Volume acceleration as an index of respiratory drive during exercise

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ABSTRACT

In order to evaluate the applicability of volume acceleration ($A_I$) at the onset of inspiration as an index of neuromuscular output, CO$_2$ rebreathing in six healthy subjects and incremental-load exercise in eight healthy subjects was performed while measuring $A_I$ and mouth occlusion pressure ($P_{0.1}$). During CO$_2$ rebreathing, $A_I$ increased linearly with end-tidal CO$_2$ partial pressure and $P_{0.1}$. During incremental-load exercise, $P_{0.1}$ and $A_I$ increased exponentially with minute ventilation and mean inspiratory flow, and $A_I$ increased linearly with $P_{0.1}$. Dyspnoea sensation at rest and exercise with or without the circuit system in eight healthy subjects was examined. Dyspnoea sensation increased markedly with the circuit system in some subjects. Incremental-load exercise was carried out by 13 healthy subjects and 21 patients with chronic obstructive pulmonary disease (COPD) to evaluate the difference in $A_I$ as respiratory drive between the two groups in the absence of a respiratory circuit. In patients with COPD, $A_I$ responses to minute ventilation, mean inspiratory flow and carbon dioxide output ($V_{\text{dCO}_2}$) were greater than those in healthy subjects. In patients with COPD, the $A_I$ response to $V_{\text{dCO}_2}$ was greater in those with a lower $\text{FEV}_1.0$ (forced expiratory volume in 1.0 s), but the ventilatory response to $V_{\text{dCO}_2}$ was lower in those with a lower $\text{FEV}_1.0$. These data suggest that $A_I$ reflects neuromuscular output during CO$_2$ rebreathing and incremental-load exercise under conditions where mechanical properties of the respiratory system are expected to be involved. During exercise, flow increased markedly, and the influence of the resistance of the respiratory circuit also increased. Therefore the use of $A_I$ has the advantage of less resistance (no respiratory circuit) and less additional respiratory effort, in comparison with the use of $P_{0.1}$, especially in patients with COPD.

INTRODUCTION

During load exercise, the respiratory drive increases in association with an increase in ventilation. To evaluate this elevated respiratory drive during exercise, mouth occlusion pressure ($P_{0.1}$) has been used as an index of neuromuscular output in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD) [1,2]. However, the application of $P_{0.1}$ requires respiratory circuits that contain an occluding valve and a

Key words: chronic obstructive pulmonary disease, CO$_2$ rebreathing, load exercise, mouth occlusion pressure, neuromuscular output, volume acceleration.

Abbreviations: $A_I$, volume acceleration; COPD, chronic obstructive pulmonary disease; $\text{FEV}_1.0$, forced expiratory volume in 1.0 s; FVC, forced vital capacity; $P_{0.1}$, mouth occlusion pressure; $P_{\text{CO}_2}$, partial pressure of CO$_2$; $P_{\text{ETCO}_2}$, end-tidal $P_{\text{CO}_2}$; $V_{\text{dI}}$, chest flow during initial inspiratory phase; VAS, visual analogue scale; $V_{\text{dCO}_2}$, carbon dioxide output per min; $V_{\text{d}}$, inspiratory minute ventilation; $V_O$, oxygen uptake per min; $V_{\text{d}}/T_{\text{I}}$, mean inspiratory flow.

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two-way valve that lead to an increase in external airway resistance, and therefore additional respiratory effort by the subject is required because of greater resistive influence, especially when flow and respiratory drive are markedly increased during exercise. In patients with COPD, an additional respiratory circuit requires more respiratory effort, and load exercise using the additional respiratory circuit cannot be carried out in some cases because of elevated dyspnoea sensation.

