Concordance between side-stream end-tidal carbon dioxide and arterial carbon dioxide partial pressure in respiratory service setting

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Objective To explore the correlation and concordance between end-tidal carbon dioxide and arterial carbon dioxide partial pressure, and confirm the experience of the general consensus among service environments.

Design A prospective cross-sectional analysis.

Setting Two respiratory service units in Hong Kong.

Participants Two hundred respiratory patients were recruited, in whom 219 sets of observations were recorded. Patients deemed to require arterial blood gas determination also had their end-tidal carbon dioxide partial pressure measured at that time, using two LifeSense LS1-9R Capnometers.

Main outcome measures The agreement of end-tidal carbon dioxide partial pressure and arterial carbon dioxide partial pressure was studied by correlation coefficients, mean and standard deviation of their difference, and the Bland-Altman plot.

Results Overall, the correlation was low and insignificant (r=0.1185, P=0.0801). The mean of the difference was 7.2 torr (95% confidence interval, 5.5-8.9) and significant (P<0.001). The limits of agreement by Bland-Altman analysis were -18.1 to 32.5 torr, which were too large to be acceptable. In the sub-group on room air, the mean difference was reduced to 2.26 torr, the correlation between end-tidal carbon dioxide partial pressure and arterial carbon dioxide partial pressure was 0.2194 (P=0.0068), though statistically significant, the extent of correlation was still low.

Conclusion End-tidal carbon dioxide partial pressure did not show significant correlation or concordance with arterial carbon dioxide partial pressure, especially when supplemental oxygen was used. End-tidal carbon dioxide partial pressure currently cannot replace arterial blood gas measurement as a tool for monitoring arterial carbon dioxide partial pressure. Possible reasons for the discrepancy with previous studies include small sample size in previous studies, lack of research facilities in service settings, and publication bias against negative studies.

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Introduction

Non-invasive monitoring of arterial oxygen using percutaneous pulse oximetry is well established. Although some studies show a good correlation of transcutaneous end-tidal carbon dioxide partial pressure ($PetCO_2$) with arterial carbon dioxide partial pressure ($PaCO_2$), they were performed in research settings and involved restricted populations such as paediatric, accident and emergency, or intensive care patients.[1-5] The validity of non-invasive carbon dioxide (CO_2) monitoring has never been as well accepted as transcutaneous oxygen saturation (SaO_2). Nevertheless, the qualitative application of $PetCO_2$ on validating endo-tracheal tube placement, dislodgement of tubing, efficacy of cardiopulmonary resuscitation is well established.[5] There are also case reports of pulmonary embolism being detected based on $PetCO_2$.[6] This study attempted to correlate $PetCO_2$ with $PaCO_2$ in respiratory patients with near-normal lung function, and those with mild respiratory failure, with a view to assessing the reliability of end-tidal capnometry in service settings.

End-tidal capnometry uses non-dispersive infrared spectroscopy to measure the amount of CO_2 during each breath. The side-stream type samples the specimen from a side-stream port and operates on both invasive and non-invasive ventilators. The main-stream models analyse CO_2 concentration from sensors outside the main-stream ventilator tubing, and can only operate on invasive ventilators. They are less prone to interference from condensation, and the latest models are much lighter, and cause less traction on the tubing and hence on any tracheostomy tube. The exhaled CO_2 produces a waveform known as a capnogram. The CO_2 level at inhalation is zero. As exhalation commences, the exhaled CO_2 rises to a peak known as $PetCO_2$. With normal lung physiology, $PaCO_2$ and $PetCO_2$ are within 1 to 5 mm Hg of each other, known as $P(a-e)CO_2$ gradient.[5] When there is ventilation-perfusion mismatch, the gradient is higher, because not all the CO_2 in the blood passes is exhaled into the alveoli.[7] In this study, we tried to examine the relationship between two groups of patients—those having mild respiratory failure (probably with some degree of ventilation-perfusion mismatch), and patients who were near normal (hospitalised for an elective bronchoscopy). If $PetCO_2$ showed good concordance with $PaCO_2$, patients with respiratory failure, the group most in need of monitoring, could be spared painful blood sampling for arterial blood gas (ABG) determination.

