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Development and characterization of a point-of care rate-based transcutaneous respiratory status monitor

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Abstract

Blood gas measurements provide vital clinical information in critical care. The current “gold standard” for blood gas measurements involves obtaining blood samples, which can be painful and can lead to bleeding, thrombus formation, or infection. Mass transfer equilibrium-based transcutaneous blood gas monitors have been used since the 1970s, but they require heating the skin to 42°C to speed up the transcutaneous gas diffusion. Thus, these devices have a potential risk for skin burns. Here we report a new generation of noninvasive device for respiratory status assessment. Instead of waiting for mass transfer equilibrium, the blood gas levels are monitored by measuring the transcutaneous diffusion rate, which is proportional to blood gas concentration. The startup time of this device is almost independent of skin temperature, so the measurement can be made at any body temperature. The test results show that this device can track the blood gas levels quickly even at normal body temperature.

Keywords

Noninvasive; transcutaneous; respiration; blood gas; sensor; monitor

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Ethical approval

The research was approved by the Office for Research Protections and Compliance of University of Maryland Baltimore County (Protocol #: Y12XG26011). The experimental subjects were informed about the test and its characteristics and gave consent for use of the data.

Conflict of interest statement

None declared.

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1. Introduction

Partial pressures of arterial oxygen (paO_2) and carbon dioxide (paCO_2) are two of the most important respiratory parameters in intensive care. PaO_2 reflects the adequacy of oxygen delivery to the blood via lungs, and paCO_2 reflects the adequacy of ventilation to clear the metabolic byproducts from blood. Hypoxia is a condition in which the body or a region of the body is deprived of adequate oxygen supply. Severe hypoxia can cause multiple organ failure or even death. Hyperoxia occurs when tissues and organs are exposed to an excess supply of oxygen or higher than normal partial pressure of oxygen, and can lead to oxygen toxicity. During oxygen therapy for preterm neonates, the occurrence of hyperoxia increases the risk of retinopathy of prematurity [1–3]. Hypocapnia, a state of reduced carbon dioxide in the blood, may contribute to intraventricular hemorrhage, cerebral palsy, cognition developmental disorder, and auditory deficit whereas severe hypercapnia can cause intracranial hemorrhage, consciousness alterations, catapora, and hyperspasmia [4–6].

Currently, arterial blood gas (ABG) measurement remains the gold standard for guiding respiratory management in intensive care units (ICU). Although reliable and accurate, it requires access to arterial blood by placing arterial line or repeated arterial punctures. Breaking the skin to collect blood samples is painful and can lead to bleeding, thrombus formation, or infection. For very small-size preterm neonates, the blood loss due to sampling sometimes even necessitates blood transfusions.

Transcutaneous blood gas monitor using electrochemical sensor has been introduced into ICU since its invention in the 1970s [7–9]. Although noninvasive, it needs to heat the skin to 42°C or higher to accelerate the response, but still requires ~20 minutes for startup before any meaningful results can be provided. Due to the elevated temperature, skin burns can occur if the measurement lasts more than a few hours. Additionally, current devices drift and need to be recalibrated frequently. Capnography, the monitoring of CO_2 partial pressure in the respiratory gases, has been used as a monitoring tool during anesthesia and intensive care. Its disadvantages include frequent inaccuracy and low reliability in patients with chronic obstructive pulmonary disease. Since the 1980s, pulse oximetry has been used to measure the proportion of hemoglobin in arterial blood that is bound to oxygen [10,11]. Pulse oximetry is easy to use, and does not require heating the skin or calibration. However, its detection mechanism limits its usefulness only for the detection of hypoxia.

Given the disadvantages and limitations of current technologies, there is a need for the development of a new generation of noninvasive monitoring devices for fast assessment of respiratory status to better guide clinical practice [12]. Our goal is to develop a noninvasive respiratory status monitor that is safer and faster than current sensors.