To avoid this need for additional respiratory effort, Cotton et al. [3] used volume acceleration ($A_v$) at the transition from expiration to inspiration as an index to reflect neuromuscular output. They calculated $A_v$ and $P_{0.1}$ during CO$_2$ rebreathing in healthy subjects, and showed that $A_v$ increased significantly with both increasing partial pressure of CO$_2$ (PCCO$_2$) and increasing $P_{0.1}$. Further, the influence of the mechanical properties of the respiratory system on $A_v$ was demonstrated by Mishima et al. [4]. The present investigation was aimed at assessing the application of $A_v$ as a respiratory drive during exercise. The following studies were carried out. (1) CO$_2$ rebreathing was performed in six healthy subjects while measuring $A_v$ and $P_{0.1}$ for a comparison with the previous study by Cotton et al. [3], because we calculated $A_v$ somewhat differently. (2) Incremental-load exercise was performed in eight healthy subjects in order to compare $A_v$ with $P_{0.1}$. (3) We examined dyspnoea sensation with a visual analogue scale (VAS) at rest and during exercise with or without the circuit system in eight healthy subjects, to evaluate the influence of the circuit system and the measurement of occlusion pressure. (4) Incremental-load exercise without the respiratory circuit system was performed in 13 control subjects and 21 patients with COPD to evaluate the difference in $A_v$ between the two groups, and the relationship between respiratory impairment and $A_v$ in the COPD patients was discussed. (5) Finally, a dynamic model of the respiratory system was adopted for analysis in evaluating the influence of resistance and compliance of the respiratory system on $A_v$.

**METHODS**

**Subjects**

The following subjects were studied: experiment 1 ($P_{0.1}$ and $A_v$ during CO$_2$ rebreathing), six healthy males aged 25–36 years (age 34 ± 1.4 years; height 171 ± 6.0 cm; body weight 71.5 ± 7.0 kg; means ± S.D.); experiment 2 ($P_{0.1}$ and $A_v$ during incremental-load exercise), eight healthy males aged 26–37 years (age 31 ± 1.7 years; height 169 ± 3.7 cm; body weight 70 ± 6.6 kg); experiment 3 (VAS at rest and during exercise in the presence and the absence of the circuit system), eight healthy males aged 31–39 years (age 34 ± 3.3 years; height 169 ± 2.3 cm; body weight 67.5 ± 5.2 kg); experiment 4 ($A_v$ during incremental-load exercise in control subjects and patients with COPD), 13 healthy males aged 24–36 years (age 30 ± 3.8 years; height 172 ± 5.2 cm; body weight 68 ± 5.6 kg) and 21 patients with COPD aged 52–79 years (age 66 ± 7.3 years; height 162 ± 6.5 cm; body weight 55 ± 10.2 kg). Patients were clinically stable and had clinical histories consistent with COPD. Informed consent was obtained from all subjects, and the study was approved by the institutional ethics committee.

**Procedures**

In experiment 1, hypercapnic respiratory responses were obtained using Read’s method, as previously reported [5]. The subjects were studied in a sitting position, and breathed through a mouthpiece with a noseclip. The subjects rebreathed 5 litres of 6–8% CO$_2$ in O$_2$ through a closed-circuit system containing a low-resistance one-way valve and an electromagnetic occlusion valve (Fukuda, Tokyo, Japan).

In experiment 2, pulmonary function tests were performed to determine vital capacity using a FUDAC 60 instrument (Fukuda). Incremental-load exercise was performed on an electronically braked cycle ergometer (Ergomet 840; Siemens Medical Systems). The subjects were wearing a noseclip and breathed through a mouthpiece. The workload was increased by 20 W per min until volitional exhaustion. The subjects breathed through an open-circuit system containing a low-resistance one-way valve and an electromagnetic occlusion valve (Fukuda).

In experiment 3, the VAS consisted of a horizontal line 100 mm in length with descriptors of the sensation of dyspnoea ranging from ‘no breathlessness’ at one end of the line to ‘extremely severe breathlessness’ at the other. The open-circuit system contained a low-resistance one-way valve and an electromagnetic occlusion valve (Fukuda). Resting trials and 2 min of loaded cycling at 120 W were performed. At rest and during the final 60 s of the loaded cycling, subjects breathed on a mouthpiece attached to a flow transducer for 30 s, and subsequently breathed on it with the circuit system and with airway occlusion several times for 30 s. Subjects indicated their level of dyspnoea using the VAS at the end of each trial, and 30 s averages of inspiratory minute ventilation ($V_i$) were computed at each trial.

In experiment 4, forced vital capacity (FVC) and forced expiratory volume in 1.0 s (FEV$_{1.0}$) were measured in all subjects using a FUDAC 60. Arterial blood gas values were measured in patients with COPD. Incremental-load exercise was performed on an electronically braked cycle ergometer (Ergomet 840). The subjects were seated on the cycle ergometer and breathed through a face mask. The workload was increased by 20 W per min in control subjects and by 10 W per min in patients with COPD until volitional exhaustion.

