Reliability of cerebral oximeter in non-invasive diagnosis and follow-up of hypercapnia

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In this study, aimed to evaluate the sensitivity and specificity of cerebral oximetry and EtCO2 values in non-invasive diagnosis and monitoring of hypercapnia. This study enrolled pediatric patients admitted to and mechanically ventilated at the Pediatric Intensive Care Unit of Gaziantep University Faculty of Medicine Hospital between January 2014 and January 2015. Patients' age, gender, diagnosis, ventilatory parameters, a measured of the mean end-tidal carbon dioxide value stream method, and the simultaneously monitored arterial blood gas $PaCO_2$ level and near infrared spectroscopy device (NIRS) measurements were recorded. The mean age of patients was 61 months (min 4-max 193), and there were 8 (53.4%) female and 7 (46.6%) male subjects. A significant correlation was found between PCO_2 and NIRS, PCO_2 and $EtCO_2$ ($r = 0.571$, $p < 0.001$). There was a significant positive correlation between $EtCO_2$ and NIRS ($r = 0.479$, $p < 0.001$). NIRS levels were significantly higher ($p < 0.001$) in the group with $pCO_2 > 45$; $EtCO_2 > 40$ and pH <7.35, compared to the group with $PCO_2 < 45$ $EtCO_2 < 40$ and $ph \geq 7.35$. The best cut-off point for NIRS to distinguish the groups with $PCO_2 > 45$ with $PCO_2 < 45$ was 80.5, with a sensitivity of 65.3%, specificity of 84.3%, and positive and negative predictive values of 81.9% and 69.1%, respectively. The best cut-off point for NIRS to distinguish the groups with $EtCO_2 > 40$ and $EtCO_2 < 40$ was 81, with a sensitivity of 62.2%, specificity 77.9%, and positive and negative predictive values of 61.2% and 72.3%, respectively. As for pH <7.35 and $PaCO_2 > 45$, while sensitivity of $EtCO_2$ (at a cut-off point of 40) was 64.9%; the sensitivity of NIRS (at a cut-off point of 80.5) was 28.1%, with $EtCO_2$ being significantly more sensitive than NIRS ($p < 0.001$). The results of the present study suggest that NIRS values of above 80 should alert clinicians for hypercapnia associated with increased cerebral blood flow.

Key words: end-tidal carbon dioxide, hypercapnia, near infrared spectroscope.

Hypercarbia results in cerebral vasodilation and increases the cerebral blood flow, a phenomenon termed as the CO_2 cerebrovascular reactivity[1]. Intracranial pressure increases in hypercarbia, which can cause a decrease in cerebral perfusion pressure in patients with significant neurological damage[2]. Although there are individual differences, every 1 mmHg increase in $PaCO_2$ causes an increase in cerebral blood flow of 3% to 5%. Hypercarbia is also known to lower seizure threshold[3,4]. By virtue of its systemic vasodilatory action, hypercapnia may cause hypotension especially in hypovolemic patients, and it may worsen tissue injury in injured lungs by imparing wound healing and, augmenting inflammation[5]. Animal experiments have shown that hypercapnia stimulates the secretion of gastric hydrogen ions and increases the incidence of gastrointestinal bleeding[6]. Tateyama et al.[7] showed in dogs that hypercapnia formed by adding 10% carbon dioxide to the breathing gas after normocapniac ventilation, increased cardiac lactate/pyruvate ratio coronary blood flow, and myocardial tissue oxygenation while it impaired myocardial aerobic metabolism.

Maintaining normocapnia and normoxemia is the main goal unless indicated otherwise in patients undergoing mechanical ventilation; with the early diagnosis of hypercapnia and taking the necessary measures being a great importance in critically ill patients.

Monitoring of end-tidal carbon dioxide ($EtCO_2$) is an important component of monitorization of critically ill patients in anaesthesiology and pediatric intensive care units as well as in the emergency department. Normal $EtCO_2$ is 38 ± 4 mmHg. This level is closely correlated with $PaCO_2$ level and is lower than that by about 3.5 mmHg[8].

The near infrared spectroscopy device (NIRS) that has been used in clinics in recent years can show instant responses in cerebral oxygenation. NIRS is an optical method monitoring primarily regional oxygenation of the brain. The method is based on the Beer-Lambert law for cerebral monitoring from the forehead. An oximeter probe measures concentrations of different wavelengths of light waves in the neck in the frontal cortex [650-850 nm, oxyhemoglobin (810 nm) and deoxyhemoglobin (730 nm)] through a cross-sectional tissue. INVOS used as one of the first examples of NIRS calculates regional saturation using two wavelengths in brain or the relevant tissue and measures both oxyhemoglobin and deoxyhemoglobin concentrations, giving a value defined as the regional oxygen saturation index (rSO_2 index = oksiHb/deoksiHb+oksiHb). rSO_2 can be calculated without being connected to the pulse and can rapidly change in response to cerebral ischemia. From this standpoint, studies with healthy young adults and children have shown that the average cerebral rSO_2 is 70%, with reductions down to below 40-50% or 20% from baseline being reported as an indicator of hypoxic-ischemic neuronal damage[9-11].

