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A rate-based transcutaneous CO_2 sensor for noninvasive respiration monitoring

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Abstract

The pain and risk of infection associated with invasive blood sampling for blood gas measurements necessitate the search for reliable noninvasive techniques. In this work we developed a novel rate-based noninvasive method for a safe and fast assessment of respiratory status. A small sampler was built to collect the gases diffusing out of the skin. It was connected to a CO_2 sensor through gas-impermeable tubing. During a measurement, the CO_2 initially present in the sampler was first removed by purging it with nitrogen. The gases in the system were then recirculated between the sampler and the CO_2 sensor, and the CO_2 diffusion rate into the sampler was measured. Because the measurement is based on the initial transcutaneous diffusion rate, reaching mass transfer equilibrium and heating the skin is no longer required, thus, making it much faster and safer than traditional method. A series of designed experiments were performed to analyze the effect of the measurement parameters such as sampler size, measurement location, subject positions, and movement. After the factor analysis tests, the prototype was sent to a level IV NICU for clinical trial. The results show that the measured initial rate of increase in CO_2 partial pressure is linearly correlated with the corresponding arterial blood gas measurements. The new approach can be used as a trending tool, making frequent blood sampling unnecessary for respiratory status monitoring.

Keywords

noninvasive; transcutaneous; respiration; CO_2; rate-based

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1. Introduction

The amount of CO_2 produced in the mitochondria is mainly related to the metabolic rate and the quantity of food metabolized. Optimal cellular functioning depends on an adequate supply of oxygen and an appropriate amount of CO_2 to maintain an acid-base balance. Arterial partial pressure of CO_2 ($paCO_2$) is an indicator of the body's ventilation status. Deviations from the normal range, which are known as hypocapnia and hypercapnia, contribute to neonatal morbidities. Hypocapnia or hypercapnia in the first few days of life contributes to altered cerebral blood flow. Potential consequences include intraventricular hemorrhage (IVH), periventricular leukomalacia, and cerebral palsy (Erickson et al 2002, Gannon et al 1998, Murase and Ishida 2005). Hypocapnia resulting from overventilation contributes to volutrauma and the development of bronchopulmonary dysplasia and brain injury (Garland et al 1995, Jobe 1999, Jobe and Bancalari 2001). Early exposure to hypercapnia and associated acidosis increases the risk for severe retinopathy of prematurity (Hauspurg et al 2011), IVH (Kaiser et al 2006), brain injury and developmental impairment (Hagen et al 2008). Clearly, rapid recognition of and response to extremes in $paCO_2$ is critical for survival and minimizing morbidities.

Although arterial blood gas (ABG) measurements remain the gold standard for guiding respiratory management in the neonatal intensive care unit (NICU), the necessity for placement of indwelling arterial lines or intermittent arterial or heel blood sampling are associated with potential complications such as bruising, inflammation, infection, anemia, and procedure-associated pain (Vertanen et al 2001). Sometimes, blood transfusions may be needed for preterm neonates to replenish the relatively large volume of blood withdrawn for diagnosis (Hack et al 2008, Rezende et al 2010). Moreover, ABG measurements only provide intermittent information concerning the dynamic changes in blood gases. Another often used method for respiratory status monitoring is capnography. However, it typically underestimates $paCO_2$. Several factors such as airway impediment, decreased cardiac output and large alveolar dead space affect the readings from capnographic $paCO_2$ measurements (Proquitté et al 2004, Saura et al 1996, Wahba and Tessler 1996).

Noninvasive transcutaneous gas monitors have been developed since the late 1970s and adopted for routine use in intensive care to measure the transcutaneous partial pressure of CO_2 ($tcpCO_2$) (Beran et al 1978, Greenspan et al 1981, Lübbers et al 1973). Measurements of $tcpCO_2$ depend on an increased capillary blood flow by increasing the temperature of underlying tissue with a heating element in the electrode. Manufacturers like Radiometer, SenTec, Medlab and Mekics have come up with several CO_2 monitoring systems within the last decade or two (Eberhard 2007). The major challenges they face are calibration, site changes, elevated temperature and associated burns. Due to the large mass transfer resistance of human skin, these transcutaneous gas monitors take >2 hours to stabilize at regular body temperature. To accelerate the stabilization process, the skin underneath the sensor is usually heated to 42°C or higher. Nevertheless, the measurement still requires 15–20 minutes of preheating. This may cause skin burns especially to neonatal patients if not handled properly, and necessitates frequent relocation of the sensor site (Restrepo et al 2012).

