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.

Key words
Blood gas monitoring, transcutaneous; Capnography; Critical care; Monitoring, physiologic; Respiratory insufficiency

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 (PetCO₂) with arterial carbon dioxide partial pressure (PaCO₂), they were performed in research settings and involved restricted populations such as paediatric, accident and emergency, or intensive care patients. The validity of non-invasive carbon dioxide (CO₂) monitoring has never been as well accepted as transcutaneous oxygen saturation (SaO₂). Nevertheless, the qualitative application of PetCO₂ on validating endo-tracheal tube placement, dislodgement of tubing, efficacy of cardiopulmonary resuscitation is well established. There are also case reports of pulmonary embolism being detected based on PetCO₂. This study attempted to correlate PetCO₂ with PaCO₂ 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\textsubscript{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\textsubscript{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\textsubscript{2} produces a waveform known as a capnogram. The CO\textsubscript{2} level at inhalation is zero. As exhalation commences, the exhaled CO\textsubscript{2} rises to a peak known as PetCO\textsubscript{2}. With normal lung physiology, PaCO\textsubscript{2} and PetCO\textsubscript{2} are within 1 to 5 mm Hg of each other, known as P(a-e)CO\textsubscript{2} gradient.\textsuperscript{1} When there is ventilation-perfusion mismatch, the gradient is higher, because not all the CO\textsubscript{2} in the blood passes is exhaled into the alveoli.\textsuperscript{2} 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\textsubscript{2} showed good concordance with PaCO\textsubscript{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\textsubscript{2} monitor port of the machine to monitor SaO\textsubscript{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\textsubscript{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\textsubscript{2} during blood taking was recorded, together with the SaO\textsubscript{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\textsubscript{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\textsubscript{2} and PetCO\textsubscript{2} was measured using the Bland-Altman method.\textsuperscript{3} The difference between PaCO\textsubscript{2} and PetCO\textsubscript{2} was plotted against the mean of the two measurements. The limits of agreement were calculated separately for each patient and each service unit. The coefficient of variation was calculated for PaCO\textsubscript{2}, PetCO\textsubscript{2}, and the difference between the two measurements.

The concordance between the two measurements was calculated using the correlation coefficient (r), the mean difference, and the standard deviation of the differences. The correlation coefficient was calculated between PaCO\textsubscript{2} and PetCO\textsubscript{2} for each service unit. The correlation coefficient was calculated using the Pearson correlation coefficient. The correlation coefficient was calculated using the Spearman rank correlation coefficient.

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studied by correlation coefficients, mean and SD of the PaCO\textsubscript{2}–PetCO\textsubscript{2} difference, and the Bland-Altman plot.\textsuperscript{6} Paired \textit{t} tests were used to study the significance of any difference. The agreement between PaCO\textsubscript{2} and PetCO\textsubscript{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\textsubscript{2} and PetCO\textsubscript{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.\textsuperscript{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\textsubscript{2} was 33.2 (SD, 7.6) torr and the mean F\textsubscript{io}\textsubscript{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\textsubscript{2}, 40 (11.0) torr for PaCO\textsubscript{2}, and 97.2 (31.0) torr for arterial oxygen tension (Pao\textsubscript{2}).

Comparison for the whole sample

The correlation between PaCO\textsubscript{2} and PetCO\textsubscript{2} was 0.1185 (P=0.0801), which is low and insignificant. Figure 1 shows the scatter plot of PaCO\textsubscript{2} against PetCO\textsubscript{2}. The variation of the scatters around the regression line was large.

The mean of the difference between the readings (PaCO\textsubscript{2} minus PetCO\textsubscript{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 \textit{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\textsubscript{2} and PetCO\textsubscript{2} values was 0.3500 (P<0.001). The linear trend showed that on average, the difference between the PaCO\textsubscript{2} and PetCO\textsubscript{2} readings increased. Therefore, the bias was not constant but depended on the value of the reading, and thus the PaCO\textsubscript{2} value could not be obtained by simply adding a consistent bias to the PetCO\textsubscript{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 PetCO₂ and PaCO₂ group was 3.7 (SD, 11.1) torr, (P<0.05 by ANOVA). The mean of the difference for 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 PetCO₂ and PaCO₂ values among females was 5.5 (SD, 11.8) torr, which was insignificant. The correlation between the difference and the average for females was (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), Fio₂ (0.4978, P<0.01), and heart rate (0.2002, P<0.01) were positively correlated with the difference between PaCO₂ and PetCO₂, while PaO₂ (-0.1372, P<0.05) and pH (-0.1607, P<0.05) were negatively correlated. The Fio₂ was positively correlated to the average of PaCO₂ and PetCO₂ values, while pH (-0.1607, P<0.05) was negatively correlated.

The impact of these diverse characteristics was further studied by dividing them into subgroups. The results are shown in Table 1. Age, Fio₂, heart rate, SaO₂ and PaO₂ had a significant effect on the difference. The Fio₂ and pH had significant effects on the average. The mean differences were reduced for patients having: an age of less than 60 years, an Fio₂ of 0.21, a heart rate of 90 beats/min or below, an SaO₂ 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

### Table 1. Group mean (SD) for difference (PaCO₂ – PetCO₂) and average (of PaCO₂ and PetCO₂) Group correlation between difference and average

