**Review**

**Recent Insights into the Measurement of Carbon Dioxide Concentrations for Clinical Practice in Respiratory Medicine**

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**Abstract:** In the field of respiratory clinical practice, the importance of measuring carbon dioxide (CO\textsubscript{2}) concentrations cannot be overemphasized. Within the body, assessment of the arterial partial pressure of CO\textsubscript{2} (PaCO\textsubscript{2}) has been the gold standard for many decades. Non-invasive assessments are usually predicated on the measurement of CO\textsubscript{2} concentrations in the air, usually using an infrared analyzer, and these data are clearly important regarding climate changes as well as regulations of air quality in buildings to ascertain adequate ventilation. Measurements of CO\textsubscript{2} production with oxygen consumption yield important indices such as the respiratory quotient and estimates of energy expenditure, which may be used for further investigation in the various fields of metabolism, obesity, sleep disorders, and lifestyle-related issues. Measures of PaCO\textsubscript{2} are nowadays performed using the Severinghaus electrode in arterial blood or in arterialized capillary blood, while the same electrode system has been modified to enable relatively accurate non-invasive monitoring of the transcutaneous partial pressure of CO\textsubscript{2} (PtcCO\textsubscript{2}). PtcCO\textsubscript{2} monitoring during sleep can be helpful for evaluating sleep apnea syndrome, particularly in children. End-tidal PCO\textsubscript{2} is inferior to PtcCO\textsubscript{2} as far as accuracy, but it provides breath-by-breath estimates of respiratory gas exchange, while PtcCO\textsubscript{2} reflects temporal trends in alveolar ventilation. The frequency of monitoring end-tidal PCO\textsubscript{2} has markedly increased in light of its multiple applications (e.g., verify endotracheal intubation, anesthesia or mechanical ventilation, exercise testing, respiratory patterning during sleep, etc.).

**Keywords:** carbon dioxide; transcutaneous partial pressure; end-tidal partial pressure; Bland–Altman analysis; blood gas analysis

1. Introduction

Atmospheric carbon dioxide (CO\textsubscript{2}) concentration is increasing worldwide by the increasing consumption of carbon-based combustibles along with progressive deforestation [1,2]. Increases in atmospheric CO\textsubscript{2} concentrations are thought to cause elevation...
of atmospheric temperature as a result of the greenhouse effect. High concentrations of atmospheric CO$_2$ can facilitate the onset of human health problems, such as increased fatigue, headache, and tinnitus. Inhalation of 0.1% CO$_2$ for a short time has been reported to cause marked changes in respiratory, circulatory, and cerebral electrical activity [3,4]. More recently, continuous measurements of atmospheric CO$_2$ concentrations have been viewed as being helpful for the evaluation of ventilation conditions in rooms or buildings, and it has been utilized as guidance to avoid the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. SARS-CoV-2 can cause the coronavirus disease 2019 (COVID-19), which has emerged as a serious problem in respiratory clinical practice [6–8].

On the other hand, arterial blood gas analysis (ABGA) is very commonly implemented in routine clinical practice of respiratory medicine [9–11]. Arterial partial pressure of CO$_2$ (PaCO$_2$) is commonly evaluated in any type of respiratory disease. PaCO$_2$ is useful for the diagnosis of hypo- or hyperventilation and to evaluate potential respiratory drive depression and CO$_2$ narcosis in patients with chronic obstructive pulmonary disease (COPD) or other conditions. The evaluation of acid–base imbalance in the context of respiratory acidosis can be performed using pH and PaCO$_2$ data. Non-invasive alternative methods such as end-tidal CO$_2$ partial pressure of exhaled gas (PetCO$_2$) and transcutaneous partial pressure of CO$_2$ (PtcCO$_2$) have been developed, and their accuracy and usefulness have been evaluated by Bland–Altman analysis [12].

Another use of CO$_2$ concentration measurements in exhaled air involves assessment of CO$_2$ production [9]. The respiratory quotient (RQ) can be calculated using the data of CO$_2$ production (VCO$_2$) and oxygen (O$_2$) consumption (VO$_2$). Then, the difference of partial pressure of oxygen (PO$_2$) between mean alveolar gas and arterial blood can be calculated [10]. This approach has been used for the evaluation of gas exchange impairment in various lung diseases [9,10,13]. Energy expenditure can be also evaluated, and this is particularly of interest in obese patients with obstructive sleep apnea syndrome (OSAS) using CO$_2$ production data and oxygen consumption data [14].