In the present study, we aimed to evaluate the sensitivity and specificity of cerebral oximetry and $EtCO_2$ values in non-invasive diagnosis and monitoring of hypercapnia.

Material and Methods

After the ethics committee approval, this study enrolled children aged between 1 month and 17 years who were admitted to a 7-bed pediatric intensive care unit (PICU) of a tertiary university hospital and received mechanical ventilation between January 2014 and January 2015. The patients were not intentionally subjected to hypoventilation, and the NIRS levels of patients with elevated EtCO2 levels and hypercarbia in arterial blood gas analysis were recorded. Those with a preliminary or definitive diagnosis of ICP (intracranial pressure increase syndrome), those with increasing ICP levels during monitoring, and those that had congenital heart disease or metabolic acidosis were excluded from the study. Patients' age, sex, comorbidities, mechanical ventilation mode, and mortality scoring were recorded.

$EtCO_2$ values were measured continuously with the Nihon Kohden BSM-4114 intensive care monitor using an invasive infrared spectroscopy and mean-stream methods. rSO_2 values were measured with a somatic-cerebral oximeter (INVOS 5100C, Somanetics). The NIRS probe was applied to the forehead, just above the eyebrows. To assess acid-base and to determine respiratory balance, partial pressures of arterial blood oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were measured with arterial blood gas analysis. Patients with metabolic acidosis were excluded from the study protocol.

Statistical analysis

Data analysis was done with SPSS for Windows 11.5 software package. The distribution of

Table I. Diagnosis of Patients

Diagnosis	The number of cases (n)	Percentage (%)
Kidney diseases	6	40
Respiratory disorders	4	26.6
Nervous system diseases	3	20
Hemato-oncological diseases	1	6.7
Scorpion stings	1	6.7
Total	15	100

Table II. NIRS measurements according to $PaCO_2$, $EtCO_2$ and pH

Variables	n	The mean (min-max)	P value+
$PaCO_2$			
>45	173	83 (47-99)	<0.001
<45	159	72 (46-95)	
$EtCO_2$			
>40	119	83 (47-98)	<0.001
<40	213	74 (46-99)	

+ Mann Whitney U test $PaCO_2$: Partial pressure of arterial carbon dioxide $EtCO_2$: End-tidal carbondioxide

quantitative variables was investigated using Kolmogorov-Smirnov or Shapiro-Wilk test. Descriptive statistics included mean ± standard deviation for continuous variables and number and percentage (%) of for nominal variables.

The significance of the difference of the median values of pairs of groups was analysed with the Mann-Whitney U test. Spearman's correlation test was used to test the significance of the relationship between continuous variables. Nominal variables were evaluated with Pearson's Chi-square or McNemar test.

Whether NIRS value was a significant marker that differentiated groups with PCO_2> 45 and PCO_2<45 and $EtCO_2$> 40 with $EtCO_2$<40 was explored using 95% confidence intervals and area under ROC curve. When a significant area under the curve was obtained, the maximum possible sum of the sensitivity and specificity levels was considered the best cut-off point. Then, the sensitivity, specificity, positive and negative predictive values of the best NIRS cut-off points were calculated. A p-value of less than 0.05 was considered statistically significant.

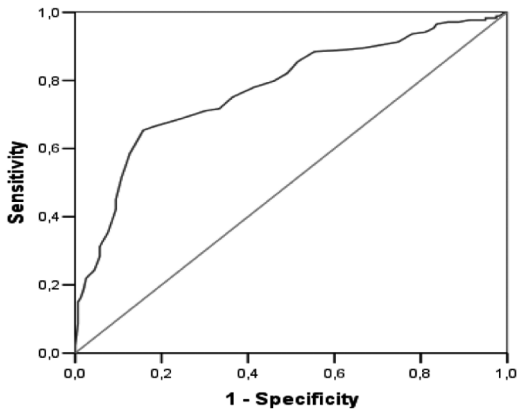

Fig. 1. The ROC curve regarding NIRS measurements to differentiate groups with pCO_2 > 45 and pCO_2<45