The resistance of the circuit in experiments 1, 2 and 3 was 0.05 kPa·1$^{-1}$·s at a flow rate of 1.0 litre·s$^{-1}$ and had
linear pressure–flow characteristics up to a flow rate of 3.0 litres·s⁻¹. In experiments 1, 2 and 4, CO₂ and O₂ were measured by an infrared CO₂ analyser and a polarographic O₂ analyser respectively (MG360; Minato, Osaka, Japan). In all experiments, respiratory flow was measured with a hot-wire flowmeter (Respirometer RM-300; Minato). In experiments 1 and 2, mouth pressure was monitored by use of a differential pressure transducer (LPU-0.1; Toyo Baldwin, Tokyo, Japan).

**Data analysis**

In experiment 1, the airway was randomly occluded during rebreathing by an electromagnetic occlusion valve during the preceding expiration, without the subject’s knowledge of the timing. The test lasted for about 4 min, and occlusion was performed 5–10 times during one rebreathing run. In experiment 2, the airway was occluded during exercise by an electromagnetic occlusion valve during the preceding expiration about every 30 s, and occlusion was performed 5–10 times during one exercise bout. The test lasted for about 4 min, and the breath-by-breath fluctuations.

The flow signals, the pressure signals, O₂ data and CO₂ data were digitized at 200 Hz using an analogue–digital conversion board (AD12-16RT; Contec, Osaka, Japan). In experiments 1 and 2, mouth pressure was monitored by use of a differential pressure transducer (LPU-0.1; Toyo Baldwin, Tokyo, Japan).

The flow signals, the pressure signals, O₂ data and CO₂ data were digitized at 200 Hz using an analogue–digital conversion board (AD12-16RT; Contec, Osaka, Japan) and an NEC computer (PC9801FA), and were recorded on a magnetic disk simultaneously. V̇ᵣ and end-tidal PCO₂ (PETCO₂) in experiment 1, V̇ᵣ and mean inspiratory flow (V̇ᵣ/TV) in experiment 2, and V̇ᵣ in experiment 3 were computed breath-by-breath from the data stored on a magnetic disk using the NEC computer and the BASIC program. Occlusion pressure read at 0.1 s from the onset of inspiration was computed from pressure signal data stored on the magnetic disk.

Cotton et al. [3] calculated Aᵣ at end-expiratory flow using a pneumotachograph, but we calculated Aᵣ during the initial part of inspiratory flow using a hot-wire respiratory flowmeter. In the present study, Aᵣ (l·s⁻²) at the onset of inspiration was the slope of the regression line that was obtained from the segment of the flow curve after the onset of inspiration. As this segment was relatively short, the value of Aᵣ was nearer to the ideal value of acceleration at the onset of inspiration, but the fitting of the regression became less accurate. We calculated Aᵣ for each breath at seven points (30 ms) from the onset of inspiration using the NEC computer, because all regression lines were significant at P < 0.05 by statistical F-test (Figure 1). V̇ᵣ, Aᵣ and PETCO₂ in experiment 1, and V̇ᵣ, Aᵣ and V̇ᵣ/TV in experiment 2, were obtained as the averages of values for three successive breaths preceding the one utilized for occlusion. In experiment 4, Aᵣ, V̇ᵣ, V̇ᵣ/TV, oxygen uptake per min (VO₂), and carbon dioxide output per min (VCO₂) were measured, breath-by-breath, using the RM-300 and the NEC computer, and the moving average filter of five points was used to smooth the breath-by-breath fluctuations.

**Statistical analysis**

Linear regression analysis was carried out by the method of least squares. The model of the exponential curve (Y = a·e⁻ᵇ·X) was linearized by transforming Y to ln(Y), and linear regression analysis was then carried out by the method of least squares. The strength of the relationship in the data was evaluated using the coefficient of determination (R²). A statistical F-test was applied to examine whether the regression model fitted the experimental data points significantly [6]. VAS scores and V̇ᵣ values were compared by paired t-tests. The significance of differences between the two groups was analysed using non-paired t-tests. The level of significance was P < 0.05. All data are presented as means ± S.D.

