A quick and easy method of measuring the hypercapnic ventilatory response in patients with COPD

Annabel H. Nickol a,b,d,*, Helen Dunroy a, Michael I. Polkey b, Anita Simonds a, Jeremy Cordingley c, Douglas R. Corfield a,e, Mary J. Morrel a

a Clinical and Academic Unit of Sleep and Breathing, National Heart and Lung Institute, Royal Brompton Hospital, Fulham Road, London SW3 6NP, UK
b Respiratory Muscle Laboratory, National Heart and Lung Institute, Royal Brompton Hospital, Fulham Road, London SW3 6NP, UK
c Department of Anaesthetics, National Heart and Lung Institute, Royal Brompton Hospital, Fulham Road, London SW3 6NP, UK
d Oxford Centre for Respiratory Medicine, Oxford OX3 7LJ, UK
e Institute of Science and Technology in Medicine, Keele University, Keele, ST5 5BG, UK

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KEYWORDS
Hypercapnic ventilatory response; COPD; Steady state; Rebreathing; Arterial PCO2; End-tidal PCO2

Summary
Background: Hypercapnic ventilatory response (HCVR) techniques have not previously been adequately validated in patients with chronic obstructive pulmonary disease (COPD). We have tested the hypothesis that end-tidal PCO2 may be used to test the HCVR in COPD during non-steady-state rebreathing, despite the fact that large (arterial—end-tidal) PCO2 differences (Pa(a− et)CO2) exist during air breathing.

Methods: Eight patients and 11 healthy volunteers underwent steady-state HCVR testing and non-steady-state rebreathing HCVR testing, using Pa and PetCO2.

Results: In COPD patients, PetCO2 was lower than PaCO2 by a constant amount throughout steady-state HCVR, but equalised with PaCO2 during non-steady-state HCVR. Consequently there were no differences in HCVR slope using either method (steady-state p = 0.91; rebreathing p = 0.73), or HCVR intercept in rebreathing (p = 0.68) whether PaCO2 or PetCO2 was used. The steady-state HCVR intercept using PetCO2 was greater than that using PaCO2 (p = 0.02). In healthy volunteers PetCO2 equalised with PaCO2 during steady-state HCVR, but was progressively greater than PaCO2 during non-steady-state. Consequently, there was no difference in HCVR slope (p = 0.21) or intercept (p = 0.46) whether PaCO2 or PetCO2 was used. During non-steady-state there was a Pa(a− et)CO2 difference in slope (p = 0.03) and intercept (p = 0.04).

* Corresponding author. Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK. Tel.: +44 (0)779 356 3358; fax: +44 (0)1865 225221.
E-mail address: annabel@medex.org.uk (A.H. Nickol).
Introduction

The hypercapnic ventilatory response (HCVR) provides information on chemosensitivity.\(^1,^2\) It can also be used to investigate mechanisms leading to respiratory failure.\(^3\) In particular, it has been utilised to examine the effects of long-term domiciliary nocturnal non-invasive ventilation (NIV) on gas exchange in patients with symptomatic hypercapnic respiratory failure.\(^4-^6\) These studies suggest that measurements of HCVR may be of use in targeting treatments in patients with respiratory failure. However, presently there is no quick and easy method of assessing HCVR that has been and well validated in patients with respiratory failure and chronic obstructive pulmonary disease (COPD).

Measurement of the HCVR is dependent on precise measurements of PaCO\(_2\). In COPD patients the end-tidal PCO\(_2\) (PetCO\(_2\)), which is often used as a surrogate measure of PaCO\(_2\),\(^7\) is known to be a poor estimator of arterial PCO\(_2\). This is due to prolonged Pa–etCO\(_2\) equilibration times and increased dead space,\(^8,^9\) which leads to an attenuated PetCO\(_2\) and a large Pa–etCO\(_2\) difference at rest. How this difference varies during different methods of measuring HCVR is unknown. The accurate assessment of the HCVR is also compromised in COPD patients due to poor neuro-mechanical coupling, which attenuates the translation of central ventilatory drive into alveolar ventilation.\(^10\) These issues are magnified by factors that commonly co-exist in COPD patients with hypercapnic respiratory failure, such as obesity. We have therefore chosen to study patients with hypercapnic respiratory failure secondary to COPD and obesity.

