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Ventilatory response to positive and negative work in patients with chronic obstructive pulmonary disease

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Department of Pulmonary Diseases, University of Nijmegen, Medical Centre Dekkerswald, Groesbeek, The Netherlands

In healthy subjects, oxygen consumption and cardiorespiratory responses are lower during eccentric exercise (negative work, $W_{neg}$) than during concentric exercise (positive work, $W_{pos}$) at the same work load. The aim of the present study was to investigate the ventilatory response to $W_{neg}$ in patients with chronic obstructive pulmonary disease (COPD). The study population consisted of 12 subjects with COPD [forced expiratory volume in 1 s (FEV$_1$) mean (sd): 1.5 (0.4) l, 46 (16) % of predicted].

Concentric and eccentric exercise tests (6 min exercise; interval > 1 h) were performed in random order at constant work loads of 25 and 50% of the individual maximal (positive) work capacity. Expired ventilation per minute ($V_e$), oxygen consumption ($VO_2$) and carbon dioxide production ($VCO_2$) were 30% lower during $W_{neg}$ than during $W_{pos}$ for both work intensities. The breathing reserve during 25%$W_{neg}$ was 11 (8)% and during 50%$W_{neg}$ was 18 (14)% higher than during $W_{pos}$ at corresponding work loads ($P<0.01$). $V_e/VO_2$ and $V_e/VCO_2$ were similar during $W_{pos}$ and $W_{neg}$. Arterial carbon dioxide tension (PaCO$_2$) increased by 0.1 (0.4) kPa during 50%$W_{neg}$ and by 0.7 (0.5) kPa during 50%$W_{pos}$ ($P<0.01$). During 50%$W_{neg}$, perceived leg effort (modified Borg scale) tended to be higher than perceived breathlessness (2.4 (1.2) vs. 2.0 (1.1)).

It was concluded that in subjects with COPD, the ventilatory requirements of $W_{neg}$ were considerably lower than those of $W_{pos}$ at similar work loads up to 50% of maximal work capacity. During $W_{neg}$, the ventilatory reserve was higher and gas exchange was less disturbed as a result of a lower $VO_2$ and $VCO_2$.

Introduction

Dynamic work is performed either as concentric (positive work, $W_{pos}$) or as eccentric (negative work, $W_{neg}$) exercise. Both types of exercise are used during many activities of daily life. During $W_{pos}$ (lifting a weight, walking upstairs), the contracting muscle shortens. During $W_{neg}$, the muscle, while contracting, lengthens in a controlled way (1). $W_{neg}$ is performed when walking downstairs or when lowering a weight to the floor.

In healthy subjects, the oxygen cost of $W_{neg}$ is lower than that of $W_{pos}$, as higher forces can be generated during $W_{neg}$ (1). At similar work loads, electromyographic (EMG) activity is lower during $W_{neg}$ as compared with $W_{pos}$ because fewer motor units are activated (2). This is accompanied with a lower cardiocirculatory and ventilatory response, as well as a lower score for perceived exertion during $W_{neg}$ (1,3–9).

Little attention has been paid to $W_{neg}$ in patients who have a limited ventilatory reserve during exercise. In patients with chronic obstructive pulmonary disease (COPD), the airway obstruction, the loss of elastic recoil, a diffusion limitation and ventilation to perfusion inequality lead to dyspnoea and abnormalities in gas exchange during exercise (10). As a result, they
are unable to exert their peripheral muscles and have a reduced exercise tolerance. If the ventilatory load during $W_{neg}$ would be substantially lower in patients with COPD, it might be a useful part of a training programme in these patients. However, it is not evident that the ventilatory response to $W_{neg}$ is equally reduced in patients with COPD and in normal subjects. In patients with COPD, the ventilatory requirement during exercise is increased (10). Even at rest, the ventilatory load may be increased by hypermetabolism and by the increased work of breathing (11). Moreover, in healthy subjects, the differences between $W_{pus}$ and $W_{neg}$ became less at lower work loads (2,4,8,9).

The aim of the present study was to investigate the metabolic cost and ventilatory requirements of $W_{neg}$ in comparison with $W_{pos}$ in patients with COPD. Therefore, the ventilatory and subjective responses to $W_{pos}$ and $W_{neg}$ were studied at sub-maximal constant work loads in 12 patients with COPD.

