Decreased mechanical efficiency in clinically stable patients with COPD

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Abstract

Background – It has recently been reported that total daily energy expenditure (TDE) is increased in patients with chronic obstructive pulmonary disease (COPD) and it was hypothesised that these patients may have a decreased mechanical efficiency during activities. The purpose of the present study was to measure the mechanical efficiency of submaximal leg exercise, and to characterise patients with a potentially low efficiency in terms of body composition, resting energy expenditure, lung function, and symptom limited exercise performance.

Methods – Metabolic and ventilatory variables were measured breath by breath during submaximal cycle ergometry exercise performed at 50% of symptom limited achieved maximal load in 33 clinically stable patients with COPD (23 men) with forced expiratory volume in one second (FEV_1) of 40 (12)% predicted. Net mechanical efficiency was calculated adjusting for resting energy expenditure (REE).

Results – Median mechanical efficiency was 15.5% and ranged from 8.5% to 22.7%. Patients with an extremely low mechanical efficiency (<17%, n = 21) demonstrated an increased $\dot{V}O_2/\dot{V}E$ compared with those with a normal efficiency (median difference 4.7 ml/l, p = 0.005) during submaximal exercise. There was no difference between the groups differentiated by mechanical efficiency in blood gas tensions at rest, airflow obstruction, respiratory muscle strength, hyperinflation at rest, resting energy expenditure or body composition. There was a significant difference in total airways resistance (92% predicted, p = 0.03) between the groups differentiated by mechanical efficiency.

Conclusions – It is concluded that many patients with severe COPD have decreased mechanical efficiency. Furthermore, based on the results of this study it is hypothesised that an increased oxygen cost of breathing during exercise contributes to the decreased mechanical efficiency.

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Keywords: mechanical efficiency, chronic obstructive pulmonary disease, exercise.

Patients with chronic obstructive pulmonary disease (COPD) often suffer from a severely impaired exercise tolerance. Over the years it has become increasingly clear that the limited exercise capacity in patients with COPD is multifactorially determined. After considering factors such as an impaired ventilatory capacity, respiratory muscle dysfunction, impaired gas exchange and cardiovascular problems,[1] recent studies have focused on peripheral muscle weakness and impaired muscle metabolism as factors that contribute to the decreased exercise capacity in patients with COPD.[2][3] Muscle strength and muscle metabolism are closely related to body composition.[4] In patients with COPD a disturbed body composition is frequently present[5] owing to loss of body weight as well as to a selective depletion of fat free mass (FFM). In particular, loss of FFM negatively influences the exercise capacity in patients with COPD[6][7] independently of lung function impairment.

The reason for the observed disturbances in body composition is not completely understood, but loss of body weight implies a negative energy balance. We have recently shown that total daily energy expenditure is increased in patients with COPD compared with healthy subjects.[8] Furthermore, it was demonstrated that, in particular, the non-resting component (predominantly the energy expenditure for activity) contributes to the increased total daily energy expenditure (TDE). In a subsequent study it was shown that the variation in TDE in patients with COPD was not strongly related to resting energy expenditure (REE) but was mainly a reflection of the energy expenditure for activities.[9] Based on the results of these two studies it was hypothesised that patients with COPD could have a reduced mechanical efficiency during exercise.

To test this hypothesis we measured the mechanical efficiency of submaximal leg exercise in a group of patients with COPD, and investigated whether mechanical efficiency is related to patient characteristics such as body composition, resting energy expenditure, lung function, and symptom limited exercise performance.

Methods

PATIENTS

Thirty three patients (23 men) with moderate to severe COPD according to the criteria of the American Thoracic Society[10] were studied (table 1). Patients exhibiting an increase in forced expiratory volume in one second (FEV_1) of >10% after inhalation of β_2 agonists or those requiring oxygen supplementation (Pao_2 at rest <7.3 kPa) were not included. All patients were admitted to a pulmonary rehabilitation centre in a stable clinical condition. None of the

Table 1 Characteristics and maximal exercise capacity of the study group

Characteristics	Median (range)	% pred
Age (years)	61 (38–82)	
BMI (kg/m^2)	22.8 (18–44)	
REE (%HB)	112.6 (76–166)	
FEV$_1$ (% pred)	36.7 (17–69)	
FVC (% pred)	84.2 (64–110)	
TLC (% pred)	125.3 (87.7–144.6)	
TLCO (% pred)	50.9 (36–112)	
Pao$_2$ (kPa)	9.3 (7.7–12.5)	
Exercise capacity		
Peak load (W)	58 (24–145)	36 (16–77)
Peak V̇o$_2$ (l/min)	0.96 (0.59–2.14)	36 (21–81)
Peak V̇E (l/min)	38 (24–72)	95 (56–185)
Peak HR (/min)	128 (85–176)	83 (56–108)

