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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_2) concentrations cannot be overemphasized. Within the body, assessment of the arterial partial pressure of CO_2 ($PaCO_2$) has been the gold standard for many decades. Non-invasive assessments are usually predicated on the measurement of CO_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_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 $PaCO_2$ 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_2 ($PtcCO_2$). $PtcCO_2$ monitoring during sleep can be helpful for evaluating sleep apnea syndrome, particularly in children. End-tidal PCO_2 is inferior to $PtcCO_2$ as far as accuracy, but it provides breath-by-breath estimates of respiratory gas exchange, while $PtcCO_2$ reflects temporal trends in alveolar ventilation. The frequency of monitoring end-tidal PCO_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

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1. Introduction

Atmospheric carbon dioxide (CO_2) concentration is increasing worldwide by the increasing consumption of carbon-based combustibles along with progressive deforestation [1,2]. Increases in atmospheric CO_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 ($\dot{V}CO_2$) and oxygen (O_2) consumption ($\dot{V}O_2$). 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.).

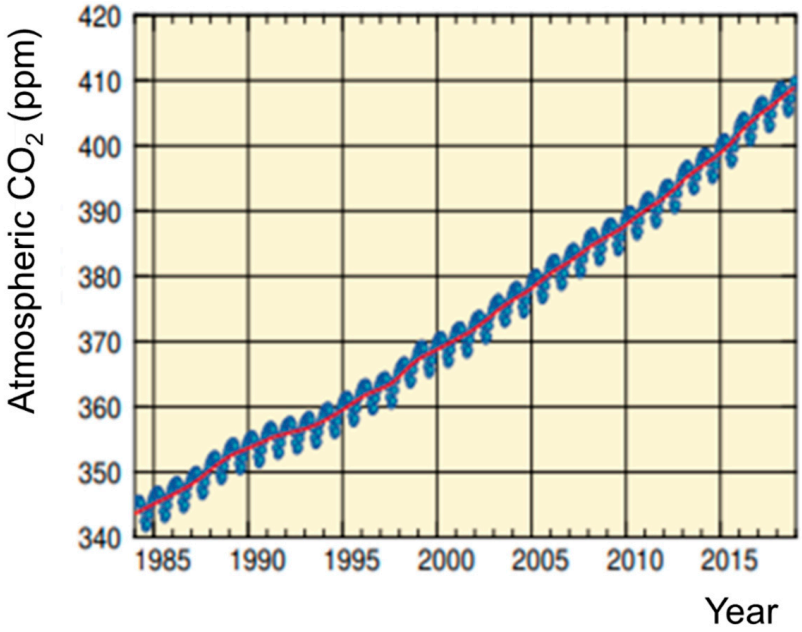


Figure 1. Globally averaged monthly mean mole fraction of CO_2 from 1984 to 2018 and the deseasonalized long-term trend shown as a red line (Adapted with permission from Ref. [2]. Copyright 2020 WMO WDCGG).

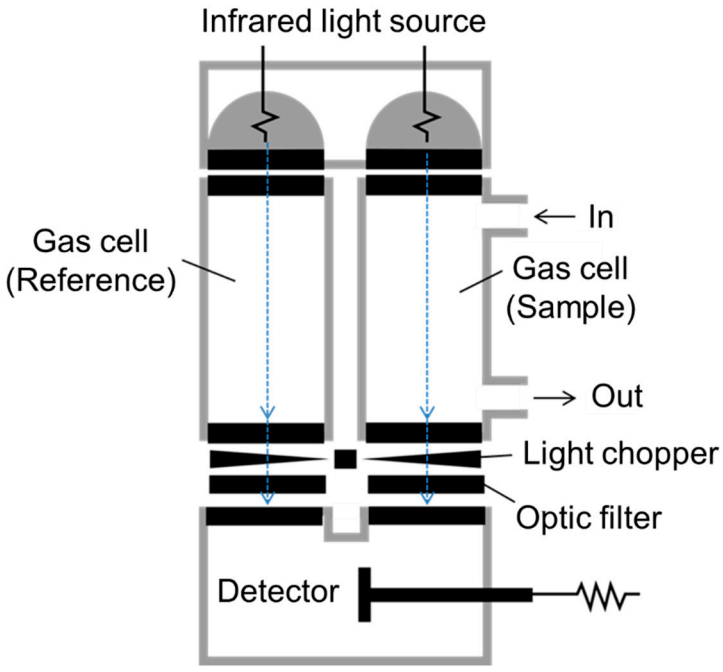


Figure 2. Measuring system of CO_2 by using the non-dispersive infrared analyzer. The light chopper delivers the data of infrared intensity as a continuous alternating current signal to the detector through the optic filter (Adapted with permission from Ref. [18]. Copyright 2021 HORIBA).

