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Hypercapnic Ventilatory Responses Measured by Transcutaneous PCO_2 Are More Linear Than those Measured by End-Tidal PCO_2

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ABSTRACT

We used transcutaneous PCO_2 ($PtcCO_2$) and end-tidal PCO_2 ($PetCO_2$) measurements to examine ventilatory responses to hypercapnia. The correlation between $PtcCO_2$ and CO_2 tension in arterial blood ($PaCO_2$) was examined in 15 patients to determine whether $PtcCO_2$ can be an alternative to $PaCO_2$. The regression line had a slope of 1.03 and was almost parallel to the identity line. The difference between the $PtcCO_2$ and $PaCO_2$ was 3.9 ± 0.47 mmHg (mean±SE, $n=15$) at 44°C and when the skin metabolism offset corrective factor was set per the manufacturer's instructions at 4 mmHg. In 3 healthy men, hypercapnic ventilatory responses were obtained from three points : at rest and during two steps in which CO_2 loading was changed. When responses were plotted with $PetCO_2$ values, the slope of the second step was significantly steeper than that of the first step, but when $PtcCO_2$ values were used the first- and second-step slopes did not differ significantly. We conclude that the relationship of steady-state ventilation to increased $PaCO_2$ is more linear than when plotted against $PetCO_2$ owing to the decreased $PaCO_2$-$PetCO_2$ difference with inspired CO_2 and deeper ventilation. (Jikeikai Med J 2002 ; 49 : 127-32)

Key words : transcutaneous PCO_2 sensors, CO_2 response curve, hypercapnia, control of breathing

INTRODUCTION

When end-tidal PCO_2 ($PetCO_2$) is used to measure the steady-state hypercapnic ventilatory response (HCVR), the initial slope of the increase in ventilation is often smaller than with subsequent changes in the $PetCO_2$, resulting in a dog-leg curvilinear response curve[1-3]. We attempted to determine whether this dog-leg response is attributable to differences between resting arterial PCO_2 ($PaCO_2$) and $PetCO_2$, which are reduced or eliminated with inspired CO_2 and higher ventilation.

Measurement of transcutaneous PCO_2 ($PtcCO_2$) has several advantages for assessing HCVR. It is less invasive than measuring arterial CO_2 tension ($PaCO_2$) and provides continuous data. The time lag of the transcutaneous CO_2 electrode, 90% in 2 to 3 minutes[4], is similar to that of the central chemoreceptor response to a steep rise in $PaCO_2$.

To determine whether measurement of $PtcCO_2$ could be used as a substitute for measurement of $PaCO_2$, we evaluated the linearity of the $PaCO_2$-$PtcCO_2$ relationship. We also evaluated whether measurement of $PtcCO_2$ is a suitable alternative to arterial blood sampling to examine whether the steady-state ventilatory response to increased $PaCO_2$ is linear from its resting value or also has a lower initial slope.

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Subjects and Methods

This study was approved by the Ethics Committee of the Jikei University Hospital. All subjects gave their written informed consent to participate.

Correlation between $PtcCO_2$ and $PaCO_2$

To prepare for measuring hypercapnic ventilatory responses, we first assessed the linearity and optimal CF for the $PtcCO_2$ measuring device used in this study (TCM3, Radiometer Trading Co., Ltd., Copenhagen, Denmark). With this device, a Severinghaus electrode attached to the skin and heated to a prescribed temperature is used to measure the pressure of CO_2 at the heated surface of the skin, a function of both skin metabolism and $PaCO_2$. The $PaCO_2$ is then calculated with the following equation: $PaCO_2 = PtcCO_2 \times e^{[0.045(37-Te)]} - CF$, where 0.045 is the exponential temperature coefficient of blood PCO_2 (in vitro), Te is the electrode temperature, and CF is an empiric factor assumed to account for skin metabolism, which increases with heating.