BMI = body mass index; REE (%HB) = resting energy expenditure as percentage of the Harris and Benedict equations; FEV$_1$ = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; TLCO = carbon monoxide transfer factor; Pao$_2$ = arterial oxygen tension; V̇o$_2$ = oxygen consumption; V̇E = minute ventilation; HR = heart rate.

patients had a respiratory tract infection or clinically visible signs of oedema at the time of the study, and none had any known cardiovascular, neurological, endocrine, or locomotor diseases. The patients were fully informed of the nature and purpose of the study and gave informed consent. The study was approved by the ethical committee of the Maastricht University and was performed in accordance with the Helsinki declaration of 1977 as revised in 1983.

PULMONARY FUNCTION TESTS
Flow volume measurements included FEV$_1$ and forced vital capacity (FVC), the highest value of at least three measurements being used. Total lung capacity (TLC), intrathoracic gas volume (ITGV) and airways resistance (Raw) were measured by body plethysmography (Masterlab, Jaeger, Wurzburg). The values were expressed as a percentage of reference values.[11] A value of Raw of <0.3 kPa × s/l was considered normal.[12] The carbon monoxide transfer factor (TLCO) was measured by a single breath method (Masterlab, Jaeger, Wurzburg) and expressed as a percentage of the reference value.[11] Inspiratory muscle strength was assessed by maximal inspiratory mouth pressure (PImax) according to the method described by Black and Hyatt and expressed in positive values.[13] Blood was drawn from the brachial artery at rest while breathing room air. Arterial oxygen and carbon dioxide tensions (Pao$_2$ and Paco$_2$) were analysed with a blood gas analyser (Radiometer, ABL 330, Copenhagen, Denmark).

METABOLIC PROFILE
Body height was determined to the nearest 0.5 cm (Lameris, WM 715, Breukelen, The Netherlands) with subjects standing barefoot. Body weight was measured with a beam scale to the nearest 0.1 kg (SECA, Germany) with subjects barefoot and in light clothing. To adjust body weight for body surface area the body mass index (BMI) was calculated as weight/height^2.

Fat free mass (FFM) was assessed by bioelectrical resistance measurements at 50 kHz (Xitron 4000b, Xitron Technologies, San Diego, California, USA). Resistance (R) was measured in the supine position at the right side as described by Lukaski.[14] FFM was calculated from height^2/R and body weight using a patient specific regression equation[15] and also adjusted for body height (FFM-index: FFM/height^2).

Resting energy expenditure (REE) was measured by indirect calorimetry using a ventilated hood system (Oxycon β, Mijnhardt, Bunnik, The Netherlands). Measurements were performed in the early morning after an overnight fast with the subject lying supine on a bed.[16] The system was calibrated before measurements were taken, and the accuracy of the system (3–4%) was regularly tested with an ethanol combustion test.

EXERCISE TESTS
During exercise tests heart rate (HR) (Sporttester, Polar Electro cy, Kempele, Finland) and transcutaneous oxygen saturation (Sto$_2$) (Sensor Medics Co, Anaheim, California, USA) were monitored. Oxygen consumption (V̇o$_2$), carbon dioxide production (V̇co$_2$), minute ventilation (V̇E), breathing frequency (BF) and tidal volume (VT) (Oxyconbeta, Jaeger BV, Bunnik, The Netherlands) were measured and calculated from breath by breath analysis using a breathing mask. The equipment was calibrated before the tests which were performed in the two weeks before the patients entered the rehabilitation exercise programme.

INCREMENTAL CYCLE ERGOMETRY TEST
The incremental cycle ergometry test was performed on an electromagnetic braked ergometer (Corival 400, Lode, Groningen, The Netherlands). After a two minute resting period and one minute unloaded cycling, power was increased every minute by 10 W. The load cycled was unknown to the patients who were encouraged to cycle for as long as possible. Immediately before and two minutes after reaching the peak workload a venous blood sample was taken to measure the concentration of lactate. The blood samples were stored on ice (4°C) and were centrifuged for five minutes at 3000 rpm (Sigma 2–15, Lameris, Breukelen, The Netherlands). The plasma lactate concentration was determined by an enzymatic method[17] using an automated system (Cobas Mira, Roche, Basel, Switzerland). Peak V̇o$_2$ was predicted using formulae for healthy elderly subjects[18] and peak V̇E was predicted from the formula of Carter *et al*[19] (37.5 × FEV$_1$). Maximal HR was calculated using the equation 220 – age in years.

