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

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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 $\geq$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 ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) 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 ($P<0·01$). $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}O_2$ and $\dot{V}CO_2$.

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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.

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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

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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_{pos} 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.

TABLE 1. Patient characteristics ($n=12$)

	Mean	SD
Age (years)	56	12
Height (m)	1·75	0·08
Weight (kg)	73	8
TLC % predicted	100	18
FRC % predicted	118	27
RV % predicted	133	35
IVC % predicted	89	21
FEV_1 (l)	1·5	0·4
% predicted	46 16	
*K*CO % predicted	55	25
PaO_2 (kPa)	10·1	1·4
$PaCO_2$ (kPa)	5·1	0·5

TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; IVC, inspiratory vital capacity; FEV_1, forced expiratory volume in 1 s; *K*CO, carbon monoxide transfer coefficient; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension. Reference values derived from Quanjer (13).

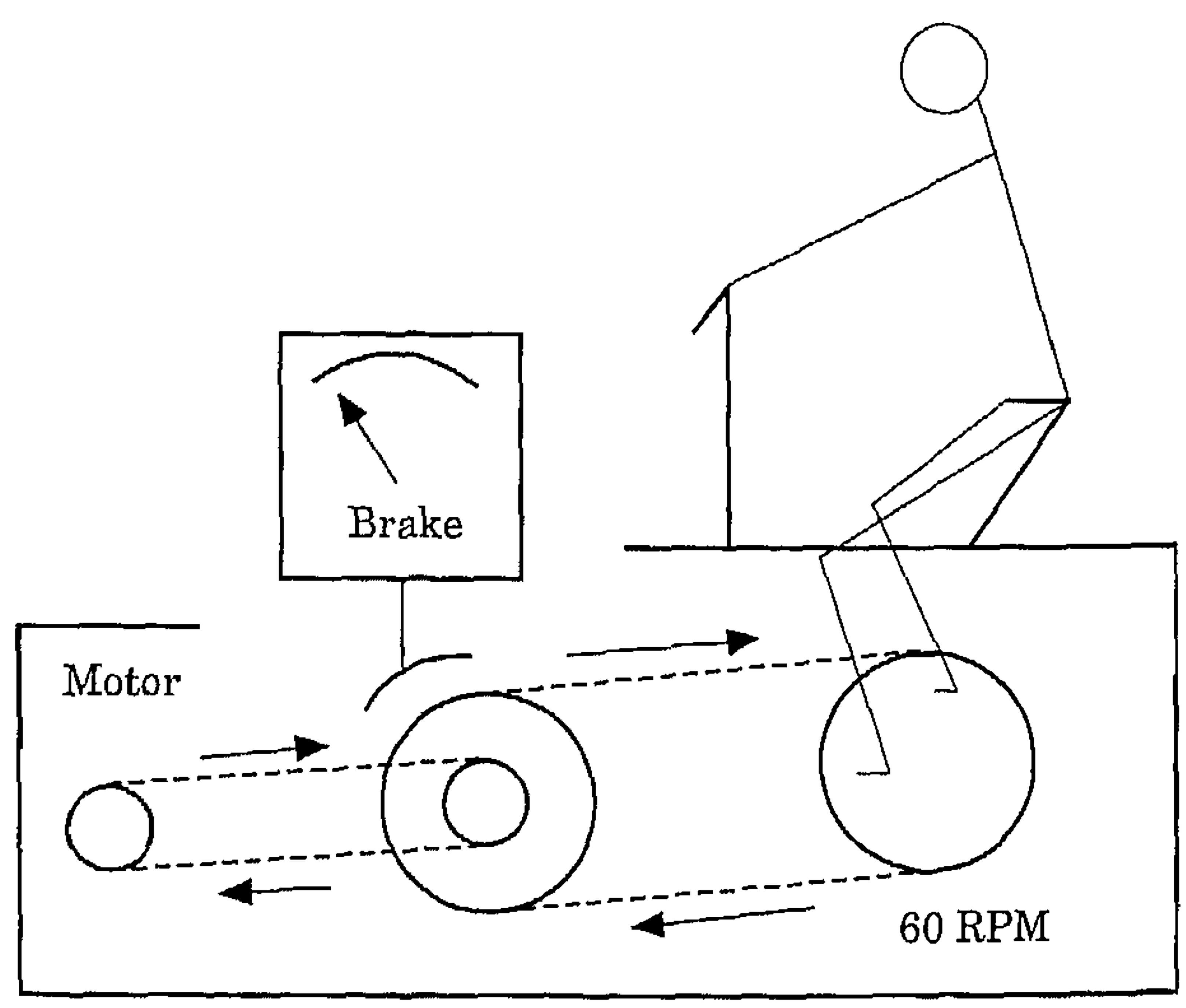

FIG. 1. Schematic presentation of a cycle ergometer for eccentric exercise. The pedals are driven in backward direction at a rate of 60 revolutions min^{-1} (RPM) by the electric motor, which has to overcome the adjustable resistance of the electromagnetic brake. After withdrawal of the brake, the subject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

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 2. Maximal incremental exercise test (n=12)

	Mean	SD
max W_{pos} (W)	88	29
HRmax (beats min^{-1})	141	26
% predicted HRmax	87	17
$\dot{V}E$max (l)	45	13
% predicted $\dot{V}E$max	82	19
$\dot{V}O_2$max (l min^{-1})	1·3	0·3
$\dot{V}CO_2$max (l min^{-1})	1·3	0·3
PaO_2 (kPa)	9·1	2·2
$PaCO_2$ (kPa)	5·7	1·0
δbase-excess (mmol l^{-1})	− 6·3	1·9
Dyspnoea	6·0	2·0
Leg effort	5·8	1·8

max W_{pos}, positive work; HR, heart rate; $\dot{V}E$, expired ventilation per minute; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; δbase-excess, change in base-excess after exercise minus value before the test.

