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Functional outcome of patients with chronic obstructive pulmonary disease and exercise hypercapnia

A-A. Simard, F. Maltais, P. LeBlanc

Functional outcome of patients with chronic obstructive pulmonary disease and exercise hypercapnia. A-A. Simard, F. Maltais, P. LeBlanc. ©ERS Journals Ltd 1995.

ABSTRACT: Chronic hypercapnia is associated with a poor prognosis in chronic obstructive pulmonary disease (COPD). Some patients are normocapnic at rest but retain CO_2 during exercise. The significance of this abnormality on the course of the disease is unknown.

Sixteen stable COPD patients (13 males and 3 females, aged 60±5 yrs, mean±SD) who had previously undergone pulmonary function tests and progressive exercise testing with arterial blood sampling at rest and maximal capacity, entered the study. At first evaluation (E1), subjects were normocapnic at rest (arterial carbon dioxide tension (P_{a,CO_2}): 4.9–5.7 kPa, (37–43 mmHg)) and all presented exercise-induced hypercapnia (end-exercise P_{a,CO_2} >5.7 kPa (43 mmHg) with a minimal 0.5 kPa (4 mmHg) increase from resting value). The subjects were re-evaluated 24–54 months later (34±8 months) (second evaluation (E2)).

At E2, forced expiratory volume in one second (FEV_1) had decreased from 42±13 to 38±15% of predicted values, and mean resting P_{a,CO_2} had increased from 5.2±0.3 to 5.7 + 0.4 kPa. Maximal exercise capacity (W_{max}) decreased between E1 and E2 from 76±30 to 56±22 W. Even if W_{max} was lower at E2, end-exercise P_{a,CO_2} was higher than at E1 (6.6±0.8 *vs* 6.4±0.5 kPa). At E2, eight subjects presented resting hypercapnia (group H), whilst the others remained normocapnic (Group N). Group H subjects had higher P_{a,CO_2}, at W_{max} than Group N and lower W_{max} than Group N at E2. Group H and N were not significantly different for physiological dead space/tidal volume ratio (V_D/V_T), FEV_1, lung volumes and transfer factor of the lungs for carbon monoxide ($T_{L,CO}$), both at E1 and E2.

In half of the patients studied, exercise hypercapnia was a step in the progression of COPD towards resting hypercapnia, and was associated with severe exercise limitation. During exercise, patients who responded to a deterioration in their lung function by increasing minute ventilation remained normocapnic at rest, whilst those who did not increase their ventilation developed chronic hypercapnia at rest during the 2–4 year follow-up period.

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Unité de recherche
Centre de pneumologie
Hôpital Laval et Université Laval
Sainte-Foy
Canada.

Correspondence: P. LeBlanc
Hôpital Laval
2725 Chemin Sainte-Foy
Sainte-Foy
Québec
Canada GlV 4G5

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Chronic hypercapnia frequently occurs in severe obstructive pulmonary disease (COPD) and is associated with a poor prognosis. It is always associated with reduced exercise capacity and high morbidity and mortality [1–5]. The mechanisms leading to hypercapnia have often been discussed, but they are still not fully understood. The relationship between the arterial carbon dioxide tension (P_{a,CO_2}) and indices of airway obstruction or ventilation-perfusion mismatch, such as the forced expiratory volume in one second (FEV_1) or physiological dead space/tidal volume ratio (V_D/V_T), is weak [6, 7]. An excessive load on the respiratory muscles [8], alterations in respiratory timing and pattern [9, 10], and a decreased central inspiratory drive [11] have also been proposed, but it is difficult to demonstrate if these are primary or secondary mechanisms.

In normal subjects, P_{a,CO_2} decreases during exercise, despite the additional stress imposed on the respiratory system. In contrast, some COPD patients who are normocapnic at rest become hypercapnic during exercise [12, 13]. Although the prognostic value of this abnormality is unknown, exercise hypercapnia is associated with reduced exercise capacity and with changes in breathing pattern [14].