SUBMAXIMAL LEG EXERCISE TESTS
The patients performed a submaximal leg exercise test at 50% of individually measured peak load for seven minutes at a fixed pedal rate of 60/minute. The mean values of the last three minutes of the metabolic and ventilatory
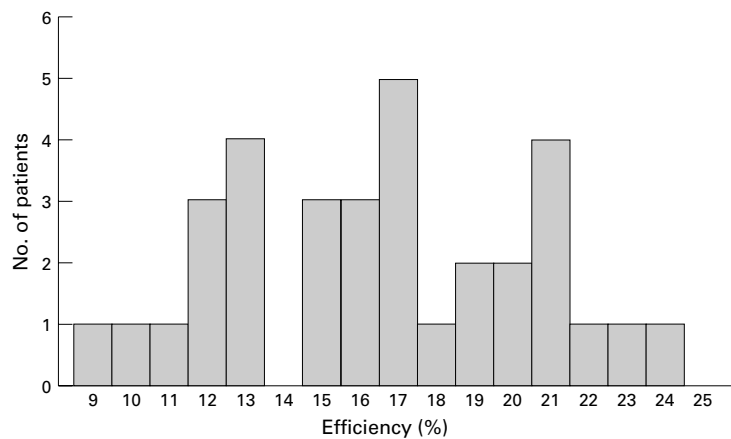
Figure 1 Frequency distribution for mechanical efficiency.

Table 2 Submaximal exercise response in patients with low and normal mechanical efficiency

	Low efficiency (<17%) (n=21)	Normal efficiency (>17%) (n=12)	p value
$\dot{V}O_2$ (% peak)	85.1 (74.4–104.5)	73.6 (60.8–95.8)	0.002
RQ (% peak)	93.0 (60.9–120.2)	91.1 (86.8–101.9)	NS
$\dot{V}E$ (% peak)	89.2 (72.9–110.0)	75.8 (64.5–100.6)	0.02
$\dot{V}O_2/\dot{V}E$ (ml/l)	25.6 (17.5–36.8)	20.9 (16.1–28.9)	0.005
$\Delta\dot{V}O_2$/load* (ml/watt)	20.6 (17.6–33.7)	14.6 (12.8–17.1)	0.000
VT (% peak)	102.3 (80.6–131.5)	89.6 (77.0–115.0)	NS
BF (% peak)	90.0 (67.0–100.6)	86.1 (70.6–100.9)	NS
HR (% peak)	88.7 (77.6–103.6)	87.4 (64.3–105.9)	NS
StO_2 (% peak)	101.1 (93.2–108.4)	101.5 (98.9–104.9)	NS
$\dot{V}O_2$/HR (ml/x)	7.1 (4.6–12.4)	6.2 (5.0–11.8)	NS

Data are presented as median (range). RQ = respiratory quotient: VT = tidal volume; BF = breathing frequency; StO_2 = transcutaneous oxygen saturation. For further abbreviations see legend to table 1.
*$\Delta\dot{V}O_2$/load = steady state $\dot{V}O_2$ during submaximal exercise minus resting oxygen consumption (obtained from REE measurement) divided by submaximal cycled load.

Table 3 Characteristics of patients differentiated by mechanical efficiency

	Low efficiency (<17%) (n=21)	Normal efficiency (>17%) (n=12)	p value
Age (years)	60 (38–82)	67 (43–74)	NS
BMI (kg/m²)	24.1 (17.9–44.1)	22.3 (18.1–27.9)	NS
FFM-index (kg/m²)	17.5 (13.1–21.9)	16.9 (13.0–21.2)	NS
REE (kcal/24h)	1524 (1174–2148)	1522 (1168–2121)	NS*
FEV_1 (% pred)	36.1 (17.4–67.9)	44.0 (30.1–62.7)	NS
FVC (% pred)	82.9 (63.9–107.0)	86.8 (75.2–109.8)	NS
TLC (% pred)	126.5 (87.7–142.4)	121.6 (92.9–144.6)	NS
ITGV (% pred)	169.8 (105.5–225.7)	166.7 (120.8–205.9)	NS
Raw (% pred)	250.0 (113.3–373.3)	158.3 (103.3–273.3)	0.03
TLCO (% pred)	58.9 (36.4–111.6)	45.9 (36.5–80.4)	NS
PImax (cm H_2O)	79 (35–137)	62 (44–117)	NS
PaO_2 (kPa)	9.3 (8.3–12.5)	9.6 (7.7–11.4)	NS
$PaCO_2$ (kPa)	5.7 (4.4–7.1)	5.3 (4.0–8.2)	NS