Methods

Patients in the respiratory ward of two service units, who were deemed to require an ABG determination, were enrolled in the study. The population comprised patients with mild respiratory impairment receiving oxygen supplementation and those with near-normal lung function on room air. Another group consisted of patients scheduled for elective bronchoscopy due to localised lesions on their chest X-ray. Informed consent was waived by the Ethics Committee of the Hospital Authority Kowloon West Cluster. Two identical Capnometers (LifeSense LS1-9R: Medair; Nonin Medical, Inc Co; Delsbo, Sweden) that were the most up-to-date models were used. A finger probe was connected to the SaO_2 monitor port of the machine to monitor SaO_2. A double-lumen nasal catheter—one channel for supplemental oxygen and the other for sampling—was set up on each patient. If the patient was breathing room air, the oxygen catheter was left open and the sampling catheter was connected to the capnometer. If the patient was breathing supplemental oxygen, the same fraction of inspired oxygen (FiO_2) as previously prescribed to the patient was given through the oxygen channel. When the system reached the steady state with a good waveform, blood for ABG assay was taken. The highest reading of $PetCO_2$ during blood taking

於醫院呼吸部測量旁流型呼氣末二氧化碳分壓及動脈血二氧化碳分壓的一致性

目的 測量呼氣末二氧化碳（CO_2）分壓及動脈血CO_2分壓的關係及一致性，並確定不同部門之間的共識。

設計 橫斷面預後分析。

安排 香港兩所醫院的呼吸部。

參與者 共邀請200位病人參與，其中分析了219組數據。需要進行動脈血氣監測的病人，我們同時會用兩個便携式CO_2監測儀（LifeSense LS1-9R Capnometers）量度其呼氣末CO_2分壓。

主要結果測量 分別使用相關系數、平均值、標準差，以及Bland-Altman圖來量度呼氣末CO_2分壓及動脈血CO_2分壓的一致性。

結果 總括來説，兩者的相關性低及不顯著（$r=0.1185$，$P=0.0801$）。平均差距為7.2托（95％置信區間：5.5-8.9），達顯著性（$P<0.001$）。Bland-Altman分析發現一致性極限太大至不能接受：-18.1至32.5托。房間空氣方面，平均差距減至2.26托，呼氣末CO_2分壓及動脈血CO_2分壓的相關數為0.2194（$P=0.0068$）；雖然統計學上達顯著性，但一致性仍然偏低。

結論 呼氣末CO_2分壓與動脈血CO_2分壓未達明顯相關及一致性，尤其是當額外提供氧氣時。目前來説，呼氣末CO_2分壓未能替代動脈血CO_2分壓為病人作動脈血氣監測。本研究的結果與文獻記載不同，可能是由於以往研究的病人數目少，診所環境缺乏研究設備，以及對有負面結果的研究發表有偏倚。

was recorded, together with the SaO_2, heart and respiratory rates. If the patient was breathing with the mouth open, he/she was instructed to breathe with a closed mouth. If that could not be achieved, the mouth was closed during recording with support from an assistant. To avoid patient distress, we did not terminate supplemental oxygen during recording of the $PetCO_2$. A patient might have more than one set of readings taken, if more than one ABG determination was deemed necessary at different points of time. Patients in severe respiratory distress were excluded. The study was conducted in two service hospitals, Wong Tai Sin Hospital and Kwong Wah Hospital. The former was a hospital for patients with sub-acute illness, with a case mix of mild-to-severe chronic respiratory patients and patients admitted for investigation of lung shadows; while the latter was an acute hospital, where most patients were less stable.