Given the disadvantages and limitations of current technologies, there is clearly a need for developing a new generation of monitoring devices for safer and faster assessment of ventilation status. Here we report a noninvasive method for ventilation status monitoring by measuring the initial transcutaneous CO_2 diffusion rate. Since the measurement is based on the initial diffusion rate, reaching the mass-transfer equilibrium is no longer required, and each measurement can be done in only two minutes. In addition, because heating the skin is not required, skin stimulation and burns are completely eliminated. In this paper, the factors affecting the measurement process were analyzed by a series of specially designed experiments. The prototype was then tested in a level IV NICU and the results were correlated with the corresponding arterial blood gas measurements.

2. Materials and methods

2.1. Experimental setup and operation procedures

The rate-based noninvasive method requires a stethoscope-shaped chamber called the sampler to collect the gases diffusing out of the skin. The measurement mechanism is shown in Figure 1. To make a measurement, the sampler was first placed on the skin surface with the opening facing the skin. The system was then purged with N_2 until the CO_2 present in the sampler was completely removed (N_2 flush stage). The 4-way valve was then switched to recirculation mode to allow the gases in the sampler to flow to the CO_2 sensor for monitoring of the CO_2 concentration (recirculation stage). The CO_2 sensor used in the prototype is a LI-820 CO_2 Analyzer (LI-COR Biosciences, Nebraska, USA), which is a sensitive (0–20,000 ppm), user friendly, economical and low maintenance device based on a single path, dual wavelength infrared detection system. The CO_2 concentration was recorded continuously throughout the sampling process. To isolate the gases in the system from the environmental air, a slight pressure (<14 kPa) was exerted on the sampler to keep it in a steady contact with the skin. Any higher pressure can disturb the capillary circulation and should be avoided.

2.2. Design of samplers

To carry out a series of designed experiments, two samplers were designed and fabricated. The samplers (Figure 2) have an inner circular chamber of 1 cm and 2 cm in diameter, with a volume of 0.235 ml and 1.256 ml, respectively. An O-ring is attached to the circumference of the circular chamber to prevent external leakage when attached to human skin. The samplers were designed for easy placement on the forearm, leg or palm. The smaller sampler was especially applicable for monitoring $tcpCO_2$ of neonates.

2.3. Mathematical modeling of CO_2 transcutaneous diffusion

Assuming that the gases in the recirculation system are well mixed, and the CO_2 diffusion in the skin follows Fick's law, then, the CO_2 accumulation in the system equals the amount of CO_2 diffusing out of the skin. If the measurement is made at regular body temperature, then

$$V\frac{dP}{dt}=DA\frac{dp}{dx}\Big|_{x=0} \quad (1)$$

where V is the total inner volume of the system, P is the CO_2 partial pressure in the system, t is time, D is the diffusion coefficient of CO_2 in the skin, A is the total mass transfer area, p is the CO_2 partial pressure in the skin, x is the distance from the surface of the skin. Suppose that the rate of CO_2 formation underneath the skin is r_0, mol/m^{3}s, the rate of CO_2 formation at the surface of the stratum corneum is 0, and the rate of CO_2 formation in the skin linearly decreases from inside to the surface, i.e.,

$$r=\frac{x}{L}r_0 \quad (2)$$

where L is the thickness of the skin. Although the CO_2 partial pressure in the system during the recirculation stage increases with time, the change is very small compared to the concentration gradient in the skin. In this case, the CO_2 mass transfer in the skin can be considered to be at a pseudo steady state, and the mass transfer of CO_2 in the skin follows

$$-\frac{D}{RT}\frac{d^2p}{dx^2}=\frac{x}{L}r_0 \quad (3)$$

Where R is the Boltzmann constant, T is temperature. The boundary conditions of equation (3) are at $x = 0$, $p = P$, at $x = L$, $p = p_a$. p_a is the CO_2 partial pressure in the tissue underneath the skin. Integrating equation (3), equation (4) is obtained

$$\frac{dp}{dx}=-\frac{r_0RT}{2DL}x^2+\frac{1}{L}(p_a-P)+\frac{LRTr_0}{6D} \quad (4)$$