**RESULTS**

**P₀,₁ and Aᵣ during CO₂ rebreathing**

The responses of V̇ᵣ, P₀,₁ and Aᵣ to PETCO₂ are shown in Figures 2(A)–2(C). V̇ᵣ, P₀,₁ and Aᵣ increased linearly with the increase in PETCO₂ in all cases. The linear regression lines relating V̇ᵣ, P₀,₁ and Aᵣ to PETCO₂ in all six subjects were significant (P < 0.05) (Table 1). Aᵣ increased linearly with P₀,₁ (Figure 2D), and the linear regressions relating Aᵣ to P₀,₁ were significant in all subjects (Table 1).

**P₀,₁ and Aᵣ during incremental-load exercise**

The mean values for vital capacity and maximal V̇ᵣ of the subjects were 4.32 ± 0.32 litres and 65.9 ± 17.2 litres·min⁻¹ respectively. V̇ᵣ, V̇ᵣ/TV, P₀,₁ and Aᵣ increased with increasing load (Figure 3). P₀,₁ increased curvilinearly with increasing V̇ᵣ and V̇ᵣ/TV (Figures 4A and 4B), and Aᵣ increased curvilinearly with increasing V̇ᵣ and V̇ᵣ/TV (Figures 4C and 4D), in all cases. The exponential regressions relating P₀,₁ to V̇ᵣ, P₀,₁ to V̇ᵣ/TV, Aᵣ to V̇ᵣ and Aᵣ to V̇ᵣ/TV in all subjects fitted the

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**Figure 1** Flow data at the transition from expiration to inspiration

Aᵣ is the slope of the regression line obtained from seven points (total 30 ms) after the onset of inspiration.
Figure 2  $V_I$ (A), $P_{0.1}$ (B) and $A_I$ (C) plotted against $P_{ETCO_2}$, and relationship between $P_{0.1}$ and $A_I$ (D), in six subjects during CO$_2$ rebreathing. Different symbols denote data points obtained from individual subjects.

Table 1 Slopes ($a_1$–$a_4$), y intercepts ($b_1$–$b_4$) and coefficients of determination ($R^2_1$–$R^2_4$) in the linear regressions relating $V_I$ to $P_{ETCO_2}$, $P_{0.1}$ to $P_{ETCO_2}$, $A_I$ to $P_{ETCO_2}$ and $A_I$ to $P_{0.1}$ during CO$_2$ rebreathing runs in six subjects. All linear regressions fitted the experimental data points significantly (statistical $F$-test; $P < 0.05$).

<table>
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<tr>
<th>Subject</th>
<th>$a_1$</th>
<th>$b_1$</th>
<th>$R^2_1$</th>
<th>$a_2$</th>
<th>$b_2$</th>
<th>$R^2_2$</th>
<th>$a_3$</th>
<th>$b_3$</th>
<th>$R^2_3$</th>
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<td>26.33</td>
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<tr>
<td>3</td>
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<td>–27.3</td>
<td>0.73</td>
<td>0.15</td>
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<td>3.65</td>
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<td>–3.20</td>
<td>0.64</td>
<td>7.05</td>
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<tr>
<td>6</td>
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<td>–620.9</td>
<td>0.98</td>
<td>2.10</td>
<td>–14.49</td>
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<td>52.78</td>
<td>–360.2</td>
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<td>18.86</td>
<td>7.67</td>
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Experimental data points significantly by statistical $F$-test (Table 2). $A_I$ increased linearly with increasing $P_{0.1}$ in all cases (Figure 4E), and the linear regressions relating $A_I$ to $P_{ETCO_2}$, $P_{0.1}$ to $A_I$, $A_I$ to $P_{ETCO_2}$ and $A_I$ to $P_{0.1}$ during CO$_2$ rebreathing runs fitted the experimental data points significantly by statistical $F$-test (Table 3).

**VAS at rest and during exercise in the presence and the absence of the circuit system**

At rest, the VAS score in the absence of the circuit system was $3.4 \pm 4.8$ mm, and in the presence of the circuit system it was $8.6 \pm 6.7$ mm. The average increase was $5.3 \pm 5.7$ mm, which was statistically significant ($P < 0.05$). At exercise, the VAS score in the absence of the circuit system was $20.0 \pm 14.3$ mm, and that in its presence was $32.5 \pm 12.1$ mm. The average increase was $12.5 \pm 7.4$ mm, which was also statistically significant ($P < 0.05$). At rest, $V_I$ in the absence of the circuit system was $11.2 \pm 3.2$ litres/min, and that in its presence was $13.6 \pm 6.3$ litres/min (average change $2.5 \pm 4.3$ litres·min$^{-1}$). At exercise, $V_I$ in the absence of the circuit system was $39.6 \pm 8.9$ litres·min$^{-1}$, and that in its presence was $43.2 \pm 11.3$ litres·min$^{-1}$ (average change $3.6 \pm 5.0$ litres·min$^{-1}$). The relationship between the changes in...
Figure 3  Effects of increasing workload on $V_I$, $V_I/T_I$, $P_{0.1}$, and $A_I$

