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Influence of exercise and CO_2 on breathing pattern in patients with chronic obstructive lung disease (COLD)

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Influence of exercise and CO_2 on breathing pattern in patients with chronic obstructive lung disease (COLD). G. Scano, F. Gigliotti, A. van Meerhaeghe, A. De Coster, R. Sergysels.

ABSTRACT: In ten eucapnic patients with chronic obstructive lung disease (COLD) we evaluated the breathing pattern during induced progressive hypercapnia (CO_2 rebreathing) and progressive exercise on an ergometric bicycle (30 W/3 min). The time and volume components of the respiratory cycle were measured breath by breath. When compared to hypercapnia, the increase in ventilation ($\dot{V}E$) during exercise was associated with a smaller increase in tidal volume (VT) and a greater increase in respiratory frequency (fR). Plots of tidal volume (VT) against both inspiratory time (TI) and expiratory time (TE) showed a greater decrease in both TI and TE during exercise than with hypercapnia. Analysis of $\dot{V}E$ in terms of flow (VT/TI) and timing (TI/TT) showed $\dot{V}E$ to increase by a similar increase to that in VT/TI during both exercise and hypercapnia, while TI/TT did not change significantly. When the patients were matched for a given $\dot{V}E$ (28 $l \cdot min^{-1}$), exercise induced a smaller increase in VT ($p < 0.05$), a greater increase in fR ($p < 0.025$); TI ($p < 0.025$) and TE ($p < 0.01$) were found to be smaller during exercise than hypercapnia. The change in the off-switch mechanism during exercise and hypercapnia could account for our results.

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Many recent studies have been devoted to the analysis of breathing patterns and ventilatory control at rest in patients with chronic obstructive lung disease (COLD) [27, 30–33]. Rapid and shallow breathing characterizes the breathing pattern in patients with chronic hypercapnia when compared with normocapnic ones [27, 33]. The increased neuromuscular drive noted in patients with COLD during induced hyperventilation [30–32] seems to depend not only on mechanical input to the respiratory centre [5] but also on mechanical afferences from the thoraco-pulmonary system [5, 7, 30, 32]. Alternatively, the rapid shallow breathing could depend on the mechanical limitation for ventilation [4, 15].

In both normal subjects and patients with COLD, hyperventilation may be achieved in different ways, such as CO_2 inhalation and metabolic load during exercise. In the former, chemical input to the respiratory centre is mainly related to the stimulation of central chemoreceptors [25]. In the latter, several factors such as CO_2 production [25, 28, 36], changes in arterial oxygen tension (PaO_2) [17, 23, 25], mechanical afferences from the lung [26], and proprioceptive muscular afferent information [7, 10] could play a role.

Comparisons between stimulation with exogenous CO_2 and metabolic load have been made in normal subjects [2, 18, 21] and show a variable relationship between ventilation and tidal volume (Hey's plot) [18] during CO_2 inhalation and exercise.

In patients with COLD, however, comparative data have been reported only in terms of ventilatory response to carbon dioxide and exercise without analysing the breathing pattern [19].

To control the different behaviour during induced hyperventilation in COLD patients who underwent CO_2 rebreathing and progressive exercise, we analysed the breathing pattern by measuring the time and volume components of the respiratory cycle.

Materials and methods

We studied ten normoxic and eucapnic male patients with chronic obstructive lung disease (COLD), according to the American Thoracic Society criteria [1]. Spirometric pulmonary functional data (Pulmonet Godart) included vital capacity (VC), forced expiratory volume in one second (FEV_1), and functional residual capacity (FRC) by the helium dilution technique, which allowed us to calculate residual volume (RV) and total lung capacity (TLC); thoracic gas volume (TGV) and the resistance of the airway (Raw) were measured by a pressure-variable body plethysmograph, which allowed the calculation of specific airway resistance ($sRaw = Raw \times TGV$). Diffusing lung properties and the permeability coeffi-

cient for carbon monoxide (KCO) were determined by the single-breath technique. The normal values for lung volumes and KCO are those proposed by GRIMBY and SÖDERHOLM [16] and ENGLERT [12], respectively. The patients were selected on the basis of both clinical history and functional evidence of airway obstruction ($FEV_1/VC \leq 60\%$) when they were clinically stable; any therapy which was being taken was withheld for at least 12 h before the study. Functional data are summarized in table I.