Substitution of equation (4) into equation (1) gives

$$\frac{dP}{dt}=\frac{DA}{LV}(p_a-P)+\frac{ALRTr_0}{6V}=\alpha(p_a-P)+\beta \quad (5)$$

At the beginning of the recirculation, the CO_2 partial pressure in the system is zero. Integrating equation (5), the formula for calculating the CO_2 partial pressure in the system is obtained,

$$P=\left(p_a+\frac{\beta}{\alpha}\right)[1-\exp(-\alpha t)] \quad (6)$$

The function $\exp(-\alpha t)$ in equation (6) can be expanded into a Taylor series at $t = 0$:

$$\exp(-\alpha t)=1-\alpha t+\frac{1}{2}(\alpha t)^2-\frac{1}{6}(\alpha t)^3+\cdots\cdots \quad (7)$$

As $\alpha t \ll 1$ in the first few minutes, the third and later items are negligible. Thus, equation (6) can be simplified into

$$P \approx (\alpha p_a + \beta)t \quad (8)$$

From equation (8), the initial rate of increase in CO_2 partial pressure can be expressed by

$$\frac{dP}{dt}\Big|_{t=0} = \alpha p_a + \beta \quad (9)$$

It can be seen that the initial rate of increase in CO_2 partial pressure in the system is linearly proportional to the CO_2 partial pressure in the blood.

2.4. Design of experiments for factor analysis

From equation (9), it can be seen that in addition to the CO_2 partial pressure in the tissue underneath the skin, many other factors also affect the measured initial rate of increase in CO_2 partial pressure. To make sure that the measurement is reliable, it is very useful to know how the interfering factors affect the readings. The factor analysis study subject was a healthy female adult (age 28, height 157 cm, weight 51 kg). To avoid the changes in p_a to complicate the analysis, the tests were conducted at stable blood CO_2 level so that the readings were only affected by the other factors. As the blood CO_2 level is relatively stable when the body is in a fasting state, all the tests were conducted in the morning before any food intake. Other interferences such as exercise, drug intake, changes in breathing patterns, etc. should also be avoided during the factor analysis tests. After initial screening, 4 factors were considered to possibly affect the measurement results. The 4 factors are the location of the measurements, the size of the sampler, the movement of the subject and the position of the subject. To check the effect of the measurement location, 4 different locations (i.e., different levels) were selected: dorsum of hand, forearm, palm and dorsum of wrist. The number of levels for the other 3 factors is 2. To minimize the number of experiments, a very efficient experimental design, the Taguchi method, was used (Peng et al 2007, Tekade and Chougule 2013, Yang 2002). The orthogonal array that can accommodate the selected factors and levels is shown in Table 1. The designed experiments are listed in Table 2. As Table 1 can hold 5 different factors but there were only 4 different factors in this analysis, the column for factor 5 was left blank and used as a reference for variance analysis. Before the experiments shown in Table 2 were carried out, the air tightness of the system was checked to ensure no leakage during the tests. Each experiment was then done in triplicate to ensure reproducibility of the results. The initial rate of increase in CO_2 partial pressure, i.e., the slope of the profile at time 0, was calculated by fitting the CO_2 partial pressure profile in the first two minutes to a linear equation.

