At identical isowork rates, ageing influences cardiorespiratory adaptations in COPD out-patients

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Summary
Purpose: To determine the extent to which younger COPD patients improve their cardiorespiratory function during exercise in comparison with older COPD patients, as a result of exercise training.
Methods: Thirty-nine COPD patients underwent an exercise program. They were divided into two groups: a younger group (57.2 ± 1.0 years, $n = 18$ patients) and an older group (68.8 ± 0.6 years, $n = 21$ patients). Forced expiratory volume in 1 s was lower than 55% of the predicted value for all patients.
Results: After training, $\dot{V}O_2$ symptom-limited significantly improved by 10.3% and 8.4% for the younger and older COPD patients, respectively ($P < 0.05$). Peak power significantly improved by 25.2% and 17.8% in the younger and older groups, respectively ($P < 0.05$) with a greater improvement for the younger group ($P < 0.05$). At submaximal exercise, ventilation and heart rate significantly decreased after training in the younger COPD patients ($P < 0.05$) with no significant modification in the older COPD patients.
Conclusions: The results suggest that all patients with COPD benefit from exercise rehabilitation at maximal exercise workload, however, according to their age, submaximal cardiorespiratory adaptations were greater in younger patients.
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Introduction

Activity limitation and breathlessness are the main clinical features of advanced COPD. It is now generally recognized that pulmonary rehabilitation including exercise training can partly reverse these deficits.[1,2] However, the range of the physiological responses after endurance training is large. For example, the improvement in maximal O_2 uptake in the literature varies from 0% to 14% for the same training period or frequency of the session, and the same moderate intensity training.[2] In the literature, exercise training can significantly modify the breathing pattern or not, at isowork rates during submaximal exercise.[3] Several possible

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hypotheses can explain these differences. Plankeel et al.[4] have demonstrated that exercise outcomes after pulmonary rehabilitation depended on the initial mechanism of exercise limitation. The choice of the exercise intensity can also be a decisive factor in cardiorespiratory adaptations. Indeed, an individualized training intensity at the ventilatory threshold induces significantly better cardiorespiratory adaptations in submaximal and maximal exercises, compared with a standardized intensity.[3] The duration of exercise training in pulmonary rehabilitation also influences cardiorespiratory responses. Out-patient exercise training with 2 or 3 weekly sessions for 4 weeks showed less benefit than similar training for 7 weeks.[4,5]

Among several studied factors, which help to understand the different cardiorespiratory adaptations between subjects following aerobic training, the age of the patients on cardiorespiratory adaptations is not actually taken into account. The COPD patients present a wide age bracket (generally 50–80 years) and some studies excluded COPD patients as they were more than 70 years old, without explaining the reasons for this exclusion.[6,7] To our knowledge, one single study[8] has dealt in particular with patient age. This investigation[8] demonstrated no difference between the younger and the older COPD patients in terms of a 12 min walking test and self-assessment scores. However, these field test measurements were not associated with directly measured physiological data.

In healthy elderly subjects, several investigations have demonstrated that the improvement in cardiorespiratory function after aerobic training is not linked with the age of the subject; in other words, age does not influence the improvement in terms of the cardiorespiratory responses.[9,10] However, the decrease in cardiorespiratory functions due to ageing, together with COPD-linked pulmonary limitation could act synergistically and could delay the outcomes of the rehabilitation in comparison with those for younger patients. The aim of this study was to identify if ageing, associated with a diagnosis of COPD, could affect the cardiorespiratory responses at different submaximal (40% and 80% of the initial peak power, and at the ventilatory threshold) and maximal workloads, after an individualized training program.

Patients and methods

Patients

Written informed consent was obtained from each patient and the study protocol was approved by the local University Ethics Committee. The entry criteria were (1) clinical diagnosis of COPD; (2) stable phase of the disease; (3) no cardiac disease, determined by clinical interview or occurring during the incremental exercise test, or other medical problem which would limit participation in the rehabilitation program; (4) an absence of oxyhemoglobin desaturation at rest or during exercise and an absence of oxygen therapy; (5) a no-longer reversible bronchodilatatory response above 12% from baseline spirometry of forced expiratory volume in 1 s (FEV_1). Patients with hospitalization or severe exacerbations 1 month prior to the initiation of the rehabilitation were excluded.

