enough time to set up the P_{tcCO_2} sensor) and patients who refused or whose relatives refused to participate in the study were not included. In addition, subjects could not be included twice in the study. The evaluation period spanned from the decision to intubate before preoxygenation to 3 h after the start of mechanical ventilation.

P_{tcCO_2} Measurement

A P_{tcCO_2} sensor (TCM5, Radiometer, Copenhagen, Denmark) was placed before preoxygenation on the subject's chest, as recommended by the manufacturer. The transcutaneous measurement of P_{CO_2} is based on the phenomenon of CO_2 gas diffusing through the skin. CO_2 is detected by a sensor placed on the subject's skin; the diffusion of CO_2 is increased by heating the sensor between 42°C and 44°C. CO_2 is finally measured electrochemically by determining the change in pH in an electrolyte solution separated from the skin by a highly permeable membrane. The change in pH is considered proportional to the logarithm of P_{aCO_2}. A temperature correction is also performed to avoid errors in measurements related to CO_2 produced by heating the skin.[23-25] The sensor was placed at the upper

part of the chest between the collarbone and the nipple. This sensor allows P_{tcCO_2} to be measured every second. As the sensor requires a few minutes for calibration, P_{tcCO_2} was considered stable when its value varied by < 1 mm Hg within 1 min. The sensor's membrane was changed every 28 d, following the manufacturer's recommendations, to obtain reliable measurements.

Procedures

The intubation and preoxygenation procedures were performed in the same way as in usual care because of the observational nature of our study. The type of preoxygenation device was therefore selected by the physician: standard O_2 involved a nonrebreather mask or bag-valve-mask, while HFNC and NIV were the available alternatives. Preoxygenation occurs before the induction of anesthesia. In accordance with our usual care protocol, preoxygenation was performed in the semi-recumbent position at 30° for 3–5 min according to the guidelines previously reported for preoxygenation.[26] Rapid-sequence induction using a hypnotic drug (ie, etomidate, propofol, pentothal, or ketamine) was performed, and either succinylcholine or rocuronium was administered before immediate intubation. Endotracheal intubation was performed by the resident or the physician in charge of the subject. The residents were considered junior operators, and the doctors of medicine were considered senior operators. During the apneic period before the first endotracheal intubation attempt, no bag-mask ventilation was provided. Its use was permitted after in case of emergency by the physician in charge. After endotracheal intubation, the subjects were ventilated using the volume control mode with a tidal volume of 6–8 mL/kg of predicted body weight. The breathing frequency, PEEP, and F_{IO_2} were left to the discretion of the physician. Sedation and analgesia, including either midazolam or propofol and morphine, were started immediately after intubation. A neuromuscular block with cisatracurium was introduced if it was considered necessary by the physician in charge of the subject. Throughout the procedure, fluid therapy was not mandatory but was provided when the physician requested it.

Definitions and Subgroup Analyses

Three groups were established according to the preoxygenation method chosen by the physician: standard O_2, HFNC, and NIV. In the standard O_2 group, F_{IO_2} was estimated as 0.21 + oxygen flow × 0.03.[1-4]

Postintubation hypotension was defined as the recorded systolic blood pressure being < 65 mm Hg or < 90 mm Hg despite 500–1,000 mL of fluid loading or the introduction or enhancement of vasoactive support.[27,28] This measure was recorded within 3 h after endotracheal intubation.

Adverse events during endotracheal intubation were classified as severe (eg, death due to any cause, cardiac arrest, S_{pO_2} < 80%, severe hypotension defined by a systolic blood pressure < 80 mm Hg) or moderate (eg, ventricular or supraventricular arrhythmia requiring intervention, esophageal or selective intubation, macroscopic aspiration, dental injury, difficult intubation defined by the need for > 3 laryngoscopies or the need to call another senior physician).[1,27]

ARDS was defined according to the Berlin definition.[29] According to the Task Force criteria,[30] the diagnosis of COPD was considered in subjects with symptoms of chronic cough and sputum production or dyspnea in addition to history of smoking. The diagnosis was retained when the postbronchodilator FEV_1/FVC was ≤ 0.7 and not fully reversible on a previous spirometry. Subjects with no previous results for pulmonary function tests were screened for emphysema via chest radiograph and via scanner when available, and for intrinsic end-expiratory pressure during mechanical ventilation.

Obesity was defined as a body mass index of ≥ 30 kg/m^2, and obesity-hypoventilation syndrome was defined as a combination of obesity, daytime hypercapnia, and sleep-disordered breathing.[31] Obesity-hypoventilation syndrome was diagnosed before admission to the ICU. Restrictive disease was diagnosed in subjects with restrictive patterns on the pulmonary function test and a reduced vital capacity, residual volume, and total lung capacity.[32] Subjects with bilateral bronchiectasis, asthma, and lung cancer were classified as "other" underlying respiratory disease. Chronic cor pulmonale was diagnosed when right-ventricular dilation and dysfunction associated with pulmonary hypertension were present.[33] Right-ventricular dilatation was considered when the apical right ventricle at base was > 41 mm and right-ventricular dysfunction when tricuspid annular plane systolic excursion was < 17 mm or measurement of tissue Doppler of the free lateral wall < 0.095 ms^{-1}.