2.5. Clinical trial

After the factors affecting the measurements were tested and analyzed, a clinical trial was conducted in a level IV NICU. Prior to the clinical trial, all the samplers and tubing were sterilized and sealed in separate packages. The samplers were sterilized by autoclaving. The tubing which is not autoclavable was sterilized by ethanol followed by UV irradiation. Eligible patients for the clinical trial were infants admitted to the NICU requiring supplemental oxygen and blood gas monitoring. Excluded from the study were patients that

were non-viable or planned for withdrawal of support, or had major lethal congenital anomalies. Four preterm neonates that satisfied the above criteria were enlisted in this study. The subjects had gestational ages of 23, 24, 26, 36 weeks and weighed 500g, 620g, 1.8kg and 2.0 kg, respectively. To check the correlation of the initial rates of increase in CO_2 partial pressure with the corresponding ABG values, the diffusion rate measurements and the ABG measurements were made simultaneously. The number of paired measurements for each baby was 6, 6, 4, and 5, respectively. The intervals between measurements were random as a blood draw for ABG measurement was only made when it was clinically necessary.

3. Results

3.1. Factor analysis

Figure 3 shows a typical CO_2 partial pressure profile recorded during the study. Just as equation (8) predicts, the CO_2 partial pressure increases linearly with time in the first few minutes as recirculation is commenced.

Because we are reporting a newly developed method, it is necessary to investigate potential interferences and how these affect the measurements. To realize this goal, a series of specially designed experiments in Table 2 were conducted. The initial rates of increase in CO_2 partial pressure for each experiment were calculated and shown in Table 3. Based on the results in Table 3, the initial rates of increase in CO_2 partial pressure for each factor at different levels were calculated and given in the top part of Table 4. As there are 5 factor columns in the orthogonal array $L_8(4\times2^4)$, but there are only 4 factors being tested, the variation of the values in Table 4, 6^{th} column (Reference) were only caused by measurement error as the experimental conditions for the two different levels were actually the same, and thus can be used as a reference for the variance analysis. The variation of the values in the Reference column shows the repeatability of the measurements. As the two values are very close and have a very small variance, this confirms that the CO_2 measurements are stable and reliable.

The 2^{nd} column (Location) gives the CO_2 diffusion rates measured at 4 different locations on the subject as indicated in Table 2. The variance analysis shows that the measurements at the 4 locations were not significantly different. In other words, the location did not significantly affect the measurement results. Thus, the location of the sampler is not a critical factor when doing a measurement. Selection of location can be made simply for convenience.

The 3^{rd} column (Sampler Size) gives the variance analysis of the CO_2 diffusion rates measured using the two different samplers. The F value was much larger than the criterion F value for $p = 0.05$, so the chance that the two rate values in this column are the same is less than 5%. In other words, the two rate values are significantly different at 95% confidence level. From equation (5), it can be seen that for the same subject, the rate of increase in CO_2 partial pressure is linearly proportional to the area to volume ratio (A/V) of the device. The ratio of the A/V values of the two samplers is 2.8. It is close to the ratio of the amounts of

CO_2 collected by the two samplers, which is 2.5. These results also shows that the measured CO_2 diffusion rates are real and reliable.

The 4th column (Movement) gives the variance analysis of the CO_2 diffusion rates when the subject was either still or moving during the measurements. The results show that moving has a significant effect on the measurement at 95% confidence level. The reason may be that moving increased the respiration rate of the subject or made it more difficult to keep a steady sampler-skin contact, thus, compromising the airtightness of the system.

The 5th column (Subject Position) gives the CO_2 diffusion rates when the subject was either standing or seated. It shows that they are not significantly different. This means that the subject can be either standing or seated during the measurement. However, for convenience, it is better for the subject to be in a comfortable position. From the above analysis, it can be concluded that the rate-based approach is a reliable method for measuring transcutaneous CO_2. Among the tested factors, only moving has a significant effect on the results and should be avoided.