latter situation, the pedals were rotated in the backwards direction by an electric motor at a rate of 60 RPM. The electromagnetic brake of the ergometer was set at 25 or 50% of the individual maximal positive work load (max W_{pos}). The motor had to generate the same power to overcome this resistance. During this procedure, the subjects were asked to let their legs be moved passively. Subsequently, the electric brake was withdrawn and the subjects were instructed to brake the speed of the pedals and to maintain a backward pedalling rate of 60 RPM. From that moment, the power generated by the motor to overcome the resistance of the electric brake was absorbed by the patient, who then performed W_{neg} at an equivalent load.

As it is not a common activity, the physiological response to W_{neg} depends on the skill involved in performing eccentric cycling exercise (4). Furthermore, W_{neg} is associated with delayed muscle soreness and muscle damage, but adaptation may occur after a repeated bout of the same exercise at a low intensity and of short duration (15). Therefore, the subjects performed eccentric exercise at work loads between 50 and 100% of max W_{pos}, 2–4 weeks before the start of the study.

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 $\dot{V}E\text{max}=37{\cdot}5 \times FEV_1$ (17). Breathing reserve was calculated by $[1-\dot{V}E/$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 (max W_{pos}) was 88 (29) W (range 30–135 W), mean $\dot{V}O_2$max was 1·3 (0·3) l min^{-1} (Table 2). $PaCO_2$ rose by 0·6 kPa from rest to maximum, indicating a ventilatory limitation. Three subjects were hypoxic (PaO_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 μg 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)

	25% max W_{pos}		50% max W_{pos}	
	W_{pos}	W_{neg}	W_{pos}	W_{neg}
Work load (W)	22 ± 7		44 ± 14	
HR (beats min^{-1})	95 ± 16	84 ± 17	98 ± 13	92 ± 14
% predicted HRmax	58 ± 8	53 ± 12	64 ± 6	57 ± 11
$\dot{V}E$ (l min^{-1})	22 ± 3	16 ± 4*	29 ± 6	19 ± 7*
% predicted $\dot{V}E$max	42 ± 15	31 ± 12*	55 ± 14	37 ± 16*
Breathing reserve (%)	58 ± 15	69 ± 12*	45 ± 14	63 ± 16*
$\dot{V}O_2$ (l min^{-1})	0·65 ± 0·06	0·45 ± 0·07*	0·85 ± 0·14	0·54 ± 0·10*
$\dot{V}CO_2$ (l min^{-1})	0·58 ± 0·06	0·38 ± 0·07*	0·83 ± 0·13	0·49 ± 0·14*
$\dot{V}E/\dot{V}O_2$	33·3 ± 5·3	34·8 ± 5·5	34·7 ± 4·7	34·1 ± 7·2
$\dot{V}E/\dot{V}CO_2$	36·8 ± 4·5	41·5 ± 6·2	35·4 ± 4·0	38·6 ± 5·5
O_2 pulse (ml O_2 $beat^{-1}$)	6·8 ± 1·2	5·20·7*	8·1 ± 1·1	5·9 ± 1·2*
PaO_2 (kPa)	9·8 ± 1·6	9·9 ± 1·7	9·8 ± 2·1	10·2 ± 1·5
$PaCO_2$ (kPa)	5·3 ± 0·5	5·1 ± 0·5	5·3 ± 0·8	5·1 ± 0·6
$\delta PaCO_2$	0·6 ± 0·6	0·4 ± 0·4	0·7 ± 0·5	0·1 ± 0·4*
δbase-excess (mmol l^{-1})	0·7 ± 1·6	0·6 ± 0·6	− 0·3 ± 1·3	0·4 ± 1·0
VD/VT	34 ± 8·6	39 ± 11·8	34 ± 7·6	35 ± 13·4
Dyspnoea	2·0 ± 1·1	1·4 ± 0·9	2·7 ± 1·0	2·0 ± 1·1
Leg effort	1·5 ± 1·0	1·3 ± 1·1	1·8 ± 1·3	2·4 ± 1·2

