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The accuracy of transcutaneous PCO_2 in severe brain injury patients: a comparison with end-tidal PCO_2

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Abstract

Background: In patients suffering from brain injury, end-tidal PCO_2 ($P_{ET}CO_2$) monitoring is controversial but transcutaneous PCO_2 ($PtcCO_2$), which is noninvasive and utilizes real-time display, may be an alternative method. We hypothesized that $PtcCO_2$ would be more accurate than $P_{ET}CO_2$ for monitoring $PaCO_2$ in severe brain injury patients.

Methods: A prospective observational study included consecutive mechanically ventilated adult subjects who had acute brain injury and an arterial catheter in place. When an arterial blood gas analysis was required, the $P_{ET}CO_2$ and $PtcCO_2$ values were simultaneously recorded. The agreement between the $P_{ET}CO_2$, $PtcCO_2$ and arterial PCO2 ($PaCO_2$) measurements (reference) was determined using the Bland-Altman method. The number of outliers defined by the formula ([$P_{ET}CO_2$ or $PtcCO_2$] - $PaCO_2$) > ± 4 mmHg indicated the proportion of measurements that were considered clinically unacceptable.

Results: A total of 25 subjects were included in the study, and 85 simultaneous measurements of $PaCO_2$, $PtcCO_2$ and $P_{ET}CO_2$ were obtained. The bias and precision between $PaCO_2$ and $PtcCO_2$ were -0.75 and 6.23 mmHg, respectively. The limits of agreement ranged from -12.97 to 11.47 mmHg. The bias and precision between $PaCO_2$ and $P_{ET}CO_2$ were 0.68 and 5.82 mmHg, respectively. The limits of agreement ranged from -10.72 to 12.08 mmHg. There were 34 (40%) outliers for the $PtcCO_2$ sensor and 34 (40%) outliers for the $P_{ET}CO_2$ sensor ($P = 1$).

Conclusions: The accuracy of $PtcCO_2$ was not superior to that of $P_{ET}CO_2$ for assessing PCO_2 levels and should not be used to monitor these levels in severe brain injury subjects.

Key words: Respiratory monitoring, end-tidal PCO_2, transcutaneous PCO_2, brain injury, accuracy.

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Introduction

Patients who suffer from a brain injury require maintaining blood carbon dioxide pressure (PCO_2) within the physiological range to avoid cerebral spinal fluid pH change and prevent cerebral vasodilatation and vasoconstriction [1]. The "gold standard" technique for monitoring PCO_2 is the determination of arterial PCO_2 ($PaCO_2$) using arterial blood gas. However, the arterial blood gas test is time-consuming, requires a significant amount of blood, must be repeated, particularly in brain injury patients, and does not display real-time data.

Therefore, techniques that can avoid these pitfalls are needed. End-tidal PCO_2 ($P_{ET}CO_2$) is a non-invasive tool that allows for the continuous monitoring of PCO_2. However, in subjects with severe brain injuries, the use of $P_{ET}CO_2$ as a surrogate of $PaCO_2$ has been disappointing [2-5]. Therefore, $P_{ET}CO_2$ is only recommended for use in out-of-hospital settings when arterial blood gas is not available [6-8].

New devices that measure transcutaneous PCO_2 ($PtcCO_2$) have recently become available. The general principle of $PtcCO_2$ measurement is that CO_2 diffuses from capillary through tissue and across the semi-permeable membrane of the device sensor, which is a modified Severinghaus electrode [9]. The agreement between the measured $PtcCO_2$ and $PaCO_2$ is dependent on the high tissue solubility of CO_2, which is further promoted by warming of the skin under the electrode. However, studies of this technology in intensive care units have produced conflicting results, with accuracy varying between studies according to the type of subjects who were evaluated [10-14]. In studies that have compared both $PtcCO_2$ and $P_{ET}CO_2$ to blood gas-measured $PaCO_2$, the former technology does appear to be more accurate [15,16].