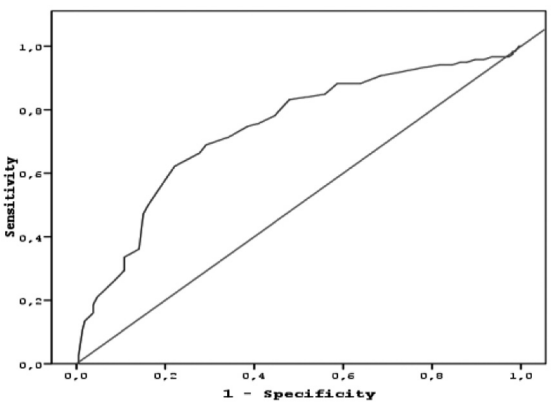

Fig. 2. The ROC curve regarding NIRS measurements to differentiate groups with $EtCO_2$> 40 and $EtCO_2$<40

Results

The mean age of the patients was 61 (4- 193) months. There were 8 (53.4%) female subjects and 7 (46.6%) male subjects. All patients were provided with respiratory support by mechanical ventilation in SIMV-PS (pressure support-synchronised intermittent mandatory ventilation) mode. A mean PIP of 22 cm H_2O (min 12-max 39), a mean PEEP of 7 cm (min 1-max 15), a mean FiO_2 of 0.6 (min 0.3- max 1), and a mean frequency of 25/min (min 14-max 60) were applied. Nephrological disorders constituted 40% of the patients' diseases, followed by respiratory system diseases and neurological diseases. Diagnoses of the patients were presented on Table I.

A significant correlation was found between PCO_2 and NIRS, and between PCO_2 and $EtCO_2$ ($r = 0.571$, $p < 0.001$). A significant positive correlation was also detected between $EtCO_2$ and NIRS ($r = 0.479$, $p < 0.001$).

NIRS levels were significantly higher in the

Table III. The Distribution of $PaCO_2$ and $EtCO_2$ Measurements

	$PaCO_2$<45	$PaCO_2$> 45	Total
$EtCO_2$<40	132 (39.8%)	81 (35.2%)	213 (81.6%)
$EtCO_2$> 40	24(7.2%)	95 (28.6%)	119 (18.4%)
Total	156 (47.0%)	176 (53.0%)	332 (100%)

group with PCO_2>45, $EtCO_2$>40 and pH <7.35 compared to the group that had PCO_2<45, $EtCO_2$<40, and pH ≥7.35 (p <0.001) (Table II).

The mean NIRS value was 79 (min 46-max 99) when pCO_2 was >35 and 68 (min 55, max 86) when pCO_2 was <35 (p<0.001).

The area under the ROC curve for NIRS was able to reliably distinguish the groups with $PaCO_2$> 45 and PaCO2<40 (area under the curve: 0.775, 95% confidence interval: 0.724-0.825, p <0.001) (Fig.1). To distinguish the groups with pCO_2> 45 with PCO_2<45, 80.5 was the best cut-off point for NIRS, having a sensitivity of 65.3%, specificity of 84.3%, and positive and negative predictive values of 81.9% and 69.1%, respectively.

The area under the ROC curve for NIRS could reliably distinguish the groups with $EtCO_2$> 40 and $EtCO_2$<40 (area under the curve: 0.737, 95% confidence interval: from 0.687 to 0.784, p <0.001) (Fig. 2). The best cut-off point for measurements to distinguish between the groups with $EtCO_2$> 40 and $EtCO_2$<40 was 81, having a sensitivity of 62.2%, specificity of 77.9%, and positive and negative predictive values of 61.2% and 72.3%, respectively.

While the proportion of patients with $PaCO_2$> 45 was 53%, those with $EtCO_2$> 40 was 28.6%, with the ratio of patients with pCO_2>45 being significantly higher than the proportion of those with $EtCO_2$>40 (P <0.001). There was a statistically significant, albeit a very low level concordance between the distribution of $PaCO_2$ and $EtCO_2$ levels (Kappa 0.378 and p <0.001). The distributions of $PaCO_2$ and $EtCO_2$ measurements were shown on Table III.

In patients with $PaCO_2$> 45; the median $EtCO_2$ level was 40 (max 70, min-21), while the median $EtCO_2$ level was 35 in patients with $PaCO_2$<45 (min 15, max 50), with the median $EtCO_2$ level being significantly higher in those with $PaCO_2$>45 (p <0.001).

As for pH <7.35 and $PaCO_2$> 45, while the sensitivity of $EtCO_2$ (at a cut-off point of 40) was 64.9%, NIRS had a sensitivity (at a cut-off point of 80.5) of 28.1%, with $EtCO_2$ being significantly more sensitive than NIRS (p <0.001). NIRS measurement results in relation to to $PaCO_2$ and pH levels were presented on Table IV.