After the evaluation of the baseline respiratory pattern, each patient, from a seated position, underwent a CO_2 rebreathing test. The apparatus has been previously described [31] and the procedure was that recommended by READ [29]. A gas mixture containing $7\%CO_2 + 50\%O_2 + 43\%N_2$ was inhaled for 3–4 min from a 6 to 8 litre bag. The inspiratory line was separated from the expiratory one by a one-way valve (Hans-Rudolph), connected to a Lilly type pneumotachograph. The flow signal was integrated into ventilation. The mouth occlusion pressure against an occluded airway at end-expiratory level 0.1 s after the onset of inspiration ($P_{0.1}$) [37] was measured as previously described [30–32, 35]. A pressure transducer (Statham SC 1001) was used to measure the mouth pressure developed at 0.1 s. On the expiratory side of the valve, gas was continuously sampled with an infrared CO_2 meter (Godart) to measure the CO_2 level; the sampled gas was returned to the rebreathing bag. The dead space and the resistance of the system were evaluated as 178 ml and 0.09 $kPa \cdot l^{-1} \cdot s$, respectively.

Table I. - Pulmonary function data at rest in 10 patients with COLD breathing room-air

n	Age y	VC *l*	RV *l*	FRC *l*	TLC *l*	sRaw $kPa \cdot s^{-1}$	FEV_1 *l*	FEV_1/VC %	Kco min^{-1}
1	61	2.04 (43)	4.2 (158)	4.9 (119)	6.25 (85)	1.47	1.0	49	2.05 (57)
2	38	3.2 (70)	2.0 (125)	3.4 (104)	5.2 (84)	1.08	1.9	60	4.16 (97)
3	49	4.15 (91)	2.6 (120)	3.9 (107)	6.8 (102)	0.49	2.5	59	1.76 (44)
4	55	3.0 (69)	3.8 (165)	5.1 (141)	6.9 (104)	1.76	1.0	35	2.12 (57)
5	63	3.5 (67)	3.7 (161)	4.6 (116)	7.2 (96)	1.57	1.6	42	2.24 (58)
6	74	2.16 (44)	5.5 (186)	6.0 (134)	7.7 (98)	2.65	0.6	28	3.0 (79)
7	38	2.7 (61)	3.5 (140)	4.9 (132)	6.3 (90)	1.27	1.4	51	5.5 (128)
8	51	2.4 (52)	3.9 (165)	4.5 (132)	6.3 (96)	2.29	0.82	35	3.1 (80)
9	56	3.5 (74)	4.3 (173)	5.4 (135)	7.6 (107)	1.27	1.3	40	1.65 (45)
10	40	4.0 (80)	2.4 (114)	4.4 (116)	6.5 (91)	0.95	2.3	57	3.5 (84)
$\bar{x}$	52.5	3.1	3.58	4.7	6.67	1.48	1.44	45.6	2.9
SD	11.8	0.73	1.03	0.73	0.74	0.63	0.63	11.2	1.21

Values between parenthesis are in % of the predicted value. VC: vital capacity; RV: residual volume; FRC: functional residual capacity; sRaw: specific resistance of the airways; FEV_1: forced expiratory volume in 1 sec; Kco: Krogh's factor for lung transfer for CO.