Statistical analyses

The characteristics of the patients were summarised as means (standard deviations [SDs]) and frequencies (%). The agreement between $PaCO_2$ and $PetCO_2$ was
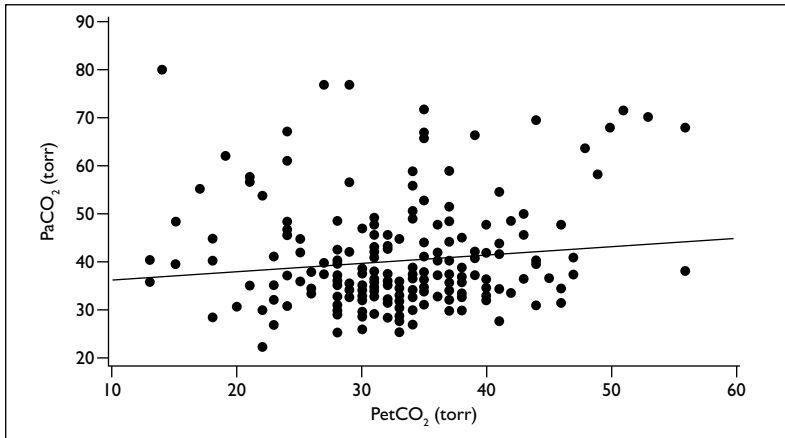
FIG 1. Plot of PaCO₂ against PetCO₂

$PaCO_2$ denotes arterial carbon dioxide partial pressure, and $PetCO_2$ end-tidal carbon dioxide partial pressure
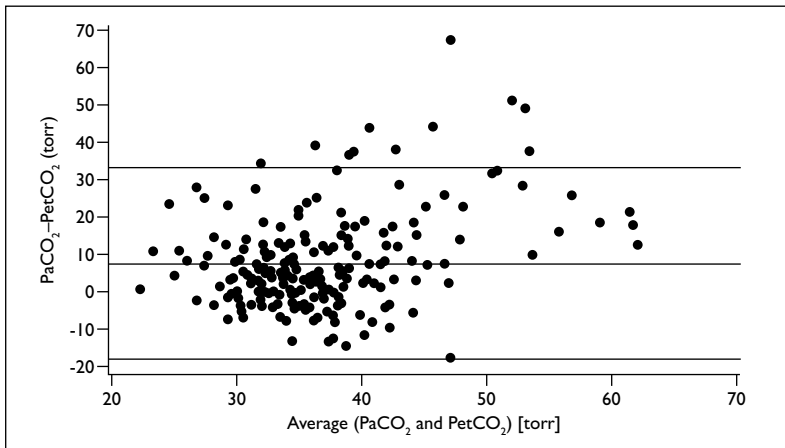
FIG 2. Bland-Altman plot of the difference ($PaCO_2$ minus $PetCO_2$) against the average of $PaCO_2$ and $PetCO_2$

$PaCO_2$ denotes arterial carbon dioxide partial pressure, and $PetCO_2$ end-tidal carbon dioxide partial pressure

studied by correlation coefficients, mean and SD of the $PaCO_2$–$PetCO_2$ difference, and the Bland-Altman plot.[8] Paired *t* tests were used to study the significance of any difference. The agreement between $PaCO_2$ and $PetCO_2$ was further studied by exploring associations with specific patient characteristics. The group means, SDs and correlations of the difference between and the average of $PaCO_2$ and $PetCO_2$ measurements were studied. The correlation coefficients between the quantitative characteristics and the difference, as well as the averages were studied. Analysis of variance (ANOVA) was employed to study the differences between group means. Subsets of patients were further investigated when the mean and the SD of the differences were reduced. The independence between the difference and the average was shown by Bland-Altman method.[8] The significance level was set as 5%. Statistical analyses were performed with

SAS version 9.1.3 (SAS Institute Inc, US).

Results

Summary of patient characteristics

There were 200 recruited patients, who had 219 sets of observations; their mean age was 70 (SD, 14) years, and 57 (26%) were female and 162 (74%) male. Machines 1 and 2 provided 158 (72%), and 61 (28%) of the readings, respectively. The mean $PetCO_2$ was 33.2 (SD, 7.6) torr and the mean F_{IO_2} was 0.23 (SD, 0.05). At the time of sampling, their mean heart and respiratory rates were 85 (SD, 5) beats/min and 20 (SD, 6) breaths/min, respectively. Corresponding mean (SD) values were 7.41 (0.04) for arterial pH, 94.4 (6.4) torr for SaO_2, 40 (11.0) torr for $PaCO_2$, and 97.2 (31.0) torr for arterial oxygen tension (Pao_2).

Comparison for the whole sample

The correlation between $PaCO_2$ and $PetCO_2$ was 0.1185 (P=0.0801), which is low and insignificant. Figure 1 shows the scatter plot of $PaCO_2$ against $PetCO_2$. The variation of the scatters around the regression line was large.