The subjects were 15 patients (9 men and 6 women; mean age, 56 ± 13.7 years [mean±SD]) who were receiving mechanical ventilation during general anesthesia. The anesthetic was inhalational (with sevoflurane or isoflurane) in 13 cases and intravenous (with propofol, midazolam, or fentanyl) in 2 cases. In 11 cases, epidural anesthesia was also used. The minute volume (V_E) was adjusted to maintain the $PetCO_2$ between 30 and 45 mmHg as measured with an expiratory gas analyzer (Capnomac Ultima, Datex Co., Ltd., Helsinki, Finland). After the $PetCO_2$ had been confirmed to be stable for longer than 30 minutes, a probe for $PtcCO_2$ measurement was attached to the subject's palmar aspect of the brachium. Two minutes after the $PtcCO_2$ had become stable and its variation had decreased to less than 0.8 mmHg/min, arterial blood was sampled and the $PaCO_2$ was measured with an (ABL505, Radiometer Trading Co., Ltd., Copenhagen, Denmark). The electrode temperature and CF for the probe used to measure $PtcCO_2$ were set at 44°C and 4 mmHg, respectively. The data obtained were analyzed to determine the correlation between $PaCO_2$ and $PtcCO_2$ values and to determine the optimal CF.

Hypercapnic ventilatory responses

Hypercapnic ventilatory responses were measured in 3 healthy men (mean age, 44 ± 6.2 years). Four sets of measurements were carried out for each subject as they remained seated. The subjects inhaled mixtures of room air, oxygen, or expired gas through a face mask via a one-way valve that was attached to a rebreathing circuit, similar to the one used by Sato et al.[5].

When the subject was at rest, the inlet of the circuit was kept open to ambient air and the circuit was used as a nonrebreathing circuit. When the circuit was used for rebreathing, the open circuit was closed and the oxygen inflow was adjusted to control the CO_2 concentration in the inhaled gas. The $PetCO_2$ was measured with the sampling tube placed near the subject's mouth in the face mask, with an expiratory gas analyzer (Capnomac Ultima, Datex). A skin electrode for transcutaneous measurement of $PaCO_2$ (TCM3, Radiometer Trading Co.) was attached to the palmar aspect of the brachium. The V_E was measured with a respiratory flow meter (RF-2, Minatoika Co., Ltd., Osaka, Japan) interposed between the face mask and the circuit. The oxygen concentration in the inhaled air was maintained at greater than 50% throughout the experiment.

After the skin electrode was mounted, subjects breathed a mixture of room air and oxygen. When ventilation, $PetCO_2$, and $PtcCO_2$ had been stable for 2 minutes (variation less than 0.8 mmHg/min), i.e., about 5 minutes after the start of the experiment, control $PetCO_2$, $PtcCO_2$, and V_E were measured. The CO_2 loading was performed in two steps: in step 1 $PetCO_2$ was raised by 3 to 5 mmHg and in step 2 $PetCO_2$ was raised by another equal step of 3 to 5 mmHg, with $PetCO_2$ held constant at each step for at least 5 minutes or until ventilation was constant. The V_E was calculated for each breath from tidal volume and time, averaged over the final minute and indexed to a body surface area of 1 m^2.

Statistical analysis

Data are expressed as means±SE. The paired Student's *t*-test was used to compare variables between groups. A P value less than 0.05 was considered to indicate statistical significance. A software package (StatView, Abacus Concepts, Berkeley, CA, USA) was used for regression analysis.

Results

Correlation between $PtcCO_2$ and $PaCO_2$ values

Regression analysis revealed that $PaCO_2$ and $PtcCO_2$ were strongly correlated ($r=0.91$, $n=15$, $P<0.0001$). The regression line had a slope of 1.03 and was almost parallel to the identity line (Fig. 1). The difference between the $PtcCO_2$ and $PaCO_2$ values in individual subjects was 3.9±0.47 mmHg ($n=15$). This results suggests that this difference must be added to the 4 mmHg, which is the CF recommended by the manufacturer. The optimal calculated CF was thought to be about 8 mmHg.