Data Collection

P_{tcCO_2} was recorded at several time points during and after the intubation procedure: before preoxygenation, at the induction of anesthesia, at endotracheal intubation, at the initiation of mechanical ventilation, and at 30 min, 1 h, 2 h, and 3 h after the initiation of mechanical ventilation. The highest P_{tcCO_2} and the lowest S_{pO_2} observed during the endotracheal intubation procedure were recorded by a nurse or a physician not involved in the procedure. The time from anesthetic induction to intubation was also noted. The time required for the sensor calibration was retrieved from the sensor's internal memory. All P_{tcCO_2} values recorded during the study were double checked against those recorded in the sensor's internal memory. P_{tcCO_2} values reported were excluded if they varied by > 1 mm Hg within a second to avoid false measures related to noise in the signal. These

values were considered incorrect. Technical issues leading to data collection failure, such as accidental or voluntary removal, were also recorded.

Hemodynamic and respiratory parameters were collected at the same time as were P_{tcCO_2} values. Demographic characteristics of the subjects, main reason for intubation, preoxygenation and intubation procedures, and complications were also recorded. In addition, we determined the severity of illness by using the Sequential Organ Failure Assessment (SOFA)[34] and the Simplified Acute Physiology Score II (SAPS II) tools.[35] When requested by the physician, the blood gas results obtained simultaneously with the P_{tcCO_2} measures were collected. The simultaneous P_{tcCO_2} value was noted. The P_{tcCO_2} values < 35 and > 45 mm Hg were reported, based on normal P_{aCO_2} levels recorded in our laboratory.

End Points

The primary end points were the assessment of the variability of P_{tcCO_2} during endotracheal intubation and within the first 3 h of mechanical ventilation initiation and the comparison of the P_{tcCO_2} values performed according to the preoxygenation method used. The secondary end points were the reliability of P_{tcCO_2} to estimate P_{aCO_2} and the relationship between the changes in P_{tcCO_2} and the onset of postintubation hypotension.

Statistical Analysis

Continuous variables are expressed as medians with interquartile ranges (IQR); comparisons between 2 groups were performed using the Mann-Whitney U test, and comparisons across 3 or more groups were performed with the Kruskal-Wallis test. The proportions were compared using the chi-square test or Fisher exact test, as required. Repeated measurements for P_{tcCO_2} that were recorded before, during, and after intubation were first compared according to whether the subjects underwent standard O_2, HFNC, or NIV using one-way analysis of variance and the Bonferroni Dunn test for post hoc analysis. In addition, a linear effects mixed model was used to determine association of the preoxygenation method used with change of P_{tcCO_2} values during the study period. The continuous variables of age and body mass index were dichotomized for analysis of repeated measures. Subjects were differentiated by whether they were > 65 y old and whether they were obese. In addition, subjects were differentiated depending on whether minute ventilation increased by ≥ 100 mL/min from the value recorded at onset of mechanical ventilation and the value recorded after 30 min of mechanical ventilation; the threshold of 100 mL/min was arbitrarily chosen.

The level of agreement between P_{tcCO_2} and P_{aCO_2} was assessed using a Bland-Altman plot[36] when the blood gas values were measured at the same time that the P_{tcCO_2} measurements were available. Receiver operating characteristic curves were constructed to determine the threshold values of P_{tcCO_2} associated with postintubation hypotension. P_{tcCO_2} during preoxygenation, at induction, at intubation, and at the initiation of mechanical ventilation and the difference in P_{tcCO_2} between the initiation of mechanical ventilation and 30 min after the start of mechanical ventilation (ie, δP_{tcCO_2}-MV30min) were used. The areas under the curve were compared based on their associated P values to determine which value had the best predictive ability for postintubation hypotension.

We conducted logistic regression analysis to determine whether this value was independently associated with postintubation hypotension. On the basis of previous studies,[9,27,37-39] age, SAPS II score, COPD, cardiac comorbidity, the use of propofol for anesthetic induction, and minute ventilation at initiation of mechanical ventilation were selected as the variables to be used for adjustment. The results are expressed as odds ratios with 95% CIs. All probability values that are reported are two-sided. We considered P values $< .05$ to be statistically significant. The statistical analysis was performed using SPSS 25 (IBM, Armonk, New York) and MedCalc 18.6 (MedCalc BVBA, Ostend, Belgium).