3.2. Clinical trial

Figure 4 shows the correlation between the initial rates of increase in CO_2 partial pressure measured by the rate-based method at room temperature and the corresponding ABG values. The correlation is significant ($p < 0.001$) with a high correlation coefficient (Figure 4), suggesting that the arterial blood CO_2 partial pressure is indeed linearly proportional to the initial rate of increase in CO_2 partial pressure. Based on the clinical data, a Bland-Altman plot was built, which is shown in Figure 5. The Bland-Altman plot shows a very small bias, and almost all the data points are within the boundaries. Among the 21 measurements, there is only one outlier, showing that the rate-based method can be used as an alternative method for blood gas monitoring.

4. Discussion

By now, arterial blood gas (ABG) sampling is still considered the gold standard for blood gas analysis. However, it requires frequent arterial or heel blood sampling, which has many side effects especially pain. The rate-based method of determining CO_2 as reported here is a noninvasive, safer and faster alternative to current methods. The rate-based method does not require blood draws, thus, the complications associated with blood sampling are completely avoided. On the other hand, transcutaneous gas monitors such as Radiometer TCM4 (Radiometer, Copenhagen, Denmark) can also measure the transcutaneous partial pressure of CO_2 noninvasively, but these require a long wait until the transcutaneous mass transfer equilibrium is established. To accelerate the stabilization process, the skin underneath the sensor is usually heated to 42°C or higher. At this temperature, the stabilization time can be shortened from 2 hours to 15 minutes, but it poses the risk for skin burns if not handled properly. In contrast, the rate-based method can be done at body temperature with no effect on the response time. In addition, the measurement depends on the initial rate and each measurement takes only 2 minutes or less to obtain. It should be noted that ABG measurements can provide only intermittent information and does not provide instantaneous results. Compared to the ABG measurements, the rate-based method has a very small bias

(−0.2 mm Hg) and the deviation from ABG is less than 4 mm Hg for the most data points. As blood sampling is on longer required, the rate-based method will allow for more frequent testing and more immediate results.

Like any other indirect methods, the rate-based method requires calibration as it measures the initial rate of transcutaneous CO_2 diffusion rather than direct arterial blood CO_2 levels. Thus, the rate of CO_2 diffusion has to be converted to the arterial blood CO_2 level to be clinically relevant. From equation (9), it can be seen that the calibration needs two corresponding ABG values. The slope of the equation is a constant that is related to the diffusion coefficient of CO_2 through the skin and the thickness of the skin. The intercept of the equation is a constant that is related to the respiration rate and thickness of the skin and temperature. The intercept is positive because CO_2 is produced in the skin. As the permeability of the skin may change with time, a re-calibration may be required from time to time. The re-calibration frequency will be determined in the future clinical trials. In addition to the two-point calibration, a one-point calibration is also possible based on the following equation:

$$\ln\left(\frac{dP}{dt}\right) = -\alpha t + \ln(\alpha p_a + \beta) \quad (10)$$

However, the one-point calibration takes longer time. As the rate of increase in CO_2 partial pressure only changes slightly during the 2 minutes of an ordinary measurement, the recirculation stage has to be extended (>20 minutes) so that term *dP*/*dt* on the left side of equation (10) can have a significant change.

It should be mentioned that even without calibration, the rate-based approach has shown very good correlation with ABG (Figure 4) among the 4 neonatal subjects of various gestational ages and weight. A larger sample population is expected to improve the statistical correlation. Nevertheless, the rate-based approach in its present form can be used as a trending tool to monitor the changing trend of the blood CO_2 levels. This can significantly reduce the frequency of blood draws and potential blood loss due to frequent sampling.

5. Conclusions

The current studies characterized a novel rate-based approach to noninvasive transcutaneous gas monitoring that is painless, safe and fast. No invasive blood draws are required unlike standard ABG measurements. Unlike commercially available transcutaneous CO_2 monitors, this approach requires no heating of the skin that can lead to measurement-related burns in patients. We investigated the potential factors that can affect the measurement of the transcutaneous CO_2 diffusion using specially designed experiments. Movement of the subject was found to have a statistical effect on the measurements but not the location of the measurement or the position (sitting or standing) of the subject. The clinical trial of the prototype conducted in a NICU shows that the measured initial rate of increase in CO_2 partial pressure is linearly correlated to the arterial blood CO_2 levels. The rate-based device

can be used as a trending tool for respiratory status monitoring to significantly reduce the frequency of blood sampling.