**Methods**

**STUDY POPULATION**

Twelve subjects (10 male) with COPD according to American Thoracic Society criteria (12), who were referred to the authors’ centre for pulmonary rehabilitation, participated in the study. They had moderate to severe airway obstruction, and most of the subjects had signs of hyperinflation and a reduced diffusion capacity for carbon monoxide (Table 1). In each subject, reversibility of FEV$_1$ was less than 15% after inhalation of 400 μg salbutamol. All subjects used inhaled β-adrenergics and corticosteroids, eight subjects used oral theophylline and two used 10 mg day$^{-1}$ oral prednisone. They were all non- or ex-smokers. They had no exacerbations for at least 8 weeks and were familiar with the procedures of exercise testing. The subjects had no neuromuscular or cardiovascular disease, and a normal ECG. Informed consent was obtained from each patient. The study was approved by the hospital Ethical Committee.

**EXERCISE PROTOCOL AND MEASUREMENTS**

Exercise was performed at a pedalling rate of 60 revolutions min$^{-1}$ (RPM) on an electrically braked cycle ergometer (Lode, Groningen, The Netherlands), which had been adapted for positive and negative work (Fig. 1) (14). In the

### Table 1. Patient characteristics (n=12)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.75</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73</td>
<td>8</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>FRC % predicted</td>
<td>118</td>
<td>27</td>
</tr>
<tr>
<td>RV % predicted</td>
<td>133</td>
<td>35</td>
</tr>
<tr>
<td>IVC % predicted</td>
<td>89</td>
<td>21</td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>% predicted</td>
<td>46</td>
<td>16</td>
</tr>
<tr>
<td>KCO % predicted</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>$PaO_2$ (kPa)</td>
<td>10.1</td>
<td>1.4</td>
</tr>
<tr>
<td>$PaCO_2$ (kPa)</td>
<td>5.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; IVC, inspiratory vital capacity; FEV$_1$, forced expiratory volume in 1 s; KCO, carbon monoxide transfer coefficient; $PaO_2$, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension. Reference values derived from Quanjer (13).

**Fig. 1.** Schematic presentation of a cycle ergometer for eccentric exercise. The pedals are driven in backward direction at a rate of 60 revolutions min$^{-1}$ (RPM) by the electric motor, which has to overcome the adjustable resistance of the electromagnetic brake. After withdrawal of the brake, the subject has to maintain a backward pedalling rate of 60 RPM by braking the speed of the pedals.
TABLE 2. Maximal incremental exercise test (n = 12)

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>max (W_{\text{pos}}) (W)</td>
<td>88</td>
</tr>
<tr>
<td>HRmax (beats min(^{-1}))</td>
<td>141</td>
</tr>
<tr>
<td>% predicted HRmax</td>
<td>87</td>
</tr>
<tr>
<td>(\dot{V}E_{\text{max}}) (l)</td>
<td>45</td>
</tr>
<tr>
<td>% predicted (\dot{V}E_{\text{max}})</td>
<td>82</td>
</tr>
<tr>
<td>(\dot{V}O_2_{\text{max}}) (l min(^{-1}))</td>
<td>1.3</td>
</tr>
<tr>
<td>(\dot{V}CO_2_{\text{max}}) (l min(^{-1}))</td>
<td>1.3</td>
</tr>
<tr>
<td>(P_aO_2) (kPa)</td>
<td>9.1</td>
</tr>
<tr>
<td>(P_aCO_2) (kPa)</td>
<td>5.7</td>
</tr>
<tr>
<td>(\delta_{\text{base-excess}}) (mmol l(^{-1}))</td>
<td>-6.3</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6.0</td>
</tr>
<tr>
<td>Leg effort</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Arterial blood samples were drawn from an indwelling catheter in the brachial artery at rest, at the end of exercise and after 3 min of recovery, and they were analysed immediately (Ciba Corning 178 DMS, Houten, The Netherlands). Heart rate (HR) was monitored by one-lead ECG recording. The predicted maximal heart rate was calculated as 220 minus age (16). Minute ventilation (\(\dot{V}E\)), oxygen consumption (\(\dot{V}O_2\)) and carbon dioxide production (\(\dot{V}CO_2\)) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands). Maximal exercise ventilation was predicted by the formula: predicted \(\dot{V}E_{\text{max}}\) = 37.5 x FEV\(_1\) (17). Breathing reserve was calculated by \([1 - \dot{V}E ÷ \text{predicted} \dot{V}E_{\text{max}}] \times 100\%\). The dead space/tidal volume ratio (VD/VT) was calculated by means of the Bohr equation. At the end of the test, perceived exertion was scored for breathlessness and for leg effort on a modified Borg scale (range 0–10) (18).