Ergometer load was increased from a starting load of 20 W to symptom limit by 20 W per min. Values for (A) $V_I$ (●) and $V_I/T_I$ (◆ 4) and (B) $P_{0.1}$ (●) and $A_I$ (◆ 4) are given during exercise from the start point to 10 min. Values are means ± S.D. for eight subjects.

Figure 4  Relationships between $P_{0.1}$, $A_I$, $V_I$ and $V_I/T_I$ during exercise

Values of $P_{0.1}$ are plotted against $V_I$ (A) and $V_I/T_I$ (B), and values of $A_I$ are plotted against $V_I$ (C) and $V_I/T_I$ (D), during exercise in eight subjects. Exponential regression analysis was carried out. (E) The relationship between $P_{0.1}$ and $A_I$ was linear. Different symbols denote data points obtained from individual subjects.
Table 2  Values of constants (a5–a8; b5–b8) and coefficients of determination (R25–R28) in the exponential regressions relating P0.1 to V0I, P0.1 to VT/TI, AI to V0 and AI to VT/TI during incremental-load exercise in eight subjects

All exponential regression curves fitted the experimental data points significantly (F-test; P < 0.05).

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<th>b5</th>
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<th>b6</th>
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Table 3  Slope (a9), y intercept (b9) and coefficient of determination (R29) in the linear regression relating AI to P0.1 during exercise in eight subjects

The linear regression fitted the experimental data points significantly (F-test; P < 0.05).

<table>
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<tr>
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<tr>
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<tr>
<td>S.D.</td>
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VAS score and the changes in V0I is shown in Figure 5. V0I clearly increased with an increase in the VAS score in some of cases at rest and during exercise.

**A1 during incremental-load exercise in healthy subjects and patients with COPD**

FVC, FEV1.0, FEV1.0/FVC, maximal VO2/body weight and maximal V0 were 4.68 ± 0.50 litres, 3.99 ± 0.55 litres, 87.6 ± 7.0%, 30.9 ± 4.3 litres·min⁻¹·kg⁻¹ and 75.5 ± 13.5 litres·min⁻¹ respectively in the healthy subjects, and 2.46 ± 0.60 litres, 1.19 ± 0.36 litres, 45.1 ± 10.6 %, 15.3 ± 4.3 litres·min⁻¹·kg⁻¹ and 38.9 ± 10.6 litres·min⁻¹ respectively in patients with COPD. Arterial PO2 and PCO2 values were 10.14 ± 1.26 kPa and 5.58 ± 0.38 kPa respectively in patients with COPD. Figure 6 shows that A1 increased curvilinearly with increasing V0, VT/TI and VCO2 and V0I increased linearly with increasing VCO2 in a representative control subject and a representative patient with COPD. The exponential regressions relating A1 to V0, A1 to VT/TI and A1 to VCO2, and the linear regressions relating V0I to VCO2, for all subjects in the two groups fitted the experimental data points significantly.

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Volume acceleration during exercise

Figure 6 Relationships between $A_i$, $V_d$, $V_T/T_i$, and $V_{CO_2}$ in a control subject and in a patient with COPD

$A_i$ is plotted against $V_d$ (A), $V_T/T_i$ (B) and $V_{CO_2}$ (C), and $V_d$ is plotted against $V_{CO_2}$ (D), during exercise for one representative control subject (○) and one representative patient with COPD (△). All data were measured breath-by-breath, and a moving average filter of five points was used.