We studied 16 normocapnic COPD patients who had previously been found to develop exercise hypercapnia, in order to verify the hypothesis that exercise hypercapnia is a precursor and predictor of chronic hypercapnia. If so, exercise-induced hypercapnia should be considered as a significant abnormality. We also attempted to evaluate the functional outcome of COPD patients with exercise-induced hypercapnia.

Methods

Subjects

We reviewed the charts of all the patients who had undergone a progressive exercise test with arterial blood samples between June 1989 and July 1991 (first evaluation=E1). Those who met the following criteria were selected: 1) a clinical diagnosis of COPD; 2) an FEV1 lower than 70% of predicted with no significant improvement after bronchodilator, and an FEV1/forced vital capacity (FVC) ratio lower than 60%; 3) normal resting P_{a,CO_2} (4.9–5.7 kPa) (37–43 mmHg); and 4) end-exercise P_{a,CO_2} >5.7 kPa (43 mmHg) with a minimal 0.5 kPa (4 mmHg) increase from rest.

Individuals with an unstable chronic disease, such as cardiac failure, diabetes and arrhythmias, and those who had changed cardiovascular status or had had lung resection since the initial evaluation, were excluded. Stable clinical status, *i.e.* no change in usual medication, absence of respiratory infection during the preceding month, and no hospitalization during the previous 3 months, was also required.

Twenty nine out of the 735 patient charts examined fulfilled the above criteria. Of these, four had died (two of respiratory failure, and 2 of lung cancer), seven refused or could not participate in the study, and two could not be located. Sixteen stable subjects were therefore re-evaluated for this study (second evaluation=E2).

Measurements

At E1 and E2, patients had pulmonary function tests, exercise testing and arterial blood sampling at rest and maximal capacity. The same equipment was used for both evaluations.

Spirometry was performed with a rolling seal spirometer (P.K. Morgan, Chatham, UK). Lung volumes were measured with a pressure body plethysmograph (Gould #2800, Dayton, Ohio, USA). Transfer factor of the lungs for carbon monoxide ($T_{L,CO}$) was measured by the single-breath method (P.K. Morgan, Chatham, UK). Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured according to the technique described by BLACK and HYATT [15], using an aneroid manometer (Boehringer #7273, Winnewood, PA, USA).

A progressive exercise test was performed on a calibrated ergometer (Bosch ERG 551, Berlin, Germany). Ventilation (V'_E) was measured by a flow resistance turbine (Volume cartridge, Sensor Medics #764040, Anaheim, CA, USA). Mixed expired O_2 and CO_2 concentrations were measured by means of rapid gas analysers (Sensor Medics #2900, Anaheim, CA, USA). Arterial blood was sampled through an in-dwelling radial artery catheter and analysed on an AVL 995 polarographic analyser (Graz, Austria). Arterial plasma lactate level was measured by an enzymatic assay (Kit Lactate, Boehringer Mannheim, France).

Procedure

All subjects were evaluated during a single visit to the laboratory. They were asked to take their usual bronchodilator medication on the study day. They gave written consent as accepted by our Ethics Committee, and standard spirometry was performed. Under local anaesthesia, a catheter was introduced into the radial artery and the patients were then comfortably seated on an electrically braked ergometer. Subjects were connected by a mouthpiece to an open circuit, and V'_E, respiratory rate, tidal volume, 20 s averages of oxygen uptake (V'_{O_2}) and carbon dioxide production (V'_{CO_2}) were measured on expired gas, at rest, during exercise and during the recovery period. Heart rate was monitored using a modified V-5 derivation. The exercise began when the gas exchange ratio (RQ) was stable (at least a 2 min rest period). During exercise, the power was increased by 10 W steps every minute, up to maximal capacity [16]. Arterial blood P_{a,O_2}, P_{a,CO_2}, pH, O_2 saturation, and lactic acid were measured in stable conditions before exercise (with the patient seated on the ergometer), and during the last 20 s of exercise.

