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Research Article

Correlation of Partial Pressure of Arterial Carbon Dioxide and End-Tidal Carbon Dioxide in Intubated Premature Infants

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Keywords

- Transcutaneous apnometry; Mechanical ventilation; Blood gas analyses; Hypercapnia; Premature infants; Respiratory insufficiency

Abstract

Background: Capnometry can reduce arterial blood sampling and allow fast and noninvasive assessments using end-tidal of carbon dioxide (EtCO2).

Objectives: The aims of this study were to evaluate the correlation of partial pressure of arterial CO2 (PaCO2)levels and EtCO2, and to verify whether capnometry would be useful for noninvasive monitoring of CO2 levels in intubated premature infants with and without diffuse parenchymal lung diseases (DPLD).

Methods: This study was conducted in premature infants admitted to the Neonatal Intensive Care Unit (NICU) from August 2014 to November 2016. EtCO2 levels were compared with PaCO2 levels, in intubated premature infants with and without DPLD. Both parameters were obtained daily until tracheal extubation. The correlation coefficient and degree of bias between them was determined.

Results: Overall, 221 measurements of EtCO2 and PaCO2 levels were obtained from 51 neonates. Twenty-eight were obtained from neonates without DPLD (12.7%) and 193 from those with DPLD (87.3%). The most frequent cause of DPLD was respiratory distress syndrome (RDS) in 86.5%. There was a positive correlation between PaCO2 and EtCO2 levels ($n = 221$; $r = 0.853$; $p < 0.0001$) in the overall cohort. Both groups showed a good correlation between both parameters, without DPLD (mean bias = 0.21, SD, 7.05; 95% CI -13.61 – 14.05), and with DPLD (mean bias = 0.37, SD, 7.66; 95% CI -14.65 – 15.39).

Conclusions: Capnometry is a useful noninvasive technique to monitor intubated premature infants. EtCO2 measurement may be a valid adjunctive parameter when titrating ventilator support.

INTRODUCTION

In the United States, approximately one out of nine live births occurs prematurely [1]. Preterm birth is associated with serious respiratory illnesses and often requires ventilatory support [1-3]. Prematurity is the most important cause of death in the first month of life and contributes to increased mortality in the first year [3]. In Brazil, premature births occurred in 9.8% of the 2.913.160 births registered in 2011 [4].

Premature infants on mechanical ventilation require special attention to ventilation parameters and oxygen levels. Arterial blood gas analysis is the gold-standard test to verify both parameters. However, it is expensive, requires multiple blood sampling, and may cause distress, pain, infection, and arterial vasospasm [5,6]. Continuous noninvasive monitoring of carbon dioxide (CO_2) levels in the neonatal intensive care unit (NICU) may protect infants from the consequences of hypocapnia and hypercapnia [7]. Capnometry may bean alternate procedure that can prevent repeated arterial blood sampling and allow a fast and noninvasive estimate of $PaCO_2$ [5,8].

Premature infants with impending respiratory failure due to lung immaturity or poor respiratory efforts generally present with a high respiratory rate and low tidal volume in mechanical ventilation (MV), leading to considerable ventilation-perfusion imbalance, which can potentially influence the correlation of the $PaCO_2$ and the $EtCO_2$ [9]. Accurate, noninvasive measurements of CO_2 production areparticularly troublesome in ventilated premature infants due to technical limitations [10].

Capnometry has the advantage of responding fast to changes in blood CO_2 levels, and provides useful information about the efficacy of alveolar ventilation [11]. A large sample cuvette lumen is used in capnometry in order to minimize the work of breathing. Additionally, pulmonary secretions generally do not interfere with the CO_2 analysis, although the airway cuvette is relatively bulky and can add to dead space [12]. In addition, accurate and noninvasive assessment of $EtCO_2$ in premature infants has some disadvantages and remains controversial because of technical challenges. Disadvantages of capnometry include a delay between sampling and measurement of $EtCO_2$, falsely low $EtCO_2$ with high aspirating flow rates, and possible contamination of the analyzer with mucus or water [6].

Another well-documented technique used in newborn infants for evaluated the CO_2 levels is non-invasive transcutaneous (Tc) blood gas monitoring. The non-invasive Tc have shown agreement with the arterial measurements for $PaCO_2$ in others studies[13,14]. This technique uses electrodes in contact with the skin surface and it is based on obtaining the balance of carbonic acid combined with the temperature that facilitates blood flow and the stabilization of the partial pressure of carbon dioxide transcutaneously ($PtcCO_2$) [15].

This study aimed to correlate $PaCO_2$ levels measured in arterial blood and $EtCO_2$ by means of a capnometer in intubated premature infants presenting with and without DPLD, and to verify whether capnometry would be a useful method for noninvasive monitoring of effective ventilation in these infants.