Of 54 out-patients with a moderate airflow obstruction class IIA[11] enrolled in the rehabilitation program, only the data of 39 men were analysed and 15 subjects were excluded. Two suffered from arthritis, two from diabetes, three had not regularly followed the rehabilitation program, two for exercise-induced hypoxemia and one for ST-segment changes on ECG, five for higher bronchodilatatory reversibility. The patients were divided into two groups according to their age (Table 1). The first group (younger group) comprised 18 patients aged from 50 to 64 and the second group (older group) was composed of 21 patients aged 65 or over. The choice of this age bracket for the patients came from the fact that the pulmonary system declines extremely gradually during most of adulthood, but the process may accelerate in later years, beyond the age of 60–65.[12] There was no significant difference between the groups at rest in pulmonary function and arterial blood gases (Table 1). Medical therapies used by the patients were bronchodilatator drugs (β_2-agonists and/or anticholinergics) and/or inhaled glucocorticosteroids. Medication remained unchanged 3 months before the training period and during the training period. In each group, four patients continued to smoke.

Protocol

Patients were tested before and after a 7-week rehabilitation program including aerobics training. The tests consisted of physical and clinical examinations followed by incremental exercise testing. At least 2 days separated the

Table 1 Anthropometric characteristics and pulmonary function of the patients before training.

	Younger (<65 years) ($n = 18$)	Older (⩾65 years) ($n = 21$)
Age (years)	57.2 ± 1.0	68.8 ± 0.6***
Height (cm)	172.3 ± 0.7	168.7 ± 1.7
Weight (kg)	87.8 ± 4.4	74.3 ± 3.6*
BMI	29.6 ± 1.4	26.1 ± 1.2**
FEV_1 (l)	1.6 ± 0.2	1.4 ± 0.1
%FEV_1 (pred. va.)	51.4 ± 4.3	52.8 ± 3.5
TLC (l. min^{-1})	7.6 ± 0.3	7.0 ± 0.3
%TLC (pred. va.)	111.3 ± 4.8	107.2 ± 3.6
PaO_2 rest (mmHg)	73.8 ± 6.7	71.4 ± 7.2
$PaCO_2$ rest (mmHg)	40.6 ± 4.8	41.2 ± 4.3

Values are means (S.E.M.); n, number of subjects; younger, COPD group aged <65 years; older, COPD group aged ⩾65 years; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; %FEV_1, percentage of predicted values; pred. va., predicted values; TLC, total lung capacity; %TLC, percentage of predicted values; PaO_2, arterial partial pressure in O_2 measured at rest; $PaCO_2$, arterial partial pressure in CO_2 measured at rest.
*$P < 0.05$.
**$P = 0.01$.
***$P < 0.001$.

aerobics training from the final incremental exercise test. After the first incremental exercise test, the powers corresponding to 40% and 80% of the measured peak power were determined. After the rehabilitation program, the physiological values were analysed at the same powers determined during the first incremental exercise test. The choice of 40% and 80% of peak power was due to the fact that, in general, 40% represents a load below the ventilatory threshold and 80% represents a load higher than the ventilatory threshold. Lastly, the data reported at the ventilatory threshold and at the peak of exercise were the values measured at the first and the final incremental exercise tests.

Blood gas and spirometric measurements

Arterial blood gases were measured at rest from an artery of the nondominant arm at 37 °C using a gas analyser (IL2 meter, Milan, Italy). Each patient underwent pulmonary function tests at rest (Table 1) including spirometry, and lung volume measurement (Medisoft, Dinant, Belgium).

Exercise testing

Graded electromagnetically bicycle exercise testing (Ergoline, Schiller, Sweden) was performed with a system designed to continuously measure oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$) and ventilation ($\dot{V}E$) using a breath-by-breath automated exercise metabolic system (Medisoft, Dinant, Belgium). The exercise protocol for this test was: following 3 min of rest, a 3-min warm-up pedalling at 20 W, the work rate being increased by 5–10 W every minute, according to the patient's obstructive pulmonary disorder. The incremental test was terminated when the patient was unable to maintain the imposed pedalling rate of 60 rpm, limited generally by dyspnea and/or leg fatigue. Each incremental test was symptom-limited. An active (2 min) and passive (3 min) recovery followed the incremental test. Blood pressure and heart rate (HR) measured by a 12-lead ECG (Medisoft) and oxyhemoglobin saturation (SaO_2) were also continuously monitored during the exercise test.