Thus, depending on the objectives driving the measurement of CO$_2$ concentrations, the most suitable method should be adopted. In order to better understand the considerations involved in such choices, we will discuss the principles, sensitivity, and limitations of the various methods available for measuring CO$_2$ concentrations.

2. Atmospheric Carbon Dioxide Concentration

The World Data Centre for Greenhouse Gases reported that atmospheric CO$_2$ concentrations are increasing worldwide, and they are currently around 410 ppm (Figure 1) [2]. The method to measure this concentration is by non-dispersive infrared technology (Figure 2) [15–18]. This increase in CO$_2$ level has been mainly attributed to increasing the consumption of carbon-based energy sources (e.g., coal, oil) with significant concomitant deforestation due to unregulated expansion of industrial agriculture initiatives [1,2].

When atmospheric CO$_2$ concentration rises, human PaCO$_2$ will rise, but its toxicity has been reported to be little, if any, at 5% (50,000 ppm) or lower [19]. Atmospheric CO$_2$ concentrations of more than 50,000 ppm may cause hypercapnia, respiratory acidosis, and increased respiratory rate. Severe acidosis will ultimately result in depression of the respiration and the circulation. Atmospheric CO$_2$ concentrations of more than 10% (100,000 ppm) may cause convulsions, coma, and death [19].

Duarte et al. showed the standard CO$_2$ levels in air in indoors environments (i.e., >15,000 ppm: accident by CO$_2$ intoxication; 10,000 ppm: submarines; 5000 ppm: crowded indoors; 600 ppm: well-ventilated indoors) [20].

According to the documents of the World Health Organization, the amplitude (depth) of respiratory movements was reduced by the inhalation of 0.1% (1000 ppm) CO$_2$, while peripheral blood flow was increased, and the amplitude of brain electrical waves was increased [3,4]. In these documents from the 1960s, it was suggested that the indoors concentrations of CO$_2$ should not exceed 1000 ppm. A man engaged in light work exhales
about 22.6 L of CO$_2$ per hour [4], and since the recent normal concentration of CO$_2$ in the atmosphere is 0.04% (0.4 L/m$^3$), the volume of required fresh air per person to ensure CO$_2$ concentrations not exceeding 0.1% (1.0 L/m$^3$) would be $22.6/(1.0 - 0.4) = 38$ m$^3$ per hour. Thus, strict monitoring of air circulation and CO$_2$ concentrations are essential in indoor locations where the density of humans is high (e.g., cinemas, theaters, office buildings, hospitals, etc.).

Figure 1. Globally averaged monthly mean mole fraction of CO$_2$ from 1984 to 2018 and the deseasonalized long-term trend shown as a red line (Adapted with permission from Ref. [2]. Copyright 2020 WMO WDCGG).

Figure 2. Measuring system of CO$_2$ by using the non-dispersive infrared analyzer. The light chopper delivers the data of infrared intensity as a continuous alternating current signal to the detector through the optic filter (Adapted with permission from Ref. [18]. Copyright 2021 HORIBA).
Measuring atmospheric CO\(_2\) concentrations has been helpful for evaluation of the ventilation conditions in rooms of buildings aiming to decrease the transmission risk of SARS-CoV-2, which can cause COVID-19 (Figure 3) \([5,21,22]\). Smaller droplets (<10 \(\mu\)m) with SARS-CoV-2 content expired from COVID-19 patients can travel tens of meters in the air while indoors and cause airborne transmission \([23,24]\). The Japanese government recommended the use of atmospheric CO\(_2\) sensors in rooms such as restaurants in order to prevent COVID-19 especially in cold weather \([25]\). Guidelines for indoor CO\(_2\) concentrations to reduce indoors COVID-19 infection risk should be more helpful if they account for environment and activity types \([5]\). Marr et al. suggested that indoor CO\(_2\) concentrations should not exceed 700 ppm in classrooms and 550 ppm in hallways in order to limit the COVID-19 transmission in schools \([26]\). Teachers in many countries may be required to keep the indoor CO\(_2\) concentrations low and decrease the students’ risk of inhaling SARS-CoV-2 floating in the air in classrooms. By measuring indoor CO\(_2\) concentrations, teachers can evaluate how widely the windows should be opened (e.g., fully or partially open) in classrooms considering the meteorological conditions (especially wind) and estimate the overall rate of ventilation in the classroom \([26]\).