Data analysis

Results for expiratory flows, lung volumes, $T_{L,CO}$, and exercise capacity are expressed as percentage of predicted values. Normal values are those of: KNUDSON *et al.* [17] for vital capacity and FEV1; COTES and HALL [18] for $T_{L,CO}$; GOLDMAN and BECKLAKE [19] for lung volumes; and JONES *et al.* [20] for maximal exercise capacity (W_{max}). In two subjects, $T_{L,CO}$ could not be measured by the same technique at both evaluations and they are not included in the analysis for this variable. The results for E1 and E2 were compared using the two-tail paired t-test, and a p-value of less than 0.05 was considered significant. At E2, subjects were divided into two groups according to the presence or absence of hypercapnia at rest. The criteria used to define resting hypercapnia (P_{a,CO_2} >5.7 kPa (43 mmHg)) was selected before the second evaluation. These groups were compared by the unpaired t-test. A multivariate analysis was performed with FEV1, functional residual capacity (FRC), the increase in P_{a,CO_2} during exercise at E1, and changes in FEV1 between E1 and E2 as independent variables, and the change in resting P_{a,CO_2} from E1 to E2 as dependent variable. Values are reported as mean ±SD.

Results

Sixteen subjects (13 males and 3 females) were included in the study. E2 was completed 34±8 months after E1. Mean age at E2 was 60±5 yrs and mean FEV1 was 38±15% of predicted value. Anthropometric and pulmonary function test results at E1 and E2 are shown in table 1. There was a significant decrease in FEV1 ($p<0.05$) and in $T_{L,CO}$ ($p<0.01$) between E1 and E2.

Table 1. – Anthropometric characteristics and pulmonary function tests at the first (E1) and second (E2) evaluations

	E1 (n=16)	E2 (n=16)
Age yrs	58±5	60±5
Weight kg	65.0±17.2	63.8±16.2
FEV_1 % pred	42±13	38±15*
FEV_1/FVC %	41±10	39±11
FRC % pred	154±38	163±33
TLC % pred	128±18	122±17
RV/TLC % pred	62±11	61±11
$T_{L,CO}$ % pred†	73±19	62±22**

Data are presented as mean±SD. †: n=14. *: p<0.05 E1 *vs* E2; **: p<0.01 E1 *vs* E2. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity; $T_{L,CO}$: transfer factor of the lungs for carbon monoxide

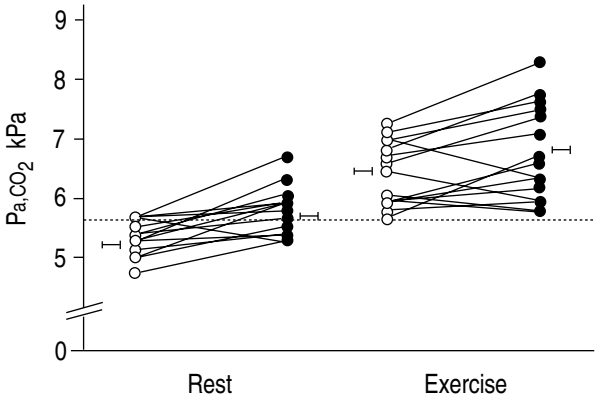

Fig. 1. – Individual resting and end-exercise arterial carbon dioxide tension (P_{a,CO_2}) at first evaluation (E1) (open circles) and second evaluation (E2) (closed circles). P_{a,CO_2} increased significantly during exercise, both at E1 (p <0.01) and at E2 (p <0.01). Resting and end-exercise P_{a,CO_2} increased significantly between E1 and E2 (p <0.01 and p <0.05, respectively). Horizontal bars show mean/median. Note that the vertical axis is cut off from zero. The dotted line identifies the upper normal limit of P_{a,CO_2} (5.7 kPa).