HR, heart rate; VD/VT, 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; δbase-excess, change in base-excess after minus before the test. W_{pos} *vs.* W_{neg} for corresponding work loads: *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}.

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.

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 0·7–1·1 l min^{-1}] was achieved during 50%W_{pos}. $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ were approximately 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 (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 (VD/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 maxW_{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.

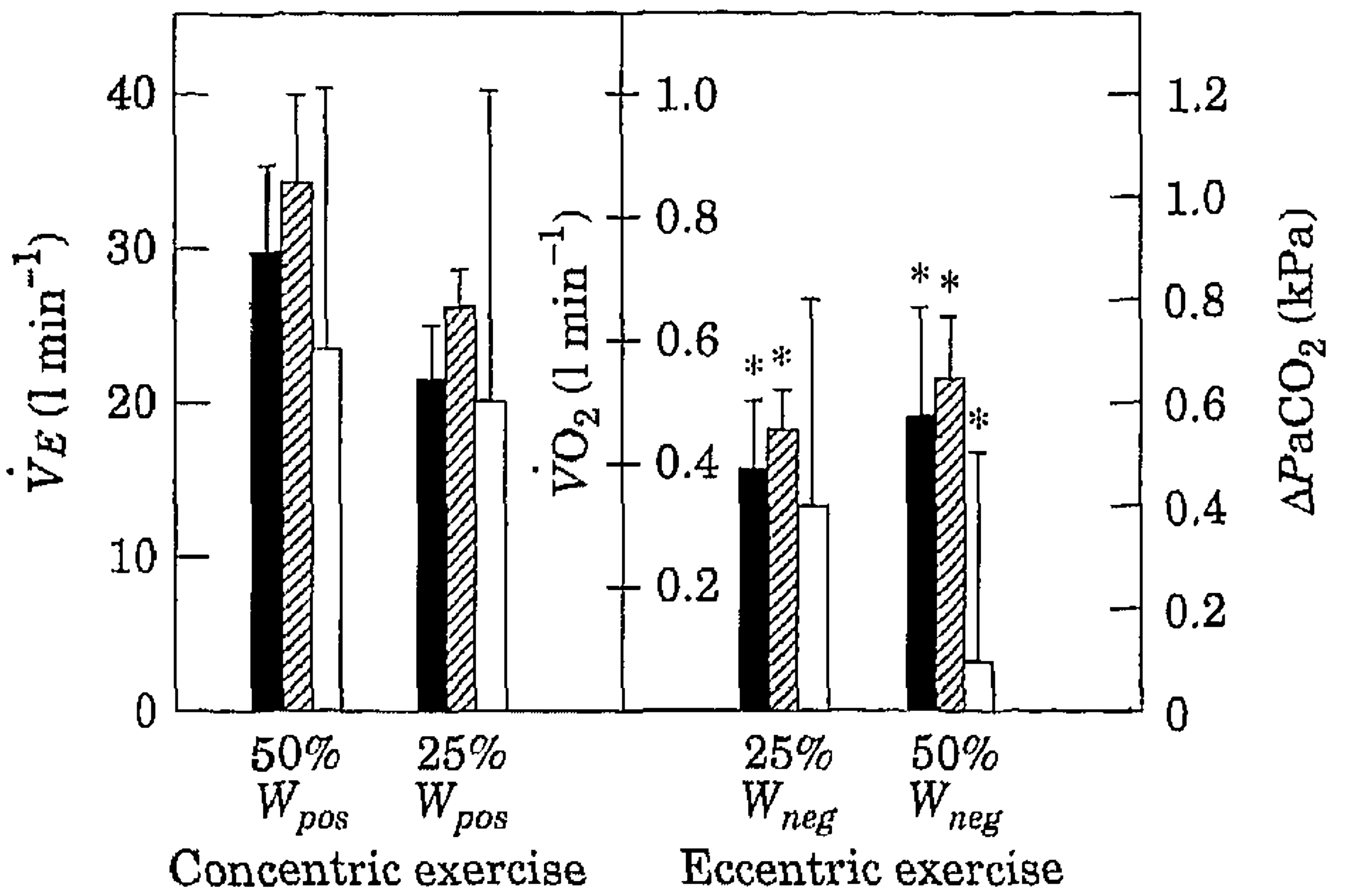

FIG. 2. Mean minute ventilation ($\dot{V}E$, solid bars), oxygen consumption ($\dot{V}O_2$, hatched bars) and change in $PaCO_2$ after minus before the test ($\delta PaCO_2$, open bars) in 12 subjects with chronic obstructive pulmonary disease after 6 min of positive (W_{pos}) and negative work (W_{neg}) at 25 and 50% of maximal (positive) work capacity. Error bars represent standard deviation. Differences were tested between W_{pos} and W_{neg} for corresponding work loads: *P<0·01.

Differences in heart rate between W_{pos} and W_{neg} were small, but for any given $\dot{V}O_2$, the heart rate was higher during W_{neg}. In consequence, oxygen pulse ($\dot{V}O_2$/HR) was significantly lower during W_{neg} than during W_{pos}.

The scores for perceived breathlessness and leg effort were less during single-stage exercise than during maximal incremental exercise. The sensation of dyspnoea was less during W_{neg} than during W_{pos}, and leg effort scored higher during 50%W_{neg} than during 50%W_{pos}, but the differences between W_{pos} and W_{neg} were not significant.

Discussion

This study in patients with COPD showed that $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ during W_{neg} were 30% lower than during W_{pos} at similar work loads of 22 and 44 W. As a result, the patients had a greater ventilatory reserve during W_{neg}.