HCVR can be measured using steady-state and non-steady-state techniques. The traditional steady-state technique is carried out by varying the concentration of inspired CO\(_2\) until steady-state ventilation is attained.\(^11,^12\) This method is lengthy and poorly tolerated. Another quicker and easier steady-state method, known as the Fenn and Craig technique, has been developed.\(^13-^15\) It involves bleeding in fixed flow rates of CO\(_2\) in step-wise increasing amounts every 5 min whilst measuring ventilation.\(^16\) It has the advantage that delivered CO\(_2\) load is independent of ventilation. A further advantage of this method is that the HCVR is measured close to normal physiological CO\(_2\) levels. The Read rebreathing technique is a non-steady-state method of assessing the HCVR.\(^17\) It is widely used clinically\(^18,^19\) and in research.\(^20-^22\) It is even quicker than the non-steady-state tests, easy to perform and well tolerated. The disadvantage of the technique is that the HCVR is measured well above eucarbia, with the assumption that the slope of the HCVR is linear and can be extrapolated. In healthy volunteers rebreathing typically produces a higher HCVR compared to steady-state techniques.\(^17,^23,^24\) We are unaware however, of any studies in patients with respiratory failure which have validated the use of PetCO\(_2\) during either steady-state or non-steady-state techniques.

The aim of the present study is to establish a quick and easy technique for measuring HCVR in patients with COPD. We therefore assessed the utility of PetCO\(_2\) for testing HCVR during both steady-state and non-steady-state in COPD patients, and healthy volunteers. We reasoned that during the steady-state HCVR there would be a large Pa–etCO\(_2\) difference in patients with COPD, but that this would be attenuated during non-steady-state, since mixed venous PCO\(_2\) (reflected by PetCO\(_2\)) and PaCO\(_2\) would approach an equilibrium. Thus we tested the hypotheses that HCVR slope and intercept derived using PetCO\(_2\) (HCVR\(_{etCO2}\)) would provide an adequate estimate of that derived using PaCO\(_2\) (HCVR\(_{PaCO2}\)) in patients with COPD using the non-steady-state Read rebreathing technique, but not the steady-state Fenn and Craig technique.

Methods

Subjects

Eight COPD patients with hypercapnic respiratory failure and 11 healthy volunteers were studied. Patients had been established on NIV for control of symptoms of hyperventilation and improvement in gas exchange for at least 3 months. Subjects underwent measurement of height, weight and screening spirometry; no healthy volunteers had evidence of cardio-pulmonary disease (on history or lung function), and all were non-smokers. Absolute contraindications were: any evidence of valvular heart disease, a history of previous advice to take prophylactic antibiotics prior to dental or other minor procedures, a history or examination suggestive of poor circulation to the hand or un-arterial supply or vaso-vagal tendency. The study was approved by the ethics committee of the Royal Brompton and Harefield NHS Trust, and all subjects gave written informed consent.

Techniques

Subjects sat comfortably reclining, breathing through a well-sealed full-facemask (Fleximask, 0611 Y, B and D Electromedical, Stratford-Upon-Avon, Warwickshire, UK). In some patients prominent facial creases made it difficult to form a good seal, and so a mouthpiece and nose clip were used. The facemask or mouthpiece was connected to a pneumotachograph (3700 Hans Rudolf Inc, Missouri, USA) and a non-rebreathing respiratory valve (Model 3700 Hans Rudolphi Inc, Missouri, USA) with a combined dead space of 215 mls. The integrated flow signal from a pressure transducer (MP 45, ±2.25 cm H\(_2\)O, Validyne, California, USA) enabled determination of minute ventilation. Tidal PCO\(_2\) was measured using an infra-red CO\(_2\) analyser (Morgan

Conclusions: In COPD patients non-steady-state HCVR using PetCO\(_2\) is well tolerated, which is as accurate as PaCO\(_2\). HCVR slope may be derived using PetCO\(_2\) during steady-state testing, though there may be errors in intercept compared to use of PaCO\(_2\). In healthy volunteers PetCO\(_2\) may be used to estimate PaCO\(_2\) during steady-state but not rebreathing HCVR.