From the flow signal we derived time and volume components of the respiratory cycle: tidal volume (V_T), mean inspiratory flow (V_T/T_I), 'duty cycle' (T_I/T_T), respiratory frequency (f_R) and ventilation ($\dot{V}_E$). V_T/T_I was related to mouth occlusion pressure ($P_{0.1}$) measured during the following breath. Since $P_{0.1}$ represents an index of inspiratory drive [37], the relationship between $P_{0.1}$ and V_T/T_I represents the effectiveness of the thoraco-pulmonary system to convert this signal into mean inspiratory flow and ventilation. Therefore, the relationship between $P_{0.1}$ and V_T/T_I is considered as the 'effective' inspiratory impedance [8].

The resistance of the circuit used on rebreathing was such that the mouth pressure during unoccluded breathing was always between +0.2 kPa (expiration) and −0.2 kPa (inspiration) with respect to the atmospheric pressure.

The output of the CO_2 meter and the integrated flow signal, as well as the mouth pressure, were continuously recorded on a multi-channel linear recorder. The patients, who wore a noseclip, were comfortably seated and were not able to predict which breath would be occluded.

The following day the study was repeated under control conditions and during progressive exercise with the subject seated on an ergometric bicycle with a progressive increase in load (30 W/3 min) until the patient felt dyspnoea or pain in the legs. Pedalling was held at 50 rpm; the breathing circuit was the same as that used during the rebreathing test in terms of both resistance and dead space. The same parameters, as well as CO_2 output ($\dot{V}CO_2$), obtained by analysing mixed fractional expiratory carbon dioxide ($FECO_2$) in a 'mixing box', were measured at the end of each level of exercise. The maximal achieved load which prevented the test from being continued was 60 W in one patient, 90 W in six patients and 120 W in three patients. Under control conditions, no data were collected after the first four min in which the patients equilibrated with the circuit. Ventilatory measurements were calculated from data averaged from five breaths preceding each of the two random occlusions at the end of each minute of rebreathing and each step of exercise. The breaths following the occlusions were discarded to eliminate the artefacts induced by the occlusions. In each patient arterial blood was sampled at rest and at each minute of rebreathing and at each step of 30 W during exercise in order to measure PaO_2, arterial carbon dioxide tension ($PaCO_2$) and pH values (Radiometer ABL I).

The following day we repeated the same protocol in four out of the ten patients, while the pedalling frequency was at 40 and 70 rpm for loads of 60 and 90 W. A rest period of 20 min separated the two exercises with different pedalling frequencies.

The results were compared by Student's t-test for paired variables when variances were equal and by Wilcoxon-Mann-Whitney test when variances were unequal; $p < 0.05$ was considered to be significant.

Table II. - Respiratory pattern in 10 COLD patients (mean values ±1SD)

	Before rebreathing	Before exercise
$\dot{V}_E$ $l \cdot min^{-1}$	13.9 ± 1.69	13.95 ± 3.2
V_T l	0.61 ± 0.11	0.72 ± 0.3
T_I sec	1.13 ± 0.24	1.3 ± 0.25
T_E sec	1.5 ± 0.3	1.76 ± 0.46
T_T sec	2.66 ± 0.56	3.0 ± 0.68
V_T/T_I $l \cdot s^{-1}$	0.55 ± 0.09	0.56 ± 0.15
T_I/T_T	0.43 ± 0.03	0.42 ± 0.04
f_R $cycles^{-1}$	23.5 ± 5.8	20.0 ± 5.2

There was no significant difference between the two experimental conditions. V_E: minute ventilation; V_T: tidal volume; T_I: inspiratory time; T_E: expiratory time; T_T: total time of the respiratory cycle; V_T/T_I: mean inspiratory flow; T_I/T_T: ratio between inspiratory time and total breath duration (duty cycle); f_R:respiratory frequency, $P_{0.1}$: mouth occlusion pressure.

Results

The respiratory pattern of the patients under control conditions is shown in table II. There was no significant difference between the values obtained on the two different days, before ventilatory stimulation.