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 μm) 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].

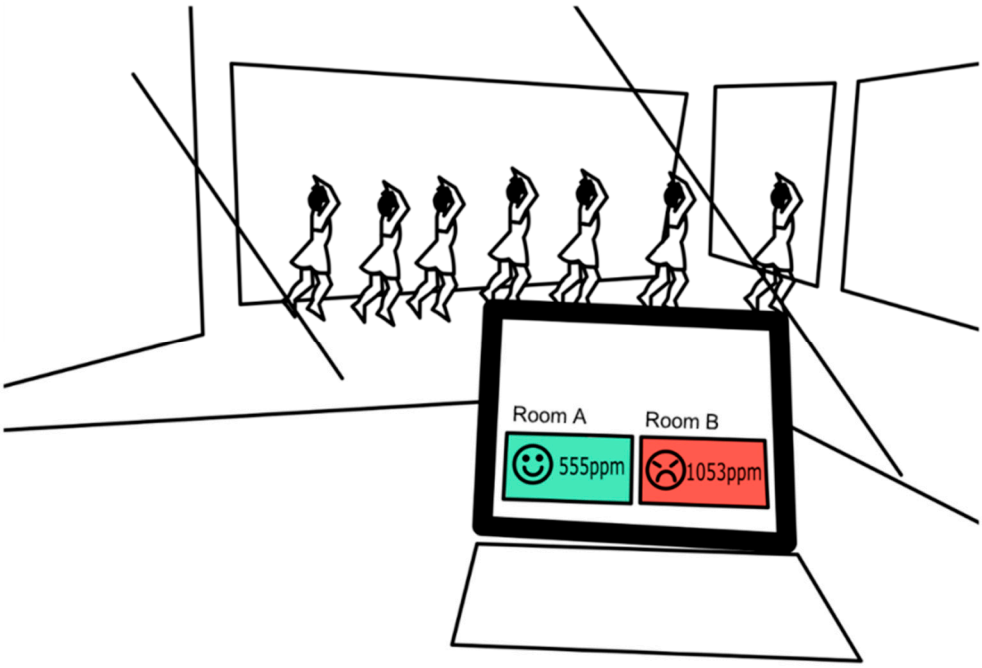


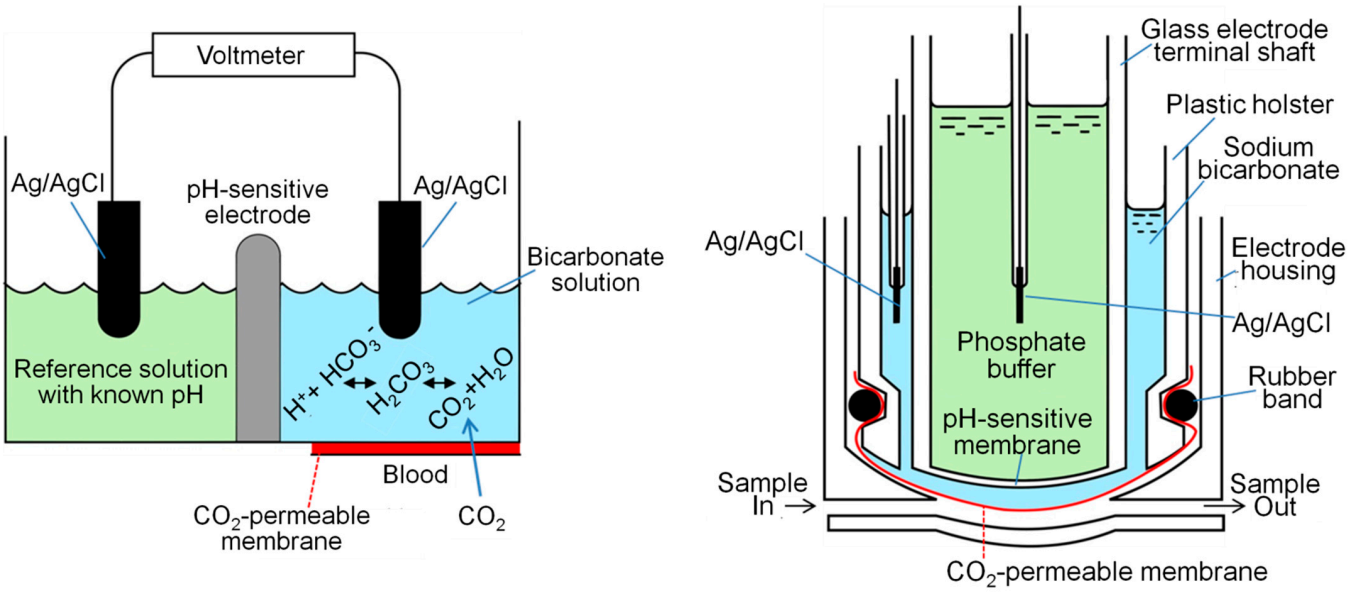
Figure 3. Monitoring of CO_2 levels in rooms. Higher levels of CO_2 in a room can mean there is a greater risk of viral transmission (Adapted with permission from Ref. [21]. Copyright 2020 Kyodo).