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Medical, Kent, England). The tip of the sampling tubing was placed inside the nares (facemask) or connected to a side port of the mouthpiece. Gas for sampling passed through a 13 cm long drying tube (Nafion, Perma Pure Inc, Toms River, New Jersey 08754, USA). Arterial oxygen saturation was measured continuously using pulse oximetry (Nellcor N-200 Pulse oximeter, Nellcor Inc, Pleasanton, California). The oximeter had an averaging time of 5–7 s. A three lead ECG (Diascope 2, S&W Medico Teknik A/S, Albertslund, Denmark) was monitored by the clinician; no patients developed ectopics or arrhythmias. Monitoring equipment was shielded from view of the subjects and they watched a video during the HCVR.

**Fenn and Craig steady-state HCVR**

The breathing circuit is illustrated in Fig. 1. The inspiratory limb of the valve was connected to a three-way tap via tubing (internal diameter 35 mm, length 1.50 m). The tap could be turned so that the subject breathed from room air or from an oxygen reservoir consisting of a 200-l Douglas bag, which was continuously being filled with warmed and humidified 100% oxygen. 100% CO₂ could be bled into the inspirate via a port near the respiratory valve at a low, controlled flow rate. Subjects underwent a 10 min rest period during which the inspiratory limb was connected to room air. At the start of the steady-state test, the inspiratory limb was switched to the oxygen reservoir, and 100% CO₂ was added to the inspirate at a rate of 200 mls/min for 5 min. The flow rate was increased in 200 mls/min increments every 5 min up to a maximum of 800 mls/min.

Arterial blood samples were taken at the end of minutes 9 and 10 of rest, and at the end of minutes 4 and 5 of each CO₂ increment.

**Rebreathing HCVR**

The breathing circuit is illustrated in Fig. 2. Subjects underwent a 10 min period breathing room air. At the start of rebreathing, a 6-l anesthetic bag containing 5% CO₂ balance oxygen was connected to the inspiratory limb, and tubing joined the inspiratory and expiratory limbs in a circuit. Arterial blood samples were taken at the end of minutes 9 and 10 of the rest period, and at the end of each minute of rebreathing.

**Arterial blood gas sampling and analysis**

To enable repeated arterial blood gas sampling, an arterial cannula (22G Abbocath™, Abbot Ireland, Sligo, Republic of Ireland) was inserted into the radial artery of the non-dominant hand under local anesthetic (Lidocaine 1%, Antigen Pharmaceuticals Ltd, Roscrea, Ireland) by a consultant intensivist using an aseptic technique. It was attached to a standard pressure transducer set (Edwards Life Sciences, Irvine, CA 92614-5686 USA) including a three-way tap for sampling arterial blood. A 250 ml bag of normal saline (Baxter Health Care Ltd, Thetford, Norfolk, England) pressurized to 300 mmHg was connected to the transducer set. The dead space between the arterial catheter and sampling port of the three-way tap was 0.5 mls. Arterial blood samples of 2.5 mls were taken over approximately 4–7 s, with the start and end of each sampling period marked on the data acquisition system. Immediately prior to sampling, 1–1.5 mls of blood was withdrawn and discarded. Samples were taken in pre-heparinized (Heparin 1000 U/ml, Leo Laboratories Ltd, Princes Risborough, Bucks, HP27 9RR, UK) syringes. These were sealed immediately with an airtight cap, and stored in crushed ice up to a maximum of 30 min before analysis on an arterial blood gas analyser.

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Figure 1  Breathing circuit for the Fenn and Craig steady-state hypercapnic ventilatory response. The subject starts by breathing via a mask or mouthpiece from room air for 10 min. A three-way tap is then turned so they breathe from humidified 100% oxygen. 100% CO₂ is bled into the inspiratory airflow, at progressive flow rates (200–800 mls/min) every 5 min. A pneumotachograph measures airflow, integrated to give ventilation breath by breath, and fine tubing in the nares enables measurement of tidal PCO₂.