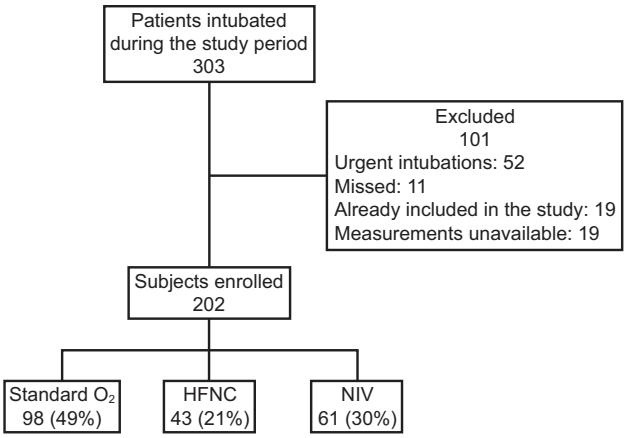

Fig. 1. Flow chart. Measurements were considered unavailable to take if the sensor was already used for another intubation or if there was a technical issue (eg, calibration failure, medical team was too busy). HFNC = high-flow nasal cannula; NIV = noninvasive ventilation.

Results

From February 2018 to March 2019, 303 patients were intubated in the ICU; 202 subjects were included in the study. The main reason for exclusion was that endotracheal intubation needed to be performed immediately in emergencies, without enough time to calibrate the P_{tcCO_2} sensor. Ninety-eight subjects (49%) received preoxygenation with standard O_2, 43 (21%) received preoxygenation with HFNC, and 61 (30%) received preoxygenation with NIV (Fig. 1).

Table 1. Baseline Subject Characteristics

Variables	All Subjects ($N = 202$)	Oxygen Device Used for Preoxygenation Before Intubation			P
		Standard O_2 ($n = 98$)	HFNC ($n = 43$)	NIV ($n = 61$)	
Age, y	63 (52–72)	61 (46–68)*	65 (51–73)	67 (58–77)	.02
Body mass index, kg/m^2	25 (22–29)	25 (22–28)†	24 (21–27)	27 (23–34)	.008
SAPS II score	48 (36–66)	47 (34–62)	43 (33–63)	52 (41–69)	.08
SOFA score	8 (5–11)	7 (5–10)	7 (4–11)	9 (6–11)	.40
Male	124 (61)	61 (62)	27 (63)	36 (59)	.90
Underlying respiratory disease					< .001
COPD	34 (17)	5 (5)	4 (9)	25 (41)‡	
Obesity-hypoventilation syndrome	13 (6)	5 (5)	2 (5)	6 (10)	
Restrictive lung disease	11 (5)	2 (2)	4 (9)	5 (8)	
Other	5 (2)	2 (2)	1 (2)	2 (3)	
None	139 (69)	84 (86)	32 (74)	23 (38)	
Underlying cardiac disease					.37
Atrial fibrillation or flutter	10 (5)	4 (4)	3 (7)	3 (5)	
Ischemic or hypertrophic cardiomyopathy	43 (21)	16 (16)	10 (23)	17 (28)	
Systemic arterial hypertension	13 (6)	7 (7)	2 (5)	4 (7)	
Chronic cor pulmonale	2 (1)	0	0	2 (3)	
Other	4 (2)	2 (2)	0	2 (3)	
None	130 (64)	69 (70)	88 (65)	33 (54)	
Main indication for intubation					< .001
Respiratory	111 (55)	25 (26)†	34 (79)	52 (85)	
Neurological	69 (34)	59 (60)†	3 (7)	7 (11)	
Hemodynamic	14 (7)	7 (7)	5 (12)	2 (3)	
Other	8 (4)	7 (7)	1 (2)	0	
ARDS	50 (25)	14 (14)	19 (44)§	17 (28)	< .001

Data are presented as median (interquartile range) or n (%).
* Standard O_2 vs HFNC and NIV ($P < .01$).
† Standard O_2 vs NIV ($P < .05$).
‡ NIV vs Standard O_2 and HFNC ($P < .001$).
§ HFNC vs Standard O_2 and NIV ($P < .05$).
SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation

The baseline characteristics of the subjects were compared according to the preoxygenation method used (Table 1). In 5 subjects, COPD was diagnosed on the basis of the clinical and radiological criteria for suspected COPD only.[30] For the other COPD subjects, the first pulmonary function test revealing obstructive syndrome were performed, depending on the subject, between 5 y and 6 months before admission to the ICU. Subjects with COPD or ARDS more frequently received preoxygenation with NIV and HFNC, respectively, than did other subjects. Age and body mass index differed significantly by preoxygenation method and were dichotomized as follows: individuals were grouped according to whether they were > 65 y old and whether they were obese. Subjects more frequently received preoxygenation with standard O_2 when they were intubated for neurological reasons.

Data regarding intubation conditions in the 3 groups are presented in Table 2. The number of laryngoscopy attempts was 1 (IQR, 1–2) in the 3 groups of subjects distinguished according to the preoxygenation method used. Ten junior operators failed intubation, which was then successfully performed by the senior operator in charge of the subject's care. Severe complications occurred significantly more frequently in the HFNC group ($P = .048$) than in other 2 groups. The respiratory and hemodynamic parameters are shown in Table 3. Notably, the tidal volume per predicted body weight applied did not differ significantly across the 3 groups; in addition, the total PEEP was significantly higher in the NIV group, and the plateau pressure was significantly higher in the NIV and HFNC groups than in the standard O_2 group within the 3 h after initiation of mechanical ventilation.