A ventilatory level of 28 $l \cdot min^{-1}$ was chosen to compare exercise and CO_2 rebreathing, because this level was achieved by all patients and located below the maximum symptom-limited Vo_2 achieved and probably below the anaerobic ventilatory threshold. At that level of ventilation (28 $l \cdot min^{-1}$) V_T ($p < 0.05$), T_I ($p < 0.025$), T_T ($p < 0.01$) and T_E ($p < 0.01$) were found to be larger during rebreathing when compared to exercise, while f_R was smaller ($p < 0.025$). These changes are schematized in figure 1.

Figure 2 (left panel) is a plot of $\dot{V}_E$ against V_T during both exercise and rebreathing. A lower

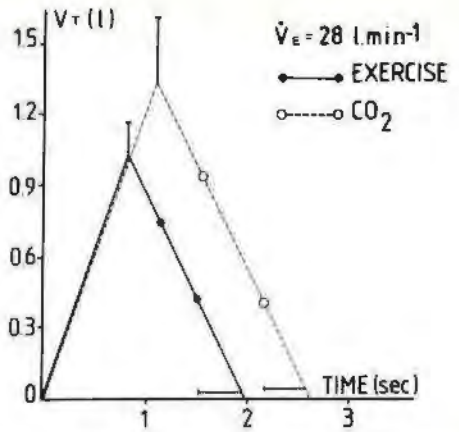

Fig. 1. Schematic representation of the respiratory cycle of 10 COLD patients during exercise (●——●) and CO_2 rebreathing (○---○) for a given ventilation ($\dot{V}_E = 28.1$ $l \cdot min^{-1}$). Bars indicate 1 SD. V_T = tidal volume. The slope of the ascending limb of the spirogram represents mean inspiratory flow (V_T/T_I).

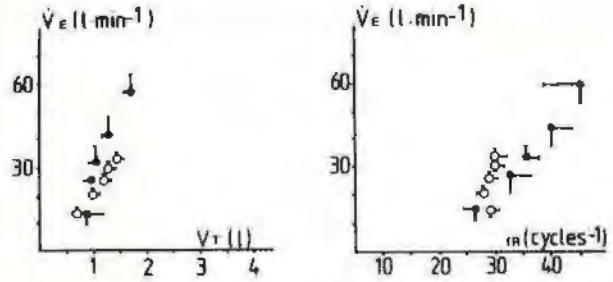

Fig. 2. Analysis of pulmonary ventilation (VE) in terms of tidal volume (VT) (left panel) and respiratory frequency (fR) (right panel). Mean values ±1 SE for all subjects are shown at rest and at each level of exercise (30 to 120W) or minute of rebreathing (1st to 4th). (●) exercise; (○) rebreathing.

increase in VT during exercise (from rest to 90 W) is evident when compared to CO_2 rebreathing (from control to the 4th minute). Furthermore, an increase in $\dot{V}E$ was also related to a significant increase in fR ($p<0.001$), but only in the former condition (right panel of fig. 2).

The relationships between VT, TI and TE are shown in figure 3; significant decreases in both TI ($p<0.01$) and TE ($p<0.001$) were observed during exercise only.

The analysis of ventilation in terms of 'central' inspiratory activity measured by inspiratory flow (VT/TI) and timing (TI/TT) (fig. 4.) shows that these parameters are related to $\dot{V}E$ in a similar way for the two types of hyperventilation. Mean inspiratory flow showed a progressive increase while TI/TT did not change significantly. For the given ventilation (28 $l \cdot min^{-1}$), $P_{0.1}$ was similar in the two conditions (0.76 kPa ± 0.2 SD and 0.75 kPa ± 0.2 SD, for exercise and rebreathing, respectively). Furthermore, plots of change in $P_{0.1}$ against changes in VT/TI during both exercise and rebreathing were found to be similar, the corresponding slope being 1.24 kPa per $l \cdot s^{-1}$ and 1.21 kPa per $l \cdot s^{-1}$ respectively (p = NS).