Figure 2  Breathing circuit for the Read rebreathing hypercapnic ventilatory response. The subject starts by breathing via a mask or mouthpiece from room air for 10 min. A closed circuit breathing system is then attached, which contains a 6-l anesthetic bag filled with 5% CO₂/balance oxygen. The subject breathes through the closed circuit for 4 min. A pneumotachograph measures airflow, integrated to give ventilation breath by breath, and fine tubing in the nares enables measurement of tidal PCO₂.
The patients hand was wrapped in a blanket to keep it warm.

**Circulation time**

An estimation of the (mouth—lung—hand) circulation time was made to enable $PaCO_2$ to be aligned to the corresponding $PetCO_2$. Subjects were asked to hold their breath at end-expiration until breaking point (the point at which they could hold their breath no longer), following which they took a breath of 100% oxygen from a 6 l anesthetic bag and held their breath for 5 s. The time taken from breaking point to the start of the rise in Sa$_O_2$ was taken to be equivalent to the lung—hand circulation time. This technique has been previously described to measure the lung—ear circulation time, with the pulse oximeter placed on the ear lobe.

**Protocol**

Subjects refrained from caffeine for at least 4 h before the study. They were assessed clinically and the arterial line was then inserted. The HCVR testing, both steady-state Fenn and Craig technique and modified Read rebreathing technique were carried out in a randomised order with >30 min between tests. In the breaks patients were allowed snacks and non-caffeinated drinks.

**Data analysis**

Flow, $PCO_2$ and Sa$_O_2$ signals were recorded via an analogue to digital interface (1401 Micro, Cambridge Electronic Design Ltd, Cambridge, UK). The signals were then analysed (Spike2, Cambridge Electronic Design Ltd, Cambridge, UK) to provide breath-by-breath measurements of inspired minute ventilation and $PetCO_2$. Adjustments to standardise measurements at body temperature, with fully saturated water vapour pressure at 37°C were made. Breaths corresponding to each arterial blood gas sample were determined by subtracting the (mouth—lung—hand) circulation time from the start and end of each arterial blood sample time. Measurements of circulation time were carried out in all patients with COPD, but only 5 of 11 healthy volunteers as it was not introduced into the protocol until after the study was in progress. In the healthy volunteers in whom an estimate was not made, a circulation time of 15 s was used. Linear regression analysis of minute ventilation on $PaCO_2$ or $PetCO_2$ was used to determine the hypercapnic ventilatory response (HCVR$_{a}$ or HCVR$_{et}$) slope (L/min/mmHg) and intercept (mmHg) during steady-state testing and rebreathing. The slope was also expressed in degrees for statistical analysis. This enabled small variations in the angle of the slope to be equally weighted irrespective of a blunted HCVR (flat slope) or brisk HCVR (steep slope).

**Sample size**

The $P(a–et)CO_2$ difference measured during air breathing in 40 COPD patients with a similar severity of lung disease compared to our group (FEV$_1$, 32% predicted, versus 34% predicted in our study) has previously been observed to be $7.0 \pm 5.2$ mmHg. Assuming 80% power and significance at the 0.05 level, a sample size of at least 6 would be required to detect a similar difference in $P(a–et)CO_2$ in our study.

**Statistical analysis**

Group results are given as mean ± SD, unless otherwise stated. Unpaired $t$-tests were used to compare healthy volunteers with COPD patients, and ANOVA to compare sequential $P(a–et)CO_2$ differences during the HCVR. Pearson’s correlation was used to examine the relationship between steady-state and rebreathing HCVR, for the slope and intercept.

HCVR$_{a}$ and HCVR$_{et}$ are compared using a Bland–Altman plot both for the slope and intercept, in which (HCVR$_{a}$–HCVR$_{et}$) difference is plotted against the mean of HCVR$_{a}$ and HCVR$_{et}$. The horizontal axis crosses the vertical axis at the mean (HCVR$_{a}$ – HCVR$_{et}$) difference, and 2SD above and below the mean are denoted by dashed lines. If there is good agreement between two parameters, the mean difference is close to zero, and data points are tightly clustered around this line. Bland–Altman plots have the advantage over simple regression that they not only illustrate whether there is a relationship between two variables, but also whether it is close to unity (x-axis passes through zero on the y-axis) or not (x-axis is displaced up or down).