Data are presented as median (range). BMI = body mass index; FFM-index = fat free mass index; REE = resting energy expenditure; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; ITGV = intrathoracic gas volume; Raw = airway resistance; TLCO = carbon monoxide transfer factor; PImax = inspiratory mouth pressure; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension.
* Also not significantly different corrected for FFM (ANOVA).

variables were used for analysis. Net efficiency[20] was calculated by the following equation:

$$\text{Net efficiency} = \frac{\text{load (watt) of exercise} \times 0.01433 \text{ (kcal/min)}}{\text{(energy expenditure during exercise} - \text{REE) (kcal/min)}} \times 100\%$$

Energy expenditure during exercise was calculated from the steady state values of $\dot{V}O_2$ and $\dot{V}CO_2$ using the abbreviated Weir formula.[21]

The steady state values of the metabolic and ventilatory variables during submaximal exercise were expressed as percentages of the peak values.

REPRODUCIBILITY OF THE TEST

In a pilot study the reproducibility of a submaximal cycle ergometry test was determined in 11 patients with COPD (FEV_1 49.8 (10.5)% predicted). There was no significant difference between the first and the second test in all measured metabolic and ventilatory variables as well as in net efficiency. The mean differences in $\dot{V}O_2$ and $\dot{V}CO_2$ between the first and the second test were respectively 26.7 ml/min (95% confidence interval (CI) −9.9 to 63.3) and 22.4 ml/min (95% CI −11.6 to 56.6), respectively, resulting in a mean difference of 0.6% in net efficiency (95% CI −1.6 to 0.4%). For the other variables ($\dot{V}E$, BF, VT, and HR) the mean difference was also between 0% and 3%.

DATA ANALYSIS

The characteristics of the study group are given as median (range). The Wilcoxon rank test was used to test within group differences. In order to identify characteristics of the patients with decreased efficiency, the group was split into patients with a low efficiency and those with a normal efficiency. In healthy subjects the net mechanical efficiency of cycle ergometry is 23%.[22] Efficiency can be lower (approximately 19 (1)%) at low work rates,[20] comparable to the load of the submaximal exercise tests in the present study. We therefore considered an efficiency of 17% or lower (twice the standard deviation below the lowest mean mechanical efficiency reported in healthy subjects) as low.

The Mann-Whitney U test was used to compare groups. A p value of <0.05 was considered to be statistically significant. The Bonferroni correction was applied when necessary.

Results

The median net mechanical efficiency was 15.5% (range 8.5–22.7%). The frequency distribution for the mechanical efficiency is shown in fig 1. There were 21 patients (13 men) with a low mechanical efficiency (14.0%, range 8.5–16.7%) and only 12 (10 men) with a normal mechanical efficiency (19.3%, range 17.2–22.7 %, p<0.001).

As shown in table 2, patients with a low mechanical efficiency had a significantly higher $\dot{V}O_2$ (% peak), $\dot{V}E$ (% peak), a higher $\dot{V}O_2$/load relationship, a higher $\dot{V}O_2/\dot{V}E$ (ml/l), and tended to achieve a higher VT (% peak; p = 0.03) than the patients with a normal mechanical efficiency during submaximal exercise. BF (% peak), StO_2 (% peak), HR (% peak), and oxygen pulse ($\dot{V}O_2$/HR) were comparable between the two groups.

No significant differences in body composition, REE, flow-volume measurements, static lung volumes, carbon monoxide transfer factor, or blood gas tensions at rest were found between the patients with a low mechanical efficiency and those with a normal mechanical efficiency (table 3). Raw was significantly higher (p<0.05) in the patients with a low mechanical efficiency.