Table 2. Intubation Parameters at Baseline

Variables	All Subjects ($N = 202$)	Oxygen Device Used for Preoxygenation Before Intubation			P
		Standard O_2 ($n = 98$)	HFNC ($n = 43$)	NIV ($n = 61$)	
First operator					.92
Junior	106 (52)	50 (51)	23 (53)	33 (54)	
Senior	96 (48)	48 (49)	20 (47)	28 (46)	
Cardiac rhythm					.24
Sinus rhythm	184 (91)	91 (93)	41 (94)	52 (85)	
Atrial fibrillation or flutter	14 (7)	6 (6)	2 (6)	6 (10)	
Pacemaker	4 (2)	1 (1)	0	3 (5)	
Vasopressor use	20 (10)	9 (9)	2 (5)	9 (15)	.22
Use of Eschmann introducer	14 (7)	8 (8)	2 (5)	4 (7)	.74
Hypnotic agent used for endotracheal intubation					.08
Etomidate	180 (89)	85 (87)	39 (94)	56 (92)	
Penthotal	7 (4)	6 (6)	0	1 (1)	
Propofol	10 (5)	7 (7)	2 (3)	1 (1)	
Ketamine	5 (2)	0	2 (3)	3 (5)	
Neuromuscular blocking agent used for endotracheal intubation					.037
Succinylcholine	166 (82)	88 (90)	34 (79)	44 (72)	
Rocuronium	35 (17)	10 (10)	9 (21)	16 (22)	
None	1 (1)	0	0	1 (2)	
Highest F_{IO_2} preoxygenation, %	99 (66–1)	66 (66–99)†	100 (100–100)	100 (100–100)	<.001
Intubation duration, s	148 (105–218)	148 (94–233)	142 (86–184)	156 (124–226)	.25
Complication during intubation*					.048
Severe	54 (27)	19 (19)	19 (44)	16 (26)	
Moderate	9 (4)	5 (5)	1 (2)	3 (5)	

Data are presented as n (%) or median (interquartile range).
* Complication during intubation was defined as severe (eg, death, cardiac arrest, $S_{pO_2} < 80\%$, severe hypotension defined by systolic blood pressure < 80 mm Hg) or moderate (eg, ventricular or supraventricular arrhythmia requiring intervention, esophageal or selective intubation, macroscopic aspiration, dental injury, difficult intubation defined by need for > 3 laryngoscopies or need to call another senior physician).
† Standard O_2 vs HFNC and NIV ($P < .001$).
HFNC = high flow nasal cannula
NIV = noninvasive ventilation

Calibration Process and Failure of the Sensor

Technical issues were observed for 13 of 202 subjects (6%) at some time points in the study period, despite appropriate initial calibration and availability of P_{tcCO_2} results at the time of preoxygenation and anesthetic induction. Consequently, we did not exclude these subjects from analysis. In 8 (4%) cases, the sensor was accidentally removed during care-related procedures. In 1 (0.5%) case, monitoring was interrupted due to electrocardiogram interference. In 2 (1%) cases, there were errors in measurement with major, rapid variability in P_{tcCO_2} without any sensor stabilization being obtained. In 2 (1%) cases, the technical problem was not specified by the physician. No physical complications related to the sensor, such as burns, were reported during the study. The median calibration time for the sensor was 6 min (interquartile range 5–8), with the values ranging from 1 min to 21 min.

Agreement Between P_{tcCO_2} and P_{aCO_2}

The Bland-Altman analysis of concordance between P_{tcCO_2} and P_{aCO_2} is shown in Figure 2. The P_{tcCO_2} bias was 0.15 mm Hg, with the 95% limits of agreement ranging from 9.6 to –9.3 mm Hg. P_{tcCO_2} values > 100 mm Hg were noted in 5 subjects only and were distributed as follows: 102, 107, 116, 135, and 150 mm Hg. The values for P_{aCO_2} recorded at the same time were 108, 101, 102, 133 and, 148, respectively.