Analysis comparing $P(a–et)CO_2$ during the steady-state HCVR was carried out on six COPD patients up to 600 ml/min and on eleven healthy volunteers up to 800 ml/min. During non-steady-state HCVR, one of eight patients with COPD and one of eleven healthy volunteers were unable to complete minute 4 of the test. Therefore, analysis comparing $P(a–et)CO_2$ during rebreathing HCVR was therefore carried out on seven patients with COPD and ten healthy volunteers up to 4 min. Analysis of the HCVR was carried out on all subjects (ie eight COPD patients and eleven healthy volunteers), as three data points were considered sufficient to determine the HCVR.

**Results**

**Subject characteristics**

Eight patients with hypercapnic COPD, established on NIV for at least three months (five male) and eleven healthy volunteers (seven male) were studied (Table 1). COPD patients had a pack-year history of 43 (17) years (range 20–60 years), with two being current smokers and six being ex-smokers. None of the healthy volunteers had ever smoked. The patients with COPD had obstructive spirometry, one was overweight (defined as body mass index (BMI) 25–29.9 kg/m$^2$), and seven of eight were clinically obese (BMI > 30 kg/m$^2$). Four had symptoms suggestive of obstructive sleep apnoea prior to initiation of NIV. The COPD patients had a group mean ± SD Pa$_O_2$ of 58 ± 7 mmHg, and Pa$_CO_2$ of 49 ± 10 mmHg, while breathing room air through a mouthpiece. The healthy volunteers were younger ($p < 0.001$) had normal spirometry (FEV$_1$ higher than COPD patients, $p < 0.001$), normal arterial blood gases (Pa$_O_2$ higher, $p < 0.001$; Pa$_CO_2$ lower, $p = 0.01$) and none had
Comparison of arterial and end-tidal PCO$_2$ during air breathing and steady-state HCVR

Fig. 3 shows the mean and S.E.M. $P_a$ and $P_{et}CO_2$ during air breathing (first data point in each panel). Consistent with previous reports $P_{et}CO_2$ was less than $P_{a}CO_2$ (7.1 ± 3.9 mmHg; $p = 0.001$) in COPD patients. In healthy volunteers, $P_{et}CO_2$ was greater than $P_{a}CO_2$ (1.4 ± 1.4 mmHg; $p = 0.009$). As expected, the $P(a\text{-}et)CO_2$ difference was greater in COPD patients than healthy volunteers ($p < 0.001$).

In patients with COPD the $P(a\text{-}et)CO_2$ difference observed during air breathing was maintained during the steady-state HCVR (Fig. 3, top left panel) and there was no change in the magnitude of the difference as CO$_2$ supplementation was increased ($p = 0.44$). Therefore there was no difference between the HCVR$_a$ and HCVR$_{et}$ slope ($p = 0.91$, Table 2). This is shown in the Bland–Altman plot (Fig. 4, top left panel) where the HCVR$_a$ – HCVR$_{et}$ difference in slope is plotted against the mean of HCVR$_a$ and HCVR$_{et}$ slope. Notice that the data points for COPD patients are evenly distributed either side of zero. The HCVR$_a$ intercept, however, was greater than HCVR$_{et}$ intercept ($p = 0.02$). This is shown in Fig. 4 (bottom left panel) where data points for COPD patients tend to be greater than zero. It should be noted however that there was one extreme outlier (>2SD from the group mean) for the plot of $P(a\text{-}et)CO_2$ intercept during steady-state HCVR (mean $P(a\text{-}et)CO_2$ intercept: outlier −179 mmHg, group mean ±2SD = −146–154). This data point was therefore were omitted from the Bland–Altman plot (Fig. 4, bottom left panel) and from statistical analysis.

In the healthy volunteers, there was no difference between $P_{et}CO_2$ and $P_{a}CO_2$ during steady-state HCVR (Fig. 3, bottom left panel), and thus no difference between the HCVR$_a$ and HCVR$_{et}$ slope ($p = 0.21$; Table 2) or intercept ($p = 0.46$; Table 2). This is shown in Fig. 4 (left panels) where data points for healthy volunteers are evenly distributed around zero for both slope (top panel) and intercept (bottom panel).