The mean of the difference between the readings ($PaCO_2$ minus $PetCO_2$) was 7.2 torr (SD, 12.7; 95% confidence interval [CI], 5.5-8.9 torr). The mean difference was significant (P<0.001) based on a paired *t* test. The Bland-Altman analysis is shown in Figure 2. The limits of agreement (mean±2 SDs) were -18.1 to 32.5 torr. The range was too large to be acceptable. It was evident that the differences did not scatter around zero, and there was a linear trend. The correlation between the difference and the average of $PaCO_2$ and $PetCO_2$ values was 0.3500 (P<0.001). The linear trend showed that on average, the difference between the $PaCO_2$ and $PetCO_2$ readings increased. Therefore, the bias was not constant but depended on the value of the reading, and thus the $PaCO_2$ value could not be obtained by simply adding a consistent bias to the $PetCO_2$ value.

Comparison for the whole sample after controlling for various patient characteristics

The large SDs could have resulted from the extremely variable patient characteristics in the whole data set. Therefore, Bland-Altman analyses were repeated for different predefined specific subgroups, so as to facilitate the revelation of any consistent trends. By this means, concordance might be improved in any given subgroup when (1) the SD was reduced, (2) there was no dependence between the difference and the average of the readings observed in the Bland-Altman plot, or (3) the correlation between them was reduced.

Group means and standard deviations for the difference between arterial carbon dioxide partial pressure and end-tidal carbon dioxide partial pressure and the average value of these two parameters as determined by the two machines and for each gender

Machine 1 was used for 158 readings and machine 2 was used for 61 readings. For machine 1, the mean of the difference for the PetCO$_2$ and PaCO$_2$ group was 3.7 (SD, 11.1) torr, (P<0.05 by ANOVA). The mean of the average of the two groups was 36.6 (SD, 6.5) torr, which was not significant. Correlation between the difference and average was 0.3389 (P<0.05 by testing for correlation coefficients). For machine 2, the corresponding mean of the difference was 16.1 (SD, 12.2 torr; P<0.05). The mean of the average was 37.5 (SD, 8.4) torr, which was not significant. The correlation between the difference and average values for machine 2 was 0.4091 (P<0.05).

There were 57 readings from females and 162 from males. The mean of the average for females was 36.2 (SD, 6.1) torr. The mean of the difference between PetCO$_2$ and PaCO$_2$ values among females was 5.5 (SD, 11.8) torr, which was insignificant. The correlation between the difference and the average for females was significant (P<0.05). For males, the mean of the average was 37.0 (SD, 7.4) torr. The corresponding mean value of the difference was 7.8 (SD, 12.9) torr, which was insignificant. Moreover, the correlation between the difference and average values was 0.3665 torr (P<0.01).

Neither machine nor gender had any effect on the mean values of the average. However, the differences obtained by machine 1 were smaller than those based on machine 2. The mean differences obtained by machine 1, for both male and female patients, were smaller than the overall mean differences. The SD for either machine and for either gender was close to that obtained from the combined sample. For each gender and machine, the correlations were significant, and were only slightly different from the overall correlation coefficients.

Effects of age, inspired oxygen concentration, cardiac and respiratory parameters, and arterial pH on the difference between arterial carbon dioxide partial pressure and end-tidal carbon dioxide partial pressure and the average value of each

Age (0.2645, P<0.01), F$_{IO_2}$ (0.4978, P<0.01), and heart rate (0.2002, P<0.01) were positively correlated with the difference between PaCO$_2$ and PetCO$_2$, while Pao$_2$ (-0.1372, P<0.05) and pH (-0.1607, P<0.05) were negatively correlated. The F$_{IO_2}$ was positively correlated to the average of PaCO$_2$ and PetCO$_2$ values, while pH (-0.1607, P<0.05) was negatively correlated.