P_{tcCO_2} Variability During Endotracheal Intubation

The evolution of P_{tcCO_2} over time in the overall population is shown in Figure 3A. During intubation and the beginning of mechanical ventilation, we observed a significant increase in P_{tcCO_2} compared to that noted during the preoxygenation period. Then P_{tcCO_2} decreased but remained higher than that noted before preoxygenation. At initiation of mechanical ventilation, 151 subjects (75%) had P_{tcCO_2}

Table 3. Respiratory and Hemodynamic Parameters

Variables	All Subjects ($N = 202$)	Oxygen Device Used for Preoxygenation Before Intubation			P
		Standard O_2 ($n = 98$)	HFNC ($n = 43$)	NIV ($n = 61$)	
Breathing frequency, breaths/min					
During preoxygenation	28 (22–35)	24 (16–30)	30 (26–36)[§]	30 (24–36)	< .001
At initiation of mechanical ventilation	21 (19–23)	20 (18–22)	22 (20–25)[§]	22 (20–24)	< .001
At 30 min of mechanical ventilation	22 (20–25)	20 (19–24)	25 (22–28)[§]	22 (20–25)	< .001
At 1 h of mechanical ventilation	22 (20–26)	22 (18–24)[*]	24 (22–28)	22 (20–25)	< .001
At 3 h of mechanical ventilation	22 (20–25)	22 (20–25)[*]	24 (21–28)	22 (20–25)	.09
Expiratory V_T/PBW, mL/kg					
At initiation of mechanical ventilation	6.33 (5.95–6.99)	6.32 (5.98–6.93)	6.13 (5.93–6.95)	6.46 (5.93–7.02)	.68
At 30 min of mechanical ventilation	6.35 (5.97–6.88)	6.40 (6.00–6.82)	6.06 (5.95–6.82)	6.39 (5.94–7.08)	.40
At 1 h of mechanical ventilation	6.32 (5.94–6.92)	6.35 (5.92–7.00)	6.15 (5.96–6.79)	6.35 (5.95–6.90)	.53
At 3 h of mechanical ventilation	6.11 (5.94–6.75)	6.11 (5.97–7.02)	6.05 (5.92–6.49)	6.25 (5.93–6.66)	.54
Total PEEP, cm H_2O					
At initiation of mechanical ventilation	5 (5-5)	5 (5-5)[‖]	5 (5-5)	6 (5–10)	.005
At 30 min of mechanical ventilation	6 (5–7)	5 (5–6)	5 (5–6)	7 (6–9)[‡]	< .001
At 1 h of mechanical ventilation	5 (5–7)	5 (5–6)	5 (5–7)	8 (5–10)[‡]	.01
At 3 h of mechanical ventilation	6 (5–7)	5 (5–6)	5 (5–6)	9 (7–11)[‡]	.003
Plateau pressure, cm H_2O					
At initiation of mechanical ventilation	17 (15–21)	17 (15–20)	18 (15–22)	20 (16–22)[†]	.03
At 30 min of mechanical ventilation	18 (15–21)	17 (14–20)	20 (15–22)	20 (18–22)[†]	.003
At 1 h of mechanical ventilation	18 (15–21)	17 (14–20)	20 (16–22)	20 (18–22)[†]	.004
At 3 h of mechanical ventilation	19 (16–22)	16 (14–21)	20 (17–22)	21 (19–23)[†]	.02
Heart rate during pre-oxygenation, beats/min	105 (89–120)	101 (88–117)	112 (91–128)	102 (85–118)	.13
SBP during pre-oxygenation, mm Hg	125 (105–144)	128 (107–148)	116 (91–132)	127 (103–141)	.19
SBP at 30 min of mechanical ventilation, mm Hg	103 (87–136)	111 (89–136)	101 (85–143)	101 (81–122)	.24

Data are presented as median (interquartile range).
[*] Standard O_2 vs HFNC and NIV ($P < .01$).
[†] Standard O_2 vs NIV ($P < .05$).
[‡] NIV vs standard O_2 and HFNC ($P < .001$).
[§] HFNC vs standard O_2 and NIV ($P < .05$).
[‖] HFNC vs standard O_2 ($P < .05$).
V_T = tidal volume
PBW = predicted body weight
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
SBP = systolic blood pressure

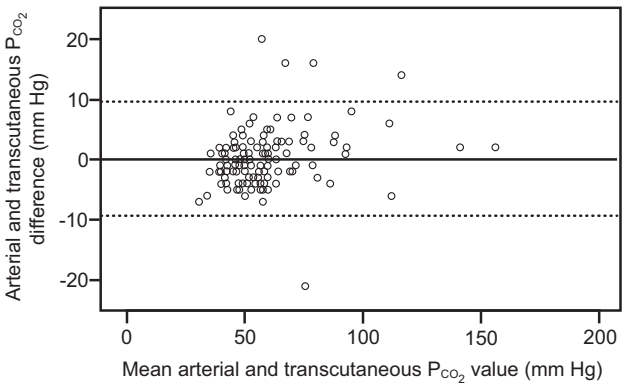

Fig. 2. Bland-Altman plot showing differences in arterial and transcutaneous measurements of partial pressure of CO_2 (P_{CO_2}) vs the mean of the 2 values among 131 critically ill subjects.

values that were not between 35 and 45 mm Hg, including 111 (55%) subjects with P_{tcCO_2} values > 45 mm Hg.