In this study, we hypothesized that $PtCO_2$ would be more accurate than $P_{ET}CO_2$ in predicting $PaCO_2$ in brain injured patients. Therefore, we compared simultaneous $PtcCO_2$ and $P_{ET}CO_2$ values to the reference $PaCO_2$ value in brain injury subjects.

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Methods

This prospective observational study was performed at the surgical ICU of a university hospital from June 2011 to January 2012. The study was approved by the local ethics committee, which waived the requirement for informed consent from subjects or their relatives (law relative to the French public health policy no. 2004-806 – Ethics Committee, CHU de Rennes, avis n°12.03).

Consecutive mechanically ventilated subjects who were >15 years of age, had a brain injury (Glasgow Coma Scale ≤8), had an arterial catheter in place and required arterial blood gas were included.

All brain injury patients were managed according to standardized protocols in order to maintain a mean arterial pressure (MAP) ≥ 85mm Hg, an ICP ≤ 20mm Hg, and a cerebral perfusion pressure (CPP) ≥ 65mm Hg [1]. Other types of therapy to avoid secondary insults were applied as recommended [1]. In patients suffered from subarachnoid hemorrhage, MAP was maintained ≥ 90 mmHg. All patients were in a semi-recumbent position (>30°) and received sedatives agents but none were paralyzed.

The following data were recorded during the first 24 hours of admission to the ICU: age, sex, body weight, the nature of the brain injury, the Glasgow Coma Scale upon admission, the Simplified Acute Physiology Score II and the Sequential Organ Failure Assessment score. Norepinephrine was administered when necessary, and the dose was recorded. For each comparison, the following variables were reported: the body core temperature, the tidal volumes, the respiratory rates, the use and level of positive end expiratory pressure (PEEP), the presence of mottling on the legs, the capillary refilling time, the arterial pH, and the hemoglobin level provided by the arterial blood gas analysis.

When the inclusion criteria were met and arterial blood gas measurement was ordered, the $PtcCO_2$ and $P_{ET}CO_2$ were simultaneously recorded.

Carbon dioxide measurement

Arterial blood gas was sampled using an arterial catheter (Seldicath 3F, Plastimed-Prodimed, Le Plessis Bouchard, France) in a heparinized syringe and assessed using an analyzer (700/800 series, Radiometer Medical ApS, Brønshøj, Denmark). PtcCO2 was measured using the SenTec monitor via a V-Sign™ Sensor (Sentec AG,

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Therwil, Switzerland) according to the manufacturer's instructions. All of the measurements were taken at the right or left earlobe. The V-sign Sensor was inserted into the docking station of the monitor, and the calibration was automatically performed. Then, the V-sign Sensor was clipped into the multi-site attachment at the earlobe ring. The earlobe was chosen because it appeared more accurate than the forehead or cheek [13]. The quality of the signal was estimated by the pulsatility index provides by the Sentec monitor (normal range: 1 to 2). As a warm-up period (≈ 30 min) is necessary for the electrode to reach its optimal working conditions, all of the measurements were performed after this period.

$P_{ET}CO_2$ was measured via a non-aspirated infrared capnograph (M1460A, Hewlett Packard, Andover MA, USA), which was inserted at the tip of the tracheal tube and connected to a multi-parameter monitor (SC 9000 XL; Siemens Elema AB, Solna, Sweden). The quality of the $P_{ET}CO_2$ measurement was the visualization on the monitor of a typical waveform with a rapid and abrupt inspiratory/expiratory segments separated by a near horizontal alveolar plateau. All of the measurements were taken at least 30 minutes after any modifications in the mechanical ventilation parameters and/or changes in the norepinephrine rate.