TABLE 1. Group mean (SD) for difference (PaCO$_2$ – PetCO$_2$) and average (of PaCO$_2$ and PetCO$_2$). Group correlation between difference and average*

	No.	Mean (SD)		Correlation between difference and average
		Difference	Average	
Age (years)				
<60	43	0.34 (7.97)†	36.13 (4.90)	0.2293
≥60	176	8.83 (13.03)†	36.99 (7.51)	0.3618§
F$_{IO_2}$				
0.21	151	2.26 (7.52)†	35.06 (4.70)†	-0.0537
>0.21	68	18.07 (14.80)†	40.74 (9.52)†	0.3066‖
Heart rate (beats/min)				
≤76	70	4.48 (13.55)†	36.05 (5.45)	0.3761§
76-90	76	5.46 (11.12)†	36.46 (6.01)	0.1683
>90	73	11.52 (12.27)†	37.94 (9.13)	0.4364§
SaO$_2$ (%)				
≤93	64	10.12 (13.04)‡	36.17 (7.25)	0.3677§
93-97	96	4.94 (11.54)‡	37.19 (7.00)	0.4214§
>97	59	7.59 (13.44)‡	36.93 (7.06)	0.2908‖
Respiratory rate (breaths/min)				
≤17	69	5.74 (14.49)	37.10 (6.94)	0.3843‖
17-21	73	6.31 (11.57)	36.92 (6.18)	0.2123
>21	77	9.26 (11.72)	36.47 (8.00)	0.4485§
pH				
≤7.39	65	8.34 (15.16)	40.32 (9.21)†	0.5362§
7.39-7.42	77	5.34 (10.57)	36.44 (4.75)†	0.1435
>7.42	76	7.70 (11.97)	34.03 (5.38)†	0.1971
Pao$_2$ (torr)				
≤82.5	74	10.61 (13.58)‡	36.90 (6.68)	0.2957‖
82.5-102.75	74	5.46 (13.11)‡	36.74 (8.28)	0.4451§
>102.75	71	5.36 (10.38)‡	36.82 (6.14)	0.2937‖

* F$_{IO_2}$ denotes fractional inspired oxygen, SaO$_2$ arterial oxygen saturation, Pao$_2$ arterial oxygen tension, SD standard deviation, PaCO$_2$ arterial carbon dioxide partial pressure, and PetCO$_2$ end-tidal carbon dioxide partial pressure
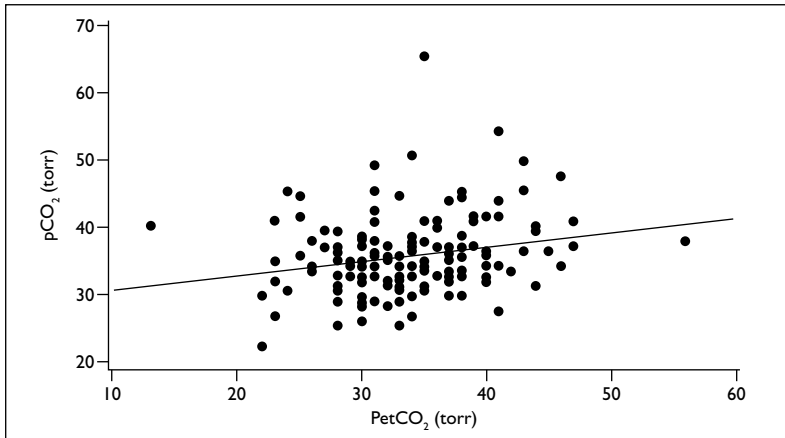† P<0.01 by analysis of variance (ANOVA)
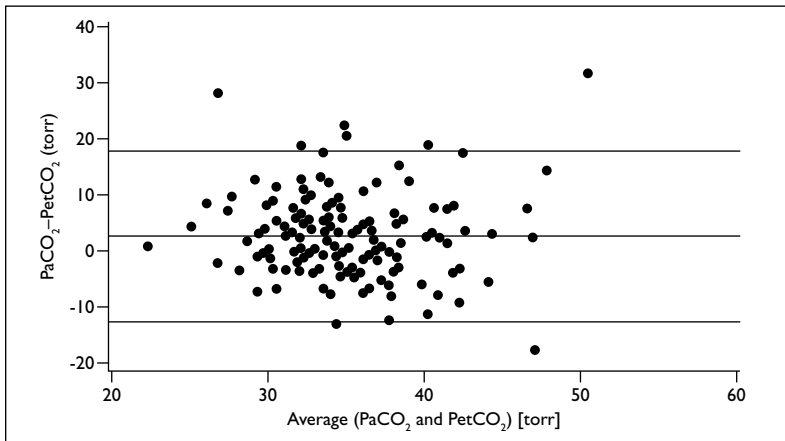‡ P<0.05 by ANOVA
§ P<0.01 by test for correlation coefficients
‖ P<0.05 by test for correlation coefficients