During exercise for a $\dot{V}E$ of 28 $l \cdot min^{-1}$, when compared to resting conditions, none of the patients became hypoxic, whilst average $PaCO_2$ showed a slight decrease ($p<0.05$). In contrast, during CO_2

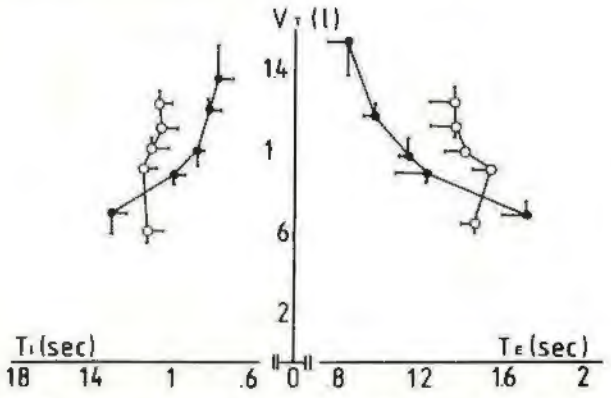

Fig. 3. Tidal volume (VT) is plotted against inspiratory time (TI) and expiratory time (TE) (for explanation see text). (●——●) exercise; (○——○) rebreathing.

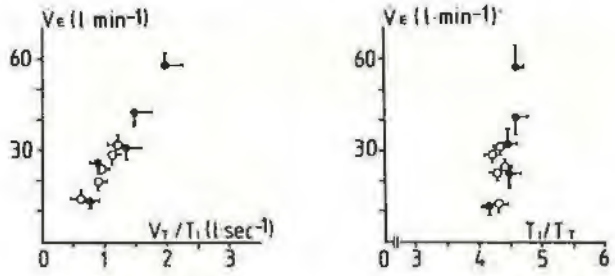

Fig. 4. Minute ventilation (VE) is analyzed in terms of mean inspiratory flow (VT/TI) and 'timing' (TI/TT). (●) exercise; (○) rebreathing.

Table III. - Arterial blood gases at rest, during exercise and CO_2 rebreathing for a given ventilation (28 $l \cdot min^{-1}$). Mean values ±1 SD and statistical comparison

		PaO_2 kPa	$PaCO_2$ kPa	pH
Rest	a	12.05±1.16	5.30±0.33*	7.370±0.04
	b	11.60±1.0 #	5.13±0.5 #	7.360±0.02 #
Exercise		11.69±1.26	4.88±0.48 *	7.378±0.05
Rebreathing		16.25±3.05 #	7.30±1.36 #	7.260±0.04 #

a: pre-exercise; b: pre-rebreathing; * $p<0.05$ (exercise *vs* rest); #$p<0.001$ (rebreathing *vs* rest)

rebreathing, both PaO_2 and $PaCO_2$ rose markedly ($p<0.001$ for both). These data are summarized in table III.

In four out of the ten patients we attempted to evaluate the possibility of synchronization of respiratory timing during exercise with pedalling speed. Pedalling frequency was set at 40 and 70 rpm for loads of 60 and 90 W. At 60 W, VT/TI was 1.4 ± 0.09 and 1.45 ± 0.1 and fR was 30.5 ± 5.6 and 31.5 ± 4.8 at 40 and 70 rpm, respectively. At 90 W, VT/TI was 1.65 ± 0.15 and 1.59 ± 0.2 and fR was 38.7 ± 6.2 and 37.4 ± 5.6 at 40 and 70 W, respectively. In no case did either VT/TI or fR significantly differ by changing pedalling speed for each given load (paired t-test). Similar results were obtained for VT.

Discussion

This study shows that, in patients with COLD, there is a different evolution of the $\dot{V}E/VT$ relationship (Hey's plot) [18] during CO_2 rebreathing and progressive exercise. The main difference we noted was a limitation of VT during exercise compared to hypercapnic stimulation and, consequently, an increase in the respiratory frequency necessary to achieve a similar level of ventilation.