![Figure 3. Monitoring of CO\(_2\) levels in rooms. Higher levels of CO\(_2\) in a room can mean there is a greater risk of viral transmission (Adapted with permission from Ref. [21]. Copyright 2020 Kyodo).](image)

In addition, there was a fatal accident involving CO\(_2\) fire extinguishing equipment in Japan in April 2021 \([27]\). Four people died and two people were injured due to the high concentrations of CO\(_2\) because the equipment in the basement parking garage was mistakenly activated. The mandate of monitoring atmospheric CO\(_2\) concentration is increasing and is likely to become mandatory in buildings and similar public structures. Currently, the measurement of CO\(_2\) concentrations using infrared is the fastest method to obtain data from atmospheric samples at low cost; as such, this method is suitable in most of the situations.

3. Blood Gas Analysis: Principle of PaCO\(_2\) Electrode

Apart from atmospheric CO\(_2\) concentration measures, it is frequently necessary to measure the partial pressure of CO\(_2\) (PCO\(_2\)) in blood in respiratory clinical practice. The analysis of blood gas values has been performed by means of electrochemical devices \([28]\). The traditionally used electrode for measuring PCO\(_2\) is termed the Severinghaus PCO\(_2\) electrode, per the last name of the inventor of this electrode, Dr. John Severinghaus.
In addition, there was a fatal accident involving CO2 fire extinguishing equipment in Japan in April 2021 [27]. Four people died and two people were injured due to the high concentrations of CO2 because the equipment in the basement parking garage was mistakenly activated. The mandate of monitoring atmospheric CO2 concentration is increasing and is likely to become mandatory in buildings and similar public structures. Currently, in Japan, CO2 concentration measures are frequently performed at high-rise buildings and large facilities. This is due to the increased attentiveness to CO2 concentration, escalating efforts to combat global warming, and CO2 narcosis in patients with COPD and many other pulmonary conditions [10,30,31].

The traditionally used electrode for measuring PCO2 is termed the Severinghaus PCO2 electrode, per the last name of the inventor of this electrode, Dr. John Severinghaus (Figure 4) [28,29]. This PCO2 electrode contains the CO2-permeable membrane and the principle of pH meter with a pH-sensitive glass membrane. PaCO2 is usually measured for the evaluation of any type of lung disease [9,10]. PaCO2 is useful for the diagnosis of hyperventilation, hypoventilation, CO2 retention, and CO2 narcosis in patients with COPD and many other pulmonary conditions [10,30,31].

The evaluation of acid–base imbalance (i.e., respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis), with the consideration of compensation, can be performed using simultaneous arterial pH and PaCO2 measurements [32,33]. The majority of CO2 is transported in the body as bicarbonate ion (HCO3−) [34]. HCO3− plays a central role in maintaining the pH level in blood [32–34]. Therefore, it is important to calculate its concentration ([HCO3−]) in blood using the Henderson–Hasselbalch equation. [HCO3−] is calculated using the following equation on devices such as Rapidlab 1265 (Siemens Healthcare Diagnostics, Sudbury, UK).

\[
[HCO_3^-] = 0.0307 \times PCO_2 \times 10^{(pH-6.105)}
\]

The normal ranges for PaCO2, arterial pH, and arterial [HCO3−] are 35–45 mmHg, 7.35–7.45, and 22–26 mEq/L, respectively [35]. These data are useful for the calculation of anion gap (AG) [32,34,36]. Using the plasma sodium concentration ([Na+]) and plasma chloride concentration ([Cl−]), AG is calculated by the following equation.

\[
AG = [Na^+] - ([Cl^-] + [HCO_3^-])
\]

The normal range for AG is 6–12 mmol/L [32]. AG is utilized for the differential diagnosis of metabolic acidosis. High-AG metabolic acidosis due to increased fixed acid includes ketoacidosis, lactic acidosis, renal failure, toxin by salicylates, etc. [32,34,36].
Normal-AG metabolic acidosis includes renal tubular acidosis, HCO$_3^-$ loss from the gastrointestinal tract, etc. [32,34,36].

The usual clinical practice for ABGA in conscious patients involves a single arterial puncture; however, the procedure may cause pain and cause hyperventilation [11]. PaCO$_2$ via the arterial puncture performed after a resting period of 20–30 min has been understood as the gold standard, because arterial blood samples must be drawn when the patient is in a steady state [11,37]. Therefore, newly developed surrogates should be compared with this gold standard PaCO$_2$ data.

PaCO$_2$ is also useful for the evaluation of the ventilatory support being provided to patients with respiratory insufficiency [38]. However, an arterial puncture is necessary for measuring PaCO$_2$, and it is sometimes difficult and painful, e.g., for pediatric patients. Therefore, less invasive or non-invasive surrogate measurements have been sought, and they include venous or capillary partial pressure of CO$_2$, PetCO$_2$, and PtcCO$_2$.