As shown in table 2, there was a significant decrease in W_{max} between E1 and E2. Subjects reached only 58±17% of their predicted maximal V'_{O_2} at E1 and 50±17% at E2 (p<0.01). Breathing pattern and gas exchange at rest and exercise, at E1 and E2, are also given in table 2. Resting P_{a,CO_2} increased significantly from 5.2±0.3 kPa at E1 to 5.7±0.4 kPa at E2 (p<0.01). Despite the decrease in W_{max} between E1 and E2, end-exercise P_{a,CO_2} also increased from 6.4±0.5 to 6.6±0.8 kPa. End-exercise V_D/V_T ratio increased significantly from 44±7 to 49±7% between the studies (p<0.05). For the W_{max} achieved, end-exercise lactic acid concentration was abnormally high both at E1 and E2. Individual resting and end-exercise P_{a,CO_2} are shown in figure 1.

Eight of the 16 subjects increased their resting P_{a,CO_2} >5.7 kPa (43 mmHg) between E1 and E2. The range of the increase was 0.3–1.1 kPa (2–8 mmHg) and was ≥0.7 kPa (5 mmHg) in six subjects. Our population was divided into two groups based on the presence or absence of resting hypercapnia at E2: one group included the eight subjects whose P_{a,CO_2} was >5.7 kPa (43 mmHg) at rest (Group H), and the other included those who were still normocapnic (Group N). Rest and exercise results for these two subgroups are shown in table 3. At E2, resting P_{a,CO_2} was 6.1±0.3 kPa in Group H and 5.4±0.2 kPa in Group N. At E2, end-exercise P_{a,CO_2} was >5.7 kPa (43 mmHg) in all subjects. It was also signi ficantly higher in Group H (7.0±1.2 kPa *vs* 6.2±0.7 kPa in Group N; p<0.05) despite the lower exercise capacity. The interval between E1 and E2 was 35±8 and 33±9 months in Groups N and H, respectively. No relationship was found between changes in resting P_{a,CO_2} from E1 to E2, and FEV_1 and FRC at E1, changes in FEV_1 between E1 and E2, and increase in P_{a,CO_2} during exercise at E1.

As can be seen in figure 2, resting and exercise V'_E was higher in Group N than Group H at E1, but this

Table 2. – Breathing pattern and gas exchange data at rest and exercise for the first (E1) and second (E2) evaluations

	Rest		End-exercise	
	E1 (n=16)	E2 (n=16)	E1 (n=16)	E2 (n=16)
W_{max} W			76±30	56±22*
HR beats·min^{-1}	94±22	91±15	152±25	132±22
V'_E L·min^{-1}	14.9±3.8	16.9±5.2	39.8±13.4	38.5±14.2
V_T L	0.74±0.19	0.74±0.18	1.20±0.39	1.19±0.39
V'_{O_2} L·min^{-1}	0.30±0.10	0.34±0.11	1.09±0.39	0.91±0.30*
V'_{CO_2} L·min^{-1}	0.27±0.07	0.30±0.10	1.00±0.38	0.86±0.33
RQ	0.94±0.20	0.89±0.07	1.02±0.15	0.96±0.09
P_{a,O_2} kPa	10.5±1.1	10.3±0.9	9.5±1.4	9.4±1.9
P_{a,CO_2} kPa	5.2±0.3	5.7±0.4*	6.4±0.5	6.6±0.8**
pH	7.43±0.02	7.40±0.02*	7.35±0.05	7.34±0.05
V_D/V_T %	49±9	50±7	44±7	49±7**
LA mmol·L^{-1}	1.08±0.37	0.88±0.26	3.51±1.57	2.58±1.42**

Values are presented as mean±SD. W_{max}: maximal exercise capacity; RQ: respiratory exchange ratio; V'_E: minute ventilation; V_T: tidal volume; LA: lactic acid. HR: heart rate; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; V_D: physiological dead space. *: p<0.01 E1 *vs* E2; **: p<0.05 E1 *vs* E2.

Table 3. – Rest and exercise data for subjects with Group (H) and without Group (N) chronic hypercapnia at rest and maximal exercise for the first (E1) and second (E2) evaluations.