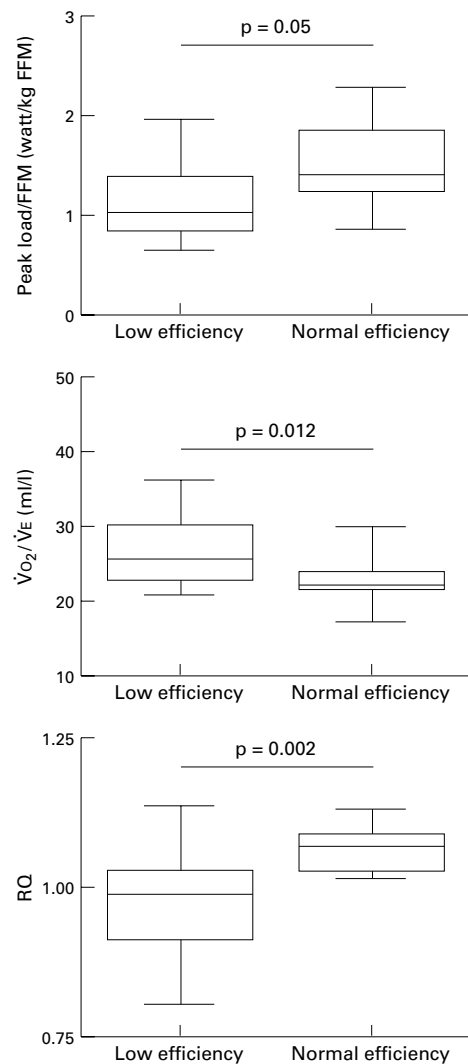Patients with a low mechanical efficiency achieved a lower peak load during the cycle

Figure 2   Peak exercise response in patients with a low or normal mechanical efficiency. Box plots indicate the 5th, 25th, 50th, 75th and 95th percentile of the data. $\dot{V}o_2 =$ oxygen consumption; $\dot{V}E =$ minute ventilation; $RQ =$ respiratory quotient; $FFM = fat$ free mass.

ergometry test, a lower peak respiratory quotient (RQ), and a higher peak $\dot{V}o_2/\dot{V}E$ as shown in fig 2. Peak $\dot{V}o_2$, peak $\dot{V}E$, peak plasma lactate concentration, peak HR, and peak Sto$_2$ were not significantly different between the groups differentiated by mechanical efficiency (data not shown).

Discussion

This study has shown that many patients with COPD have a severely impaired mechanical efficiency during exercise. The results suggest that a decreased efficiency is related to an increased oxygen cost of breathing. Patients with a severely impaired efficiency were characterised by an enhanced ventilatory response to exercise and had higher airways resistance at rest. Peak exercise capacity was slightly reduced in patients with a low efficiency, and the peak oxygen consumption per litre ventilation was increased.

Only limited data of mechanical efficiency in patients with COPD are available to date. This study confirms the recent findings by Palange *et al*[23] who reported a significantly decreased (net) efficiency of 16% in patients with COPD (which corresponds to the median mechanical efficiency in the present study) compared with 25% in healthy subjects during submaximal cycling. Owing to the limited investigations, it is not clear how a decreased mechanical efficiency can be explained, but several mechanisms might be considered including an increased oxygen cost of ventilation. Levison and Cherniack[24] showed that during exercise the oxygen consumption per litre ventilation was significantly higher in patients with COPD than in healthy subjects. Spiro *et al*,[25] however, reported that the physiological strain of ventilation during submaximal exercise was much higher in patients with COPD than in healthy subjects.

In patients with COPD the increased oxygen cost of breathing is assumed to be related to an increased inspiratory work of breathing. In clinically stable patients with COPD both the resistive and elastic components of inspiratory work are increased due to high airways resistance and hyperinflation.[26] Recent studies have focused attention on the importance of acute-on-chronic hyperinflation during exercise in patients with COPD.[27 28] The dynamic hyperinflation results in a substantial increased elastic load since VT is forced to oscillate on a stiffer portion of the pressure-volume relationship of the respiratory system. Furthermore, dynamic hyperinflation increases the inspiratory threshold loading caused by the inward elastic recoil of the respiratory system. In addition, the ability of the respiratory muscles to generate pressure is decreased during dynamic hyperinflation due to length-tension inappropriateness.[28] However, the exact effect of dynamic hyperinflation on the oxygen cost of breathing during exercise and mechanical efficiency of exercise in patients with COPD needs further study.