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

(Figure 4) [28,29]. This PCO_2 electrode contains the CO_2-permeable membrane and the principle of pH meter with a pH-sensitive glass membrane. $PaCO_2$ is usually measured for the evaluation of any type of lung disease [9,10]. $PaCO_2$ is useful for the diagnosis of hyperventilation, hypoventilation, CO_2 retention, and CO_2 narcosis in patients with COPD and many other pulmonary conditions [10,30,31].



(**a**) (**b**)

Figure 4. PCO_2 electrode. (**a**) The CO_2 from the blood diffuses through the membrane (red) into the bicarbonate solution (light blue). The hydrolysis reaction occurs in the bicarbonate solution and results in the production of hydrogen ions (H^+) in proportion to the amount of dissolved CO_2 present. The difference in voltage between the reference solution (light green) and the bicarbonate solution (light blue) is measured. Ag/AgCl, Silver electrode plated with silver chloride; HCO_3^-, Bicarbonate ion; H_2CO_3, Carbonic acid (Adapted with permission from Ref. [28]. Copyright 2005 Elsevier). (**b**) Severinghaus PCO_2 electrode. The principle of pH meter with pH-sensitive glass membrane is used (Adapted with permission from Ref. [28]. Copyright 2005 Elsevier).

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 $PaCO_2$ measurements [32,33]. The majority of CO_2 is transported in the body as bicarbonate ion (HCO_3^-) [34]. HCO_3^- plays a central role in maintaining the pH level in blood [32–34]. Therefore, it is important to calculate its concentration ($[HCO_3^-]$) in blood using the Henderson–Hasselbalch equation. $[HCO_3^-]$ 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 $PaCO_2$, arterial pH, and arterial $[HCO_3^-]$ 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 ($\dot{V}/\dot{Q}$) mismatch (especially relative increase in high $\dot{V}/\dot{Q}$ 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 $\dot{V}/\dot{Q}$ 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.

