Ventilatory response to CO2 with Read’s rebreathing method in normal infants

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Abstract

Background: Methods of evaluating the ventilatory response to CO2 (VRCO2) of the respiratory center include the steady-state and the rebreathing method. Although the rebreathing method can evaluate the respiratory center more in detail, the steady-state method has been mainly performed in infants. The aim of this study was to investigate whether we could perform the VRCO2 with the rebreathing method in normal infants. Methods: The subjects were 80 normal infants. The gestational age was 39.9(39.3-40.3) weeks, and the birth body weight was 3,142 (2,851-3,451) grams. We performed the VRCO2 with Read’s rebreathing method, measuring the increase in minute volume (MV) in response to the increase in EtCO2 by rebreathing a closed circuit. The value of VRCO2 was calculated as follows: VRCO2 (mL/min/mmHg/kg) = \( \frac{\Delta MV}{\Delta EtCO2 / Body weight} \). Results: We performed the examination without adverse events. The age in days at examination was 3 (2-4), and the examination time was 150±38 seconds. The maximum EtCO2 was 51.1 (50.5-51.9) mmHg. The value of VRCO2 was 34.6 (29.3-42.8). Tidal volume had a greater effect on the increase in MV than respiratory rate (5.4 to 14.3 mL/kg, 44.1 to 55.9 /min, respectively). Conclusion: This study suggests that the rebreathing method can evaluate the ventilatory response to high blood CO2 in a short examination time. We conclude that the rebreathing method is useful even in infants. In the future, we plan to measure the VRCO2 of preterm infants, and evaluate the respiratory center of infants in more detail.
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Methods

The subjects were 80 normal infants. The gestational age was 39.9 (39.3-40.3) weeks, and the birth body weight was 3,142 (2,851-3,451) grams. We performed the VRCO$_2$ with Read’s rebreathing method, measuring the increase in minute volume (MV) in response to the increase in EtCO$_2$ by rebreathing a closed circuit. The value of VRCO$_2$ was calculated as follow: VRCO$_2$ (mL/min/mmHg/kg) = ΔMV / ΔEtCO$_2$ / Body weight.

Results

We performed the examination without adverse events. The age in days at examination was 3 (2-4), and the examination time was 150±38 seconds. The maximum EtCO$_2$ was 51.1 (50.5-51.9) mmHg. The value of VRCO$_2$ was 34.6 (29.3-42.8). Tidal volume had a greater effect on the increase in MV than respiratory rate (5.4 to 14.3 mL/kg, 44.1 to 55.9 /min, respectively).

Conclusion

This study suggests that the rebreathing method can evaluate the ventilatory response to high blood CO$_2$ in a short examination time. We conclude that the rebreathing method is useful even in infants. In the future, we plan to measure the VRCO$_2$ of preterm infants, and evaluate the respiratory center of infants in more detail.

Introduction:

Respiration is controlled mainly by the central and peripheral chemoreceptors 1). The central chemoreceptor located in the respiratory center of the medulla oblongata increases the amount of ventilation in response to pH change due to high blood CO$_2$. The peripheral chemoreceptor in the carotid body responds to hypoxemia for the increase in the amount of ventilation. Respiratory control is mainly regulated by the respiratory center in response to change in blood CO$_2$, because the responsiveness to the change in pH is more sensitive than the change in PaO$_2$. Therefore, chemical respiratory control is evaluated as the ventilatory response to CO$_2$ (VRCO$_2$), and its evaluation methods include the steady-state and the rebreathing method 2). In the steady-state method, subjects breath gas with a fixed CO$_2$ concentration (e.g. 0%, 2%, 4%), and the change in amount of ventilation is evaluated. In the rebreathing method, subjects accumulate blood CO$_2$ by rebreathing a closed circuit, and the amount of ventilation is evaluated continuously at each CO$_2$ concentration. The value of VRCO$_2$ which evaluates the responsiveness to CO$_2$ quantitatively is calculated with this formula, VRCO$_2$ (mL/min/mmHg/kg) = ΔMinute volume (MV)/ΔEtCO$_2$/body weight.