Other factors such as test conditions, the age of the patients, and familiarisation with exercise may have influenced mechanical efficiency in the present study. Gaesser *et al*[20] have shown that at low loads the net efficiency is decreased to approximately 19%. In the present study the cycled load was relatively low which could have resulted in a slightly lower efficiency than the assumed 23% efficiency.[22] Furthermore, age is probably no confounder in the present study since it has been shown by deVries *et al* that age has no influence on mechanical efficiency.[29] In addition, in the Netherlands cycling is a very familiar activity, making it unlikely that the patients in the study had never cycled before in their life. Moreover, it was shown in the present study that the submaximal exercise test was highly reproducible.

It could also be suggested that maintenance medication influences metabolism during exercise. Unfortunately only little attention has been paid to the metabolic effects of drugs (during exercise) in patients with COPD. Recently it was suggested that inhalation of β_2

sympathicomimetics could be related to an increased total daily energy expenditure in patients with COPD[30] but the potential stimulating effects of medication on exercise induced metabolism needs further investigation.

In the present study a comprehensive analysis of potential factors contributing to a variation in mechanical efficiency in patients with COPD was performed. However, measurements performed at rest – including pulmonary function, body composition, resting energy expenditure, or information obtained by incremental exercise testing – could not characterise patients with a normal or those with an increased mechanical efficiency. We therefore analysed the response to the submaximal exercise test in detail. Patients with a decreased mechanical efficiency had a significantly higher oxygen consumption per litre ventilation during submaximal exercise than those with a normal efficiency. With respect to the possible significance of dynamic hyperinflation to an increased oxygen cost of breathing in patients with COPD, it could be hypothesised that a more pronounced level of dynamic hyperinflation is assumed in patients with decreased mechanical efficiency as suggested from the observed enhanced ventilatory response and maximal VT response during submaximal exercise. Furthermore, under resting conditions the patients with a decreased mechanical efficiency had higher airways resistance which also could have contributed to a higher oxygen cost of breathing than in patients with normal mechanical efficiency.

Enhanced oxygen cost of breathing in the patients with decreased mechanical efficiency was also suggested by the significantly increased $\dot{V}O_2$/load relationship compared with the patients with a normal mechanical efficiency since the $\dot{V}O_2$/load relationship can be interpreted as a reflection of the oxygen cost of breathing.[31] In earlier studies it was reported that patients with COPD have a normal $\dot{V}O_2$/load relationship during incremental exercise.[24 32 33] However, when the $\dot{V}O_2$/load relationship reported for healthy subjects during incremental as well as submaximal exercise (± 10 ml/min/watt) is considered,[34] it should be noted that an enhanced $\dot{V}O_2$/load relationship was found in this study in both patients with a decreased mechanical efficiency and also in those with normal mechanical efficiency, suggesting an increased oxygen cost of breathing in the latter group as well.

There are several important clinical implications of the decreased mechanical efficiency found in the present study. Although the patients with decreased mechanical efficiency were characterised by a slightly lower performance on cycle ergometry and a higher peak $\dot{V}O_2/\dot{V}E$, the presence of decreased efficiency cannot be determined from an incremental cycle ergometry test. Furthermore, as shown in this study, cycling at 50% of symptom-limited maximum workload results, in many patients with COPD, in a metabolic response which is close to the peak physiological response. We have already shown in an earlier study that supposed submaximal exercise such

as the 12 minute walking test results in a ventilatory and metabolic response close to the peak physiological response.[35] Training load should induce a certain metabolic response in order to result in a physiological training effect. The results of the present study may therefore explain why training at relatively low loads could have resulted in a significant physiological training effect in patients with severe COPD, as reported by Maltais *et al*.[36] A submaximal exercise test should therefore be performed to choose an adequate training load and the metabolic and ventilatory response it evokes. Although in patients with less severe COPD it was found that high intensity training should be performed in order to achieve a training effect,[37] the results of the present study suggest that, from a metabolic point of view, a lower intensity training programme can also be successful, particularly for patients with severe COPD.

In conclusion, the results of the present study suggest that many patients with COPD have decreased mechanical efficiency which is not related to body composition, REE, chronic hyperinflation, airflow obstruction, or respiratory muscle strength. The findings suggest that the decreased efficiency is related to an increased oxygen cost of breathing during exercise. Dynamic hyperinflation in patients with COPD is probably an important contributing factor to the increased oxygen cost of breathing during exercise, but this needs further investigation.

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