The impact of these diverse characteristics was further studied by dividing them into subgroups. The results are shown in Table 1. Age, F$_{IO_2}$, heart rate, SaO$_2$ and Pao$_2$ had a significant effect on the difference. The F$_{IO_2}$ and pH had significant effects on the average. The mean differences were reduced for patients having: an age of less than 60 years, an F$_{IO_2}$ of 0.21, a heart rate of 90 beats/min or below, an SaO$_2$ in the range of 93 to 97, a respiratory rate of 21 breaths/min or below, and an arterial pH in the range of 7.39 to 7.42. The correlations between the difference and the averages were insignificant for patients aged less

FIG 3. Scatter plot of $PaCO_2$ against $PetCO_2$ for patients with Fio_2 of 0.21
$PaCO_2$ denotes arterial carbon dioxide partial pressure, $PetCO_2$ end-tidal carbon dioxide partial pressure, and Fio_2 fraction of inspired oxygen

FIG 4. Bland-Altman plot for patients with Fio_2 of 0.21
$PaCO_2$ denotes arterial carbon dioxide partial pressure, $PetCO_2$ end-tidal carbon dioxide partial pressure, and Fio_2 fraction of inspired oxygen

TABLE 2. Diagnosis of patients on supplemental oxygen with Fio_2 of more than 0.21 (n=68)*

Diagnosis	No. of patients
COPD	30
COPD + pneumonia	7
COPD + TB	4
COPD + pneumothorax	5
COPD + HOCM	1
COPD + pneumonia + bronchiectasis	1
COPD + pneumonia + Ca lung	1
TB	1
Pulmonary fibrosis	3
TB + pneumonia	2
Bronchiectasis	5
Aspergillosis	1
Myasthenia gravis	1
Congestive heart failure	1
Ca lung	1
Pneumonia	4

* Fio_2 denotes fraction of inspired oxygen, COPD chronic obstructive pulmonary disease, TB tuberculosis, HOCM hypertrophic obstructive cardiomyopathy, and Ca lung cancer of the lung

$PetCO_2$. The variation of the scatter points around the regression line was less, but is still quite large. It had been shown earlier that the mean of the difference between the readings ($PaCO_2$ minus $PetCO_2$) was 2.26 (SD, 7.52; 95% CI, 1.05-3.47), and was significant (P<0.001), based on a paired t test. The limits of agreement (mean±2 SDs) were -12.8 to 17.3. The range was still too large to be acceptable. Figure 4 shows the Bland-Altman plot of difference against the average; the difference is no longer related to the average.

Discussion

The fact that the mean difference of $PaCO_2$ minus $PetCO_2$ using machine 1 was lower than the overall mean was caused by a population difference. Machine 1 was used mainly in Wong Tai Sin Hospital, where more patients had reasonable lung function and breathing on room air, as they were admitted for elective bronchoscopy. Machine 1 was also used on larger patient numbers (n=158 vs 61). High heart rate, low pH, high SaO_2 values (due to oxygen supplementation) were indicators of patient instability and hence poor lung function. A bigger difference was expected in patients with poor lung function, hence a positive correlation was evident.

In recording $PetCO_2$ values, we encountered the following difficulties:

1. The reading varied from second to second.

2. The highest reading appeared only for a split

than 60 years, for patients with an Fio_2 of 0.21, heart rates in the range of 76 to 90 beats/min, respiratory rates in the range of 17 to 21/min, and an arterial pH >7.39. The SD of the difference for patients with an Fio_2 of 0.21 was also substantially reduced from 12.7 to 7.5.

Patients with 0.21 fraction of inspired oxygen

There were 68 patients receiving oxygen supplementation, with Fio_2 values of more than 0.21. The diagnoses of these patients are shown in Table 2. The remaining patients were on room air (Fio_2=0.21). Since the latter patients had substantially smaller mean values—together with the SD of the difference as well as the correlation between the difference and the average—their data were selected for further analysis.