MATERIALS AND METHODS

This experimental study was conducted in premature infants admitted to the NICU at the University Hospital from August 2014 to November 2016. The study was approved by the Ethics Committee of Federal University of Parana, Curitiba, Brazil. All parents signed an informed consent form and authorization to include the data of their infants in the study. This is prospective study and the design is of the type diagnosis test study.

All infants were intubated and received ventilation therapy with pressure limited, time-cycled ventilators in either an assist-control mode or a synchronous, intermittent mandatory ventilation mode, Puritan Bennett™ 840®, Carlsbad, California. Premature infants with substantial hemodynamic instability, airway congenital malformation, or irregular breathing frequency were excluded.

$EtCO_2$ / $PaCO_2$ comparisons were obtained from all premature infants, who were separated into groups with and without DPLD. Table (1) presents the characteristics of the infants and Table (2), the clinical conditions of the infants on mechanical ventilation included in the study.

Heparinized arterial blood samples from radial artery were analyzed with the equipment GEM Premier 3000® (Instrumentation Laboratory, Lexington, MA), which was calibrated daily. Immediately before blood sampling, the $EtCO_2$ value shown on the display of the portable capnometer was recorded simultaneously to the $PaCO_2$. The interval between the measurements by capnometry and arterial blood gas did not exceed 15 minutes.

The $EtCO_2$ in exhaled air was measured by a mainstream portable capnometer (EMMA Emergency Capnometer, Phasein AB, Danderyd, Sweden) placed between the endotracheal tube and the circuit of mechanical ventilator. The capnometer has an internal calibration capability and this calibration was performed according to the manufacturer's recommendations. Values of peak CO_2 concentration were displayed breath-to-breath. Time for the signal to change from a specified low value to a specified high value was ≤ 60 ms. The mean exhaled CO_2 of three consecutive measurements was used in the analysis.

Premature infants were monitored daily, starting on the first day of mechanical ventilation until the removal of the endotracheal tube. The measurements were recorded along with information on infants' clinical diagnoses, vital parameters, and mechanical ventilation parameters. The data collection did not interfere with the routine of the ICU. Arterial blood gas analysis was performed daily per unit standard practice, but capnometry was performed only for the study purpose.

Statistical analysis

Descriptive data were analyzed with Statistica®, version 10, Pearson's correlation and Bland-Altman technique was performed with MedCalc®, version 7.4.4.1. Student's paired *t* test was used to analyze differences between $EtCO_2$ and $PaCO_2$, and the Bland-Altman technique was applied to assess agreement and bias between both measurements. The Mann-Whitney test compared the independent samples of the groups. The Shapiro-Wilk test was used to analyze the normality in the groups. Data are presented as mean (± standard deviation) or median (inter quartile range). A p value< 0.05 was considered statistically significant.

RESULTS

The study population encompassed 51 premature infants, 26 (51%) boys. The mean gestational age of the entire cohort was 28.08 + 3.19 weeks, and the median birth weight was 880 g (700

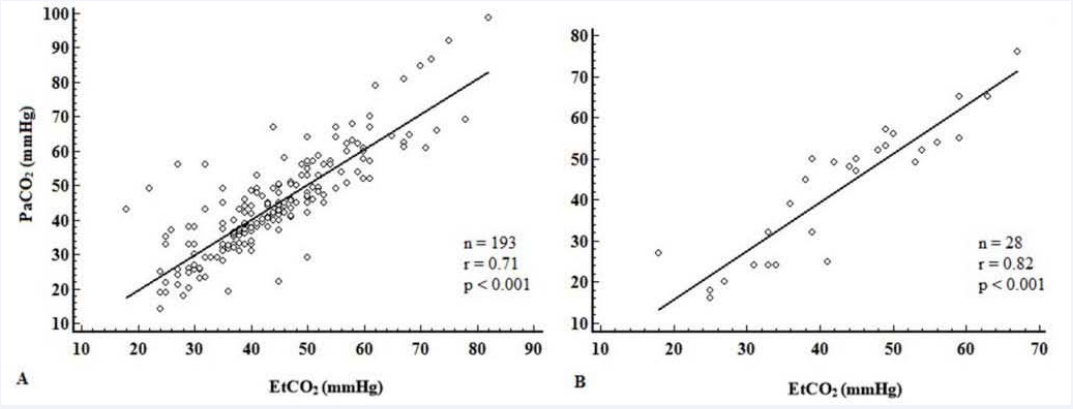

Figure 1 Scattergram showing the regression line between end-tidal CO2 and partial pressure of arterial CO2 levels. The figure (1A) shows the infants with diffuse parenchymal lung diseases (DPLD) and the figure (1B) the infants without DPLD.