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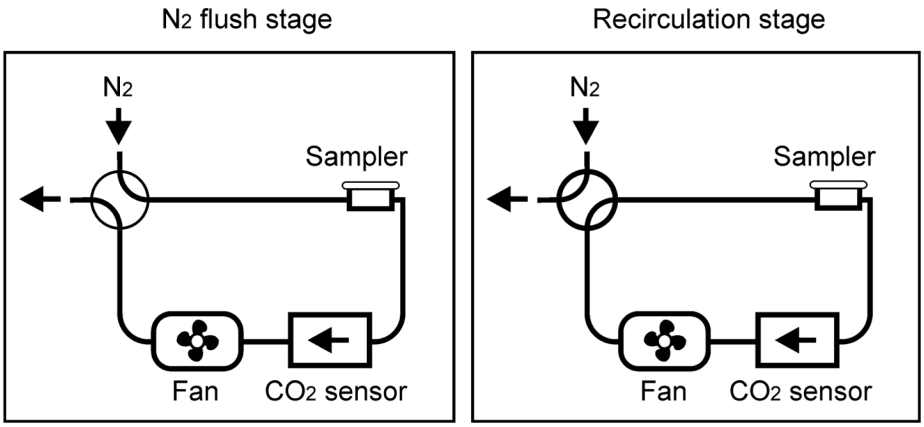

Figure 1.

The schematic of the experimental setup for rate-based measurements. Left: The N_2 flush stage of the measurement. Right: The recirculation stage of the measurement.

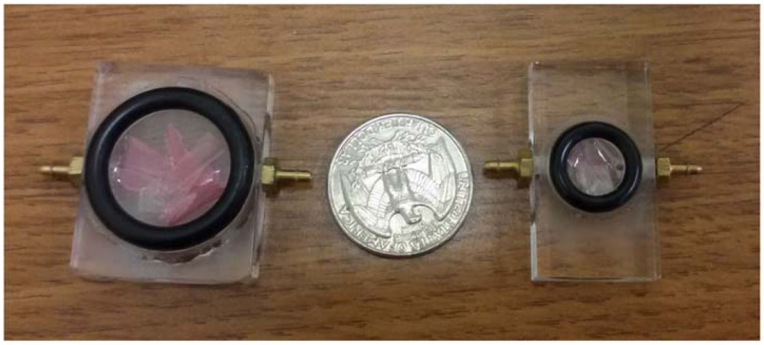

Figure 2.

The small and large samplers used to measure the initial rate of increase in CO_2 partial pressure in the recirculation system. The inner diameter of the small and large samplers is 10 mm and 20 mm, respectively.