2. Materials and methods

2.1. Principle of measurement

The principle of the noninvasive blood gas measurement is shown in Fig. 1. The system consists of a sampler, a gas pump, CO_2 and O_2 sensors, and two 3-way valves, which are connected by gas-impermeable tubing. To make a measurement, the sampler is placed on the

skin and held in place with medical grade adhesive to prevent leaking. N₂ is then introduced into the system to flush out the ambient air (N₂ flush stage). After that, the 3-way valves are switched to allow the gases to recirculate between the sampler and the sensors (recirculation stage). During the recirculation stage, the N₂ atmosphere in the system serves as a sink to provide a concentration gradient for O₂ and CO₂ to diffuse out of the skin. The O₂/CO₂ concentrations are recorded continuously and the rate of increase in CO₂/O₂ partial pressure is calculated.

2.2. Construction of prototype

The sampler used to collect the blood gases diffusing out of the skin is an acrylic cup-shaped structure with two hose barb fittings (Fig. 2). Three different samplers were made, which have a sampling area of 0.9 cm², 8.5 cm² and 12.6 cm², respectively. The CO₂ sensor is a LI-820 CO₂ analyzer (LI-COR, Lincoln, Nebraska), which has a measurement range of 0–20,000 ppm with a 1-ppm resolution. The O₂ sensor is an oxy.IQ oxygen transmitter (GE Infrastructure Sensing, Billerica, MA), which measures oxygen in the range of 0–2,000 ppm with a resolution of 2 ppm. The sensors are designed to output their digitized values in serial format (RS 232). They are connected to a computer via serial-to-USB converter (i.e. FT232 from Future technology). The gas pump is a micro-diaphragm pump produced by Parker (Hollis, NH), which provides a flow rate up to 800 milliliter per minute. The 3-way valves are solenoid valves produced by the Lee Company (Westbrook, CT). They require only a very small power to operate, have small dimensions (<2" in any direction), and are compatible with medical applications. The tubing that is used to connect the various components is tygon tubing produced by Saint Gobain (Malvern, PA), which has a very low CO₂/O₂ permeability. The electronics for activating the valves and digitizing the readings of the sensors are controlled by a dedicated microcontroller, which is also responsible for communicating the data to the computer. The program is written in LabVIEW, which controls the valves, reads the sensors, logs the data, and calculates the slopes in real time. All the time intervals are user adjustable so as to allow flexibility of the software.

2.3. Test of prototype

The prototype was extensively characterized in the lab after it was built. First, the double-sided medical grade adhesive tape produced by Adhesives Research (Glen Rock, PA) was cut into pieces in the same shape as the sampler. One piece of adhesive tape was applied to the opening of the sampler (Fig. 2). The measurement site on the body was wiped with an alcohol prep and let dry. Then, the sampler was attached to the skin by pressing the adhesive against it. In addition to using the adhesive, an elastic band was used for reinforcement, ensuring that the sampler stays well in case the skin is oily or rigorous movements are involved during measurement. The N₂ supply for purging the system was from a gas tank equipped with a pressure regulator, and the output pressure was set at ~0.5 PSI. Use of higher pressures can increase the N₂ flow rate, reduce the purging time, but can compromise the seal between the skin and the sampler, creating a leakage that will ultimately skew the results. The time intervals used in the tests were 30 seconds for N₂ flush and 60 seconds for recirculation. During the recirculation stage, the sensors were read every half a second and the slope was calculated by fitting the readings to a linear equation. The measurement cycle

would repeat until it was stopped by pressing the stop button. After the test, the sampler was gently detached from the skin and the adhesive was peeled off the sampler.

2.4. Transcutaneous mass flux and signal to noise ratio (S/N)

The mass flux of the blood gas through the skin can be expressed as

$$F = k(T)(p_a - p_f), \quad \text{ml/cm}^2\text{s} \quad (1)$$

Where $k(T)$ is the mass transfer coefficient of the blood gas through skin, p_a is the arterial partial pressure of the blood gas, p_f is the partial pressure of the gas in the system. When pure N_2 is used as purge gas, p_f is very small and negligible compared to p_a . So, equation (1) can be simplified as

$$F = k(T)p_a \quad (2)$$

As the amount of blood gas diffusing out of the skin equals to the accumulation of the gas in the system, F can also be calculated by the following equation:

$$F = \frac{\Delta \text{ppm} \cdot V}{A t_m} \quad (3)$$

Where ppm is the concentration change of the blood gas in the system during the recirculation stage, V is the internal volume of the system (ml), A is the sampling area of the sampler (cm^2), and t_m is the duration of the recirculation stage (seconds).