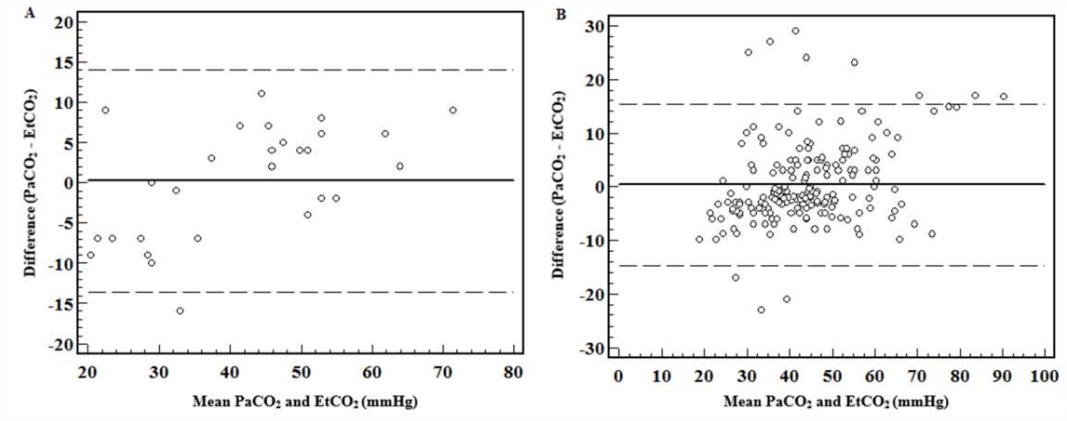

Figure 2 Bland-Altman plot for mean values of partial pressure of arterial CO2 and end-tidal CO2 in all infants, mean bias = 0.352 (standard deviation 7.57; 95% confidence interval [CI], -14.5 to 15.2). The figure 2A show the infants without diffuse parenchymal lung diseases (DPLD), mean bias = 0.21 (SD, 7.05; 95% CI, -13.61 to 14.05). The figure 2B the infants with DPLD, mean bias = 0.37 (SD, 7.66; 95% CI, -14.65 to 15.39).

– 1125 g). The Apgar scores were stratified, separated in groups and the score obtained at 5 minutes was used in the analysis. The premature infants with Apgar score less than three were classified at zero, between three to six at one and greater than six at two. For the temperature was used the body temperature and the incubator temperature data. The incubator was used for maintain the baby heated (Table 1).

All patients were received mechanical ventilation, but not all of them had pulmonary disease. Some premature infants were on mechanical ventilation due to hemodynamic instability (arterial hypotension / shock), perinatal asphyxia, fatigue, apnea (secondary to immaturity of the respiratory center), respiratory muscle failure or heart failure, but they did not present respiratory failure due to DPLD. Infants were grouped according to the presence or absence of DPLD, yielding 28 analyses in infants without DPLD (12.7%) and 193 analyses in infants with DPLD (87.3%). The most prevalent DPLD was RDS in 44 (86.5%) premature infants. The clinical conditions of the 7 (13.5%) infants without DPLD were perinatal asphyxia 2 (4%), heart failure 1 (1.9%), apnea 1 (1.9%), sepsis 1 (1.9%), hemodynamic instability 1 (1.9%), and fatigue 1 (1.9%), (Table 2).

Values of $PaCO_2$ and $EtCO_2$from all 51 patients were similar (p=0.82) and there was no significant differences in $PaCO_2$ and in $EtCO_2$ between groups with (p=0.81) and without DPLD (p=0.98).

Daily arterial blood gas results yielded 221 $PaCO_2$ / $EtCO_2$ from 51 patients. Overall, mean $PaCO_2$ was 44 + 14.4 mmHg and mean $EtCO_2$ was 43.7 + 11.8 mmHg. For the group without DPLD, the mean $PaCO_2$ was 43 + 16.06 mmHg, median 48.5 (26 – 53.5) and mean $EtCO_2$ was 42.9 + 12.3 mmHg, median 43 (33.5 – 51.5), with 28 samples. In group with DPLD, the mean $PaCO_2$ was 44.1 + 14.25 mmHg, median 43 (35 – 52) and mean $EtCO_2$ was 43.8 + 11.8 mmHg, median 43 (37 – 50) with 193 samples (Figure 1).

Significant positive correlation was noted between $PaCO_2$ and $EtCO_2$(n = 221; r = 0.853; p < 0.0001) (Figure 1), and there was a longer strong concordance [16] with mean difference of 0.352 ± 7.57 with 95% confidence interval of 14.5 – 15.2 (Figure 2).