Hypercapnic ventilatory responses

The slopes ($dV_E/dPCO_2$) of steps 1 and 2 were compared. The mean±SE of the four measurements

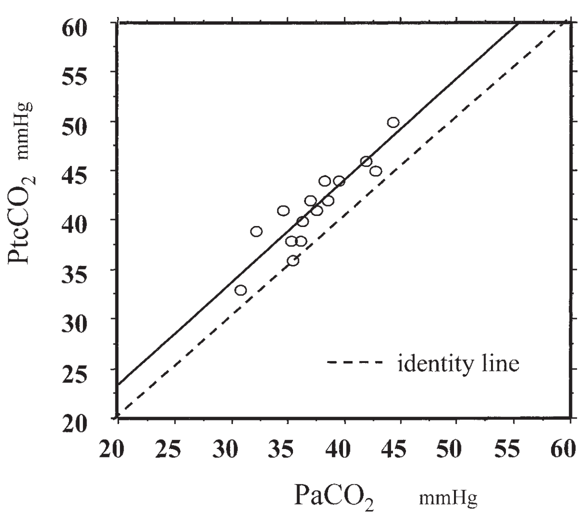

Fig. 1. A strong correlation is seen between $PaCO_2$ and $PtcCO_2$ ($r=0.91$, $p<0.0001$). The slope was 1.03, slightly above the identity line. $Y=2.7+1.03X$; $R^2=0.82$, $n=15$.

of the first and second slopes in each subject were plotted against the $PetCO_2$ (Fig. 2). The slope of step 2 was significantly steeper than that of step 1 in all three subjects ($P<0.05$). When slope was determined with $PtcCO_2$ (Fig. 2), it did not differ significantly between steps 1 and 2 in any of the three subjects.

The ventilatory responses of the three subjects were then combined and analyzed (Fig. 3). When slopes were plotted with the $PetCO_2$ values, the second slope (1.5±0.092 L/mmHg/m²) was significantly steeper than the first slope (0.73±0.054 L/mmHg/m², $P<0.05$, $n=12$). When slopes were plotted with $PtcCO_2$ values, the first and second slopes (1.8±0.31 and 1.9±0.22 L/mmHg/m², respectively) did not differ significantly. The slope between the values following the first and second CO_2 loads was significantly steeper when plotted with the $PtcCO_2$ values (1.9±0.22 L/mmHg/m²) than when plotted with the $PetCO_2$ values (1.5±0.092 L/mmHg/m², $P<0.05$, $n=12$).

Discussion

We confirmed that $PtcCO_2$ measurement accurately reflects $PaCO_2$. The results of this study suggest that the so-called dog-leg form seen in hypercapnic ventilatory response testing with $PetCO_2$ is due to the difference between arterial and end-tidal PCO_2 which narrows with increased inspired CO_2 and increased ventilation.

Correlation between $PtcCO_2$ and $PaCO_2$ values

In the present study, measurements were made in patients under general anesthesia. Anesthetic agents have no effect on the relationship of $PtcCO_2$ to $PaCO_2$[6] but do often increase the difference between $PaCO_2$ and $PetCO_2$. The CF reflects the CO_2 production associated with skin metabolism. The optimal CF in the present study was about 8 mmHg, which is higher than the CF of 4 mmHg reported by Severinghaus et al.[7]. The observed CF may be a function of age and is smaller in newborns and higher in older children[4]. The CF has not been directly determined with all manufacturers' $PtcCO_2$ electrodes nor with the new Radiometer electrodes. Therefore, we believe sett-