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No.</th>
<th>Mean (SD)</th>
<th>Correlation between difference and average</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>43</td>
<td>0.34 (7.97)</td>
<td>36.13 (4.90)</td>
</tr>
<tr>
<td>≥60</td>
<td>176</td>
<td>8.83 (13.03)</td>
<td>36.99 (7.51)</td>
</tr>
<tr>
<td>Fio₂</td>
<td>0.21</td>
<td>151</td>
<td>2.26 (7.52)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0.21</td>
<td>68</td>
<td>18.07 (14.80)</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>≤76</td>
<td>70</td>
<td>4.48 (13.55)</td>
</tr>
<tr>
<td></td>
<td>76-90</td>
<td>76</td>
<td>5.46 (11.12)</td>
</tr>
<tr>
<td></td>
<td>&gt;90</td>
<td>73</td>
<td>11.52 (12.27)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>≤17</td>
<td>69</td>
<td>5.74 (14.49)</td>
</tr>
<tr>
<td></td>
<td>17-21</td>
<td>73</td>
<td>6.31 (11.57)</td>
</tr>
<tr>
<td></td>
<td>&gt;21</td>
<td>77</td>
<td>9.26 (11.72)</td>
</tr>
<tr>
<td>pH</td>
<td>≤7.39</td>
<td>65</td>
<td>8.34 (15.16)</td>
</tr>
<tr>
<td></td>
<td>7.39-7.42</td>
<td>77</td>
<td>5.34 (10.57)</td>
</tr>
<tr>
<td></td>
<td>&gt;7.42</td>
<td>76</td>
<td>7.70 (11.97)</td>
</tr>
<tr>
<td>Pao₂ (torr)</td>
<td>≤82.5</td>
<td>74</td>
<td>10.61 (13.58)</td>
</tr>
<tr>
<td></td>
<td>82.5-102.75</td>
<td>74</td>
<td>5.46 (13.11)</td>
</tr>
<tr>
<td></td>
<td>&gt;102.75</td>
<td>71</td>
<td>5.36 (10.38)</td>
</tr>
</tbody>
</table>

* Fio₂ denotes fractional inspired oxygen, SaO₂ arterial oxygen saturation, Pao₂ arterial oxygen tension, SD standard deviation, PaCO₂ arterial carbon dioxide partial pressure, and PetCO₂ 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
than 60 years, for patients with an $F_iO_2$ 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 $F_iO_2$ 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 $F_iO_2$ values of more than 0.21. The diagnoses of these patients are shown in Table 2. The remaining patients were on room air ($F_iO_2$=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 $PetCO_2$. 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

![Figure 3](image1.png)

**FIG 3.** Scatter plot of $PaCO_2$ against $PetCO_2$ for patients with $F_iO_2$ of 0.21 $PaCO_2$ denotes arterial carbon dioxide partial pressure, $PetCO_2$ end-tidal carbon dioxide partial pressure, and $F_iO_2$ fraction of inspired oxygen

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>30</td>
</tr>
<tr>
<td>COPD + pneumonia</td>
<td>7</td>
</tr>
<tr>
<td>COPD + TB</td>
<td>4</td>
</tr>
<tr>
<td>COPD + pneumothorax</td>
<td>5</td>
</tr>
<tr>
<td>COPD + HOCM</td>
<td>1</td>
</tr>
<tr>
<td>COPD + pneumonia + bronchiectasis</td>
<td>1</td>
</tr>
<tr>
<td>COPD + pneumonia + Ca lung</td>
<td>1</td>
</tr>
<tr>
<td>TB</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>3</td>
</tr>
<tr>
<td>TB + pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>5</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>1</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Ca lung</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
</tr>
</tbody>
</table>

* $F_iO_2$ denotes fraction of inspired oxygen, COPD chronic obstructive pulmonary disease, TB tuberculosis, HOCM hypertrophic obstructive cardiomyopathy, and Ca lung cancer of the lung

![Figure 4](image2.png)

**FIG 4.** Bland-Altman plot for patients with $F_iO_2$ of 0.21 $PaCO_2$ denotes arterial carbon dioxide partial pressure, $PetCO_2$ end-tidal carbon dioxide partial pressure, and $F_iO_2$ fraction of inspired oxygen

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TABLE 2. Diagnosis of patients on supplemental oxygen with $F_iO_2$ of more than 0.21 ($n=68$)*

* $F_iO_2$ denotes fraction of inspired oxygen, COPD chronic obstructive pulmonary disease, TB tuberculosis, HOCM hypertrophic obstructive cardiomyopathy, and Ca lung cancer of the lung

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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 FiO₂
of 0.21, and no supplemental oxygen diluting exhaled
CO₂, the correlation between PaCO₂ and PetCO₂ 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). However, all except Abramo
et al² have sample sizes of smaller than 80, and many
of the corresponding studies were conducted in
academic units with research facilities. Kerr et al⁴ used
computerised averaging of PetCO₂ to obtain a more
consistent recording of PetCO₂. This implied that
PetCO₂ 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 PetCO₂ and PaCO₂. 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 al⁵) to low concordance
5.5±5.9 torr (Kerr et al⁴). 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 FiO₂ of 0.21 (n=151), the mean
difference was 2.26 (SD, 15.04) torr. The results show
that PetCO₂ is unlikely to be acceptable as a means
of replacing ABG sampling for PaCO₂ determination.
After 14 years of reported good correlation by Tobias
et al⁴ and good concordance in a few other studies,⁶,⁸,¹⁰
PetCO₂ has never received the same level of support
as a non-invasive tool. This is in sharp contrast to
SaO₂ 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, PetCO₂ may one day be an alternative
to PaCO₂. The newer generation devices to measure
PaCO₂ transcutaneously have obviated the need for
frequent calibration with sophisticated standardised
gases, and a recent study has shown promising
results.¹⁵ However, more studies with larger patient
samples are required to confirm their consistency.

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* PaCO₂ denotes arterial carbon dioxide partial pressure, PetCO₂ end-tidal carbon dioxide partial pressure, and capillary/venous PCO₂ partial pressure of carbon
dioxide in capillary/venous blood