We also observed a significant correlation between values of $PaCO_2$ and $EtCO_2$ in patients without DPLD, (mean bias = 0.21, SD, 7.05; 95% CI -13.61 – 14.05), and with DPLD (mean bias = 0.37, SD, 7.66; 95% CI -14.65 – 15.39), variations within acceptance limits of approximately 2 mmHg (Figure 2).

DISCUSSION

Monitoring of both oxygenation and CO_2 is essential in neonates submitted to mechanical ventilation. $EtCO_2$ is an

Table 1: Characteristics of the infants included in the study (n = 51).

Characteristics	No. (%)
Gender Males Females	 26 (51) 25 (49)
Gestational age (weeks) Mean ± SD	 28.08 ± 3.19
Birth weight (g) Median(lower quartile – upper quartile)	 880 (700 – 1125)
Apgar (5 minutes) <3 = 0 3-6 = 1 >6 = 2	50 (100) 6 (12) 15 (30) 29 (58)
Temperature (°C) Incubator Body	 34.5 ± 1.61 36.45 ± 1.12
SD: standard deviation.	

Table 2: Clinical conditions of patient on mechanical ventilation (n = 51).

Condition	No. (%)	Days in MV (Mean)
RDS	44 (86.5)	17
Perinatal Asphyxia	2 (4)	1
Apnea	1 (1.9)	43
Heart Failure	1 (1.9)	2
Sepsis	1 (1.9)	6
Hemodynamic Instability	1 (1.9)	2
Fatigue	1 (1.9)	4
Abbreviations: RDS: Respiratory Distress Syndrome; MV: Mechanical Ventilation.		

alternate noninvasive method to monitor CO_2 values, although this measurement in infants is not well accepted, particularly in preterm infants [5,6,17]. $EtCO_2$ values can be influenced by factors such as arterial hypotension or hypertension, temperature variations, changes in respiratory rate or ventilation-perfusion ratio [18]. In our study, DPLD did not influence the results of $EtCO_2$ as an estimate of $PaCO_2$. The correlations between $EtCO_2$ and $PaCO_2$ were similar in infants with and without DPLD.

Blood gas monitoring is critical in premature infants with respiratory insufficiency and is a priority in NICU [15]. Arterial blood gas analysis is the gold-standard method to assess the adequacy of ventilation [19]. In our study, concordant values were observed in both groups, the mean difference between $EtCO_2$ and $PaCO_2$ in infants with DPLD was small, which can be interpreted as a successful result. Thus, $EtCO_2$ monitoring can be recommended as an alternative and may be helpful in adjusting mechanical ventilation settings [20].

$PaCO_2$ and $EtCO_2$ were positively correlated in all premature infants and corroborating to different authors [5]. Wu et al. (2003), [6], showed a good correlation in premature infants with RDS. Contrariwise Watkins and Weindling in 1987 [9], found a poor correlation ($r = 0.387$, $p<0.01$, $n = 62$), between both parameters in sick preterm neonates attributed to increased physiologic dead space, different ventilation-perfusion and the severity of pulmonary disease. $EtCO_2$ monitoring has not had much support in most premature infants with DPLD, considering that these infants have higher respiratory rate, lower tidal volume, and mismatched ventilation-perfusion [6].

The most prevalent DPLD in our cohort was RDS, which can result primarily from a pulmonary surfactant deficiency [21]. This complication is common in premature infants and is associated with pulmonary hypertension, as well as abnormalities of postnatal alveolarization and neovascularization [22].

Our study attempted to show the possibility of a less invasive technique to monitor CO_2 levels, considering that premature infants require careful monitoring through frequent blood sampling, which sometimes conflicts with the nonaggressive, gentle approach of infant care in the NICU [15]. Thus, there is a need for monitoring through noninvasive techniques for the occurrence of hypercapnia in infants, minimizing blood sampling to reduce the risk of anemia, and protecting these children from discomfort and pain [23].

Our study had some limitations. One of them was the size of the sample that was small with only 51 premature infants enrolled and analyzed in a period of 2 years. The study included only intubated premature infants without neurological impairment and without hemodynamic instabilities, which also contributed to the difficulty in enrolling more infants. Further, with increasing use of non-invasive ventilation there are less infants remain intubated. Additionally hospital employees strike and ICU reform may have affected the data collection for this study.

CONCLUSIONS

The results of our study suggest that $EtCO_2$ is a valid adjunctive parameter when titrating ventilator support and may be useful for real-time analyses of abnormal $PaCO_2$ levels both premature infants with and without pulmonary disease. Measuring both $EtCO_2$ in combination with other clinical parameters allows detection of lung disease progression, appropriateness strategies of treatment and check the ventilation-perfusion inefficiency.

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