4. Non-Invasive Alternative Methods to Estimate PaCO$_2$

4.1. Venous Blood Gas Analysis (VBGA)

The pulse oximeter allows the measurement of the levels of systemic O$_2$ by determining the degree of percutaneous O$_2$ saturation (SpO$_2$) [39,40]. Therefore, peripheral VBGA with simultaneous evaluation of SpO$_2$ offers an alternative to arterial blood gas analysis [41–43]. This approach has become standard practice, particularly among pediatric patients and in the emergency department, owing to its advantages (i.e., easiness and less invasive nature) over arterial blood gas analysis [44–46]. Capillary blood gas analysis can also be performed. This is particularly useful in children and involves warming the extremity to arterialize the subcutaneous vascular bed and extracting a minute amount of blood using a lancet. The gas content of this sample should be similar to the values obtained for actual arterial blood samples [47–49]. It has been demonstrated that intentional hyperventilation increases venous–arterial PCO$_2$ differences and pH differences [50]. Moreover, in patients with respiratory alkalosis who did not receive treatment, the condition may be underestimated by the “SpO$_2$ plus VBGA” method [50]. Furthermore, hyperventilation increases differences in the concentration of venous–arterial bicarbonate [51]. Therefore, these changes may be attributed to a reduction in peripheral blood perfusion induced by hyperventilation-associated systemic vasoconstriction [50,51].

4.2. End-Tidal PCO$_2$

Traditionally, the concentration of CO$_2$ in an exhaled gas is calculated by determining the levels of chemically absorbed CO$_2$ and other gases [52–54]. The absorbed CO$_2$ is subsequently compared with the total volume of the gas, thereby revealing the levels of CO$_2$ present. The concentration of CO$_2$ in an exhaled gas can also be measured by gas chromatography and/or mass spectrometry, but these systems are voluminous, sturdy, and expensive [55–57]. The technological advancement of exhaled CO$_2$ monitoring has enabled the reduction of system size and the adequate monitoring of ventilation using the infrared analyzer. PetCO$_2$ is the highest and closest estimate of PaCO$_2$ in the time course of continuous sampling of expiratory PCO$_2$ data [54,58]. Typically, PaCO$_2$ and PetCO$_2$ differ by 2–5 mmHg. However, the presence of lung disease, such as acute respiratory distress syndrome, COPD, and asthma, ventilation/perfusion (V/Q) mismatch (especially relative increase in high V/Q regions) in the lungs can cause the PaCO$_2$–PetCO$_2$ difference to increase, in which case the non-invasive measurements may be potentially misleading. Patients with gas exchange impairments may be unable to efficiently exhale CO$_2$. Therefore, PetCO$_2$ is not a good surrogate of PaCO$_2$ for patients with pulmonary diseases. Furthermore, PetCO$_2$ cannot replace PaCO$_2$ [58,59]. Nevertheless, PetCO$_2$ has been reported to be a useful indicator of pulmonary perfusion and cardiac output during cardiopulmonary resuscitation [54,58–60], and its use was recommended by numerous guidelines (American Heart association [61], European Resuscitation Council [62], and American College of Emergency Physicians [63]). Particularly, the use of waveform capnography was recommended
during cardiopulmonary resuscitation [59,61,62]. The return of spontaneous circulation is indicated by a sudden continuous rise in PetCO\(_2\) (≥40 mmHg) [61]. Patients with an average PetCO\(_2\) of 15 mmHg are more likely to be successfully resuscitated than those with a value of 7 mmHg [64]. In patients with a low or decreasing PetCO\(_2\), reassessment of cardiopulmonary resuscitation is recommended [61]. In adults and children, capnometry or capnography can be utilized to continuously monitor alterations in exhaled CO\(_2\) from the onset of intubation to extubation [54,58,65,66]. Both PetCO\(_2\) and (PaCO\(_2\)-PetCO\(_2\)) are useful for monitoring V/Q mismatch especially (physiologic deadspace)/(tidal volume) evaluation, and useful to assess pulmonary embolism [58,59]. PetCO\(_2\) monitoring is a faster indicator than pulse oximetry or ECG tracing in order to find patient mishaps such as a ventilator becoming disconnected or other catastrophic events [58].