Determination of the ventilatory threshold (VTh)

Determination of the VTh was useful in order to personalize training intensity. VTh was determined by the technique of Beaver et al.[13] VTh determination was unclear for five patients (27.7%) in the younger group and seven subjects (33.3%) in the older group. For these 12 patients, the method of Wasserman et al.[14] was attempted, also unsuccessfully. Hence, for the latter patients, we estimated the VTh at 50% of the maximal measured power, as demonstrated by the results of Coppoolse et al.[15] Thus, to measure cardiorespiratory adaptations following aerobic training, the data were obtained for only 27 patients (13 and 14 younger and older patients, respectively).

Rehabilitation program

The rehabilitation program was composed of health advice, respiratory therapy sessions, and individualized aerobics training. The health advice and respiratory therapy consisted of three weekly group sessions. The most important components of respiratory training were pursed-lip and diaphragmatic breathing.

Training program

The training program consisted in one session of stationary bicycle exercise for 45 min, 3 days a week, over a 7-week period. The individualized training program was the following. The patients pedalled for 4 min at 90% of the power of their ventilatory threshold, followed by 1 min at 90% of their measured peak power. The patients whose ventilatory threshold was undistinguishable, pedalled 4 min at 40% of their peak power followed by 1 min at 90% of their measured peak power. This sequence was repeated nine times. This method of interval training corresponds to the square wave endurance exercise test (SWEET).[16]

During each aerobic session, oxyhemoglobin saturation and HR were monitored continuously. A physiotherapist supervised each session.

Statistical analysis

Values were expressed as means ± standard error of the mean (mean ± S.E.M.). The software used for statistical analysis was SIGMASTAT. Data were compared in relation to subject characteristics for homogeneity between the younger and the older groups using an unpaired Student's t-test. For each exercise level (40%, and 80% of the initial peak power, the ventilatory threshold and the maximal values measured before and after training), a two-way analysis of variance (ANOVA) (group and time) with repeated measurements was used to compare the mean values of cardiorespiratory adaptations to exercise for each group (younger and older) both before and after training. When the ANOVA F ratio was significant, the means were compared by using pairwise multiple comparison procedures (Newman–Keuls method). Significance was set at the 0.05 level for all analyses.

Results

Before training

The younger patients were significantly heavier than the older patients ($P < 0.05$; Table 1). There was no significant difference between groups in $\dot{V}O_{2\text{symptom-limited}}$ ($\dot{V}O_{2SL}$) normalized by the body mass, peak power, and maximal HR (Table 3). $\dot{V}E_{max}$ ($P < 0.05$) and maximal CO_2 output ($P < 0.05$) were significantly higher in the younger patients compared to the older patients (Table 3).

After training

- *Forty percent of the initial peak power* (Table 2): The younger patients presented a significant decrease in $\dot{V}E$

Table 2 Physiological variables before and after training at 40% of the initial peak power in the two groups.

	Younger (<65 years) (n = 18)		Older (⩾65 years) (n = 21)	
	Before	After	Before	After
$\dot{V}O_2$ (ml. min^{-1}. kg^{-1})	9.1±0.8	8.4±0.8	8.6±0.7	7.9±0.7
$\dot{V}E$ (l. min^{-1})	26.7±1.2	23.1±1.0*	22.5±1.4	20.0±1.3
$\dot{V}CO_2$ (l. min^{-1})	7.3±4.7	6.5±3.9	6.0±4.5	5.1±4.5
$\dot{V}E/\dot{V}O_2$	35.5±1.6	33.1±1.4	36.7±2.6	36.3±2.5
$\dot{V}E/\dot{V}CO_2$	38.6±0.9	37.7±1.1	39.8±1.0	41.1±1.2
HR (bpm)	107.7±2.1	98.8±1.6*	101.4±2.6	98.4±1.9