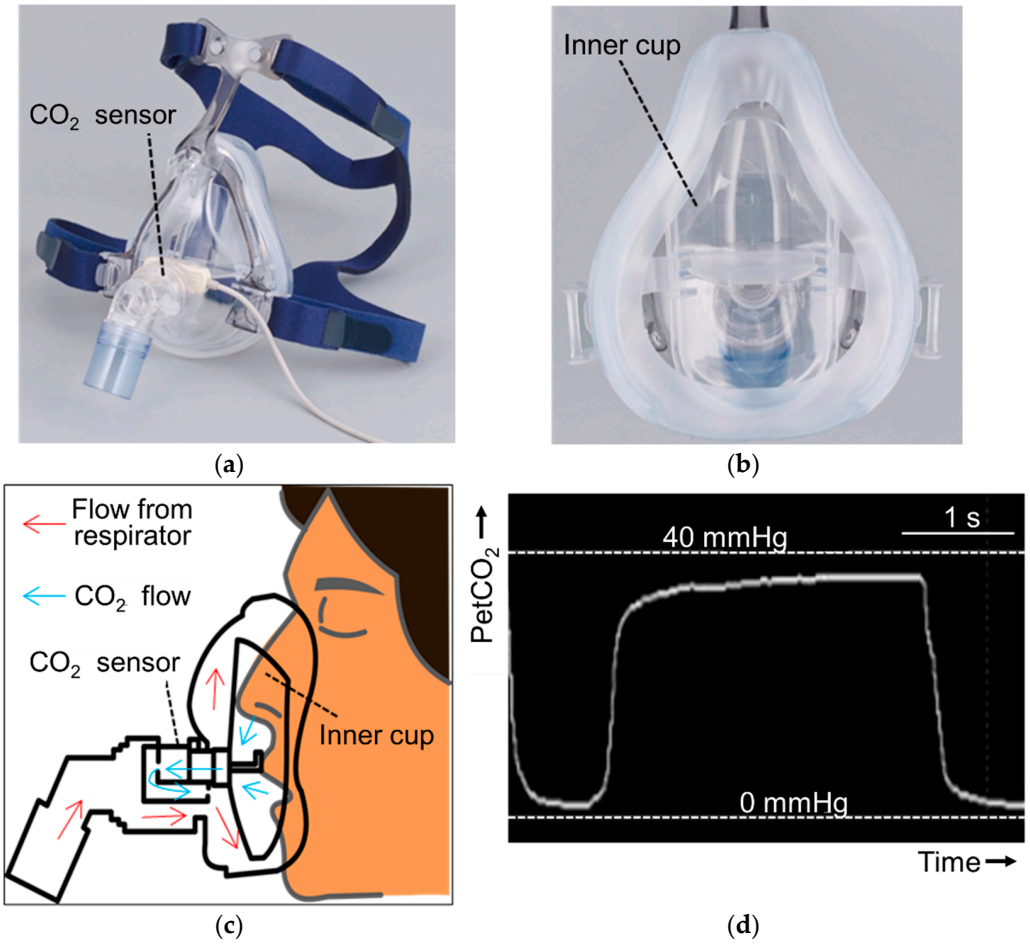


Figure 5. A system of measuring end-tidal PCO_2 during non-invasive positive pressure ventilation. (**a**) Mainstream CO_2 sensor (TG-980P, Nihon Kohden, Tokyo, Japan) is used in a mask (cap-ONE, Nihon Kohden, Tokyo, Japan). (**b**) The inner cup is attached inside the mask. (**c**) Air flow from respirator 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).

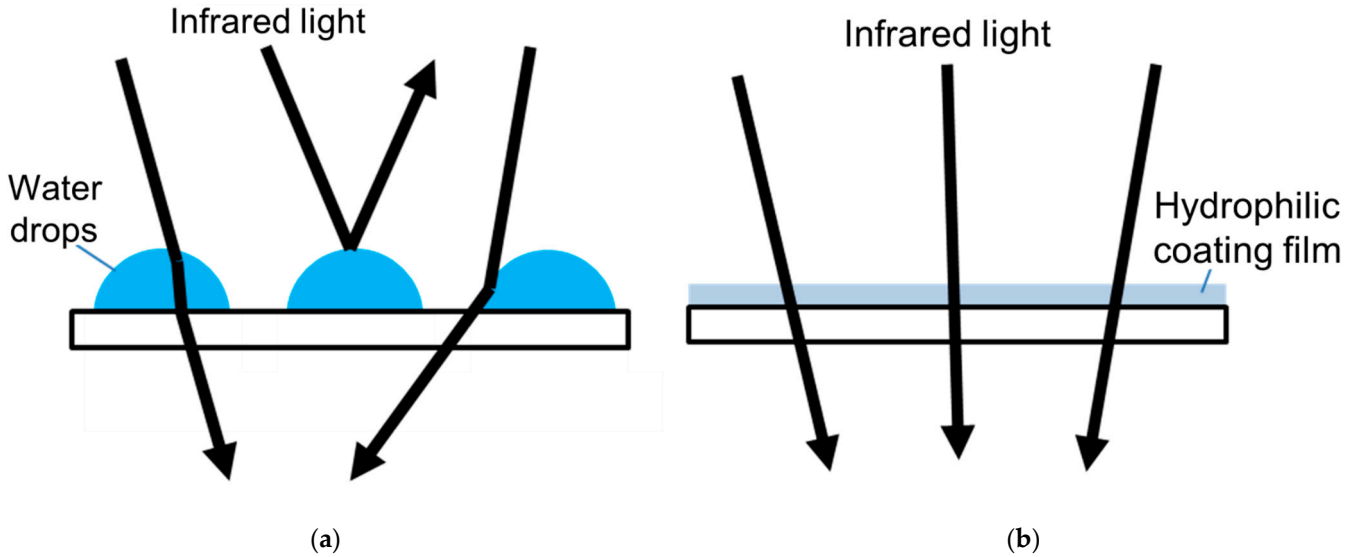


Figure 6. Technology of size reduction of end-tidal PCO_2 sensors. In the new CO_2 sensor, the use of heaters to avoid water drops is unnecessary. (**a**) In ordinary CO_2 sensors, heaters are necessary to prevent windows from being clouded by water vapor in expired air. Water drops on windows cause 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].