Monitoring with capnography is recommended not only in intubated patients but also in non-intubated patients undergoing non-invasive positive pressure ventilation (NPPV) [67]. Figure 5 shows the new CO\(_2\) sensor, TG-980P (Nihon Kohden, Tokyo, Japan) and a mask, cap-ONE (Nihon Kohden, Tokyo, Japan) in the NPPV system with the recently rolled out ventilator, NKV-330 (Nihon Kohden, Tokyo, Japan). In cap-ONE, the inner cup is included, and exhaled air will efficiently reach TG-980P. Monitoring with capnography is possible at a remote place. The electromechanical response of the new devices for NPPV (NKV-330 with cap-ONE and TG-980P), as shown by breathing on the sensor measuring atmospheric PCO\(_2\), elicited an increase in PCO\(_2\) within 3 s even at remote places such as a nurse station in a hospital ward.

Figure 5. A system of measuring end-tidal PCO\(_2\) during non-invasive positive pressure ventilation. (a) Mainstream CO\(_2\) sensor (TG-980P, Nihon Kohden, Tokyo, Japan) is used in a mask (cap-ONE, Nihon Kohden, Tokyo, Japan). (b) The inner cup is attached inside the mask. (c) Air flow from respirator and exhaled flow from mouth or nose are shown. (d) Capnographic waveform on the monitor of non-invasive positive pressure ventilator (NKV-330, Nihon Kohden, Tokyo, Japan) is shown.
There are two methods to sample and detect CO$_2$ in clinical situations: mainstream and sidestream [57,68]. Mainstream CO$_2$ is measured using a sensor inserted in an airway adapter, and the sample is directly taken from the airway, providing accurate data. Sidestream CO$_2$ is measured by pulling the patient’s exhalation air through a small tube into a CO$_2$ detector that is placed at the end of the small tube. Although mainstream CO$_2$ measurement requires a relatively large amount (150 mL/min) of sample gas, only a small amount (50 mL/min) of gas is sufficient for sidestream [68]. Currently, TG-980P is the smallest and the lightest mainstream PetCO$_2$ sensor, where special anti-fog film is used on the window of specimens, and therefore, the heater to avoid fog is unnecessary (Figure 6).

**Figure 6.** Technology of size reduction of end-tidal PCO$_2$ sensors. In the new CO$_2$ sensor, the use of heaters to avoid water drops is unnecessary. (a) In ordinary CO$_2$ sensors, heaters are necessary to prevent windows from being clouded by water vapor in expired air. Water drops on windows cause refraction and reflection of infrared lights. (b) The hydrophilic coating film used in the new CO$_2$ sensor (TG-980P, Nihon Kohden, Tokyo, Japan) disabled the surface tension of water drops. Thanks to this anti-fog film, the new sensor does not require the use of heaters.

### 4.3. Transcutaneous Blood Gas Analysis

Evaluation of dissolved gases diffusing into the surface of the skin can be used to determine the partial pressure of gases in blood [69–73]. Heating of the skin locally, occasionally accompanied by measurement of transcutaneous PO$_2$, is necessary for determining the PtcCO$_2$. This dilation of vessels increases the flow of arterial blood to the skin capillary bed below the detector, thereby accelerating the diffusion of gas [69,70,74,75] (Figure 7). According to Severinghaus et al., the PtcCO$_2$ electrode contains a relatively large solid silver reference electrode inside the glass pH sensor, which enhances the transfer of heat from the heater to the skin via the glass pH electrode [69,70]. The presence of an ultra-thin film of buffer electrolyte between the silver and glass appeared to be important. This internal electrolyte contains reference solution (e.g., phosphate buffer) (light green, Figures 4 and 7). The external electrolyte contains bicarbonate solution (light blue, Figures 4 and 7). The precise blueprints of recent PtcCO$_2$ sensors are different according to manufacturing companies. This approach is commonly used to evaluate the pulmonary gas exchange function in pediatric patients as well as in adults with acute/chronic respiratory failure [76–78]. Moreover, this methodology can be employed to monitor patients receiving mechanical ventilation and managing limb ischemia [79–81].
4.4. Comparison of Accuracy

The accuracy of an alternative new method has been evaluated by Bland–Altman analysis for use in respiratory clinical practice (Table 1) [12,45,50,82–89].