MAXIMAL INCREMENTAL EXERCISE TEST

Four to six weeks before the start of the study, a symptom-limited incremental (concentric) exercise test was performed. The subjects cycled at a pedalling rate of 60 RPM breathing ambient air. The work rate was increased each minute by 10\% of the predicted maximal work load till exhaustion (19). All subjects stopped because of dyspnoea. Mean (SD) maximal work load (\(\text{max} W_{\text{pos}}\)) was 88 (29) W (range 30–135 W), mean \(\dot{V}O_2_{\text{max}}\) was 1.3 (0.3) l min\(^{-1}\) (Table 2). \(P_aCO_2\) rose by 0.6 kPa from rest to maximum, indicating a ventilatory limitation. Three subjects were hypoxic (\(P_aO_2 < 7.3\) kPa) at maximum. Base-excess decreased by more than 4 mmol l\(^{-1}\) in all but one subject (Table 2), suggesting that work was performed above the anaerobic threshold (16).

SINGLE-STAGE CONCENTRIC AND ECCENTRIC EXERCISE TESTS

Four single-stage exercise tests were performed in random order on two consecutive days with a maximum of two tests on the same day. All subjects inhaled 400 \(\mu\)g salbutamol 2 h before the first exercise test of each day. FEV\(_1\) varied
Table 3. Exercise responses (mean ± SD) to positive ($W_{pos}$) and negative work ($W_{neg}$) at 25 and 50% of maximal positive work capacity (max $W_{pos}$) ($n=12$)

<table>
<thead>
<tr>
<th>Work load (W)</th>
<th>25% max $W_{pos}$</th>
<th>50% max $W_{pos}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W_{pos}$</td>
<td>$W_{neg}$</td>
<td>$W_{pos}$</td>
</tr>
<tr>
<td>HR (beats min$^{-1}$)</td>
<td>22 ± 7</td>
<td>44 ± 14</td>
</tr>
<tr>
<td>% predicted HRmax</td>
<td>95 ± 16</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>% predicted $\dot{V}E_{\text{max}}$</td>
<td>58 ± 8</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>Breathing reserve (%)</td>
<td>22 ± 3</td>
<td>16 ± 4*</td>
</tr>
<tr>
<td>% predicted $\dot{V}E_{\text{max}}$</td>
<td>42 ± 15</td>
<td>31 ± 12*</td>
</tr>
<tr>
<td>$\dot{V}O_2$ (l min$^{-1}$)</td>
<td>58 ± 15</td>
<td>69 ± 12*</td>
</tr>
<tr>
<td>$\dot{V}CO_2$ (l min$^{-1}$)</td>
<td>0.65 ± 0.06</td>
<td>0.45 ± 0.07*</td>
</tr>
<tr>
<td>$\dot{V}E$</td>
<td>33.3 ± 5.3</td>
<td>34.8 ± 5.5</td>
</tr>
<tr>
<td>$\dot{V}E/\dot{V}O_2$</td>
<td>36.8 ± 4.5</td>
<td>41.5 ± 6.2</td>
</tr>
<tr>
<td>O$_2$ pulse (ml O$_2$ beat$^{-1}$)</td>
<td>6.8 ± 1.2</td>
<td>5.20 ± 7*</td>
</tr>
<tr>
<td>PaO$_2$ (kPa)</td>
<td>9.8 ± 1.6</td>
<td>9.9 ± 1.7</td>
</tr>
<tr>
<td>PaCO$_2$ (kPa)</td>
<td>5.3 ± 0.5</td>
<td>4.1 ± 0.4</td>
</tr>
<tr>
<td>$\delta$PaCO$_2$</td>
<td>0.6 ± 0.6</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>$\delta$base-excess (mmol 1$^{-1}$)</td>
<td>0.7 ± 1.6</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2.0 ± 1.1</td>
<td>1.4 ± 0.9</td>
</tr>
<tr>
<td>Leg effort</td>
<td>1.5 ± 1.0</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>MD/VT</td>
<td>34 ± 8.6</td>
<td>39 ± 11.8</td>
</tr>
<tr>
<td>MD/VT</td>
<td>34 ± 8.6</td>
<td>39 ± 11.8</td>
</tr>
</tbody>
</table>