	E1		E2	
	Group H (n=8)	Group N (n=8)	Group H (n=8)	Group N (n=8)
Rest				
FEV_1 % pred	36±11	47±14	33±13	42±17
FRC % pred	169±24	140±45	169±18	157±44
TLC % pred	133±16	123±19	127±16	116±18
MIP kPa			5.9±3.8	5.7±2.2
MEP kPa			8.2±4.2	8.3±2.5
P_{a,O_2} kPa	11.0±1.1	9.8±0.7*	10.2±0.8	10.3±1.0
P_{a,CO_2} kPa	5.3±0.2	5.2±0.3	6.1±0.3	5.4±0.2**
V_D/V_T %	49±7	49±11	48±8	52±5
Maximal exercise				
W_{max} W	65±26	87±32	49±24	64±19
P_{a,CO_2} kPa	9.4±1.4	9.6±1.5	8.8±1.9	10.0±1.8
P_{a,CO_2} kPa	6.6±0.5	6.1±0.4	7.0±1.2	6.2±0.7*
V_D/V_T %	44±8	43±6	48±7	49±7
V'_{Emax}/MVV %	88±22	95±30	82±16	100±17

Data are presented as mean±SD. MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; W_{max}: maximal exercise capacity; MVV: maximal voluntary ventilation. For further abbreviations see legends to tables 1 and 2. *: $p<0.05$ E1 *vs* E2; **: $p<0.01$ E1 *vs* E2.

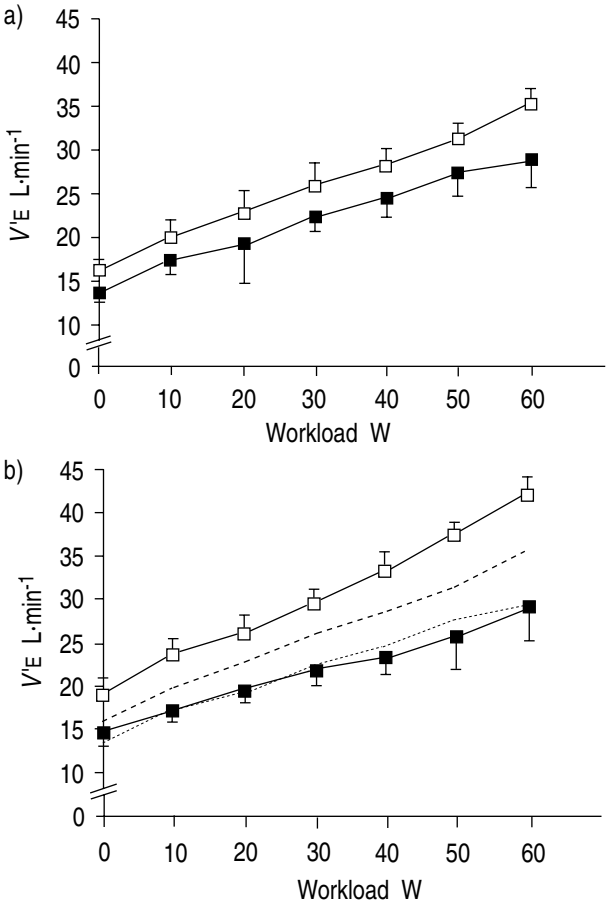

Fig. 2. – Group mean (±SEM) value for minute ventilation (V'_E) at each exercise level for: a) first evaluation (E1) and b) second evaluation (E2). –□– :subjects who remained normocapnic at rest (Group N); –■–: subjects who had resting hypercapnia at E2 (Group H). Dashed line (Group N) and dotted line (Group H) in panel b are a repetition of those in panel a. The differences in V'_E between Groups N and H become significant at every level of exercise at E2, and are due mostly to an increase in V'_E in Group N from E1 to E2. Note that the vertical axis are cut off from zero.

difference was not statistically significant. In contrast, at E2 this difference was accentuated and reached statistical significance at each level of exercise. The increased V'_E in Group N was due to combined increases in V_T and respiratory rate, the differences being nonsignificant when these parameters were taken separately.