Statistical analysis

To demonstrate the superiority of $PtcCO_2$ compared with $P_{ET}CO_2$, at least 82 measurements were required (NQuery Advisor 6.0, Statistical Solutions Ltd., Cork, Ireland) assuming an α-risk of 0.05, a β-risk of 0.2, and a proportion of outliers of 40% and 20% in the $P_{ET}CO_2$ and $PtcCO_2$ groups, respectively [4]. The $PaCO_2$ value obtained by arterial blood gas was the reference value. The statistical analysis was performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA). Data were expressed as the mean±SD and median (interquartile range) for the non-normally distributed variables and as the n (percentage). The agreement between the 2 measurement methods was assessed using a Bland-Altman analysis [17]. The study design included several measurements per patient; therefore, a correction was used in the limits of agreement calculation [18]. The outliers were defined as the differences $PaCO_2$ - $PtcCO_2$ or $PaCO_2$ - $P_{ET}CO_2$ that strictly exceeded ±4 mmHg. In addition, variables which may explain the outliers for $PaCO_2$ - $PtcCO_2$ and $PaCO_2$ - $P_{ET}CO_2$ were studied and compared using a Student's t-test or a Kruskal-Wallis test when necessary. The body temperature, the hemodynamic parameters (capillary refilling time, presence of mottling on the legs, and norepinephrine dose),

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the arterial pH, and the hemoglobin level were compared between $PaCO_2$ - $PtcCO_2$ non outliers and outliers. The body temperature, the ventilation parameters (respiratory rates, tidal volumes, PEEP), the hemodynamic parameters (capillary refilling time, mottling on the legs, and norepinephrine dose), the arterial pH, and the hemoglobin level were compared between $PaCO_2$ - $P_{ET}CO_2$ non outliers and outliers.

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Results

Twenty five subjects were included, and 85 simultaneous measurements of $PaCO_2$, $PtcCO_2$ and $P_{ET}CO_2$ were obtained. The baseline patient characteristics are provided in Table 1. The median number of measurements per patient was 4 (range: 1-5), and all the measurements were performed at the acute phase in the first 48 h after admission in ICU. Body core temperature, ventilation parameters, arterial pH and haemoglobin level measured at each comparisons are provided in Table 2.During the measurements, all of the subjects received a norepinephrine infusion at a mean dose of 0.4±0.5 $\mu g/kg \cdot min^{-1}$.

A comparison of the PCO_2 measurements using arterial blood gas and the $P_{ET}CO_2$ and $PtcCO_2$ measurements are presented in Table 3. The number of outliers did not vary between the $PtcCO_2$ and $P_{ET}CO_2$ measurements. The regression analysis and the results of the Bland-Altman analysis are provided in Table 2 and Figure 1. Variables which may explain the outliers for $PaCO_2$ - $PtcCO_2$ and $PaCO_2$ - $P_{ET}CO_2$ are provided in Table 4 and 5, respectively. There were no difference between non outliers and outliers.

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Discussion

In this population of severe brain injury subjects, $PtcCO_2$ was not superior to $P_{ET}CO_2$ and could not be used as a surrogate of $PaCO_2$. The percentage of outliers was high and did not vary between the 2 measurement methods.

The use of $P_{ET}CO_2$ as a surrogate of $PaCO_2$ in the ICU is controversial. Kerr et al. compared $P_{ET}CO_2$ with $PaCO_2$ in traumatic brain injury (TBI) subjects and found a bias of 1 mmHg and limits of agreement that ranged from -5.2 to +17.2 mmHg, but no clinical limits of agreement were defined [3]. In 21 TBI subjects, the bias was 5.5 mmHg, and the limits of agreement ranged from -4.5 to +15.5 mmHg [4]. The values that were considered clinically relevant were ±4 mmHg; therefore, $P_{ET}CO_2$ could not be used to substitute for $PaCO_2$. Moreover, the $PaCO_2$ - $P_{ET}CO_2$ differences in 40% of the cases were outside of the previously defined limit. Recently, Lee et al. found values that were outside of the limit of ±5 mmHg in 23% of TBI subjects [5].