(F-test; $P < 0.05$). Table 4 shows the mean values of the coefficients of regression equations for the two groups. The responses of $A_i$ to $V_d$ $\left( b_{10}; \Delta \ln A_i/\Delta V_d \right)$, $V_T/T_i \left[ b_{11}; \Delta \ln A_i/\Delta (V_T/T_i) \right]$ and $V_{CO_2} \left( b_{12}; \Delta \ln A_i/\Delta V_{CO_2} \right)$, and the ventilatory response to $V_{CO_2} \left( a_{13}; \Delta V_i/\Delta V_{CO_2} \right)$, were greater in patients with COPD than in healthy subjects. In COPD patients, FEV$_{1.0}$ was correlated negatively with $b_{10} \left( r = -0.67; P < 0.001 \right)$ and $b_{12} \left( r = -0.45; P < 0.05 \right)$, but positively with $a_{13} \left( r = 0.55; P < 0.05 \right)$, and $b_{10}$ was correlated negatively with $a_{13} \left( r = -0.50; P < 0.05 \right)$ (Figure 7). Therefore the responses of $A_i$ to $V_i$ and $V_{CO_2}$ were greater in subjects with a lower FEV$_{1.0}$, but the ventilatory response to $V_{CO_2}$ was lower in subjects with a lower FEV$_{1.0}$.

DISCUSSION

Manner of computing $A_i$

In the study by Cotton et al. [3], $A_i$ was calculated from flow data between an expiratory flow of 0.2 litre·s$^{-1}$ and zero flow using a pneumotachograph. It was noted that, as inspiratory flow was greater, the numbers of flow data points calculated were fewer. In the present study, $A_i$ was calculated from the flow points after the onset of inspiration using a hot-wire flowmeter, because this device discriminates the flow direction and inverts the original flow signals from the same phase to a different one electronically [7]. Therefore we calculated $A_i$ at the onset of inspiration as the slope of the regression line that was obtained from the segment of the flow curve after the onset of inspiration. As that segment was relatively short, the value of $A_i$ was closer to the theoretical value of acceleration $\left[ V(0) \right]$. We calculated $A_i$ for each breath from seven points (total 30 ms) from the onset of inspiration (Figure 1), and all the regression lines were significant at $P < 0.05$ by statistical F-test. The flow range of the calculated segments was up to 1.5–2.0 litres·s$^{-1}$. When inspiratory flow and $A_i$ increase markedly, the influence of the mechanical properties of the respiratory system should be taken into consideration.

CO$_2$ rebreathing

During CO$_2$ rebreathing, $A_i$ and $P_{0.1}$ increased with increasing $P_{ETCO_2}$, and $A_i$ was correlated significantly with $P_{0.1}$, similar to the results of Cotton et al [3]. Although there were minor differences in apparatus and the manner of calculation, the response of $A_i$ to $P_{ETCO_2}$ in the present study was similar to that observed by Cotton et al. [3].

$P_{0.1}$ during exercise

The measurement of $P_{0.1}$ provides a useful index of the output of the respiratory centre [8]. Moreover, brief
occlusions are useful in measuring output in the very first part of inspiration in conscious subjects, but $P_{0.1}$ must be treated with a great deal of caution [9]. It has been reported that the occlusion pressure wave changes significantly during incremental-load cycle exercise in healthy subjects and in patients with COPD [10]. In addition, $P_{0.1}$ was increased in a reflex manner in response to internal flow-resistive loading induced by breathing a high-density gas [11,12]. As the use of an external respiratory circuit is also a factor leading to increased resistance during high-level ventilation, it should be noted that respiratory drive may be overestimated.

### Relationships of $P_{0.1}$ and $A_{1}$ to $V_{I}$ and $V_{T}/T_{I}$

Hesser and Lind [1] reported that the relationships of $P_{0.1}$ to $V_{I}$ and $V_{T}/T_{I}$ were parabolic during incremental-load exercise. Sergysels et al. [2] reported that the relationships of $V_{I}$ and $V_{T}/T_{I}$ to $P_{0.1}$ seemed to be exponential during incremental-load exercise for normal subjects and for patients with COPD. In the present study, the relationships of $P_{0.1}$ to $V_{I}$ and $V_{T}/T_{I}$ were exponential during incremental-load exercise. However, both relationships were curvilinear, as $P_{0.1}$ rose considerably more quickly than did $V_{I}$ and $V_{T}/T_{I}$. The relationships of $A_{1}$ to $V_{I}$ and $V_{T}/T_{I}$ were also exponential, and $A_{1}$ was correlated significantly with $P_{0.1}$ during incremental-load exercise. This revealed $A_{1}$ to be a good index of neuromuscular output during exercise, similar to $P_{0.1}$.