The S/N of the system equals:

$$S/N = \frac{F}{F_x} = \frac{\Delta \text{ppm}}{R/3} = \frac{3F \cdot A \cdot t_m}{R \cdot V} \times 10^6 \quad (4)$$

where F_x is the noise of the measured mass flux, R is the resolution of the sensors. Usually, resolution is defined as 3 times of signal noise. The CO_2 and O_2 sensors used in the system have a 1-ppm and 2-ppm resolution, respectively, so the S/N of the device is approximately equal to 3 ppm for CO_2 and 1.5 ppm for O_2 .

2.5. Design of experiments for analysis of affecting factors

To check if skin preparation and measurement location significantly affect the measurement results, we used orthogonal experiment designs [13,14] to determine their effects. All the tests were conducted in the morning when the body was in a fasting state and the blood gas level was stable. As changes in breathing pattern, food or drug intake, exercise could affect the blood gas levels, these activities were not performed prior to and during the tests. Two

different skin preparation methods, alcohol prep wiping and wash with soap, were tested. To avoid mutual influence of the two different skin preparations, two separate groups of tests were designed and two affecting factors were tested each time (Table 1).

3. Results

3.1. Baseline and S/N

The baseline readings of the rate-based noninvasive respiratory status monitor were tested by bypassing the sampler (connecting the incoming and outgoing tubing directly). Fig. 3 shows the baseline readings of sampler C for 41 cycles of measurements. It can be seen that the CO₂ readings stabilized almost immediately while the O₂ readings took about 20 cycles to stabilize. There are two possible reasons for the slow stabilization of the oxygen readings: the O₂ sensor's slow response and depot effect. The CO₂ sensor measures CO₂ based on infrared spectra detection. It responds to changes in CO₂ level almost immediately. Comparatively, the O₂ sensor used in the device is an electrochemical sensor, whose response time is much longer. Thus, there will be a delay when the concentration of the analyte changes quickly. In other words, the reading will be higher than the actual value when the concentration of the analyte is decreasing. The depot effect is caused by the gradual release of adsorbed O₂. When the system is purged with N₂, the adsorbed O₂ will be released into the system and give a false higher reading until the adsorbed O₂ is completely released. The stabilized baseline readings show the fundamental leak rate of the system. The averages of the stabilized baseline signals for CO₂ and O₂ are shown in Table 2. It can be seen that the leak rate of O₂ is much higher than that of CO₂. This is expected as the leak is mainly caused by diffusion from air to the system and the O₂ concentration in air (20.95%) is hundreds of times higher than that of CO₂ (0.039%).

After the baseline test, the device was tested on a healthy adult. The readings of sampler C for 24 cycles of measurement are shown in Fig. 3. Again, the CO₂ signal quickly stabilized but the O₂ signal took more than 10 cycles to stabilize. The data analysis of the human test is also shown in Table 2. It can be seen that the average of the CO₂ readings is 0.301 ppm/s for sampler C, much higher than its baseline. The average of the O₂ readings is also higher than the baseline, but it is not so impressive due to the high leak rate. The test results for the other two samplers are shown in Table 2 as well. It can be seen that the larger the sampler the higher the signal as well as the S/N.

3.2. Transcutaneous mass transfer flux and S/N

The device has an internal volume of approximately 80 ml. Using the data in Table 2, the transcutaneous mass fluxes were calculated by Equations (3), which are 1.87×10^{-6} ml/cm²s for CO₂ and 8.06×10^{-7} ml/cm²s for O₂. The S/N was estimated to be 53.1 for CO₂ according to Equation (4), which is quite close to the S/N calculated using the real signals (Table 2). However, the estimated S/N for O₂ using Equation (4) was 11.5, which is 2 times higher than the actual S/N calculated using the real signals, suggesting that the real resolution of the O₂ sensor is lower.

As S/N is proportional to the sampling area according to Equation (4), we can easily calculate the S/N for samplers in different size. For example, the previously used small sampler has a 1-cm diameter and a sampling area of 0.8 cm². Its S/N was estimated to be 2.1 for CO₂ and 0.5 for O₂ when it is used for measurements on adults. So, although it has been successfully used for preterm neonates [15,16], it is too small for adults and the measurement results could be unreliable.