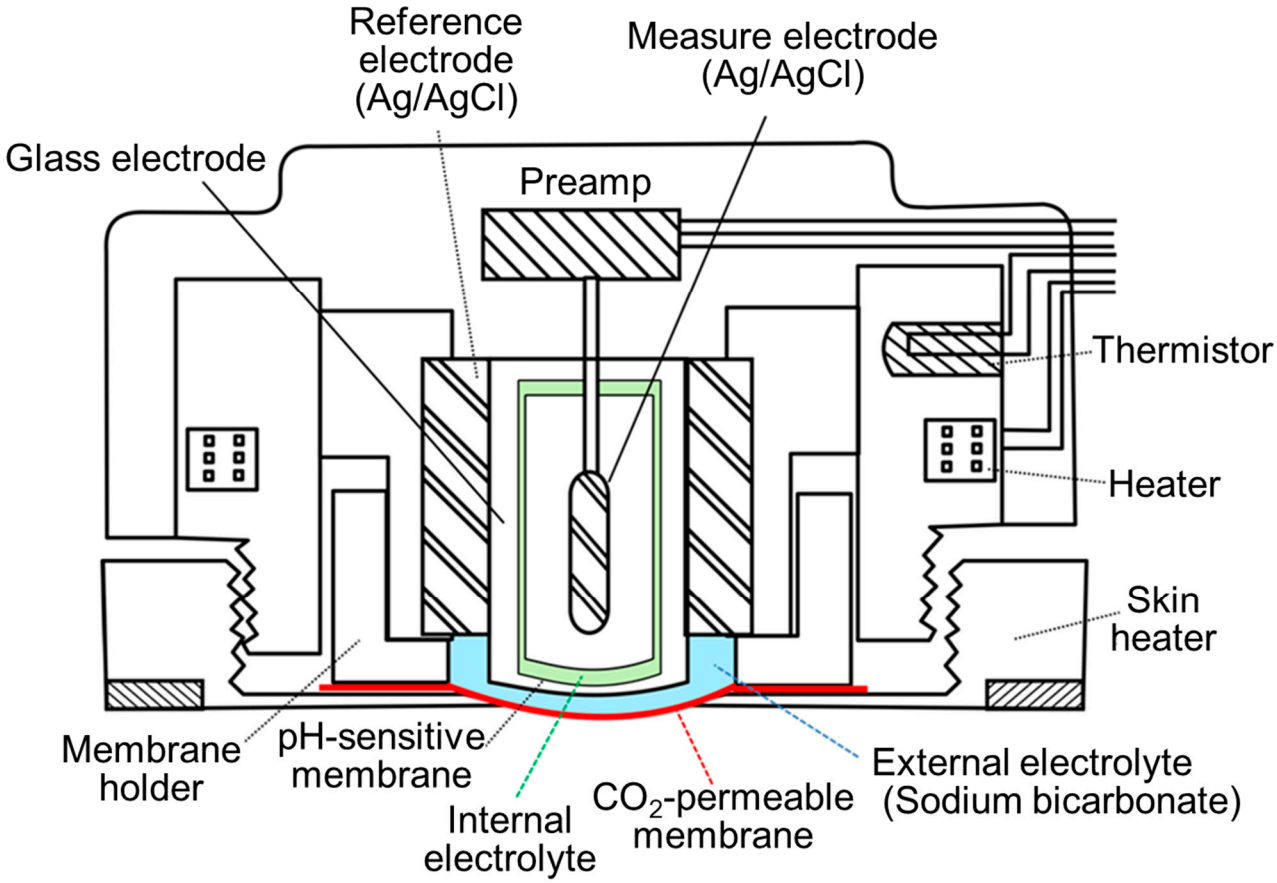


Figure 7. Transcutaneous PCO_2 sensor. The skin heater is necessary in addition to the Severinghaus electrode (Adapted with permission from Ref. [73]. Copyright 1983 Japanese Society for Medical and Biological Engineering). An ultra-thin film of buffer electrolyte (light green) is placed between the silver and glass. This internal electrolyte stabilizes the pH inside the glass electrode. The external electrolyte (light blue) contains sodium bicarbonate. According to the manufacturing companies, the precise blueprints of recent products differ.