Even with a normal P_{a,CO_2} and higher ventilation levels, Group N had a significantly higher ratio of maximal ventilation to maximal voluntary ventilation (V'_{Emax}/MVV) calculated from FEV_1 ×35 [21] than Group H (100±17 *vs* 82±16%) at E2. There was no significant difference in V_D/V_T ratio at rest and at W_{max} between the two groups at E1 and E2. No significant change in V'_E occured between E1 and E2 in Group H.

Discussion

Although resting hypercapnia has been shown to be a poor prognostic factor in COPD patients, little is known regarding the significance of isolated exercise-induced hypercapnia in this population [12, 13]. Our results indicate that, among the study population, 50% of normocapnic COPD patients who presented exercise hypercapnia developed chronic hypercapnia at rest within a few years. Initially, our population had a reduced exercise capacity, and, without major changes in airway obstruction, this exercise limitation worsened and resting hypercapnia appeared between the two evaluations. At E1, the patients who became hypercapnic during follow-up were not significantly different from those who remained normocapnic, but tended to have lower FEV_1 and $T_{L,CO}$, higher FRC and total lung capacity (TLC), and lower exercise capacity.

This study could be criticized on a few points. Firstly, it is not prospective. We think, however, that our results are still valid because, as mentioned earlier, both evaluations were made with the same equipment and an

identical exercise protocol. The 13 subjects who fulfilled the initial criteria but could not be studied at E2 would probably have been lost to follow-up for the same reasons in a prospective study. In addition, the criteria used to define resting hypercapnia were selected before E2. The second potential criticism is the lack of a control group of patients presenting similar bronchial obstruction but in whom P_{a,CO_2} remained normal both at rest and exercise. This would have allowed us to evaluate whether patients with exercise-induced hypercapnia are more susceptible to develop resting hypercapnia with time. We initially intended to carry out this step and had identified 15 COPD patients with normal CO_2 both at rest and exercise. However, their mean FEV_1 was markedly higher than in the exercise-induced hypercapnia patients (FEV_1=50±14% *vs* 42±13% predicted value, respectively; $p<0.05$). We believe that this large difference in the degree of bronchial obstruction invalidates any comparison between the two groups, and supports the notion that normocapnia and exercise-induced hypercapnia are successive stages in the natural history of COPD toward resting hypercapnia. This study, however, does not allow us to conclude that chronic hypercapnia is always preceded by exercise-induced hypercapnia. Finally, although the cut-off for defining resting hypercapnia in the present study (P_{a,CO_2} >5.7 kPa) can be debated, it has been considered abnormal in previous studies [8, 22], and the minimal 0.5 kPa (4 mmHg) increase makes our definition of hypercapnia at exercise more restrictive.

Carbon dioxide retention is frequent and usually occurs when the FEV_1 is lower than 1 L or 40% of predicted, but many severe COPD patients never become hypercapnic. SORLI *et al.* [8] showed that CO_2 retention in COPD patients was characteristically associated with a decreased tidal volume (V_T), causing an increase in V_D/V_T and, hence, a reduced alveolar ventilation. The reduced V_T was caused by a decreased inspiratory flow or a shortened inspiratory time, or both. BÉGIN and GRASSINO [22] suggested that chronic alveolar hypoventilation is likely to develop in COPD patients who have a combination of high inspiratory loads and inspiratory muscle weakness. They also proposed that hypercapnia could be a strategy to avoid overloading the inspiratory muscles that could lead to fatigue and possibly irreversible failure.

In the present study, the underlying mechanisms of CO_2 retention at rest and exercise were not thoroughly evaluated but some comments can be made. Subjects who became hypercapnic at rest tended to have lower ventilation (V'_E) during exercise at E1 than those who remained normocapnic, and this difference was significant at E2. The difference in V'_E between the groups was due to an increased V'_E in the normocapnic group from E1 to E2, and not to a decreased ventilation in the hypercapnic group. As indicated by the increase in the V_D/V_T ratio and the decrease in FEV_1, lung function and gas exchange slightly deteriorated between E1 and E2. Accordingly, one would predict that in order to maintain P_{a,CO_2} at rest and exercise at a similar level from E1 to E2, patients should have increased V'_E. It appears that some did, whilst others chose not to modify their V'_E at the cost of higher P_{a,CO_2} both at rest and exercise. Although lung function were not significantly different between Group N and H, on average the latter group had slightly more bronchial obstruction. Therefore, it is possible that patients in Group H simply represent a subset of patients with more severe lung disease. However, it appears reasonable to hypothesize that, as suggested by BÉGIN and GRASSINO [22], patients in group H, who were more mechanically disadvantaged, adopted a ventilatory pattern that reduced the stress imposed on the respiratory muscles (*i.e.* a reduction in $V'E$), and resulted in higher P_{a,CO_2}.