3.3. Effect of measurement location and skin pretreatment on measurement

To check if skin preparation and measurement location affect the measurement results, 8 tests were conducted and the measured increase rates are given in Table 1. As each affecting factor was tested at two different levels and each level was tested twice, the average increase rate for each level is equal to the mean of the two test results. For example, the average increase rate without skin treatment is equal to the mean of the results of test No.1 and test No.2. The average increase rate for the measurements performed on the forearm is equal to the mean of the results of test No.1 and test No.3. The average increase rate for all other conditions can be calculated the same way and the results are given in Table 3. F-test was used to compare the results at two different levels and the p-values are given in Table 3. It can be seen that skin pretreatment and measurement location do not significantly affect the readings. In other words, the measurement can be done at different locations on the body and the skin can be pretreated either ways before the test.

3.4. Detection of Changes in paCO₂ induced by increasing the amount of activity

After the above tests were conducted, the device was tested on two adult subjects to see if it could track the changes in blood gas level induced by increasing the amount of activity. For subject 1, the test was conducted on the forearm and the results are shown in Fig. 4. The average CO₂ increase rate is 0.270 ppm/s when the subject was sitting quietly. When the subject squatted 40 times in 2 minutes, an abrupt increase in CO₂ increase rate up to 0.46 ppm/s (70% increase) was observed. Then, the CO₂ increase rate gradually returned to normal when the subject relaxed. Although the test was conducted at a different location (chest) for subject 2, similar results were obtained. The average of the CO₂ increase rates is 0.255 ppm/s when the subject was sitting quietly. When the subject squatted 40 times, a similar abrupt increase in CO₂ increase rate was observed, but the percentage of increase is different (108% increase). The reason may be that the load of activity is different or different people respond to external stimuli differently depending on their original physiological and/or psychological state. During the relaxation phase, his CO₂ increase rates gradually returned to normal. These results show that the device can detect the changes in blood CO₂ level at normal body temperature.

4. Discussions

According to equation (4), there are 5 measures that can increase the S/N of the system. These measures include: (1) increasing the size of the sampler, (2) decreasing the internal volume of the system, (3) raising the skin temperature at the measurement site, (4) increasing the duration of the recirculation, and (5) decreasing the noise of the signal.

Increasing the size of the sampler can increase the amount of gases diffusing out of the skin. As a result, a higher signal will be detected at the same blood gas level. Thus, the sensitivity of the system will be increased. This has been confirmed by the experimental results shown in Table 2. A good sampler should be able to provide sufficient mass transfer area and a good seal between the skin and the sampler. It is not necessary to be in the shape of a cup as long as it can provide a large mass transfer area and is airtight at the skin contact. Designing a better sampler will be one of our future tasks.

Decreasing the internal volume of the system can increase the S/N of the system because a lower volume will give a higher increase rate at the same transcutaneous diffusion rate. To decrease the internal volume of the system, we will further miniaturize the system in the future and reduce its volume to a portable size. Human tests (results not shown) show that if only blood CO₂ level is to be measured, the O₂ sensor can be removed and the gas supply for purging the system can be omitted. As ambient CO₂ partial pressure (~0.3 mmHg) is much lower than arterial CO₂ partial pressure (35–45 mmHg), the CO₂ transcutaneous diffusion will not be significantly affected in the presence of ambient CO₂. In this case, the purge of the system is still needed but the recirculation pump will do the work as long as it is let run continuously and the inlet of the purge gas is left open. As the O₂ sensor and purge gas supply are removed, the CO₂-only device can be made very small.

Raising the skin temperature can increase the transcutaneous mass transfer coefficient and its corresponding diffusion rate. So the S/N of the measurement will be increase at the same blood gas level. Actually, that is why the equilibrium-based transcutaneous monitors have to raise the skin temperature to 42°C or higher. We measured the startup time of our device and compared with Radiometer TCM4, a commercially available equilibrium-based transcutaneous monitor. At 37°C, the startup of Radiometer TCM4 took 85 minutes before any meaningful results were obtained. Even at 42°C, it still needed about 20 minutes to stabilize. Comparatively, our method was almost independent of temperature. The startup of the CO₂ measurement was almost immediate at any skin temperature. The startup of the O₂ measurement was slower, but it was mainly due to the slow response of the O₂ sensor, not the rate-based approach. Right now, we are developing an optical O₂ sensor. Like the CO₂ sensor, the optical O₂ sensor responds to changes in O₂ level almost immediately. In the second generation of the device, the electrochemical sensor used in the first generation of the device will be replaced by this optical O₂ sensor. As skin temperature does not affect the rate-based approach as significantly as the equilibrium-based approach, we will remain making measurements at normal body temperature. This can avoid potential skin burns and the measurement can be made continuously for a longer time.