Comparison of arterial and end-tidal PCO$_2$ during the non-steady-state HCVR

In patients with COPD, the $P(a\text{-}et)CO_2$ difference observed during air breathing was abolished throughout the non-steady-state HCVR (Fig. 3, top right panel). Therefore there was no difference between the HCVR$_a$ and HCVR$_{et}$ slope ($p = 0.73$, Table 2) or intercept ($p = 0.68$, Table 2). This is shown in Fig. 4 (top right panel) where the data points for COPD patients during rebreathing are evenly distributed either side of zero. In contrast, in the healthy volunteers the $P(a\text{-}et)CO_2$ difference observed during air breathing was maintained during the non-steady-state HCVR (Fig. 3, bottom right panel). Post hoc analysis showed that the magnitude of the $P(a\text{-}et)CO_2$ difference varied throughout the rebreathing ($p < 0.001$), with differences between minutes 1 vs 3; 2 vs 3; and, 2 vs 4. As a consequence, there was a significant difference between the HCVR$_a$ and HCVR$_{et}$ slope ($p = 0.03$; Table 2) and intercept ($p = 0.04$; Table 2).

Table 1 Characteristics of patients with COPD and healthy volunteers.

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</table>
Figure 3  Mean ± SEM arterial (closed circles) and end-tidal (open circles) PCO₂ in mmHg during air breathing (normoxia) and assessment of the hypercapnic ventilatory response (in hyperoxia). Values for COPD patients (top panels), healthy volunteers (bottom panels), steady-state CO₂ administration (left panels) and rebreathing (right panels) are shown. Significance at the 0.01 and 0.05 levels are denoted † and *, respectively.

Table 2  HCVR slope and intercept for steady-state and non-steady-state rebreathing methods, using arterial and end-tidal PCO₂

<table>
<thead>
<tr>
<th></th>
<th>Steady-state HCVR, Fenn and Craig method</th>
<th>Non-steady-state HCVR, Read Rebreathing method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (L/min/mmHg)</td>
<td>Intercept (mmHg)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCVRₐ</td>
<td>0.61 ± 0.32</td>
<td>33.6 ± 19.2</td>
</tr>
<tr>
<td>HCVRₑᵗ</td>
<td>0.62 ± 0.36</td>
<td>26.1 ± 5.9</td>
</tr>
<tr>
<td>p value</td>
<td>0.91</td>
<td>0.02</td>
</tr>
<tr>
<td>Volunteers COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCVRₐ</td>
<td>2.19 ± 1.06</td>
<td>31.5 ± 5.11</td>
</tr>
<tr>
<td>HCVRₑᵗ</td>
<td>1.97 ± 1.01</td>
<td>30.9 ± 5.6</td>
</tr>
<tr>
<td>p value</td>
<td>0.21</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Mean ± SD HCVR slope (in L/min/mmHg) and intercept (in mmHg), using arterial (HCVRₐ) and end-tidal PCO₂ (HCVRₑᵗ). In COPD patients, for the HCVR slope during steady-state testing n = 6, and during non-steady-state testing n = 8; in the healthy volunteers n = 11 for both methods. For the HCVR intercept in COPD patients one outlier (>2 SD from the mean) was omitted from the analysis of the data obtained during both steady-state testing (n = 5) and non-steady-state testing (n = 7). Significance values comparing HCVRₐ and HCVRₑᵗ, using paired t-tests are given. Significance at the 0.05 level is denoted*.
This is shown in Fig. 4 (right panels) where data points for healthy volunteers tend to be greater than zero for the slope (top right panel), and less than zero for the intercept (bottom right panel).

There was one extreme outlier (>2SD from the group mean) for the plot of $P(a_{et})CO_2$ intercept during non-steady-state HCVR (mean $P(a_{et})CO_2$ intercept: outlier $-77$ mmHg, group mean $\pm$ 2SD = $-69$–$83$). This data point was therefore omitted from the Bland–Altman plot (Fig. 4, bottom right panel) and from statistical analysis.