In 154 subjects (76%), median P_{aCO_2} measured 1–3 h after the start of mechanical ventilation was significantly higher in subjects who received NIV (53 mm Hg [IQR 47–66]) than in those who received standard O_2 (42 mm Hg [IQR 37–49], $P < .001$ after comparison), but P_{aCO_2} did not significantly differ from the subjects with HFNC (44 mm Hg [IQR 39–55]). The variability in P_{tcCO_2} values according to the preoxygenation method is shown in Figure 3B. Results for univariate mixed model are shown in Table 4. Overall, the P_{tcCO_2} values differed significantly across the 3 preoxygenation groups and over the period studied ($P < .001$), and the values were affected by whether subjects had COPD ($P < .001$), obesity ($P = .02$), or a neurologic reason

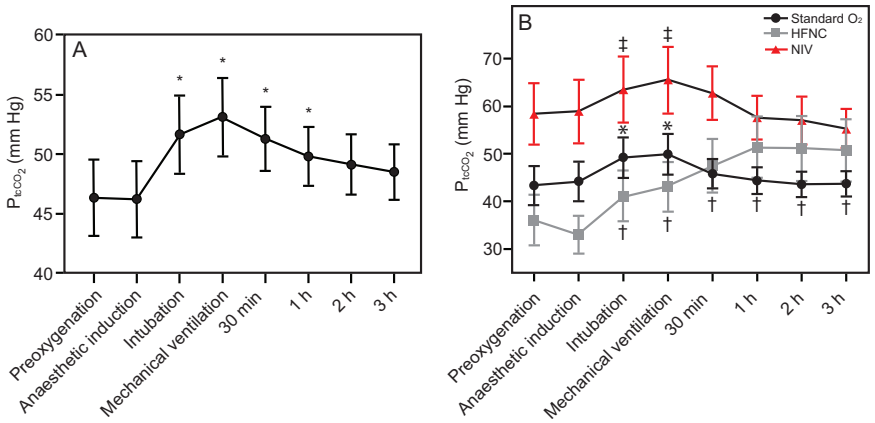

Fig. 3. Repeated measurement of P_{tcCO_2} before and after the initiation of mechanical ventilation. A: Among all the subjects in the study, and B: according to the preoxygenation method.*$P < .05$ vs preoxygenation (A) and vs preoxygenation in the standard O_2 group (B). †$P < .05$ vs preoxygenation in the HFNC group (B). ‡$P < .05$ vs preoxygenation in the NIV group (B). §$P < .05$ across all 3 groups at all time points (B). P_{tcCO_2} = transcutaneous measurement of partial pressure of CO_2; HFNC = high-flow nasal cannula oxygen therapy; NIV = noninvasive ventilation.

Table 4. Linear Mixed Model Effects for P_{tcCO_2} Variability

Effect	*F*	*P*
Oxygen device used for pre-oxygenation before intubation	16.517	< .001
Age > 65 y	0.943	.33
Male	0.148	.70
Obesity	6.486	.02
COPD	68.711	< .001
Underlying cardiac disease	0.015	.90
Neurological reason for intubation	21.543	< .001
ARDS	0.159	.69
Increased minute ventilation > 100 mL between the onset of and after 30 min of mechanical ventilation	0.917	.34

P_{tcCO_2} = transcutaneously measured partial pressure of CO_2

for intubation ($P < .001$), but not by whether they were > 65 y old, had ARDS, had underlying cardiac disease, had increased minute ventilation > 100 mL/min between initiation of and after 30 min of mechanical ventilation ($P = .89$), or were obese ($P = .07$). The maximum P_{tcCO_2} at endotracheal intubation was significantly higher in the NIV group than in the standard O_2 group ($P < .001$). The extreme values recorded at this assessment time were 18–153 mm Hg in the standard O_2 group, 22–120 mm Hg in the HFNC group, and 20–120 mm Hg in the NIV group. The preoxygenation method used remained independently associated with the variability of P_{tcCO_2} after COPD, obesity, and neurological reason for intubation were entered in the mixed model (F value 4.22, $P = .01$). The P_{tcCO_2} values decreased after the initiation of mechanical ventilation in the standard O_2 and NIV groups and increased in the HFNC group.

P_{tcCO_2} Variability and Development of Postintubation Hypotension

Postintubation hypotension occurred within 3 h of the beginning of mechanical ventilation in 37 subjects (38%) in the standard O_2 group, 30 subjects (70%) in the HFNC group, and 40 (66%) subjects in the NIV group ($P < .001$). In the overall study population, 71 (35%) experienced postintubation hypotension within 1 h of intubation, and 107 subjects (53%) experienced it within 3 h.