Increasing the duration of the recirculation can increase the S/N of the measurement, but will make the measurement cycles longer. In the tests described in this paper, the N₂ flush stage lasted 30 seconds and the recirculation stage lasted 60 seconds. So each measurement cycle lasted 1.5 minutes. Although 1.5-minute measurement intervals is fast enough for many applications, we aim to reduce this interval to less than 1 minute so that the device can track more rapid blood gas changes. For applications where accuracy is the highest priority, the duration of the recirculation can be increased for better accuracy.

Decreasing the noise of the signal is another way to increase the S/N of the measurement. This can be achieved by increasing the precision and stability of the sensors and the stability of the pump, and reducing the disturbance of the N₂ flow and the unsteady leakage caused by bad sealing. In the second generation of the device, an O₂ sensor with better performance will replace the current electrochemical sensor as mentioned previously. In addition, all other aspects will also be optimized.

It needs to be mentioned that the rate-based approach does not measure the arterial blood gas partial pressure directly. Thus, a calibration will be required if accurate blood gas levels are desired. The calibration can be performed by comparing the increase rate with the matching ABG value. Even when a proper calibration is not available, the device can still be used as a trending tool to track the changes in blood gas level, making frequent blood drawing unnecessary. We believe that the approach described here will have broad applicability to many patient populations and disease states.

5. Conclusion

A rate-based non-invasive method for respiratory status monitoring was developed and characterized. The test results show that it can track blood gas levels quickly and noninvasively. The measurement can be made at normal body temperature, so it is safer than equilibrium-based non-invasive monitors.

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Highlights

- Development of a noninvasive transcutaneous respiratory status monitor
- The device is rate-based, and faster than traditional equilibrium-based monitors
- The measurement is made at normal body temperature, so it is safer.

Fig. 1. Measurement principle and system design. Left: N₂ flush stage; Right: Recirculation stage.

Fig. 2.
Samplers used to collect the blood gases diffusing out of the skin.

Fig. 3.
Baseline readings when sampler C was bypassed and readings on human subject.

Fig. 4.
CO₂ readings of the subjects at different physical activity levels.

Experiments designed for testing the effect of skin preparation and measurement location

Table 1

Test group	Test No.	Skin preparation	Location	Increase rate (ppm/s)	
				CO ₂	O ₂
A	1	No treatment	Forearm	0.157	0.694
	2	No treatment	Leg	0.144	0.703
	3	Alcohol prep wiping	Forearm	0.112	0.665
	4	Alcohol prep wiping	Leg	0.139	0.687
B	5	No treatment	Forearm	0.227	0.537
	6	No treatment	Leg	0.193	0.618
	7	Soap wash	Forearm	0.298	0.568
	8	Soap wash	Leg	0.179	0.631

Table 2

Data analysis of baselines and human test results

Sampler	Baseline (ppm/s)		Human test (ppm/s)		Net signal (ppm/s)		Noise (ppm/s)		S/N	
	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂
A	0.042	1.860	0.082	1.885	0.040	0.025	0.007	0.021	5.7	1.2
B	0.055		0.203		0.148		0.005		29.6	
C	0.006	1.104	0.301	1.231	0.295	0.127	0.006	0.023	48.4	5.4

Table 3

Statistical analysis for the effect of skin preparation and measurement location

Test group	Level	CO ₂		O ₂	
		Skin prep	Location	Skin prep	Location
A	1	0.151	0.135	0.699	0.680
	2	0.126	0.142	0.676	0.695
	p-value	0.859	0.429	0.376	0.556
B	1	0.210	0.263	0.578	0.553
	2	0.238	0.186	0.600	0.625
	p-value	0.749	0.636	0.494	0.158