Values are means (S.E.M.); $\dot{V}O_2$, O_2 uptake; $\dot{V}E$, pulmonary ventilation; $\dot{V}CO_2$, CO_2 output; $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for O_2 and CO_2, respectively; HR, heart rate.
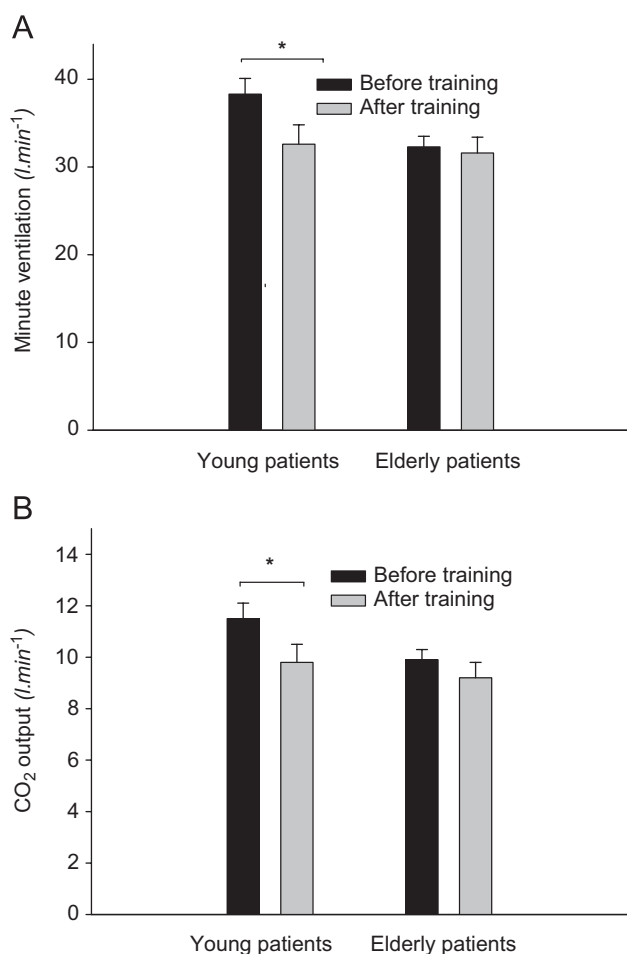*$P<0.05$, significant intragroup differences after the training period.

Figure 1 (A) Evolution of minute ventilation ($\dot{V}E$) between the two groups before and after the training period at 80% of the initial peak power. Values are expressed by means±S.E.M.; *$P<0.05$. (B) Evolution of the CO_2 output ($\dot{V}CO_2$) between the two groups before and after the training period at 80% of the initial peak power. Values are expressed by means±S.E.M.; *$P<0.05$.

($P<0.05$) and HR ($P<0.05$) whereas the older patients did not present significant physiological alteration.

- *Ventilatory threshold*: At this metabolic level, the results were presented for only 13 younger and 14 older patients because the ventilatory threshold could not be detected for 12 patients. No significant alteration was observed for $\dot{V}O_2$, $\dot{V}E$, and HR for the two groups. On the other hand, the power was significantly improved within the two groups ($P<0.05$). For the young and old patients, it was equal to before training 57.1±6.7 and 53.9±6.6 W, respectively to attain after training, 70.0±6.5 and 65.3±5.4 W.

- *Eighty percent of the initial peak power*: For the young patients, $\dot{V}E$, $\dot{V}CO_2$ (Figure 1A and B) and HR decreased significantly ($P<0.05$), whereas no significant cardiorespiratory alteration was measured in the older patients. For the young patients, HR before training was equal to 120.4±2.3 bpm which decreased to 110.5±2.1 bpm ($P<0.05$); for the old patients, it was measured 114.8±2.6 bpm to attain after training 111.5±2.0 bpm.

- *Maximal exercise* (Table 3): Peak power increased significantly in the two groups ($P<0.05$), with a significantly greater improvement for the younger patients ($P<0.05$). The improvement was 25.2% for the younger patients and 17.8% for the older patients. The $\dot{V}O_{2SL}$ was similarly improved ($P<0.05$) by 10.3% and 8.4% for younger and older patients, respectively. $\dot{V}E_{max}$ was significantly increased by 13.5% in younger COPD patients ($P<0.05$) and by 11.4% for the older COPD patients ($P<0.05$). Maximal CO_2 output ($\dot{V}CO_{2max}$) was significantly improved by 11.6% and 11.5% in younger and older patients ($P<0.05$), respectively.

Discussion

The original finding in this study was that, despite an improvement in cardiorespiratory data to the same extent at maximal exercise—except at maximal mechanical power—for younger and older COPD patients, cardiorespiratory adaptations ($\dot{V}E$ and HR) were influenced by ageing at submaximal isowork rates following an individualized training program.