The increase in respiratory frequency was achieved by a proportional decrease in TI ($p<0.01$) and TE ($p<0.001$), while the duty cycle (TI/TT) remained similar.

In normal subjects, ventilatory responses during acute hypercapnia and exercise have been compared previously [2, 18, 21]. According to ASKANAZI *et al.* [2], an increase in ventilation during hypercapnic stimulation depends mostly on an increase in tidal volume, whereas during exercise, an increase in ventilation depends on an increase in both tidal volume and respiratory frequency with a significant decrease in inspiratory time. The authors supposed that a change in the 'inspiratory off-switch' mechanism [14] during exercise could account for the different responses in terms of tidal volume and respiratory frequency [2]. In contrast, HEY *et al.* [18] showed that the relationship between ventilation and tidal volume is similar during hypercapnia and exercise.

To our knowledge, there are no comparative data in the breathing pattern during CO_2 stimulation and exercise in patients with chronic obstructive lung disease. GARRARD and LANE [15] showed a progressive decrease in inspiratory and expiratory time during rebreathing with a progressive but small increase in tidal volume, related to volume restriction due to a progressive increase in lung volume at end-expiratory level.

During exercise in patients with COLD, the slope of the relationship between tidal volume and inspiratory time tends to be shifted to the left, when compared to normal subjects [4, 32]. This results in a shorter inspiratory time and a smaller V_T with a rapid and shallow breathing [4, 32, 35]. Synchronization of respiratory rate during exercise with pedalling speed or stepping frequency has been noted in normal man [18]. However, this observation has not been confirmed in more recent papers [20-22] where respiratory frequency and both V_T/T_I and V_T/T_E relationships were found to be similar at two different pedalling speeds [20, 21]. Our data in patients are consistent with these [20, 21] and seem to indicate no link between movement frequency and respiratory frequency of bicycle exercise.

The differences we noted in the respiratory pattern during CO_2 rebreathing and exercise in patients with COLD are consistent with the data of ASKANAZI *et al.* who studied normal man in the supine position [2]. These differences could be explained as follows:

i) mechanical differences observed in COLD patients during induced hypercapnia [15] and exercise [9] could be due to different changes in lung volume at end-expiratory level. These volume changes restrict any substantial increase in tidal volume [9, 15]. We were unable to control the possible changes in lung volume at end-expiratory level during rebreathing and exercise. However, for the chosen level of ventilation (28 $l \cdot min^{-1}$), $P_{0.1}$ was found to be similar in the two experimental conditions. As an increase in lung volume put the inspiratory muscles in a less favourable condition to generate inspiratory pressure [11] we argue that end-expiratory volume was not dissimilar with exercise and CO_2 rebreathing for the chosen $\dot{V}_E$. This could also be indicated by the similarity of the slopes of the $P_{0.1}/(V_T/T_I)$ relationship, an index of the effective inspiratory impedance of the thoraco-pulmonary system [8].

ii) a decrease in T_I has been observed in response to a progressive hypoxia (8 to 4 kPa) [23]. However, our data did not show a significant decrease in arterial P_{O_2} for a given $\dot{V}_E$, during either exercise or hypercapnia, as compared to control conditions. These data are consistent with our previous ones [30, 35] in patients with COLD during moderate ergometric exercise.

iii) CO_2 stimulation is known to increase central inspiratory activity [13, 23] and to raise the volume (V_T) threshold for the reflex inspiratory off-switch [13]. Furthermore, elevated P_{CO_2} in the bronchial airways is sufficient to lower stretch receptor activity [3], necessary for reaching the threshold for the Hering-Breuer inhibitory reflex; this causes V_T to increase. In terms of changes in breathing pattern, on the one hand, larger inflation causes greater expiratory prolongation [34], *i.e.* greater V_T increases are accompanied by greater T_E and viceversa (see also fig. 1); on the other hand, a small fall in P_{aCO_2} with exercise measurably influences ventilatory pattern while the addition of CO_2, which prevents hypocapnia, enhances the V_T plateau by increasing T_I [24]. These data could, at least in part, account for our results showing a greater V_T increase and lower T_E decrease with hypercapnia compared with exercise.