Respiratory control in infants is premature and its prematurity causes respiratory diseases such as apneic attacks. Many preterm infants need oxygen therapy or mechanical ventilation due to prematurity of the respiratory center. Prematurity is also one of the risk factors in brief resolved unexplained events (BRUE) 3). Therefore, it is important to evaluate the respiratory center in infants. The VRCO$_2$ was mainly evaluated by steady-state methods in infants so far. Some report low VRCO$_2$ of infants born to smoking and drug abusing mothers 4, 5). However, the VRCO$_2$ with the rebreathing method is rarely performed in infants. While the steady-state method evaluates the increase in the amount of ventilation only at several CO$_2$ concentrations, the rebreathing method evaluates the amount of ventilation continuously in increasing CO$_2$ concentrations with rebreathing 2). The rebreathing method can evaluate the VRCO$_2$ in more detail. The aim of this study was to evaluate whether we could perform the VRCO$_2$ with the rebreathing method in normal infants, as a first step in evaluating the respiratory center in more detail.

Methods:

Subjects
The subjects were infants without congenital abnormality and maternal smoking history admitted to the normal newborn room between March and September 2011. Infants in the normal newborn room of our hospital need no medical support such as oxygen, infusion and photo therapy. We performed \( \text{SpO}_2 \) monitoring for 12 hours to infants in the normal newborn room and excluded infants with apneic attacks. The total number of subjects was 80 and we performed \( \text{VRCO}_2 \) with the rebreathing method to each subject. Basic characteristics are shown in Table 1. The gestational age was 39.9(39.3-40.3) weeks, the birth body weight was 3,142 (2,851-3,451) grams, Apgar score at 1 min and 5 min was 8 (8-9) and 9 (9-9) and the rate of caesarean delivery was 22.5%. This study was approved by the ethics committee of our institution. Written informed consent was obtained from the patient’s parents.

Ventilatory response to CO\(_2\)

We performed \( \text{VRCO}_2 \) with the rebreathing method based on Read’s method \(^6\) using ARFEL III (Aivison, Tokyo, Japan) (Figure 1). The closed circuit consists of a face mask, \( \text{EtCO}_2 \) sensor (Oridion medical, Jerusalem, Israel), pneumotachograph (Hans Rudolph, Shawnee, Kansas) and a bag filled with 5% CO\(_2\) and 95% \( \text{O}_2\). Tidal volume (TV), inspiration time (I), expiration time (E) and \( \text{EtCO}_2\) were measured with a pneumotachograph and \( \text{EtCO}_2 \) sensor, and these data were transferred to and analyzed by ARFEL III. As in Figure 1, we accumulated the subjects’ blood \( \text{CO}_2 \) by rebreathing the closed circuit during quiet sleep. Respiratory parameters of each breath were measured until the \( \text{EtCO}_2 \) elevated more than 2% from the beginning of the examination. We terminated the examination when the patient woke up. We monitored \( \text{SpO}_2 \) during the examination and confirmed that the subjects had enough spontaneous breathing to exhaust \( \text{CO}_2 \) after the examination.

The value of \( \text{VRCO}_2 \) was calculated from the relationship between \( \text{EtCO}_2 \) and MV. The formula is as follow:

\[
\text{VRCO}_2 = \Delta \text{MV} / \Delta \text{EtCO}_2 / \text{Body Weight}.
\]

In addition to \( \text{VRCO}_2 \), we investigated TV, inspiratory time/total respiratory time (I/I+E), and respiratory rate (RR) at the beginning and end of examination. The data were analyzed with JMP® 15 (SAS Institute Inc, Cary, NC, USA). The values are in mean±SD or in median (first quartile – third quartile) according to distribution. Wilcoxon test was used to compare RR, TV and I/E at the beginning and end of examination. P value < 0.05 was considered statistically significant.

Results:

We performed the examination without any adverse events in all cases. The age in days at examination was 3 (2-4), and the examination time was 150 ± 38 seconds. The maximum \( \text{EtCO}_2 \) was 51.1 (50.5-51.9) mmHg. An example of the result is shown in Figure 2. At the beginning of the examination, RR was 44.7 /min, TV was 5.4 mL/kg and I/I+E was 0.47. MV increased in response to the continuous increase of \( \text{EtCO}_2 \) by rebreathing. At the end of the examination, RR was 60.1 /minute, TV was 15.0 mL/kg, I/I+E was 0.44 and \( \text{EtCO}_2 \) was 50.7 mmHg. The value of \( \text{VRCO}_2 \) in this case was 36.5 mL/kg/min/mmHg. TV contributed to the increase in MV more than RR.