Discussion

The difference between $EtCO_2$ and $PaCO_2$ is a result of alveolar dead space, and its normal value is between 3 and 5 mmHg. Decrease in lung perfusion (air embolism, position changes, decreased cardiac output, reduced blood pressure), increases alveolar dead space, diluting exhaled carbon dioxide, and reducing $EtCO_2$. $EtCO_2$ increases when carbon dioxide production is increased such as sepsis, malignant hyperthermia, and in cases where its elimination is limited by reduced alveolar ventilation. The return of spontaneous circulation during cardiopulmonary resuscitation quickly raises $EtCO_2$[12, 13].

In a study of 32 mechanically ventilated newborns dated 2008, there was a good correlation between mainstream $EtCO_2$ and $PaCO_2$. Whereas this correlation was impared in

Table IV. NIRS Measurements According to $PaCO_2$ and pH Level

	$PaCO_2$<45	$PaCO_2$> 45	p-value †
pH<7.35	76 (62-88)	85 (47-96)	0.007
ph≥7.35	71 (46-95)	81 (61-99)	<0.001
p-value‡	0.117	<0.001	

Comparisons made between the pCO2 level when † pH levels are kept constant
Comparisons made between the pH levels when ‡ $PaCO_2$ levels are kept constant (Mann-Whitney U test)

those with pulmonary disease, it was restorated by the application of surfactant[14]. Several other studies conducted at neonatal intensive care units also supported this result[15, 16].

In a study conducted by McDonald et al.[17] in mechanically ventilated pediatric patients, the difference between $EtCO_2$ and $PaCO_2$ was ≤ 5 mm Hg in 54% of patients and ≤ 10 mmHg in 80%. Furthermore, the gap widened as the duration of mechanical ventilation was increased.

Raz et al.[18] reported that $EtCO_2$ accurately reflected $PaCO_2$ and there was a statistically significant correlation between mean $EtCO_2$ and $PaCO_2$ (in SIMV mode r:0.893, p <0.0001; in CPAP mode r: 0841 , p <0.0001; in T-Tubes r: 0.923, p <0.0001).

In a study comprising children on mechanical ventilation conducted by Mehta et al.[19] , $EtC0_2$ showed an excellent correlation with $PaCO_2$ (n = 150, r: 0.914), although it was no longer the case when P / F <200. Similarly, Bath et al.[20] reported that this correlation was impared in case of lung pathologies such as hyaline membrane disease or meconium aspiration.

De Waal et al.[21] investigated the effects of low-pressure carbon dioxide pneumoperitoneum on regional cerebral oxygen saturation and cerebral blood flow. During insufflation, an increase was reported in $EtCO_2$ and $PaCO_2$ levels; they additionally noted that their NIRS value increased by 15.7 ± 8.8%. This increase did not result from a reduction of cerebral oxygen metabolism during carbon dioxide insufflation, but an increase in cerebral blood flow due to rising carbon dioxide levels.

Hypercarbia results in cerebral vasodilation and increases the cerebral blood flow, a phenomenon which is defined CO_2 cerebrovascular reactivity. Evidence from positron emission tomography studies indicates that the cerebral blood volume changes seen during hypercapnia and hypocapnia are primarily caused by arterial volume changes[22]. Hypercapnia studies with NIRS measurement have been carried out in healty volunteers to characterize brain tissue oxygenation and blood flow changes[23].

In 2012 Quarti et al.[24] reported a study in 90 pediatric patients with congenital heart disease requiring external carbon dioxide support during cardiopulmonary bypass application to correct carbon dioxide hypocarbia. The authors assessed NIRS and $PaCO_2$ in 3 phases, namely before, during, and after the infusion. After the addition of carbon dioxide, NIRS rose to 63.4 from 52.9; and it decreased to 55.8 by stopping the application. Meanwhile, $PaCO_2$ increased to 40.6 mmHg from 31.3 mmHg and decreased to 34.4 mmHg by stopping application. We also found significant correlations between NIRS and $PaCO_2$, $PaCO_2$ and $EtCO_2$($r = 0.571$, $p < 0.001$). A significant and positive correlation existed between NIRS and $EtCO_2$ ($r = 0.479$, $p < 0.001$).

Hypocapnia induces cerebral vasoconstriction and decreases CBF. We also found lower NIRS level in hypocarbia compared to hypercarbia ($p<0.001$).

The limitations of our study included the disproportional number of samples relative to the number of patients, and the lack of the consideration given to the effects of changes in the oxygenation index while assessing the correlation between $PaCO_2$, $EtCO_2$ and NIRS. Another limitation was a wide age distribution (4-193 months) of our patients. As is known, physiological dead space may show a mild increases with aging, which may have partly affected our results.

The results of the present study suggest that NIRS values of above 80 should alert clinicians for hypercapnia associated with increased cerebral blood flow.

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