The areas under the curve and the prognostic relevance of the P_{tcCO_2} values in predicting postintubation hypotension are listed in Table 5. Only the area under the curve for δP_{tcCO_2}-MV30min was found to be significant. The threshold value determined by the receiver operating characteristic curve was 5 mm Hg for δP_{tcCO_2}-MV30min. δP_{tcCO_2}-MV30min > 5 mm Hg was significantly associated with postintubation hypotension in both the unadjusted analysis (odds ratio 2.58 [95% CI 1.37–4.88], $P =$

Table 5. Area Under the Curve for P_{tcCO_2} Values and Occurrence of Postintubation Hypotension

	Mean ± SD	95% CI	*P*
During preoxygenation	0.49 ± 0.041	0.41–0.57	.67
At induction	0.47 ± 0.041	0.39–0.55	.48
At intubation	0.46 ± 0.041	0.37–0.53	.27
At initiation of mechanical ventilation	0.41 ± 0.046	0.38–0.45	.41
δ P_{tcCO_2}-MV30min	0.57 ± 0.062	0.52–0.66	.02

P_{tcCO_2} = transcutaneously measured partial pressure of CO_2
δP_{tcCO_2}-MV30min = difference between P_{tcCO_2} at initiation of mechanical ventilation and P_{tcCO_2} recorded 30 min after the start of mechanical ventilation

.003) and in the adjusted analysis (odds ratio 2.14 [95% CI 1.03–4.44], $P = .039$). Among the 71 subjects who experienced postintubation hypotension within 1 h of intubation, 44 (62%) with δP_{tcCO_2}-MV30min > 5 mm Hg developed hypotension after 30 min of mechanical ventilation. The SAPS II score was also associated with postintubation hypotension in the adjusted analysis (odds ratio 1.04 [95% CI 1.02–1.06], $P < .001$), as was the need for vasopressors before preoxygenation (odds ratio 10.76 [95% CI 1.32–87.96], $P = .034$).

Discussion

This study is a proof-of-concept study, and further studies are required. The P_{tcCO_2} values recorded during endotracheal intubation within 3 h after initiation of mechanical ventilation in the ICU varied significantly. The first period of variability was observed at the time of apneic oxygenation, as previously reported during general anesthesia.[40] Some subjects experienced a quick increase in the P_{tcCO_2} level, and some subjects exhibited extreme values of hypercapnia during endotracheal intubation. P_{tcCO_2} variability differed significantly according to whether subjects received standard O_2, NIV, or HFNC for preoxygenation, and we noted an association between a decrease in P_{tcCO_2} within the first 30 min of mechanical ventilation and postintubation hypotension.

Thus, P_{tcCO_2} appears to be a suitable substitute for P_{aCO_2} and can safely be measured during endotracheal intubation, although it cannot provide the exact P_{aCO_2} value.[13,15,16,41,42] The sensor provided several advantages over those used for P_{aCO_2} and P_{ETCO_2} measurements. First, the sensor quickly provided P_{tcCO_2} values using a noninvasive method and recorded CO_2 values continuously, which cannot be done with blood gas analysis. Furthermore, unlike capnometry, use of the sensor enables the estimation of P_{CO_2} during the apneic period after anesthetic induction and appears to be more accurate for P_{aCO_2} estimation than P_{ETCO_2} in many situations encountered in the ICU, including shock and acute respiratory failure with hypercapnia.[11,12,15]

The issue that arises is the clinical impact of changes in P_{tcCO_2} during endotracheal intubation, which can affect the outcome for some subjects. We observed a significant increase in P_{tcCO_2} values during intubation, and most of the subjects had abnormal values during the study period. Some subjects experienced extreme P_{tcCO_2} values during intubation. This finding may be explained by apneic oxygenation, which is known to increase P_{tcCO_2} and its association with susceptibility to hypercapnia in subjects with respiratory diseases. P_{tcCO_2} should be monitored among patients in whom deleterious effects of P_{CO_2} variability can occur, such as those with brain injury[43] or individuals placed on extracorporeal membrane oxygenation.[44,45]

A clinical implication may be the relationship between CO_2 variability and the occurrence of postintubation hypotension. Rapid hypercapnia correction is commonly considered to lead to this complication.[46] However, there is little evidence available to support this assumption. Whereas cardiac output and sympathetic tone increase with an increase in CO_2,[19-21,47] no human studies have demonstrated the link between the correction of CO_2 during intubation and the occurrence of postintubation hypotension. Franklin et al[9] reported an association between hypercapnia before intubation and the occurrence of hypotension, suggesting a link between CO_2 variability and postintubation hypotension. In our study, we observed a relationship between a decrease in P_{tcCO_2} values within half an hour after the start of mechanical ventilation and the occurrence of postintubation hypotension, independent of the effects of other factors such as a history of COPD or minute ventilation at the initiation of mechanical ventilation. Of note, the recorded P_{tcCO_2} value was not associated with hypotension at any time during the intubation period. We believe that our results suggest that the risk of hypotension is related less strongly to high values of P_{tcCO_2} (and consequently to a high level of P_{aCO_2}) than to a sharp decrease in P_{tcCO_2} values and P_{aCO_2} induced by the correction of hypoventilation following the initiation of mechanical ventilation. Our results are therefore consistent with studies that have reported that a high level of CO_2 or respiratory acidosis is associated with higher cardiac output.[19-21]

We can hypothesize that a decrease in P_{CO_2} or the correction of acidosis leads to a drop in cardiac output and may induce hypotension. The definition of postintubation hypotension used in this work can be criticized. There are several definitions available[28] in the literature, and an evaluation after 1 h is often preferred.[27,48] Using this definition, Jaber et al[27] reported a rate of cardiovascular collapse of approximately 25% within the first hour after endotracheal intubation. Because we recorded postintubation hypotension within the first 3 h after endotracheal intubation and initiation of mechanical ventilation, the postintubation hypotension incidence was higher than that reported in other studies. Indeed, we found that 53% of the subjects exhibited

postintubation hypotension in this time period, with 36 subjects (18%) developing postintubation hypotension after 1 h of mechanical ventilation.