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 $PaCO_2$.

Surrogate	Average Bias	1.96 SD	Accuracy	Usefulness for Patients with Pulmonary Diseases	References
$PvCO_2$	Approximately 5 mmHg higher than $PaCO_2$	14.7–15.0 mmHg	Worst	Limited	[45,50]
$PetCO_2$	2–5 mmHg lower than $PaCO_2$	6.9–14.4 mmHg	Second best	Limited	[83–88]
$PtcCO_2$	4–5 mmHg higher than $PaCO_2$	4.6–10.4 mmHg	Best	Good (still not replaceable)	[83–89]

$PaCO_2$, arterial partial pressure of CO_2; $PetCO_2$, end-tidal CO_2 partial pressure of exhaled gas; $PtcCO_2$, transcutaneous partial pressure of CO_2; $PvCO_2$, venous partial pressure of CO_2; SD, standard deviation. The width of $\pm$ 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.

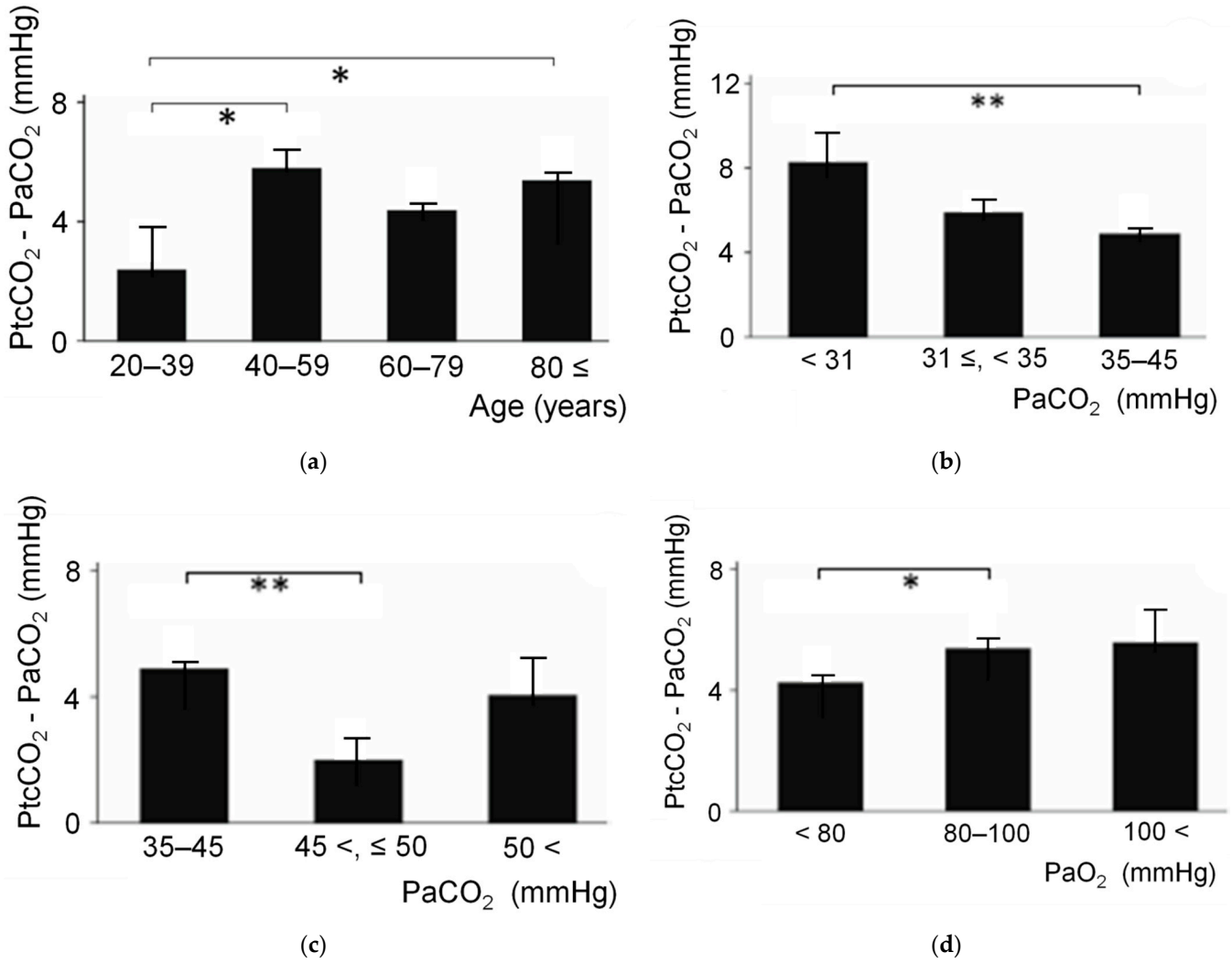