HR, heart rate; $V_D/V_T$, dead space/tidal volume ratio; $\dot{V}E$, expired ventilation per minute; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide consumption; PaO$_2$, arterial oxygen tension; PaCO$_2$, arterial carbon dioxide tension; $\delta$PaCO$_2$, change in PaCO$_2$ after minus before the test; $\delta$base-excess, change in base-excess after minus before the test.

Results

All subjects could sustain exercise for 6 min during all tests, and no significant decrease in base-excess occurred. Heart rate and $\dot{V}E$ did not reach predicted maximum values. The highest $\dot{V}O_2$ [0.85 ± 0.14, range 0.7–1.11 min$^{-1}$] was achieved during 50%$W_{pos}$. $\dot{V}E$ and $\dot{V}CO_2$ were nearly 30% lower during $W_{neg}$ than during $W_{pos}$ for both work intensities. The breathing reserve during 25%$W_{neg}$ was 11 (8)% higher, and during 50%$W_{neg}$ was 18 (14)% higher (Table 3, Fig. 2).

The ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) did not differ significantly between $W_{pos}$ and $W_{neg}$. No significant differences occurred in dead space/tidal volume ratio (MD/VT) between the two types of work at either work load. The increase of PaCO$_2$ during 50%$W_{neg}$ was significantly less than during 50%$W_{pos}$ (0.1 vs. 0.7 kPa, P<0.01) (Fig. 2). Two out of three subjects, who were hypoxic at max$W_{pos}$, had a PaO$_2$ of 6.2 kPa during 50%$W_{pos}$, whereas during 50%$W_{neg}$, PaO$_2$ did not fall below 8.1 kPa.

STATISTICAL ANALYSIS

The results were expressed as mean values (standard deviation; SD). Differences between $W_{neg}$ and $W_{pos}$ at corresponding work levels were compared by means of the Wilcoxon test for paired samples, and were corrected for multiple measurements. Significance was accepted if $P<0.01$.

less than 10% from the value measured previously. The second exercise test was performed after a resting period of at least 1 h. The subjects cycled both concentrically and eccentrically for 6 min at constant work loads of 25 and 50% of their individual max$W_{pos}$.

The ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) did not differ significantly between $W_{pos}$ and $W_{neg}$. No significant differences occurred in dead space/tidal volume ratio (MD/VT) between the two types of work at either work load. The increase of PaCO$_2$ during 50%$W_{neg}$ was significantly less than during 50%$W_{pos}$ (0.1 vs. 0.7 kPa, P<0.01) (Fig. 2). Two out of three subjects, who were hypoxic at max$W_{pos}$, had a PaO$_2$ of 6.2 kPa during 50%$W_{pos}$, whereas during 50%$W_{neg}$, PaO$_2$ did not fall below 8.1 kPa.
were small, but for any given
in normal subjects are contradictory. In
»eg
44 W. As a result, the patients had a greater
This study in patients with COPD showed that
significant.
differences between
change in PaC0
(5PaC02, open bars) in
V
O
2, W
pos,
eg
Wneg.

Differences in heart rate between
and
were small, but for any given
25% and 50%
of maximal (positive) work capacity. Error bars rep­
After minus before the test
Wneg.

The scores for perceived breathlessness and
and leg effort scored higher
during 50%
Wneg
than during 50%
Wpos
but the differences between
and
were not

Discussion
This study in patients with COPD showed that
, 
V
O
2 and
COPD were 30% lower
during
at similar work loads of 22 and
44 W. As a result, the patients had a greater
ventilatory reserve during
.