The use of the SenTec monitor in ICUs has produced contrasting data. Rodriguez et al. evaluated this monitor in 50 ICU subjects who were hospitalized for various reasons [10]. The bias was -0.2 mmHg, and the limits of agreement ranged from -9.4 mmHg to +9.0 mmHg. The authors concluded that the $PtcCO_2$ measurement was an acceptable tool for monitoring PCO_2, but they did not consider predefined limits. Bolliger et al. compared the SenTec and TOSCA 500 monitors in 50 ICU subjects [11]. For the SenTec and TOSCA 500 monitors, the bias was -2.60 and -2.75 mmHg, and the limits of agreement ranged from -14.1 to +8.8 mmHg and -11.5 to +7.2 mmHg, respectively. According to the predefined limit of ±7.5 mmHg, the authors concluded that the 2 devices were inaccurate. Baulig et al. evaluated the SenTec monitor in cardiac surgery subjects [12]. The bias was 0.37 mmHg, and the limits of agreement ranged from -9.0 to +9.75 mmHg. Using a recently available sensor, they found a bias of 1.1 mmHg and limits of agreement that ranged from -3.4 to +5.5 mmHg, with a predefined limit of ±5 mmHg [13]. In a study that evaluated the TOSCA 500 monitor including 55 subjects, of whom 10 were multiple traumatic and neurosurgical subjects, the bias was 1.2 mmHg, and the limits of agreement ranged from -10.5 to +13.0 mmHg [14]. Nevertheless, in the subgroup of brain injury subjects, the authors concluded that $PtcCO_2$ should be used with caution [14].

Few studies have evaluated simultaneous measurements of $P_{ET}CO_2$ and $PtcCO_2$ using the $PaCO_2$ measurement as a reference [15, 16]. During general anesthesia, the values obtained with the transcutaneous PCO_2 monitor

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had a lower bias and narrower limits of agreement than those obtained with the end-tidal PCO_2 monitor (0.19 vs. -4.40 mmHg and -4.6 to 4.9 mmHg vs. -10.7 to +2.9 mmHg, respectively) [15]. In mechanically ventilated subjects who required inter-hospital transport, Hinkelbein et al. found that the bias for the end-tidal measurement was higher than that obtained with $PtcCO_2$ (-5.3 vs. -0.6 mmHg) [16].

According to the *a priori* better performance of $PtcCO_2$, we expected that $PtcCO_2$ would be more accurate than $P_{ET}CO_2$. We considered that acceptable differences between $PtcCO_2$ or $P_{ET}CO_2$ and $PaCO_2$ would not exceed ±4 mmHg as previously considered to be clinically relevant in studies of brain injury subjects [4, 5, 19]. The percentage of outliers using the SenTec monitor did not differ from those that were associated with the $P_{ET}CO_2$ measurement and the limits of agreement were significant, which suggests that the $PtcCO_2$ measurement should not be used in subjects suffering from brain injury.

Our study has some limitations that must be pointed out. Indeed, it may be argued that norepinephrine may have modified the skin perfusion and $PtcCO_2$ values. These subjects often require at the acute phase such medication to maintain adequate cerebral perfusion pressure and/or MAP [1]. Nevertheless, the relationship between vasopressor use and an alteration in the bias and precision has not been demonstrated and in our study, no relationship was found between the norepinephrine dose and the difference between $PaCO_2$ and $PtcCO_2$ [14, 20]. We measured $PtcCO_2$ at the earlobe and we cannot exclude regional hypoperfusion, although the earlobe site was found to provide the better accuracy [13].

In conclusion, $PtcCO_2$ measured at the earlobe with the Sentec monitor was not superior to $P_{ET}CO_2$ in subjects who were suffering from brain injury and should not be used to monitor PCO_2 in these subjects.

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Figure Legend

Figure 1. Bland-Altman agreement between arterial PCO_2 and $PtcCO_2$ (A) and between arterial PCO_2 and $P_{ET}CO_2$ (B).

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Table 1. Patient characteristics.

Patients	**n = 25**
Age, years	46 [31–52]
Sex, male	13 (52)
Nature of the brain injury	
Trauma	16 (64)
Subarachnoid hemorrhage	3 (12)
Other*	6 (24)
SAPS II	43 [36–52]
SOFA score	8 [7–9]
Glasgow Coma Scale upon admission	6 [4–7]

The data are presented as the median [interquartile 25–75] and number (%). SAPS II: Simplified Acute Physiology Score II. SOFA: Sequential Organ Failure Assessment. *Other: stroke (n = 2), intracranial hemorrhage (n = 2), brain abscess (n = 2), and tumor (n = 1).