Table 1. Alternative non-invasive methods for measuring PaCO₂.

| Surrogate     | Average Bias                  | 1.96 SD   | Accuracy   | Usefulness for Patients with Pulmonary Diseases | References |
|---------------|-------------------------------|-----------|------------|------------------------------------------------|------------|
| PvCO₂         | Approximately 5 mmHg higher than PaCO₂ | 14.7–15.0 mmHg | Worst | Limited                                             | [45,50] |
| PetCO₂        | 2–5 mmHg lower than PaCO₂     | 6.9–14.4 mmHg  | Second best | Limited                                             | [83–88] |
| PtcCO₂        | 4–5 mmHg higher than PaCO₂    | 4.6–10.4 mmHg  | Best       | Good (still not replaceable)                        | [83–89] |

PaCO₂, arterial partial pressure of CO₂; PetCO₂, end-tidal CO₂ partial pressure of exhaled gas; PtcCO₂, transcutaneous partial pressure of CO₂; PvCO₂, venous partial pressure of CO₂; SD, standard deviation. The width of ± 1.96 SD means the 95% limits of agreement.
5. Usefulness and limitation of Transcutaneous Blood Gas Analysis

Currently, the most accurate non-invasive alternative surrogate of PaCO$_2$ is PtcCO$_2$ (Table 1). We performed various subgroup analyses on the PtcCO$_2$ bias (PtcCO$_2$—PaCO$_2$) in order to use PtcCO$_2$ efficiently in the future [89].

5.1. Various Subgroup Analyses on the PtcCO$_2$ Bias

Subgroup analyses (sex, age, PaCO$_2$ level, and PaO$_2$ level) were performed using the data at 30 min after the placement of detectors (n = 272).

5.1.1. Sex

The results of the analysis did not show significant differences in the PtcCO$_2$ bias (males/females: 168/104 [89]).

5.1.2. Age

Comparison of the PtcCO$_2$ bias between four age groups: 20–39 years (n = 11); 40–59 years (n = 12); 60–79 years (n = 138); and ≥80 years (n = 111) (Figure 8a). The PtcCO$_2$ bias was significantly lower in young adults (20–39 years) versus those aged 40–59 years and ≥80 years (p < 0.05, respectively). PtcCO$_2$ and PtcO$_2$ are frequently utilized in newborns. The increases in PtcCO$_2$ bias induced by aging may be due to the thickness of the skin with increasingly reduced permeability to gas exchange.

5.1.3. PaCO$_2$ Level

Comparison of the PtcCO$_2$ bias between the severe hypocapnia group (PaCO$_2$ < 31 mmHg; n = 7), mild hypocapnia group (31 mmHg ≤ PaCO$_2$ < 35 mmHg; n = 24), and normal range group (35 mmHg ≤ PaCO$_2$ ≤ 45 mmHg; n = 202) is shown in Figure 8b. The PtcCO$_2$ bias was significantly higher in the severe hypocapnia group versus the normal range group (p < 0.01), and this was an intensity-dependent effect. Comparison of bias between the normal range group (35 mmHg ≤ PaCO$_2$ ≤ 45 mmHg; n = 202), mild hypercapnia group (45 mmHg < PaCO$_2$ ≤ 50 mmHg; n = 26), and severe hypercapnia group (50 mmHg < PaCO$_2$; n = 13) is shown in Figure 8c. The PtcCO$_2$ bias was significantly lower in the mild hypercapnia group versus the normal PaCO$_2$ group (p < 0.01). The hypocapnic systemic vasoconstriction is thought to be the mechanism of increases in the PtcCO$_2$ bias [50]. CO$_2$ concentration in blood is very important for peripheral blood perfusion. On the other hand, severe hypercapnic subjects (>50 mmHg) frequently have comorbid conditions such as circulatory failure, heart failure, edema, infection, etc.

5.1.4. PaO$_2$ Level

Comparison of the PtcCO$_2$ bias between the hypoxemia group (PaO$_2$ < 80 mmHg; n = 158), normal range group (80 mmHg ≤ PaO$_2$ ≤ 100 mmHg; n = 102), and hyperoxemia group (100 mmHg < PaO$_2$; n = 12) is shown in Figure 8d. The PtcCO$_2$ bias was significantly lower in the hypoxemia group versus the normal PaO$_2$ group (p < 0.05), and this was thought to be a PaO$_2$ level-dependent effect. Previous studies have investigated hypoxemic systemic vasodilation [90]. The concentration of O$_2$ in blood appears to be associated with peripheral perfusion and PtcCO$_2$ bias.
Figure 8. Comparisons of PtcCO$_2$ and PaCO$_2$ bias (n = 272). (a) Comparison of bias between four age groups. The bias was significantly lower in young adults (20–39 years) versus those aged 40–59 years and ≥ 80 years. (b) Comparison of bias between the severe, mild hypocapnia group, and normal range group. The bias was significantly higher in the severe hypocapnia group than the normal range group, and this was an intensity-dependent effect. (c) Comparison of bias between the normal range group and mild, severe hypercapnia group. The bias was significantly lower in the mild hypercapnia group versus the normal range group. (d) Comparison of bias between the hypoxemia group, normal range group, and hyperoxemia group. The bias was significantly lower in the hypoxemia group versus the normal range group, and this was a PaO$_2$ level-dependent effect. Bars: SEM, *: $p < 0.05$, **: $p < 0.01$ [89]. PaCO$_2$, arterial partial pressure of CO$_2$; PaO$_2$, arterial partial pressure of O$_2$; PCO$_2$, partial pressure of CO$_2$; PtcCO$_2$, transcutaneous partial pressure of CO$_2$; SEM, standard error of the mean.