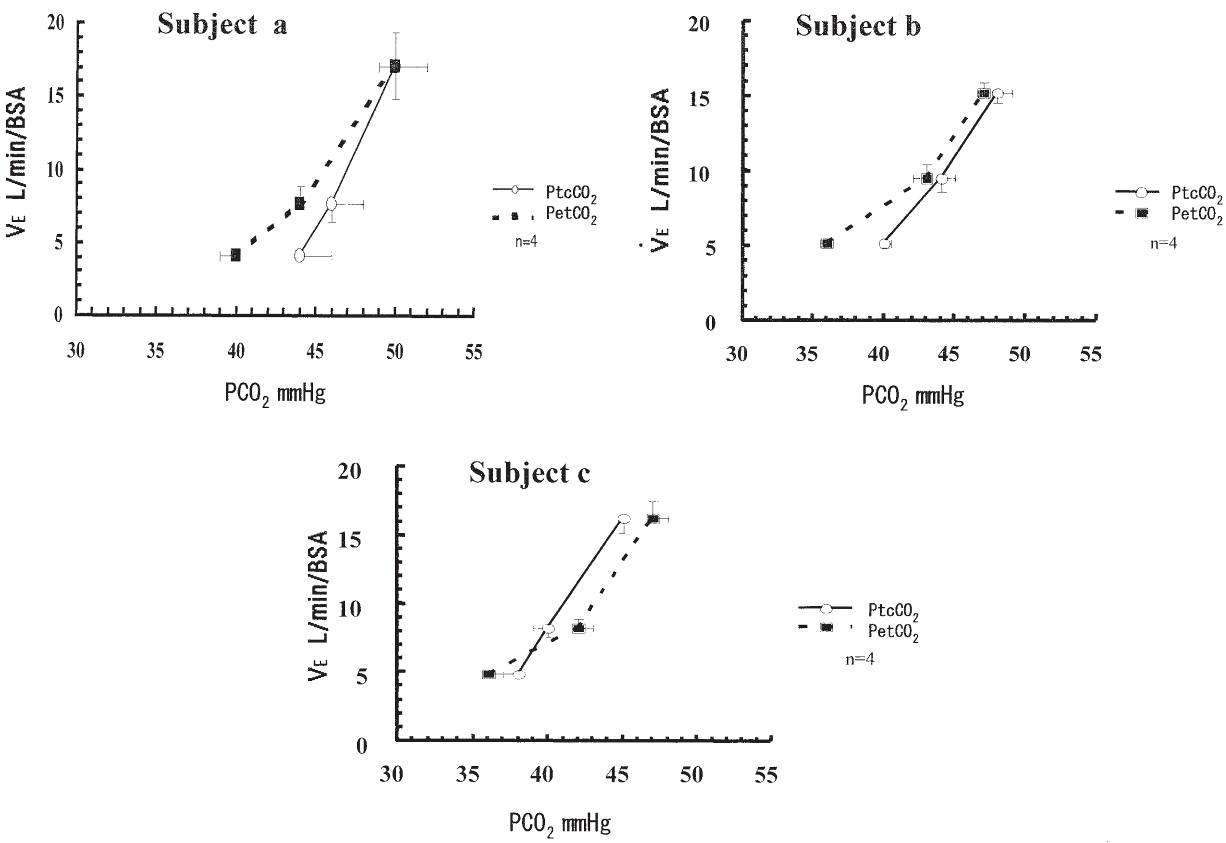

Fig. 2. Hypercapnic ventilatory response curves for 3 subjects.
a, b, c : Significant difference between the slope following low CO_2 loading and the slope following high CO_2 loading when plotted against $PetCO_2$ (*a* : 0.85±0.093 vs. 1.6±0.13, $P<0.05$; *b* : 0.66±0.094 vs. 1.3±0.096, $P<0.05$; c : 0.69±0.085 vs. 1.5±0.22, $P<0.05$; mean±SE).

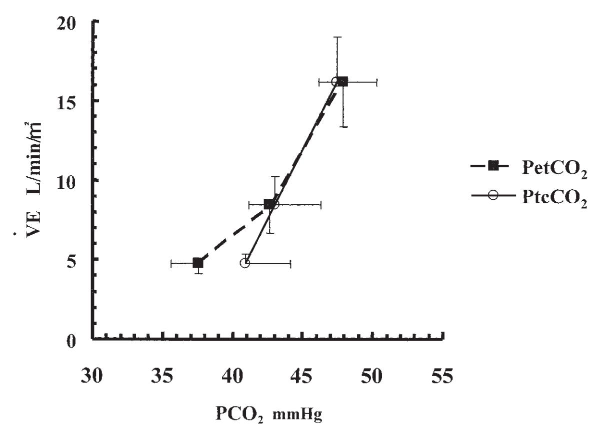

Fig. 3. Mean hypercapnic ventilatory response curves for three subjects.
The slope following low CO_2 loading and the slope following high CO_2 loading were significantly different when plotted against $PetCO_2$ (0.73±0.054 vs. 1.5±0.092, $P<0.05$; mean±SE, $n=12$) but did not differ when plotted against $PtcCO_2$.

ing the CF at 8 mmHg, as suggested by our results, is appropriate.