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Table 2. Body core temperature, ventilation parameters, hemodynamic parameters, arterial pH and hemoglobin level for each comparison (n=85).

Body core temperature, °C	37.8±0,8 [36.7 – 40.7]*
Ventilation parameters	
- Tidal volume, ml/kg	7.8±1.2
- Respiratory rate,	13±3
- PEEP, n(%)	59 (69%)
- Level of PEEP, cm H_2O	3±2
Mottling, n(%)	40 (47%)
Capillary refilling time, sec†	2 (1-3)
Arterial pH	7.41±0.06
Hemoglobin, g/dl	9.5±1.4

Values are expressed as mean±SD unless overwhise. *[minimum – maximum]. † Missing data, n=2. PEEP: Positive end expiratory pressure.

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Table 3. Arterial, transcutaneous and end-tidal carbon dioxide pressure values, linear regression and the Bland-Altman analysis results ($PtcCO_2$ or $P_{ET}CO_2$ vs. $PaCO_2$) and number of outliers.

	PCO_2 values (mmHg)	**Linear regression**		**Bland-Altman analysis**			**Outliers n (%)**
		Coefficient correlation	**p**	**Bias* (mmHg)**	**Precision (mmHg)**	**Limits of agreement (mmHg)**	
$PaCO_2$	37.0 ± 6.2 (23.0; 53.0)			-	-		
$PtcCO_2$	37.7 ± 7.2 (24.1; 61.3)	0.60	<0.001	-0.75	6.23	-12.97; 11.47	34 (40%)
$P_{ET}CO_2$	36.3 ± 6.7 (22.0; 52.0)	0.58	<0.001	0.68	5.82	-10.72; 12.08	34 (40%)

The data are presented as the mean ± SD (min; max) and number (%). PCO_2: carbon dioxide pressure. $PaCO_2$: arterial PCO_2. $PtcCO_2$: transcutaneous PCO_2. $P_{ET}CO_2$: end-tidal PCO_2.* Bias was the difference between $PaCO_2$ and $PtcCO_2$ or $P_{ET}CO_2$.

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Table 4. Body temperature, hemodynamic parameters, arterial pH and haemoglobin level in $PaCO_2$ - $PtcCO_2$ non outliers *vs* outliers.

	Non outliers n=51*	Outliers n=34*	p
Body temperature, °C	37.7±0.6	37.9±0.9	0,63
Hemodynamic parameters:			
Capillary refilling time†, sec	2 (1-3)	2 (1-3)	0,35
Mottling, n(%)	23 (45%)	16 (47%)	1.0
Norepinephrine, µg/kg.min^{-1}	0.46±0.65	0.24±0.3	0,39
Arterial pH	7.41±0.06	7.40±0.05	0,48
Hemoglobin, g/dl	9.7±1.4	9.3±1.4	0,20

Values are expressed as mean±SD.*Number of pair data. † Data are expressed as median [interquartiles range].

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Table 5. Body temperature, ventilation and hemodynamic parameters, and arterial PH in $PaCO_2$-$P_{ET}CO_2$ non outliers *vs* outliers.

	Non outliers n=51*	Outliers n=34*	p
Body temperature, °C	37.9±0.9	37.7±0.6	0,48
Ventilation parameters:			
- Respiratory rate, per min	13±2	14±4	0.53
- Tidal volume, ml/kg	7.9±1.3	7.6±1.0	0,48
- PEEP†, cm H_2O	3±2	4±2	0,33
Hemodynamic parameters:			
- Capillary refilling time††, sec	2 [1-3]	2 [1-3]	0.31
- Mottling, n(%)	21 (41%)	18 (53%)	0.40
- Norepinephrine, µg/kg.min^{-1}	0.39±0.58	0.35±0.51	0,96
Arterial pH	7.41±0.06	7.4±0.05	0,41

Values are expressed as mean±SD unless otherwhise.*Number of pair data. †Positive end expiratory pressure. †† Data are expressed as median [interquartiles range].

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Figure 1