iv) part of these data [24] are consistent with the hypothesis of metabolic drive to breathing with exercise [28, 36]. This hypothesis maintains that the hyperpnoea of exercise is completely attributable to the increased delivery of CO_2 to the lungs [28, 36]. Contrary to the metabolic hypothesis, the neurohumoral hypothesis holds that during exercise, ventilation is augmented by neural stimuli, in addition to metabolic stimuli [6, 7]. In this context it should be mentioned that in normal man and patients with COLD, pulmonary congestion during muscular exercise represents a natural stimulus for J receptors [17, 26], with an increase in the inhibitory vagal activity limiting inspiratory volume. On the contrary, the effects of acute hypercapnia on pulmonary circulation are unimportant in normal man [25]. In terms of respiratory timing, ELDRIDGE and GILL-KUMAR [10] have recently shown that stimulation of afferents from limb muscles in cats causes different changes in timing variables, *i.e.* greater frequency and shorter expiratory time than those associated with chemoreceptor afferent stimulation. These findings could provide a further explanation for the increased respiratory frequency and shorter T_E we noted with bicycle exercise.

That mechanical afferences are also involved in sustaining ventilation in patients with COLD during progressive exercise is indicated by the fact that their $P_{0.1}/\dot{V}_{CO_2}$ ratio, an index of the respiratory drive per unit of metabolic load ($\dot{V}_{CO_2}$), is higher than that of normal subjects [30, 32].

In summary, we found that in eucapnic and normoxic patients with COLD, exercise and CO_2

inhalation are associated with dissimilar responses in terms of breathing pattern. Changes in volume threshold for the reflex respiratory switching due to: i) increase in P_{ACO_2} during rebreathing and moderate hypocapnia with exercise, and ii) other mechanical afferent information with exercise, could account for our results.

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RÉSUMÉ: Chez dix malades eucapniques souffrant du syndrome respiratoire obstructif chronique (SROC) nous avons évalué le rythme respiratoire durant l'hypercapnie progressive induite (rebreathing avec CO_2) et l'exercice progressif sur bicyclette ergométrique (30 W/3 min). Les composants temps et volume du cycle respiratoire ont été mesurés pour chaque souffle. Comparé à l'hypercapnie, on a trouvé que l'augmentation de la ventilation ($\dot{V}E$) durant l'exercice est associée à une augmentation moindre du volume respiratoire (V_R) et à une augmentation plus grande de la fréquence respiratoire (f_R). Des graphiques du volume respiratoire (V_R) tracés par rapport aux temps d'inspiration (T_I) et d'expiration (T_E) ont montré une réduction plus marquée à la fois du T_I et du T_E durant l'exercice que pendant l'hypercapnie. L'analyse de la $\dot{V}E$ par rapport au débit (V_R/T_I) et au temps de chronométrage (T_I/T_T) ont démontré que la $\dot{V}E$ augmentait proportionnellement au V_R/T_I à la fois durant l'exercice et l'hypercapnie, tandis que le T_I/T_T ne changeait pas de façon significative. Quand les malades ont été comparés pour une $\dot{V}E$ donnée (28 $l \cdot min^{-1}$), on a trouvé que l'exercice provoquait une augmentation moindre du V_R ($p < 0,05$), une augmentation plus grande du f_R ($P < 0,025$); en revanche, on a constaté que le T_I ($p < 0,025$) et le T_E ($p < 0,021$) étaient plus courts durant l'exercice que pendant l'hypercapnia. Un changement dans le mécanisme d'arrêt au cours de l'exercice et de l'hypercapnie pourrait expliquer nos résultats.