5.1.5. Among Various Respiratory Diseases

There were not significant differences in the PtcCO$_2$ bias among various respiratory diseases in the data of [89] (Figure 9). The breakdown of respiratory diseases was as follows: asthma–COPD overlap (n = 39), COPD due to emphysema (n = 25), interstitial lung disease (n = 41), pneumonia (n = 74), asthma (n = 27), lung cancer (n = 10), acute bronchitis (n = 15), bronchiectasis (n = 7), sleep apnea syndrome (n = 6), pleural diseases (n = 5), and others (n = 15).
Figure 9. Subgroup analyses on PCO₂ bias (PtcCO₂—PaCO₂) of patients with various respiratory diseases (n = 272). Bars: SEM. There were no significant differences in PCO₂ bias (ANOVA with Tukey’s post hoc test). ACO, asthma-chronic obstructive pulmonary disease overlap; ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; E, emphysema; ILD, interstitial lung disease; N.S., not significant; PaCO₂, arterial partial pressure of CO₂; PCO₂, partial pressure of CO₂; PtcCO₂, transcutaneous partial pressure of CO₂; SAS, sleep apnea syndrome ([89], additional data).

5.2. Usefulness

The use of this non-invasive PtcCO₂ monitor leads to an accurate assessment of CO₂ retention. All hypercapnia patients with PaCO₂ > 50 mmHg (n = 13–20) showed PtcCO₂ ≥ 50 mmHg until 12 min [89] (additional data). Utilization of thinner films for CO₂-permeable and/or pH-sensitive membranes (Figure 7) may accelerate the speed to equilibration in order to reach the accurate data. The American Association for Respiratory Care has recommended an acceptable clinical range of agreement between PtcCO₂ and PaCO₂ (±1.96 standard deviation: ±7.5 mmHg or narrower) [80]. This range of agreement, determined through TCM4 with a tcSensor 84 (Radiometer Medical AsP, Copenhagen, Denmark), was reduced over time: ±13.6 mmHg at 4 min, ±7.5 mmHg at 12–13 min, and ±6.3 mmHg at 30 min [89].

5.3. Limitations

Although PtcCO₂ is currently the best non-invasive surrogate of PaCO₂, there were still some cases with large bias over 10 mmHg. PaCO₂ cannot be replaced with PtcCO₂ completely even after considering the average bias of 4–5 mmHg (Table 1) [89]. Other limitations include the occurrence of technical drift; therefore, the baseline calibration is necessary [91,92]. In addition, rapid results are not available, and the results are not independent of dermal perfusion, edema, or increased skin thickness [91,93].

5.4. Future Use

PtcCO₂ monitoring during sleep study has been reported to be useful for evaluating the necessity of ventilatory support especially in patients with neuromuscular
disorders [94,95]. PtcCO2 monitoring with polysomnography may become the standard method of sleep study in the future [94]. PtcCO2 monitoring during rehabilitation may be the promising method, too [96–98]. However, the actual PaCO2 will not be disregarded, because the PCO2 bias is sometimes large, and PtcCO2 cannot replace PaCO2 completely [89]. Therefore, future use of PtcCO2 monitoring will be limited and may be just focusing on relative evolution.

6. Other Applications of Measuring CO2 Mainly for Research Use

Measuring CO2 in exhaled gas is also used for assessment of the metabolic condition of subjects. Energy expenditure (EE) is determined using the Weir equation (e.g., MK-5000, Muromachi Kikai, Tokyo, Japan) (Figure 10) [99–101]. RQ is calculated using the pulmonary exchange ratio (VCO2/VO2)

\[
EE \text{ (kcal/kg/h)} = (3.815 \times \dot{V}O_2) + (1.232 \times \dot{V}CO_2) = [3.815 + (3.815 \times RQ)] \times \dot{V}O_2
\]

Figure 10. The system of measuring CO2 production and O2 consumption in mice. Inlet air routes from animal chamber, control air, and reference gases are periodically changed. CO2 concentration is measured by infrared absorption analysis. O2 concentration is measured by magneto-electrical analysis (MK-5000) [100].