Training effects at isowork rates

The results of our study demonstrated that ageing, associated with COPD, influenced the improvement in

Table 3 Physiological variables before and after training at maximal exercise in the two groups.

	Younger (<65 years) (n = 18)		Older (⩾65 years) (n = 21)	
	Before	After	Before	After
Peak power (W)	86.6 ± 5.3	$108.4 \pm 7.1^{*,\S}$	75.7 ± 5.8	$89.2 \pm 6.4^{*}$
$\dot{V}O_{2SL}$ (ml. min^{-1}. kg^{-1})	15.7 ± 0.8	$17.3 \pm 0.9^{*}$	14.9 ± 0.7	$16.2 \pm 0.7^{*}$
$\dot{V}E$, (l. min^{-1})	$47.2 \pm 2.5^{\S}$	$53.6 \pm 2.6^{*}$	40.3 ± 2.9	$46.0 \pm 3.1^{*}$
$\dot{V}CO_2$ (l. min^{-1})	$14.9 \pm 0.9^{\S}$	$16.7 \pm 1.0^{*,\S}$	12.2 ± 0.9	$13.6 \pm 0.9^{*}$
$\dot{V}E/\dot{V}O_2$	36.3 ± 2.0	36.8 ± 2.3	37.4 ± 2.2	39.8 ± 2.0
$\dot{V}E/\dot{V}CO_2$	32.3 ± 1.3	33.0 ± 1.2	33.9 ± 1.1	34.8 ± 1.3
HR (bpm)	128.9 ± 2.5	132.0 ± 3.0	126.9 ± 3.4	130.6 ± 2.5

Values are means (S.E.M.); n, number of subjects; $\dot{V}O_{2SL}$, O_2 uptake at maximal exercise; $\dot{V}E$, pulmonary ventilation; $\dot{V}CO_2$, CO_2 output; $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for O_2 and CO_2, respectively; HR, heart rate.
*$P<0.05$, significant intragroup differences between before and after the training period.
§$P<0.05$, significant intergroup differences before or after the training period.

cardiorespiratory function at submaximal exercise. At the ventilatory threshold, a significant improvement in power was measured without an associated improvement in $\dot{V}O_2$ in the two groups. This latter result could be explained by a considerable variability of this parameter ranging from 0% to 50%.[2] Nevertheless, the alteration in power translated a positive adjustment because for higher power after training, $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and HR remained stable. For a given submaximal work load after training (40% and 80% of the initial peak power), younger COPD patients presented a significant decrease in $\dot{V}E$ and HR, without any change for the older group. This finding suggests a better cardiorespiratory efficiency for a given submaximal mechanical power output. Even though we cannot explain these different adaptations with ageing, we may suggest several hypotheses. Firstly, decreased $\dot{V}E$ for a given load could be explained by a change in biochemical muscular function. Maltais et al.,[17] following training in COPD patients with a mean age of 65 ± 7 years, demonstrated an increase in citrate synthase and 3-hydroxyacyl-CoA dehydrogenase. This adaptation could induce a reduction in exercise-induced lactic acidosis, leading to a drop in $\dot{V}CO_2$ and then a reduction in $\dot{V}E$ at a given load. However, we do not know if the patients with a mean age of 60 years could present a greater adaptation than those with a mean age of 70 years. We could hypothesize that a lower supply of O_2 over many years[18] in older COPD patients could induce a more damaged muscular function at the beginning of the training, potentially leading to lower adaptability. We can also hypothesize that 7 weeks of training for the older COPD patients is too short a period to reach the results obtained in younger COPD patients. Indeed, the review of Rogers and Evans[19] showed that older subjects were able to adapt their muscular function with exercise training in a similar manner to younger subjects. However, the occurrence of this adaptation may take longer.

Secondly, with natural ageing, lung-compliance diminished and associated with a chronic respiratory disease, O'Donnell et al.[20] demonstrated that COPD patients (mean age = 66 ± 2 years), in comparison with age-matched normal elderly subjects (mean age = 64 ± 2 years), presented a higher dynamic hyperinflation during exercise. This mechanism induces an increase in mechanical respiratory constraints. These constraints induce an improvement in the working of the respiratory muscles and a greater metabolic demand[21]. Thus, it could be hypothesized that dynamic hyperinflation and associated mechanical ventilatory constraints could more greatly limit the respiratory adaptations at submaximal loads in the older COPD than the younger COPD patients.