Figure 8. Comparisons of $PtcCO_2$ and $PaCO_2$ bias (n = 272). (**a**) Comparison of bias between four age groups. The bias was significantly lower in young adults (20–39 years) versus those aged 40–59 years and ≥80 years. (**b**) Comparison of bias between the severe, mild hypocapnia group, and normal 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).

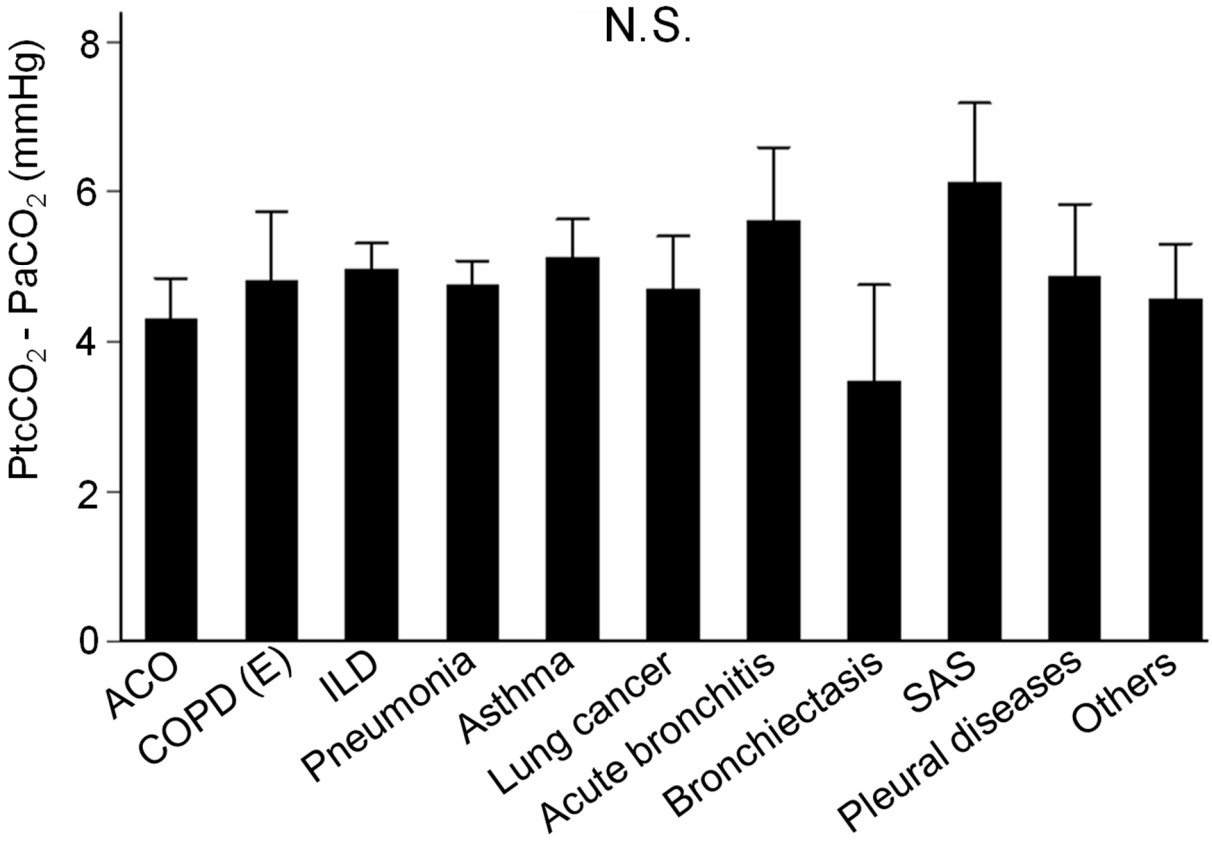


Figure 9. Subgroup analyses on PCO_2 bias ($PtcCO_2$—$PaCO_2$) of patients with various respirtory diseases (n = 272). Bars: SEM. There were no significant differences in PCO_2 bias (ANOVA with Tukey's post hoc test). ACO, asthma-chronic obstructive pulmonary disease overlap; ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; E, emphysema; ILD, interstitial lung disease; N.S., not significant; $PaCO_2$, arterial partial pressure of CO_2; PCO_2, partial pressure of CO_2; $PtcCO_2$, transcutaneous partial pressure of CO_2; SAS, sleep apnea syndrome ([89], additional data).