In normal subjects performing steady-state
exercise at equal work loads above 100 W,
, 
V
O
2 during
were 50–70% lower
than during
. At lower work loads, the differences in
and
between
and
were smaller (1,3,4,8,9). This may be
explained by the extra work performed during
eccentric cycling by the muscles of the trunk and
of the upper extremities to stabilize the body.
This unmeasured work will be relatively high at
low external work loads (8). In addition, Aura
and Komi have shown that the mechanical
efficiency during
defined as the ratio of the
output to the input energy, was positively corre­
related with work intensity (20). In the present
study’s patients with COPD, decreased work of
breathing may have contributed to the reduced
oxygen cost of
.

Knuttgen et al. found a higher ventilatory
equivalent for oxygen (\(\dot{V}E/\dot{V}O_2\)) during eccentric
exercise than during concentric exercise at
similar work loads (4). The authors suggested
a different mechanoreceptor activity or motor
activity during
. This was not supported by
others, who found that
and
were propor­tionally reduced (5,8,9). \(\dot{V}E\) appeared to be
more closely correlated with \(\dot{VT}CO_2\) (8,21). No
differences in \(\dot{V}E/\dot{V}O_2\), \(\dot{V}E/\dot{VT}CO_2\) and dead space
ventilation were found between
and
in the present study, and changes in base-excess
were negligible. Therefore, the present authors
believe that an absolute reduction in
and
and a greater ventilatory reserve rather
than an increased ventilatory drive or improved
alveolar ventilation, explain the improvements in
gas-exchange during
in contrast to
.

Data about the cardiocirculatory response to
in normal subjects are contradictory. In
most studies, HR during
was lower than
during
at similar work loads (4,6,8,9). In
contrast, during maximal leg extension, a higher
HR and cardiac output has been found during
the eccentric than during the concentric phase of
exercise (22). When
was compared with
at equal levels of
below 11 min
, HR was higher during
(5,7,8,21), whereas the
cardiac output was the same (5,7). In the present
study, differences in HR were not significant
between
and
at similar work loads, but oxygen pulse (\(\dot{V}O_2/HR\)) was lower during
. Therefore, it is assumed that the cardio­
circulatory response to
in patients with
COPD is essentially the same as in normal
subjects.

In normal subjects, the score for perceived
exertion at a given work load was lower during
than during
while for similar levels of
, 
was experienced as more strenuous
In the present study, the Borg scores for dyspnoea and perceived leg effort did not differ significantly between $W_{pos}$ and $W_{neg}$, probably because the work loads were too low. However, during $50\% W_{neg}$, perceived leg effort scored higher than perceived breathlessness, which is in agreement with the reduced ventilatory load and greater ventilatory reserve at this work level. Thus, $W_{neg}$ resulted in a subjective response which was quite similar to what has been found in normal subjects.

Work loads above $50\%$ of $max W_{pos}$ were not used in the present study for several reasons. First, in patients with COPD, the ventilatory requirements might have exceeded the ventilatory capacity at higher work loads. This would have concealed differences in exercise response between $W_{pos}$ and $W_{neg}$. Secondly, $W_{neg}$ is associated with delayed-onset muscle soreness and muscle damage resulting in loss of muscle strength (23–27). This might be more pronounced in the elderly because of a smaller muscle mass and a lower $\dot{V}O_2max$ (28). The subjects were in a moderate physical condition, untrained and not accustomed to performing heavy exercise. For this reason, they had performed eccentric exercise at least 2 weeks before the tests to induce adaptation and to prevent muscle damage at the time of the tests (15,25).

Both muscular tension and metabolic cost are stimuli which may increase muscle strength (29). In normal subjects, eccentric exercise has shown to provide a stimulus to gain static and dynamic muscle strength, and has been used in many training programmes (29–33). This was also found in an old age group (34). The results of the present study warrant further investigation into whether patients with COPD may benefit from eccentric exercise training during pulmonary rehabilitation. The reduced ventilatory load during $W_{neg}$ might enable these patients to train their peripheral muscles at a higher external work load and for a longer duration than during $W_{pos}$. If so, the increased muscular tension and total amount of work during eccentric exercise training would enhance the effects of conventional training programmes.

It was concluded that in patients with COPD, the ventilatory requirements of eccentric exercise were considerably lower than those of concentric exercise at similar work loads up to $50\%$ of the individual maximal work capacity. As a result, the ventilatory reserve was greater and gas exchange was less disturbed during $W_{neg}$ than during $W_{pos}$ in these patients.

**Acknowledgements**

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**References**

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