Thirdly, as exercise intensity increases, there is an increase in the energy derived from carbohydrate (CHO) utilization and a decline in the energy derived from the lipid oxidation.[22] This shift to CHO utilization according to a relative power output involves a progressive increase in CO_2 production. We can thus hypothesize that the utilization of the substrates according to the age group in our COPD patients could present some differences and explain the difference in ventilatory adaptation due to a different production level of CO_2. This hypothesis could be supported by a significant decrease in $\dot{V}CO_2$ in the younger COPD patients for a strenuous intensity without significant alteration in the older COPD patients.

The change in catecholamine production with age during exercise could influence $\dot{V}E$. Fleg et al.[23] demonstrated that elderly subjects generally present a higher catecholamine level than younger subjects, at submaximal exercise. We might hypothesize that the older COPD patients could produce a higher level of catecholamine than the younger COPD patients, translated by a difference in $\dot{V}E$ adaptation. In the same way, this difference in level of catecholamine production could explain a difference in HR adaptation between young and older COPD patients.

Lastly, it is recognized that COPD patients often suffer from pulmonary hypertension, which may alter hemodynamic parameters. We can speculate that the older COPD patients present vessels, which are more rigid and distorted because of "natural ageing". Nevertheless, Kessler et al.[24] demonstrated, over a period of 6.8 ± 2.9 years, a rather slow positive rate of progression of pulmonary arterial pressure (0.4 mmHg. yr^{-1}). Hence, this hemodynamic parameter does not seem to influence cardiovascular adaptations following

training, in relationship with ageing. On the other hand, the results of Mahler et al.[25] suggest that exercise performance may by limited by right ventricular dysfunction in addition to respiratory impairment. Indeed, this function is lower because of lung hyperinflation and reduced venous return, as a result of increased intrathoracic pressure.[26] The overall effect is a reduced left ventricular stroke volume. This hypothesis can be paralleled with that of higher dynamic hyperinflation in the older patients, resulting in a lack of training adaptation at submaximal exercises in the older patients compared with younger COPD ones.

Obviously, all these hypotheses need further investigations in order to understand the different physiological mechanisms in cardiorespiratory adaptations with ageing, following an individualized training program in COPD patients.

Training effects at maximal exercise

At maximal exercise intensity, younger and older COPD patients significantly improved, in the same way, their $\dot{V}O_{2SL}$, by 10.3% and 8.4%, respectively, which is consistent with the improvement encountered in the literature.[2] On the other hand, peak power, after training, was significantly higher in younger COPD patients compared to the older patients. This latter result is in agreement with the results found in the Butcher and Jones' review.[2] These latter demonstrated that the improvement in peak power depends on training intensity. Our result also suggests that peak power after training is age-dependent. A higher cost of breathing in O_2 in the older COPD patients could possibly explain this finding. Indeed, natural ageing induces a reduction in lung elastic recoil, an increase in stiffness of the chest wall and a greater utilization of O_2 by the respiratory muscles[27,28] with a consequence of a greater distribution of blood flow to the respiratory muscles at the expense of the locomotor muscles.[27,29] Thus, competition between the locomotor and respiratory muscles for the blood flow could occur, inducing a weaker maximal power by a diminished blood flow available to the locomotor muscles. However, this hypothesis would seem to be unlikely, since our results demonstrated a similar $\dot{V}E/\dot{V}O_2$ ratio between the two groups.

Secondly, a neuromuscular hypothesis could explain the different adaptation in power output between the younger and older patients. Older COPD patients could present less muscular mechanical efficiency during exercise, due to a prolongation of twitch contraction and half-relaxation times,[30] an impairment of the motor end plate and muscular coordination, as demonstrated in healthy elderly subjects in comparison with younger subjects.[30,31]

In conclusion, the $\dot{V}O_{2SL}$ improvement in the two groups of COPD patients demonstrated that younger and older patients can benefit from a complete rehabilitation program. However, for submaximal exercise intensities, which are very important in autonomy and quality of life, ageing associated with a chronic respiratory disease does not permit optimal cardiorespiratory adaptations in older COPD subjects compared with younger COPD subjects, over the same training period. Even the physiological mechanisms remain unclear; our results could explain some of the discrepancies occurring in the literature concerning cardiorespiratory adaptations after aerobics training.

Conflict of interest

None of the authors has any conflict of interest (financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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