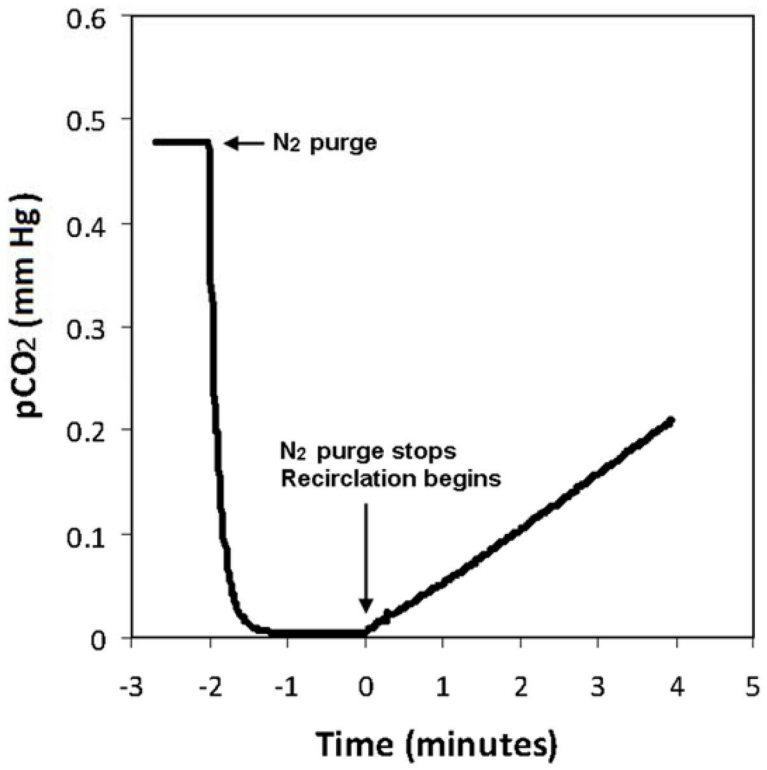

Figure 3.
A typical CO_2 partial pressure profile recorded. The CO_2 partial pressure drops to zero during the N_2 flush stage, and increases linearly when the recirculation begins.

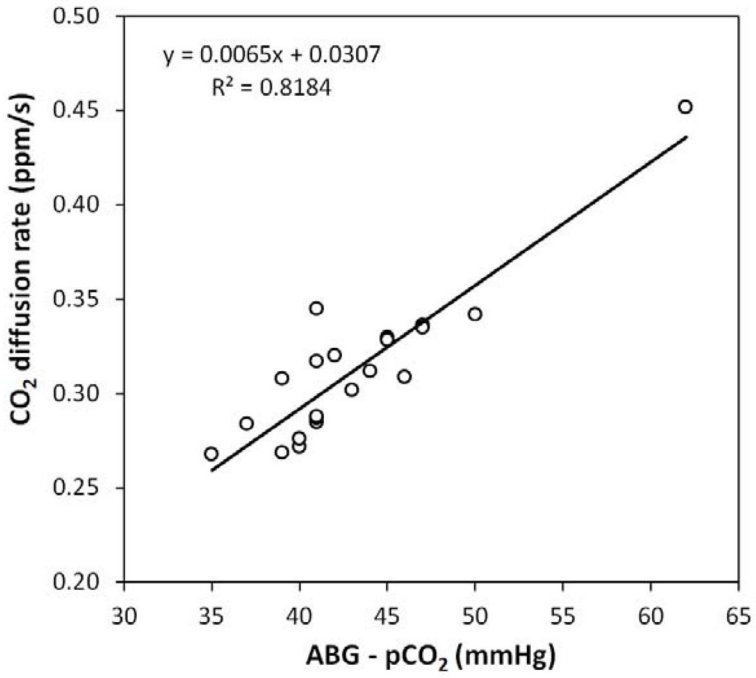

Figure 4.

The correlation between the initial rates of increase in CO_2 partial pressure measured by the rate-based method at room temperature and their corresponding ABG values. The subjects were 4 preterm neonates with gestational ages ranging from 23 to 36 weeks and weighing from 0.5 to 2.0 kg.