Hypercapnic ventilatory responses

After measuring CO_2 values with the subjects at rest breathing a high concentration of oxygen, we performed low-level CO_2 loading (step one), followed by high-level CO_2 loading (step two). Step one is believed to correspond to the point where ventilation increases linearly past the dog-leg phase. Step two is believed to induce ventilation to increase to about 40 L/min[8]. Therefore, we decided to check for the presence or absence of any dog-leg responses by comparing the two slopes yielded by these two steps. When plotted with the $PtcCO_2$ measurements, the slope between the values at rest and the values at step 1 did not differ significantly from the slope between the values at step 1 and the value at step 2. However, when plotted with the $PetCO_2$ values, the slope between the resting values and the values at step 1 was significantly less than the slope between steps 1 and 2. These results indicate that the dog-leg shape is seen when the response is plotted with the $PetCO_2$ values but is absent (i.e., the ventilatory response to $PaCO_2$ is linear) when $PtcCO_2$ values are used.

Receptors for hypercapnic ventilatory responses are present on the ventral surface of the medulla and the carotid body. Usually, hydrogen ions directly stimulate chemoreceptors on the ventral surface of the medulla, and this effect plays a central role in the normoxic and hyperoxic states. However, because hydrogen ions do not pass through the brain-blood barrier, hypercapnic ventilatory responses are actually determined by the $PaCO_2$[9,10]. Therefore, hypercapnic ventilatory responses should be viewed as changes in V_E in response to $PaCO_2$.

However, studies have yielding curvilinear dog-leg responses[1–3] with the assumption that $PaCO_2$ can be accurately estimated with $PetCO_2$[11]. On the other hand, Linton et al.[12] have reported that hypercapnic ventilatory responses, including those during the resting phase, are always linear when $PaCO_2$ is measured. Forster et al.[13] have also measured $PaCO_2$ and found that hypercapnic ventilatory responses in normoxic humans are curvilinear. In their report, however, some data were deleted because intake of meals. However, because meals are unlikely to cause acute changes in hydrogen ion concentration around the ventral surface of the medulla, we cannot rule out the possibility that ventilatory responses might have been linear if the deleted data were also included in the analysis. Reischl et al.,[14] however, could not confirm hypercapnic ventilatory responses were curvilinear with by $PaCO_2$ measurements.

Some naive subjects hyperventilate at rest owing to the wakefulness factor or anxiety. This hyperventilation may explain why some studies report a dog-leg response when $PaCO_2$ is measured. Our three experiment subjects were well-trained and experienced, and trials were repeated 4 times in each.

We found that the differences between the $PetCO_2$ and $PaCO_2$ measurements were greater at rest than following CO_2 loading. Laszlo et al.[15] attributed this difference to water and plasma in the lungs and to dead-space ventilation. Other workers have pointed out that when the tidal volume at rest is small, the effect of dead-space ventilation is increased, leading to lower $PetCO_2$ values[16–18]. We also found that the tidal volume increased following CO_2 loading. Furthermore, dead-space ventilation is reportedly increased during oxygen administration and when the subject is sitting rather than supine[19,20].

These results suggest that dead-space ventilation at rest may help explain why dog-leg hypercapnic ventilatory responses are observed only when $PetCO_2$ is measured and not when $PtcCO_2$ is measured. The increased ventilation during CO_2 loading provides a higher end-tidal CO_2, just as does a very deep expiration, and while CO_2 is inspired, the dead space (nonventilated alveoli) are filled with the inspired gas which has high CO_2 concentration and thus expirates from the dead space dilute end-tidal gas less.

We conclude that the relationship of steady-state ventilation to increased $PaCO_2$ is more linear than when related to $PetCO_2$, owing to the reduction of the $PaCO_2$-$PetCO_2$ difference with inspired CO_2 and deeper ventilation. We find that with the transcutaneous PCO_2 instrument used in this study, the empiric skin metabolism factor, CF, is 8 mmHg rather than 4 mmHg.

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