### Other indices of neuromuscular output using flow parameters

$A_{1}$ is considered to be an index of neuromuscular output using flow parameters. Other indices using flow parameters have been reported. Goldberg and Milic-Emili [13] used mean flow obtained over a fixed time after onset of inspiration as the index of neuromuscular output. Painter and Cunningham [14] analysed the respiratory flow patterns from different stimuli using initial inspiratory acceleration, which was the slope of the first 100 ms of the inspiratory phase. Mishima et al. [4]...
Volume acceleration during exercise

Figure 7 Relationships between $b_10$ and FEV$_{1.0}$ (A), $b_12$ and FEV$_{1.0}$ (B), $a_{13}$ and FEV$_{1.0}$ (C) and $a_{13}$ and $b_10$ (D) during incremental-load exercise in 21 patients with COPD

$b_{10}$, $b_{11}$ and $b_{12}$ are values of constants in the exponential regressions ($A_I = a_{10} \cdot e^{b_{10} \cdot \frac{V_I}{T_I}}$; $A_I = a_{11} \cdot e^{b_{11} \cdot V_{CO_2}}$; $A_I = a_{12} \cdot e^{b_{12} \cdot \frac{V_I}{T_I}}$), and $a_{13}$ is the value of a constant in the linear regression ($A_I = a_{13} \cdot P_{D_2} + b_{13}$).

reported that chest flow during the initial inspiratory phase ($V_{d,1}$) is a good index of chest wall acceleration, which is determined by both the neuromuscular drive and the mechanics of the respiratory system. This index is similar to $A_I$ in our study, as the two indices are calculated from chest flow or mouth flow in the initial inspiratory phase.

Influence of resistance and compliance on $A_I$

Cotton et al. [3] speculated that the influence of the resistance and compliance of the respiratory system on $A_I$ was negligible. However, Mishima et al. [4] reported that $V_{d,1}$ is influenced by both the neuromuscular drive and the mechanics of the respiratory system, and $A_I$ must also be potentially subject to the mechanical properties of respiratory impedance to the same degree as $V_{d,1}$. From our simulation shown in the Appendix, $A_I$ is also influenced by resistance and compliance. $A_I$ decreased as resistance increased and increased as compliance increased, with the influence of compliance being less than that of resistance. Thus $A_I$ was underestimated when resistance increased. These observations mean that, when estimating $A_I$ as an index of respiratory drive, the mechanical properties of the respiratory system should be taken into account.

Influence of the resistance of the respiratory circuit

It has been reported that added inspiratory resistance increases $P_{D_1}$ responses, indicating that inspiratory motor output is augmented by resistive loading [15,16]. $P_{D_1}$ was increased by added resistance, especially at a high level of ventilation [16]. In experiment 3 in the present study, changes in the VAS scores increased during exercise. An increase in $V_d$ accompanied by an increase in dyspnoea sensation is thought to be associated with an elevation of respiratory drive in some cases. Heightened inspiratory and expiratory motor outputs cause comparable increases in the sensation of breathing difficulty [17,18]. Therefore the resistance of the respiratory circuit will have an influence on respiratory drive at high levels of ventilation during exercise. The measurement of $A_I$ requires less additional resistance and respiratory drive than measurement of $P_{D_1}$.

Respiratory drive during exercise in patients with COPD

Patients with COPD have an increased respiratory drive [2], and the $P_{D_1}$ values in such patients during room air breathing are higher than in control subjects [19]. Exercise performance in patients with COPD is limited largely by impairment of ventilatory mechanics.
[2,20–22]. Sergysels et al. [2] showed that the relationship between $P_{0.1}$ and $V_t$ or $V_t/T_t$ was exponential, and that the response of $P_{0.1}$ to $V_t$ and $V_t/T_t$ for the patients with COPD was greater than that of the normal subjects during exercise. In the present study, the responses of $A_1$ to $V_t$, $V_t/T_t$ and $V_{CO_2}$ were measured for each subject, and the mean values in patients with COPD were higher than those in control subjects. Therefore it is suggested that the respiratory drive in patients with COPD is higher than that in control subjects. Light et al. [23] reported that the $\Delta V_{CO_2}/\Delta V_{CO_2}$ ratio (where $\Delta V_{CO_2}$ is expiratory minute ventilation) during exercise was higher in subjects with a high FEV$_{1.0}$, a low resting arterial PCO$_2$ and a low resting arterial O$_2$ saturation among patients with COPD. In the present study, FEV$_{1.0}$ was positively correlated with the response of $A_1$ to $V_t$, $V_t/T_t$ and $V_{CO_2}$ in patients with COPD. Therefore it is suggested that, as the degree of mechanical impairment increases, the response of the respiratory drive to incremental load is higher but the ventilatory response to incremental load is lower in patients with COPD.