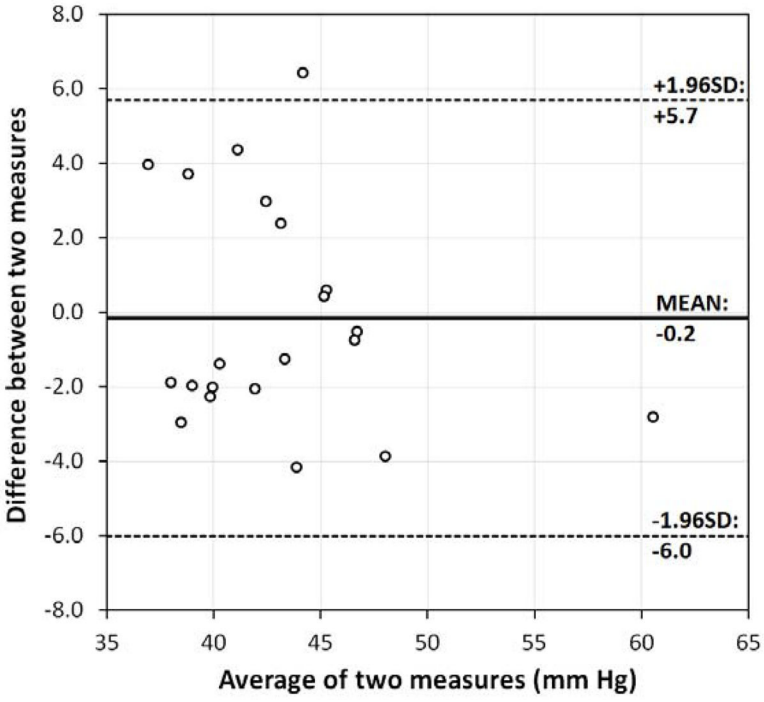

Figure 5.

The Bland-Altman Plot between the rate-based measurements and the ABG values. The subjects were 4 preterm neonates with gestational ages ranging from 23 to 36 weeks and weighing from 0.5 to 2.0 kg.

Table 1

The orthogonal array $L_8(4\times2^4)$ for factor analysis

Test No.	Factor No.				
	1	**2**	**3**	**4**	**5**
1	1	1	1	1	1
2	1	2	2	2	2
3	2	1	1	2	2
4	2	2	2	1	1
5	3	1	2	1	2
6	3	2	1	2	1
7	4	1	2	2	1
8	4	2	1	1	2

Note: Each column represents a different factor. The numbers in each column stand for the levels of that factor. Factor 1 has 4 different levels. Factors 2–5 have 2 different levels.

Table 2

The design of experiments for factor analysis

Test No.	Factor				
	Location	**Sampler size**	**Movement**	**Subject position**	
1	Dorsum of hand	Small	Moving	Standing	
2	Dorsum of hand	Large	Still	Seated	
3	Forearm	Small	Moving	Seated	
4	Forearm	Large	Still	Standing	
5	Palm	Small	Still	Seated	
6	Palm	Large	Moving	Standing	
7	Dorsum of wrist	Small	Still	Standing	
8	Dorsum of wrist	Large	Moving	Seated	

Note: Table 1 can accommodate 5 different factors. As there were only 4 different factors in this analysis, the column for factor 5 was left blank and used as a reference.

Table 3

The initial CO_2 diffusion rates (ppm/second)

Test No.	Run 1	Run 2	Run 3	Average	Stdev
1	0.1149	0.1085	0.1241	0.1158	0.0078
2	0.2007	0.1925	0.2068	0.2000	0.0072
3	0.0949	0.1052	0.0986	0.0996	0.0052
4	0.1507	0.1625	0.1595	0.1576	0.0061
5	0.0743	0.0794	0.0802	0.0780	0.0032
6	0.2574	0.2386	0.2452	0.2471	0.0095
7	0.0695	0.0581	0.0605	0.0627	0.0060
8	0.2888	0.2589	0.2709	0.2729	0.0150

Note: Each test listed in Table 2 was carried out in triplicate to ensure the reliability of the analysis.

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Table 4

The **v**ariance analysis of the initial CO_2 diffusion rates

Factor level	Location	Sampler size	Movement	Subject position	Reference
1	0.1579	0.0890	0.1839	0.1458	0.1561
2	0.1286	0.2194	0.1246	0.1626	0.1524
3	0.1626				
4	0.1678				
Variance	3.08×10^{-4}	8.50×10^{-3}	1.76×10^{-3}	1.41×10^{-4}	6.84×10^{-6} (V_0)
F-value (V/V_0)	45	1242	257	21	1
F(p=0.05)	216	161	161	161	
Same?	Yes	No	No	Yes	

Note: The results for different factor levels in the top part of the table were obtained by averaging the readings for that level. According to Table 1, the result for level 1 of factor 1 (location) is the average of the readings for Test 1 and Test 2. The result for level 2 of factor 1 (location) is the average of the readings for Test 3 and Test 4, and so on. The variance in the bottom part of the table shows the variability of the results for different levels. The variance for factor 5 shows the variability only caused by experimental error as the experimental conditions for the two different levels are the same. Thus, the variance for factor 5 can be used as a reference for variance analysis.