The correlation between $PaCO_2$ and $PetCO_2$ was 0.2194 (P=0.0068), which was significant, although still low. Figure 3 shows the plot of $PaCO_2$ against

TABLE 3. Results of previous studies[1,3,4,9-12]

Investigator	Patient type	Sample size	Mean difference of $PetCO_2$ and $PaCO_2$*	Limits of agreement	Correlation coefficient of $PetCO_2$ and $PaCO_2$
Tobias et al,[9] 1994	Post-surgery	55	2.2 torr	±0.9 torr	r^2=0.84 r=0.992
Kerr et al,[4] 1996	Severe head injury	35	5.5 torr	±5.9 torr	r^2=0.34 r=0.58
Abramo et al,[1] 1997	Paediatric seizures	165	0.33 torr	±0.16 torr	r^2=0.97 (capillary PCO_2)
Yosefy et al,[10] 2004	Respiratory distress in accident and emergency	73	Not stated	Not stated	r=0.792
Corbo et al,[3] 2005	Severe asthma	39	1 torr	95% confidence interval (-0.1 to 2 torr)	Not stated
Agus et al,[11] 2006	Paediatric patients in ketoacidosis	78	Not stated	Not stated	r=0.79 (venous PCO_2)
Yazigi et al,[12] 2007	Obese patients after surgery	25	Not stated	0.3-5.9 torr	r=0.6

* $PaCO_2$ denotes arterial carbon dioxide partial pressure, $PetCO_2$ end-tidal carbon dioxide partial pressure, and capillary/venous PCO_2 partial pressure of carbon dioxide in capillary/venous blood

second over a period of 20 to 30 minutes.

3. When supplemental oxygen was used, the value decreased.

4. If a patient opened his mouth during breathing, the value decreased. This could be partially prevented by supporting the jaw.

5. When the weather was humid, or if the monitor was used continuously for a prolonged time, condensation invariably made the readings inaccurate.

Owing to such problems, obtaining accurate and consistent readings each and every time was a challenge. In the best case scenario with an FIO_2 of 0.21, and no supplemental oxygen diluting exhaled CO_2, the correlation between $PaCO_2$ and $PetCO_2$ was only 0.2194 (P=0.0068), and the scatter points between the regression line was still large. Compared to studies by other authors, our correlation coefficient was low (Table 3[1,3,4,9-12]). However, all except Abramo et al[1] had sample sizes of smaller than 80, and many of the corresponding studies were conducted in academic units with research facilities. Kerr et al[4] used computerised averaging of $PetCO_2$ to obtain a more consistent recording of $PetCO_2$. This implied that $PetCO_2$ cannot provide a reliable reading on patients who require oxygen supplementation — the group most in need of non-invasive monitoring. Even with a good correlation, one can only infer association, not agreement between $PetCO_2$ and $PaCO_2$. The mean difference would be more reflective of concordance. In the previous studies by various authors (Table 3), the mean difference varied from high concordance 0.33±0.16 torr (Abramo et al[1]) to low concordance 5.5±5.9 torr (Kerr et al[4]). In our subgroup analysis in the under-60-year-old group (n=43) with the best results, there was a mean difference of 0.34 (SD, 7.97) torr. In those with an FIO_2 of 0.21 (n=151), the mean difference was 2.26 (SD, 15.04) torr. The results show that $PetCO_2$ is unlikely to be acceptable as a means of replacing ABG sampling for $PaCO_2$ determination. After 14 years of reported good correlation by Tobias et al,[9] and good concordance in a few other studies,[1,3,9] $PetCO_2$ has never received the same level of support as a non-invasive tool. This is in sharp contrast to SaO_2 determination. The possible reason is that when deployed in service units, consistent recording of results cannot be achieved with the available facilities and where staff are not tuned to research as in academic units. Another possible reason is publication bias. Despite the few studies with positive results published, many more with negative results were never published. With further development of new technology, $PetCO_2$ may one day be an alternative to $PaCO_2$. The newer generation devices to measure $PaCO_2$ transcutaneously have obviated the need for frequent calibration with sophisticated standardised gases, and a recent study has shown promising results.[13] However, more studies with larger patient samples are required to confirm their consistency.

Acknowledgement

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