Comparison of steady-state and non-steady-state HCVR measured using $PaCO_2$ or $PetCO_2$

Comparing the steady-state with the non-steady-state HCVR in COPD patients there was no difference in slope derived using $PaCO_2$ (HCVR$_s$ slope $p = 0.59$, intercept 0.74) or $PetCO_2$ (HCVR$_nt$ slope $p = 0.58$, intercept 0.91). In healthy volunteers there was also no difference in slope derived using $PaCO_2$ (HCVR$_s$ slope $p = 0.92$) or $PetCO_2$ (HCVR$_nt$ slope $p = 0.90$), however, the intercept was significantly higher with the non-steady-state rebreathing technique derived using $PaCO_2$ (HCVR$_s$ intercept $p = 0.001$) and $PetCO_2$ (HCVR$_nt$ intercept $<0.001$).

Discussion

We have shown that in patients with COPD and obesity the HCVR slope can be accurately measured using $PetCO_2$ or $PaCO_2$ during both steady-state and, non-steady-state techniques, and therefore either method may be used clinically to determine the slope. We did find a difference in the HCVR intercept with the steady-state method, but not with the non-steady-state rebreathing. Therefore the rebreathing technique is the method of choice when HCVR intercept is of interest. In contrast, in healthy volunteers, assessment of the HCVR using the steady-state technique is preferable. This is because during steady-state HCVR, the
HCVr intercept or slope. Our observations during HCVR testing in healthy subjects was abolished. There was therefore no difference in HCVRa or HCVRret slope or intercept. However, during non-steady-state HCVR testing the P(a–et)CO2 difference was maintained, with PetCO2 being higher in healthy volunteers during HCVR testing, as shown previously. There was a difference in both HCVRa and HCVRret slope and intercept. It has previously been speculated that the higher PetCO2 during rebreathing in healthy volunteers may arise due to failure of CO2/HCO3 reactions to complete during the passage of blood through the lungs; if the reaction completes 'downstream' by the point of arterial blood sampling, PaCO2 will be lower. Interestingly Steinbrook et al. in awake goats only found PetCO2 to be higher than PaCO2 during rebreathing under hyperoxic conditions, but not during normoxia. They attributed this to regional variations in alveolar gas composition which accompanies rebreathing.

Limitations of the study

When interpreting the findings of our study it must be noted that although circulation time was measured at rest in all patients, it was only measured in 5 of the 11 healthy volunteers. Since circulation time at rest is likely to differ to that measured during HCVR assessment this may have influenced the P(a–et)CO2 relationships described in this study. However, we think that the influence of this inaccuracy is likely to be so small that it would not change the P(a–et)CO2 relationships described. For example, during rebreathing the average increase in PetCO2 from minutes 1 to 4 was 19 mmHg for patients with COPD and 9 mmHg for healthy volunteers. Therefore, an error in the estimation of the circulation time of 5 s, would have led to an error in PetCO2 corresponding to the time of arterial blood gas sampling of 0.5 mmHg for patients with COPD and 0.3 mmHg for the healthy volunteers.

We did not attempt to match COPD patients and volunteers for age. Ventilatory responses tend to decrease with age, however, it was not the aim of this study to compare HCVR between the healthy volunteers and COPD patients.

The same inspired CO2 load was used both for healthy volunteers and for COPD patients, despite the fact the baseline PaCO2 for COPD patients was higher. The initial CO2 stimulus for volunteers would therefore be relatively greater than for patients. This simple approach was taken rather than the much more experimentally complex approach of adjusting the starting FiCO2 for each individual. It would have delayed the equilibration time in COPD patients, but should not affect HCVR slope.

P(a–et)CO2 differences in COPD patients

The reduced PetCO2 compared to PaCO2 during air breathing in patients with COPD is explained by expired gas from ventilated but under-perfused units of lung with low PCO2 content diluting the expired PCO2 fraction. As such, the single greatest determinant of the P(a–et)CO2 difference has been shown to be tidal volume, since a large tidal volume to dead space ratio will reduce the dilutional effect of returning gas from under-perfused lung units.