We compared 3 groups that were established according to the preoxygenation technique chosen by the physician. As in previous studies,[48] standard O_2 was used more frequently than the other techniques. It is noteworthy that, unlike Bailly et al,[48] who studied the impact of preoxygenation on pulse oximetry, we included a higher proportion of subjects who underwent HFNC in our cohort. This difference is probably due to this technique being used increasingly more often in the ICU.[1,3-5] In our study, P_{tcCO_2} varied differently over time in the 3 groups, and standard O_2 and NIV had the same profile trend, while HFNC had a different profile. These differences probably occurred because there was considerable cardio-respiratory disease heterogeneity across the 3 groups. On the one hand, the use of NIV was linked to a higher rate of COPD with hypercapnia. On the other hand, there were more cases of ARDS in the HFNC group. Impaired respiratory system compliance among these subjects could have led to the occurrence of hypercapnia after the start of mechanical ventilation, explaining the increasing pattern in P_{tcCO_2} over the study period.[49] In more than half of the subjects who experienced postintubation hypotension within 1 h after the start of mechanical ventilation, a δP_{tcCO_2}-MV30min $>$ 5 mm Hg was noted before hypotension occurred. Thus, we believe that the decrease in P_{tcCO_2} after intubation is a predictor of hypotension after the beginning of mechanical ventilation and not a consequence of hypotension. However, we also noted that the preoxygenation method has an impact on P_{tcCO_2} variability independent of the underlying diseases of the patient.

The main strength of our study lies in the exclusion of patients who had various diagnoses and underwent different preoxygenation techniques. In addition, their care in terms of the intubation processes was not modified. We can therefore presume that the variability in CO_2 recorded reflects the variability that occurs daily in a medical ICU. Furthermore, the use of this P_{tcCO_2} sensor during endotracheal intubation in the ICU is an innovative monitoring method that can lead to new clinical research perspectives.

Our study has several limitations to note. It is a single-center study, and it may not be possible to generalize our results to ICUs caring for subjects with particular pathologies or with specific preoxygenation practices. Lung function measurements were not available in all subjects for the diagnosis of the underlying respiratory disease in all subjects, which may have resulted in misclassification of some subjects. The evaluation of the agreement between P_{tcCO_2} and P_{aCO_2} was not possible for all subjects due to the observational nature of the study. Moreover, it would have been more accurate to assess the correlation between P_{tcCO_2} and P_{aCO_2} at all of the time points in the study. As the calibration of the sensor required a few minutes, we were not able to include extreme emergency intubations; consequently, the use of P_{tcCO_2} monitoring is excluded in emergency circumstances. It would have been interesting to assess the CO_2 variability among these subjects because they usually have higher severity scores and are therefore at a higher risk for postintubation hypotension. In addition, given that not all subjects had an arterial catheter, blood pressure measurements were recorded intermittently, so some cases of postintubation hypotension may have been missed. Fluid management was not homogenized at the time of intubation, which could have caused confusion in the analysis of the relationship between CO_2 variability and hemodynamic alterations, as it could impact postintubation hypotension incidence,[27] although a recent study failed to show an effect of fluid bolus on the occurrence of cardiovascular collapse.[50]

Additional investigations should focus on controlling P_{tcCO_2} variability, decreasing the incidence of postintubation hypotension and improving the outcomes among subjects in whom the variability of P_{CO_2} has a potential deleterious effect, such patients with brain injury[43] and those receiving with extracorporeal membrane oxygenation.[45]

Conclusions

Our study describes the evolution of transcutaneous CO_2 throughout intubation among critically ill subjects. We observed major changes in P_{tcCO_2} during and after endotracheal intubation. Among the 3 groups established according to the preoxygenation technique used, the variability in P_{tcCO_2} differed. We found that P_{tcCO_2} showed the same trend when standard O_2 or NIV was used for preoxygenation but was higher when NIV was used. In contrast, P_{tcCO_2} had a different trend when HFNC was used for preoxygenation. We also highlighted an association between a decrease in P_{tcCO_2} after the start of mechanical ventilation and the development of postintubation hypotension. Because we performed a proof of concept study, additional studies need to be conducted to verify our results and specifically, to determine whether postintubation hypotension and the deleterious variability in CO_2 can be prevented by the continuous monitoring of P_{tcCO_2} during endotracheal intubation.

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