In patients with severe airway obstruction, the function of the respiratory muscles differs from rest to exercise. During exercise, the inspiratory load is high because of the significant increase in inspiratory flow required to maintain adequate ventilation. As shown by DODD *et al.* [23], there is also some degree of dynamic hyperinflation, which reduces the ability of the respiratory muscles to generate pressure. This contrasts with normal subjects, who tend to decrease their functional residual capacity at high exercise intensity in order to improve the operating conditions of inspiratory muscles [24]. In addition, expiratory flow limitation and reduced inspiratory time to respiratory cycle ratio (t_I/t_{tot}), contribute to the dynamic weakness of inspiratory muscles [25]. Although our patients did not suffer from severe respiratory muscle weakness, exercise may have exposed a poor ventilatory reserve.

At E2, V'_E/MVV was smaller in Group H compared to Group N. This was due to the fact that Group H patients reached a smaller end-exercise $V'E$ than Group N. As stated previously, this breathing pattern was possibly adopted in an attempt to reduce the load imposed on the respiratory muscles. Given the lower V'_E/MVV in Group H, it might be suggested that these patients were not limited by ventilation. We believe that this interpretation is incorrect for a number of reasons. In the present study, MVV was estimated from the FEV_1 value and individual subjects may exhibit large deviations from the general relationship [21]. Important factors, such as inspiratory muscle function, are not taken into account in the estimated MVV [26]. Although in many COPD patients, the MVV underestimates V'_{Emax}, it is conceivable that in some patients who develop significant inspiratory muscle dysfunction during exercise, the MVV may actually overestimate the true ventilatory capacity. Interestingly, a study by LEBLANC *et al.* [27] showed that this might even be true in normal subjects. The presence of ventilatory limitation in Group H is also supported by the fact that each patient of this group stopped exercise because of severe dyspnoea. Finally, in these patients, exercise-induced increase in P_{a,CO_2} also suggests the presence of a poor ventilatory reserve. Accordingly, we believe that a V'_E/MVV ratio smaller than 1 does not indicate the absence of ventilatory limitation in COPD patients.

The subjects of this study had a significant arterial lactic acid concentration at a very low exercise intensity. At E1, the end-exercise concentration was 3.5 $mmol \cdot L^{-1}$ for a mean workload of 76 W, and it reached 2.6 $mmol \cdot L^{-1}$ at E2 for a mean maximal workload of only 56 W. As

previously shown by many authors, COPD patients produce lactic acid quite early during exercise [28–30]. Hypoxaemia, inappropriate cardiac output, and peripheral muscle deconditioning are some of the pathophysiologic mechanisms that have been proposed to explain this early lactic acid production. Added to mechanical respiratory abnormalities, the secondary increase in ventilatory demand associated with lactic acidosis and peripheral muscle fatigue may contribute to the exercise limitation.

We conclude that, in some COPD patients, exercise hypercapnia is a step towards chronic hypercapnia. Exercise hypercapnia occurs with severe airway obstruction and is always associated with reduced exercise tolerance. This poor exercise capacity is due not only to ventilatory limitation but is also associated with early lactic acid production, which further increases ventilatory demand [31]. The subjects who become hypercapnic at rest seem to be those with the more severe respiratory mechanical abnormalities. Those who remain normocapnic have higher ventilation, despite their decrease in ventilatory reserve at maximal exercise.

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