During air breathing and steady-state HCVR, PetCO2 was lower than PaCO2 in patients with COPD. As a consequence the steady-state HCVRret intercept was significantly less than the HCVRa intercept. Since the P(a–et)CO2 difference was constant, there was no difference in HCVR slope. By contrast during non-steady-state HCVR testing the P(a–et)CO2 difference was abolished, as would be expected since during rebreathing mixed venous PCO2 (reflected by PetCO2) and PaCO2 approach an equilibrium. There was therefore no difference in non-steady-state HCVRa or HCVRret intercept or slope. Our observations during rebreathing are in keeping with previous studies in COPD patients. We have extended this study by showing that there is no difference in slope between steady-state and rebreathing techniques in the patients with COPD. This is in agreement with one previous study in healthy subjects, although a number of others have tended to show a higher rebreathing HCVR compared to the steady-state23,24,29 again in healthy subjects.

P(a–et)CO2 differences in healthy volunteers

PetCO2 was slightly higher than PaCO2 during resting breathing (1.4 ± 1.4 mmHg) in healthy volunteers. This is the opposite result of some30–33 but not all34 previous studies in man. The reason for our observation is not clear; however, we have suggested several contributory mechanisms. Firstly, the respiratory cycle generates oscillations in alveolar PCO2, which in turn lead to oscillations in arterial PCO2.25 Whereas PetCO2 reflects the peak of the oscillation, PaCO2 of a sample drawn over several breath cycles reflects the mean of the oscillation. In this way PetCO2 could be greater than PaCO2. This suggestion is supported by the observation that during exercise PaCO2 oscillations increase in magnitude,36 and at higher work intensities PetCO2 becomes greater than PaCO2.27,27 To our knowledge this relationship has not previously been observed at rest. In our study such an effect may have been unmasked by body posture since subjects were tested in the semi-recumbent position rather than upright. A change in posture from standing to supine leads to decreased alveolar dead space, presumably due to the gravitational effect on blood flow in the pulmonary blood vessels leading to better ventilation–perfusion matching and therefore an increase in PetCO2 relative to PaCO2.29,40 In addition, the 215 ml respiratory apparatus dead space in our study may have caused a degree of rebreathing, thereby raising PetCO2. During the HCVR assessment we would not expect PCO2 oscillations to play an important role in the P(a–et)CO2 relationship, since the inhaled CO2 load would attenuate the oscillation profile.

During steady-state HCVR testing the P(a–et)CO2 difference during air breathing in healthy subjects was abolished. There was no difference in HCVRa or HCVRret slope or intercept. However, during non-steady-state HCVR testing the P(a–et)CO2 difference was maintained, with PetCO2 being higher in healthy volunteers during HCVR testing, as shown previously.30,31,41 There was a difference in both HCVRa and HCVRret slope and intercept. This suggestion is supported by the observation that during non-steady-state HCVR testing the P(a–et)CO2 difference was significantly less during air breathing at rest in COPD patients is consistent with previous reports.8,9 Our results should be interpreted with caution due to the small sample size, however they are consistent with expected findings.

Limitations of the study

When interpreting the findings of our study it must be noted that although circulation time was measured at rest in all patients, it was only measured in 5 of the 11 healthy volunteers. Since circulation time at rest is likely to differ to that measured during HCVR assessment this may have influenced the P(a–et)CO2 relationships described in this study. However, we think that the influence of this inaccuracy is likely to be so small that it would not change the P(a–et)CO2 relationships described. For example, during rebreathing the average increase in PetCO2 from minutes 1 to 4 was 19 mmHg for patients with COPD and 9 mmHg for healthy volunteers. Therefore, an error in the estimation of the circulation time of 5 s, would have led to an error in PetCO2 corresponding to the time of arterial blood gas sampling of 0.5 mmHg for patients with COPD and 0.3 mmHg for the healthy volunteers.

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Conclusions and implications of findings

Our study shows that even in patients with severe respiratory disease, such as those with hypercapnic respiratory failure secondary to COPD and obesity a valid measurement of HCVR can be made, which is quick and easy to perform. Despite large P(a-et)CO₂ differences observed at rest, PetCO₂ can be used during assessment of both the steady-state and an non-steady-state breathing HCVR slope in patients with COPD. Therefore, since both methods are non-invasive, relatively short and can be tolerated by patients with severe respiratory failure, either method is practical and may be used in clinical practice. The non-steady-state rebreathing method is preferred if the intercept is of particular interest. In healthy volunteers the steady-state HCVR is preferable.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgements

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References