All data is shown in Table 2. The value of \( \text{VRCO}_2 \) was 34.6 (29.3-42.8) mL/kg/min/mmHg. RR and TV significantly increased through the examination (44.1 to 55.9 /min, P<0.001, 5.4 to 14.3 mL/kg, P<0.001, respectively). The rate of increase was higher in TV than RR. There was no significant change in I/I+E through the examination (0.48 to 0.47, P=0.14).

Discussion:

The aim of this study was to perform the ventilatory response to CO\(_2\) with the rebreathing method in normal infants to evaluate the respiratory center. The examination was performed without any adverse events and the value of \( \text{VRCO}_2 \) was 34.6 (29.3-42.8) mL/kg/min/mmHg. The median examination time was 150 seconds and the median maximum \( \text{EtCO}_2 \) was 51.1mmHg. The increase in TV had a greater effect to the increase in MV than that of RR. To the best of our knowledge, this is a study with the largest number of subjects evaluating the \( \text{VRCO}_2 \) with the rebreathing method in normal infants.

The steady-state and rebreathing method are the main methods for evaluating \( \text{VRCO}_2 \). However, some stu-
dies have reported that evaluation with the rebreathing method is more precise and has higher reproducibility than the steady-state method.

Berkenbosch et al. performed the VRCO\(_2\) with the steady-state and rebreathing method in 10 males, and reported that the value of VRCO\(_2\) with the rebreathing method was 1.85 times higher than that of the steady-state\(^7\). They described that the difference between EtCO\(_2\) and the CO\(_2\) partial pressure in the central chemoreceptor in the rebreathing method was less than the difference in the steady-state method, causing the difference in VRCO\(_2\) between the 2 methods. In brief, the error between EtCO\(_2\) and blood CO\(_2\) of the respiratory center was larger in the steady-state method. As a result, the VRCO\(_2\) with the steady-state method could be lower than that of the rebreathing method. In the study of Mohan et al., the VRCO\(_2\) with the steady-state method was significantly lower than that of the rebreathing method in 5 normal adults\(^8\). This was because the examination time was longer and the VRCO\(_2\) was evaluated at a lower blood CO\(_2\) in the steady-state method. The long examination time causes respiratory muscle fatigue, and the increase in the amount of ventilation demanded by the ventilatory response of the respiratory center cannot be generated, which may result in an underestimation of the VRCO\(_2\). Hasegawa et al. demonstrated that the tolerance for respiratory load in infants was lower than in adults, and respiratory muscle fatigue was more likely to occur in infants\(^9\). We think that the short examination time is one of the advantages of the rebreathing method in infants. The increase in EtCO\(_2\) with the steady-state method could be insufficient, because the subjects breathe gas with a fixed CO\(_2\) concentration repeatedly in the steady-state method. In our study, we increased the maximum EtCO\(_2\) to up to 51 mmHg and were able to evaluate the VRCO\(_2\) at a high CO\(_2\) concentration.

Mannee et al. performed the VRCO\(_2\) with the steady-state and rebreathing method multiple times in 20 normal adults and evaluated the intraclass correlation coefficients (ICC) of the VRCO\(_2\) \(^{10}\). While the ICC of the rebreathing method was as high as 0.89, the ICC of the steady-state method was 0.56. They found that the VRCO\(_2\) with the rebreathing method had higher reproducibility than that of the steady-state method. They assumed that the cause of this difference was due to the discordance between EtCO\(_2\) and blood CO\(_2\) of the respiratory center in the steady-state method, as in the study of Berkenbosch et al. The high reproducibility is more preferable in infants, because it is difficult for them to follow our orders and to be examined multiple times. This high reproducibility is also an advantage of the rebreathing method.

After focusing on the difference between methods, we focused on the difference in results of the same rebreathing method. The value of VRCO\(_2\) (\(\Delta\text{MV}/\Delta\text{EtCO}_2\)) in three studies with the rebreathing method in normal adults were 1.2, 4.6, 1.7 L/min/mmHg, respectively \(^7, 8, 10\). In addition, Akiyama reported the value of VRCO\(_2\) in 2 studies, 2.2 for 28 patients\(^{11}\) and 1.9 for 17 patients\(^{12}\), respectively with the rebreathing method in normal adults. It was assumed that this difference was due to the different range in EtCO\(_2\) evaluated in the examination although the same rebreathing method was adopted. In the future, if we were to evaluate other pathologies using data of this study as reference, we should use the same protocol as of this study. It was difficult to compare our normal infants’ data with normal adults’ data, because the protocol and equipment were not the same and the data of normal adults’ lacked adjustment for body weight or body surface area. However, the data of 17 normal adults reported by Akiyama et al. included respiratory parameters (e.g. RR, TV) during measurement\(^{12}\), so we compared those parameters with our data. TV and RR at the beginning of examination were 0.27 L and 17.0 /min, and those at the end of examination was 1.53 L and 23.6 /min. The increase in TV was larger than that of RR, which was consistent with our data.