5.2. Usefulness

The use of this non-invasive $PtcCO_2$ monitor leads to an accurate assessment of CO_2 retention. All hypercapnia patients with $PaCO_2$ > 50 mmHg (n = 13→20) showed $PtcCO_2 \geq 50$ mmHg until 12 min [89] (additional data). Utilization of thinner films for CO_2-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 $PtcCO_2$ and $PaCO_2$ (±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, ±7.5mmHg at 12–13 min, and ±6.3 mmHg at 30 min [89].

5.3. Limitations

Although $PtcCO_2$ is currently the best non-invasive surrogate of $PaCO_2$, there were still some cases with large bias over 10 mmHg. $PaCO_2$ cannot be replaced with $PtcCO_2$ 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

$PtcCO_2$ 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]. $PtcCO_2$ monitoring with polysomnography may become the standard method of sleep study in the future [94]. $PtcCO_2$ monitoring during rehabilitation may be the promising method, too [96–98]. However, the actual $PaCO_2$ will not be disregarded, because the PCO_2 bias is sometimes large, and $PtcCO_2$ cannot replace $PaCO_2$ completely [89]. Therefore, future use of $PtcCO_2$ monitoring will be limited and may be just focusing on relative evolution.

6. Other Applications of Measuring CO_2 Mainly for Research Use

Measuring CO_2 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 ($\dot{V}CO_2/\dot{V}O_2$)

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

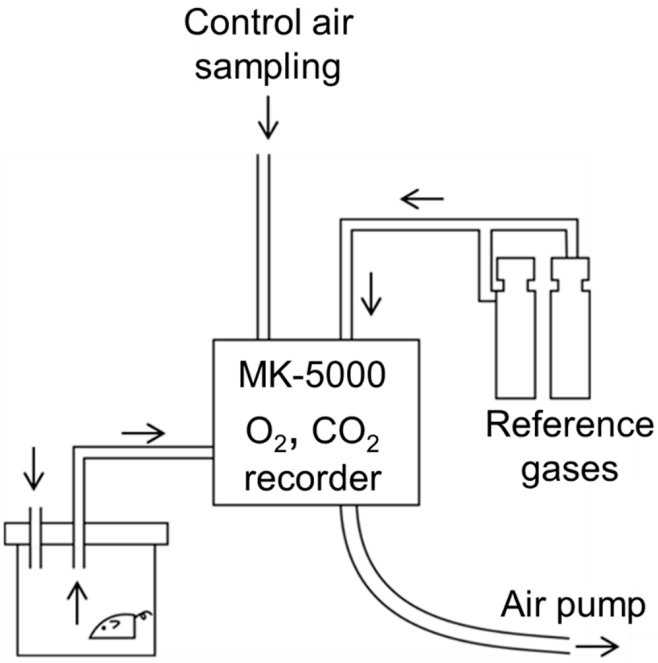


Figure 10. The system of measuring CO_2 production and O_2 consumption in mice. Inlet air routes from animal chamber, control air, and reference gases are periodically changed. CO_2 concentration is measured by infrared absorption analysis. O_2 concentration is measured by magneto-electrical analysis (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 O_2 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 oxydized, 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 sugested 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 tehcnical fragility of the mass spectrometers, which require more extensive technical support [57]. Furthermore, the method of photoinduced electron transfer is rapidly developping 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:

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
HCO_3^-	Bicarbonate ion
$[HCO_3^-]$	Bicarbonate concentration
H_2CO_3	Carbonic acid
ILD	Interstitional lung disease
$[Na^+]$	Plasma sodium concentration
NPPV	Non-invasive positive pressure ventilation
N.S.	Not significant
OSAS	Obstructive sleep apnea syndrome
O_2	Oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PCO_2	Partial pressure of carbon dioxide
$PetCO_2$	End-tidal carbon dioxide partial pressure of exhaled gas
PO_2	Partial pressure of oxygen
$PtcCO_2$	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
SpO_2	Percutaneous oxygen saturation
VBGA	Venous blood gas analysis
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption
V/Q	Ventilation/perfusion

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