The measurement of \( \dot{V}CO_2 \) and \( \dot{V}O_2 \) is based on the principles of infrared analysis [15,16] and magneto-electrical analysis [102], respectively. The administration of nasal continuous positive airway pressure (CPAP) in patients with sleep apnea has been linked to body weight gain [103,104]. Therefore, long-term exposure to intermittent hypoxia may result in greater reductions in O2 consumption and EE. Human and animal studies have examined the metabolic rates. However, the EE or metabolic rates were not found to be decreased in animal models of intermittent hypoxia or in OSAS patients compared to after the treatment with nasal CPAP [14,100]. Conversely, Tachikawa et al. reported significant decreases in basal metabolic rate in OSAS patients by nasal CPAP [14]. Non-agitated sleep without airway obstruction enabled by treatment with CPAP may contribute to this phenomenon. Measure of EE and the calculation of RQ by the pulmonary exchange ratio will undoubtedly contribute to obesity research and other research focused on lifestyle-related diseases in the future [100,105–107].
When carbohydrates, fat, and protein are oxidized, RQ are calculated to 1.0, 0.7, and 0.8, respectively [108]. Recently, Lin et al. monitored both CO$_2$ and O$_2$ concentrations in human breath samples using a home-made gas chromatography/milli-whistle analyzer and reported that the changes in CO$_2$ concentrations (and the index of CO$_2$/O$_2$ ratio) were related to the changes in blood sugar concentrations [109]. They suggested that their compact gas chromatography system may be used for a non-invasive and time-dependent (continuous and rapid) blood sugar monitoring in the future.

In addition, historically, gas chromatography and mass spectrometry had been often used as the gas analyzer in respiratory research, and the peak expired PCO$_2$ had been measured by this technology [55–57]. The advantage of these methods over the infrared CO$_2$ analysis is that concentrations of multiple gases can be simultaneously measured. Nevertheless, the use of mass spectrometry for respiratory research has decreased since 2000, which is likely because of cost and technical fragility of the mass spectrometers, which require more extensive technical support [57]. Furthermore, the method of photoinduced electron transfer is rapidly developing in various research fields, and CO$_2$ has been reported to be detected using amine-containing fluorophores [110,111]. The evaluation of local CO$_2$ concentrations in various small organs of animals might be possible by this technology.

7. Conclusions

In summary, measures of CO$_2$ concentrations in the air are done using the infrared analyzer. Data are important for both the climate problem and the regulatory monitoring of buildings to avoid poor aeration and more recently COVID-19 transmission. Measure of arterial CO$_2$ concentration is performed by measuring PaCO$_2$ using the Severinghaus electrode. The most accurate non-invasive alternative method of PaCO$_2$ is PtcCO$_2$. Measure of CO$_2$ production with O$_2$ consumption may be used for further investigation in the various fields of metabolism, obesity with obstructive sleep apnea syndrome, and lifestyle-related diseases.

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Abbreviations

The following abbreviations are used in this manuscript:

| Abbreviation | Description |
|--------------|-------------|
| ABGA | Arterial blood gas analysis |
| ACO | Asthma chronic obstructive pulmonary disease overlap |
| Ag/AgCl | Silver electrode plated with silver chloride |
| ANOVA | Analysis of variance |
| [Cl$^-$] | Plasma chloride concentration |
| COPD | Chronic obstructive pulmonary disease |
| CO$_2$ | Carbon dioxide |
| COVID-19 | Corona virus disease 2019 |
| CPAP | Continuous positive airway pressure |
| E | Emphysema |
EE Energy expenditure
H+ Hydrogen ion
HCO3− Bicarbonate ion
[HCO3−] Bicarbonate concentration
H2CO3 Carbonic acid
ILD Interstitial lung disease
[Na+] Plasma sodium concentration
NPPV Non-invasive positive pressure ventilation
N.S. Not significant
OSAS Obstructive sleep apnea syndrome
O2 Oxygen
PaCO2 Arterial partial pressure of carbon dioxide
PaO2 Arterial partial pressure of oxygen
PCO2 Partial pressure of carbon dioxide
PetCO2 End-tidal carbon dioxide partial pressure of exhaled gas
PO2 Partial pressure of oxygen
PtcCO2 Transcutaneous partial pressure of carbon dioxide
RQ Respiratory quotient
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
SAS Sleep apnea syndrome
SD Standard deviation
SEM Standard error of the mean
SpO2 Percutaneous oxygen saturation
VBGA Venous blood gas analysis
VCO2 Carbon dioxide production
VO2 Oxygen consumption
V/Q Ventilation/perfusion

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