The VRCO\(_2\) of the respiratory center has been mainly evaluated with the steady-state method in infants, and the VRCO\(_2\) of infants born to smoking and drug abusing mothers has been performed so far \(^4, 5\). Data of the VRCO\(_2\) in normal infants was measured as the control for comparison. Wingkum et al. showed that the VRCO\(_2\) in 12 infants of drug abusing mothers was lower in comparison with 12 normal infants\(^4\). In this study, EtCO\(_2\) and MV were measured with the steady-state method in which subjects breathed room air and 4% CO\(_2\) gas for 5 minutes each. The maximum EtCO\(_2\) was 40.43 mmHg, which was within normal range. The examination time of our study was 2.5 minutes, which was the shortest in all the studies quoted.
in this article. Furthermore, the maximum EtCO$_2$ in our study was 51.1 mmHg, so we were able to evaluate the VRCO$_2$ at high blood CO$_2$ levels.

Ali et al. compared the VRCO$_2$ among 34 infants born to smoking mothers, 22 infants born to drug abusing mothers and 22 normal infants. They showed that the increase in ventilation was significantly lower in order of infants born to drug abusing mothers, smoking mothers and normal infants 5). In this examination, MV was measured when breathing 0%, 2%, and 4% CO$_2$ gas, and the VRCO$_2$ was evaluated by the relationship between MV and F$_1$CO$_2$ rather than EtCO$_2$. The VRCO$_2$ using F$_1$CO$_2$ could be underestimated because the error tended to be larger between F$_1$CO$_2$ and blood CO$_2$ of the respiratory center than the error between EtCO$_2$ and blood CO$_2$, as in the study by Mannee et al.$^{10}$. In fact, the values of VRCO$_2$(mL/min/mmHg/kg) in normal infants were a median of 34.6 in our study and an average of 48.7 in the study by Wingkun et al.$^4$ compared to a low average of 10.9 in the study by Ali et al.$^5$

This study has some limitations. Normal adults were selected after respiratory function tests and interviews$^{11), 12)$. However, it was difficult to perform spirometry test to infants, so we selected newborns that did not need any medication or monitoring as normal infants. This way of selection was the same as in other studies for normal infants $^4, 5)$. Next, we measured the VRCO$_2$ once in this study. Some studies of normal adults studied the average measuring the VRCO$_2$ multiple times$^{7), 11)$. We designed to measure the VRCO$_2$ once in this study, because this physiologic test is difficult to perform in infants and the reproducibility of the rebreathing method is high $^{10}$. We plan on evaluating the respiratory center of infants in more detail by performing the VRCO$_2$ to preterm infants, infants with apneic attacks and infants treated with caffeine, using the data of normal infants obtained from this study.

Conclusion:

We measured the VRCO$_2$ with the rebreathing method in normal infants. The value of VRCO$_2$ was 34.6 (29.3 - 42.8) mL/kg/min/mmHg. This study suggested that the rebreathing method can evaluate the ventilatory response in high blood CO$_2$ concentrations in a short examination time. We conclude that the rebreathing method is useful even in infants. In the future, we plan on measuring the VRCO$_2$ of preterm infants, infants with apneic attacks, and evaluate the respiratory center of infants more in detail.

Reference:


Hosted file

Table 1, 2 VRCO2 with the rebreathing in normal infants.pdf available at https://authorea.com/users/378145/articles/494693-ventilatory-response-to-co2-with-read-s-rebreathing-method-in-normal-infants
Rebreathing bag (CO₂ 5%)

Pneumotachograph

EtCO₂ sensor

![Graph showing respiratory parameters]

![Scatter plot showing EtCO₂ vs MV]

VRCO₂ = 36.5 (mL/min/mmHg/kg)
VRCO₂ = 36.5 (mL/min/mmHg/kg)