In normal subjects performing steady-state exercise at equal work loads above 100 W, $\dot{V}E$ and $\dot{V}O_2$ during W_{neg} were 50–70% lower than during W_{pos}. At lower work loads, the differences in $\dot{V}E$ and $\dot{V}O_2$ between W_{pos} and W_{neg} 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 W_{neg}, defined as the ratio of the output to the input energy, was positively correlated 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 W_{neg}.

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 W_{neg}. This was not supported by others, who found that $\dot{V}E$ and $\dot{V}O_2$ were proportionally reduced (5,8,9). $\dot{V}E$ appeared to be more closely correlated with $\dot{V}CO_2$ (8,21). No differences in $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ and dead space ventilation were found between W_{pos} and W_{neg} in the present study, and changes in base-excess were negligible. Therefore, the present authors believe that an absolute reduction in $\dot{V}O_2$ and $\dot{V}CO_2$ and a greater ventilatory reserve rather than an increased ventilatory drive or improved alveolar ventilation, explain the improvements in gas-exchange during W_{neg} in contrast to W_{pos}.

Data about the cardiocirculatory response to W_{neg} in normal subjects are contradictory. In most studies, HR during W_{neg} was lower than during W_{pos} 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 W_{pos} was compared with W_{neg} at equal levels of $\dot{V}O_2$ below 1 l min^{-1}, HR was higher during W_{neg} (7,8,21), whereas the cardiac output was the same (5,7). In the present study, differences in HR were not significant between W_{pos} and W_{neg} at similar work loads, but oxygen pulse ($\dot{V}O_2$/HR) was lower during W_{neg}. Therefore, it is assumed that the cardiocirculatory response to W_{neg} 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 W_{neg} than during W_{pos}, while for similar levels of $\dot{V}O_2$, W_{neg} was experienced as more strenuous

(6). 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 maxW_{pos} were not used in the present study for several reasons. Firstly, 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 $\dot{V}O_2$max (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.

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