Conclusions

In the present study, $A_1$ increased linearly with $P_{0.1}$ during CO$_2$ rebreathing and incremental-load exercise. It is suggested that $A_1$ reflects neuromuscular output in a similar manner to $P_{0.1}$ under these conditions. $A_1$ is potentially subject to the mechanical properties of the respiratory system, and this has to be taken into consideration. However, during incremental-load exercise, flow increased markedly, and the influence of the resistance of the respiratory circuit also increased. Therefore it is suggested that the use of $A_1$ has the advantage of requiring less additional respiratory effort, because of lower resistance of the respiratory circuit and the absence of airway occlusion, in comparison with the use of $P_{0.1}$. This approach is likely to be particularly useful for patients with COPD, in whom respiratory drive is elevated and hence an additional respiratory circuit will often require severe respiratory effort.

REFERENCES


APPENDIX

Simulation of the respiratory system using a mechanical model

In the respiratory system, driving pressure developed by contraction of respiratory muscles can be shown as:

$$P(t) = 1/C \times V(t) + R \times \dot{V}(t) + F \times \ddot{V}(t)$$

where $P(t)$ is driving pressure, $V(t)$ is volume, $\dot{V}(t)$ is flow, $\ddot{V}(t)$ is volume acceleration, $C$ is compliance, $R$ is 

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resistance and $I$ is inertance. At the onset of inspiration ($t = 0$), $V(t)$ and $\dot{V}(t)$ are zero, and the inertance of the respiratory system is relatively constant [1]. Cotton et al. [2] denoted acceleration at the crossover from expiration to inspiration as $A_i$, and proposed that the magnitude of acceleration could be correlated with the driving pressure and hence neuromuscular output, without the influence of the resistance and compliance of the respiratory system. However, volume acceleration at the onset of inspiration must be calculated from several flow data points, so the influence of resistance and compliance of the respiratory system cannot be ignored. In order to estimate the influences of resistance and compliance on $V(t)$, we attempted to simulate respiratory dynamics using a mechanical model. Driving pressure should be regarded as the linear increase at the transition from expiration to inspiration, and is shown as:

$$P(t) = S(t + t_i)$$

where $S$ is the slope of the linear equation and $t_i$ is the delay time from the onset of driving pressure to the starting point of inspiratory flow [3]. The linear differential equation of the second order is:

$$1/C \cdot V(t) + R \cdot \dot{V}(t) + I \cdot \ddot{V}(t) = S(t + t_i)$$

This equation is solved as:

$$V(t) = c_1 e^{ct} + c_2 e^{ct} + C \cdot S \cdot t + C \cdot S \cdot (t_i - C \cdot R)$$

where $c_1$, $c_2$, $k_1$ and $k_2$ are constants.

When $t = 0$, $V(0) = 0$, $\dot{V}(0) = 0$, $P(0) = I \cdot \ddot{V}(0) = c_1 \cdot k_1 + c_2 \cdot k_2$ and $A_i$ is nearly equal to $\dot{V}(0)$. As these parameters were maintained at standard values ($R = 0.12 \text{ kPa}^{-1} \cdot \text{s}$; $C = 2.0 \text{ kPa}^{-1} \cdot \text{s}$; $I = 0.001 \text{ kPa}^{-1} \cdot \text{s}^2$; $t = 0.1 \text{ s}$; $S = 1 \text{ kPa}^{-1} \cdot \text{s}^{-1}$) [4], the influences of $R$ and $C$ on $A_i$ were estimated by varying one of these parameters (Figure A1). $A_i$ was calculated with the 30 ms flow data from the onset of inspiration. As $R$ increased, $A_i$ decreased. As $C$ increased, $A_i$ increased slightly. In other words, $A_i$ decreased as $R$ increased and $A_i$ increased as $C$ increased. This means that $A_i$, as an index of neuromuscular output, was underestimated when $R$ increased.

REFERENCES