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Research Article

The present study examined the respiratory responses involved in the maintenance of eucapnea during acute airway obstruction in 12 patients with chronic obstructive disease (COPD) and 3 age-matched normal subjects. Acute airway obstruction was produced by application of external flow-resistive loads (2.5 to 30 cm H2O/liter per s) throughout inspiration and expiration while subjects breathed 100% O2. Application of loads of increasing severity caused progressive increases in PCO2 in the patients, but the magnitude of the increase in PCO2 varied substantially between subjects. On a resistance of 10 cm H2O/liter per s, the highest load that could be tolerated by all COPD patients, the increase in PCO2 ranged from 1 to 11 mm Hg, while none of the normal subjects retained CO2. Based on the magnitude of the increase in PCO2 the patients could be divided into two groups: seven subjects whose PCO2 increased by less than or equal to 3 mm Hg (group I) and five subjects whose PCO2 increased by greater than 6 mm Hg (group II). Baseline ventilation and the pattern of breathing were similar in the two groups. During loading group I subjects maintained or increased tidal volume while all group II patients decreased tidal volume (VT). The smaller tidal volume in group II subjects was mainly the result of their shorter inspiratory time as the […]

Mechanisms Underlying CO_2 Retention during Flow-resistive Loading in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT The present study examined the respiratory responses involved in the maintenance of eucapnea during acute airway obstruction in 12 patients with chronic obstructive disease (COPD) and 3 age-matched normal subjects. Acute airway obstruction was produced by application of external flow-resistive loads (2.5 to 30 cm H_2O/liter per s) throughout inspiration and expiration while subjects breathed 100% O_2. Application of loads of increasing severity caused progressive increases in P_{CO_2} in the patients, but the magnitude of the increase in P_{CO_2} varied substantially between subjects. On a resistance of 10 cm H_2O/liter per s, the highest load that could be tolerated by all COPD patients, the increase in P_{CO_2} ranged from 1 to 11 mm Hg, while none of the normal subjects retained CO_2. Based on the magnitude of the increase in P_{CO_2} the patients could be divided into two groups: seven subjects whose P_{CO_2} increased by $\leq$3 mm Hg (group I) and five subjects whose P_{CO_2} increased by >6 mm Hg (group II). Base-line ventilation and the pattern of breathing were similar in the two groups. During loading group I subjects maintained or increased tidal volume while all group II patients decreased tidal volume (V_T). The smaller tidal volume in group II subjects was mainly the result of their shorter inspiratory time as the changes in mean inspiratory flow were similar in the two groups. The magnitude of CO_2 retention during loading was inversely related to the magnitude of the change in V_T ($r = -0.91$) and inspiratory time (T_i) ($r = -0.87$) but only weakly related to the change in ventilation ($r = -0.53$). The changes in P_{CO_2}, V_T, and T_i during loading correlated with the subjects' maximum static inspiratory pressure, which was significantly lower in group II as compared with group I patients. These results indicate that the tidal volume and respiratory timing responses to flow loads are impaired in some patients with COPD. This impairment, presumably due to poor inspiratory muscle function, appears to lead to CO_2 retention during loaded breathing.

INTRODUCTION

Recent studies suggest that in patients with chronic obstructive pulmonary disease (COPD)[1] there may be relationship between the pattern of breathing and the development of CO_2 retention (1–5). The size of the tidal volume appears to be crucial in this regard. Those patients who retain CO_2 have a smaller tidal volume and shorter duration of inspiration than those who do not (1, 2, 5). The abbreviated duration of inspiration is believed to be responsible for the reduced tidal volume, which, as a consequence, decreases alveolar ventilation. A worsening of this pattern of breathing has been observed in patients with COPD during acute respiratory failure due to exacerbation of lung disease (2, 5). In these patients, reduction in the duration of inspiration appears to be related, at least in part, to changes in the mechanics of breathing since the duration of inspiration returns toward normal values as lung function improves.

External resistive loading of ventilation is a frequently used technique to study compensatory responses to airway obstruction. Although the mechan-

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[1] *Abbreviations used in this paper:* COPD, chronic obstructive lung disease; FEV_1, forced expiratory volume is seconds; FRC, functional residual capacity; MIP, maximal inspiratory pressure; Raw, airway resistance; SRaw, specific airway resistance; T_e, expiratory time; T_i, inspiratory time; VC, vital capacity; V_T, tidal volume.

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ical effects of increased resistance to airflow produced externally are not identical to those produced by obstruction of the intrathoracic airways, the responses observed provide useful information. When normal subjects breathe continuously through an external resistance, tidal volume increases while breathing frequency slows (6–11). Hence load compensation, as evaluated by the ability to maintain a normal P_{CO_2}, seems to occur mainly through mechanisms that increase tidal volume rather than breathing rate. In the present study, we applied external resistive loads to patients with COPD to acutely alter respiratory mechanics in controlled fashion and examined the mechanisms involved in tidal volume compensation.

Tidal volume, ventilation, end-tidal CO_2, and occlusion pressure (as an index of the neuromuscular drive to breathe) were measured in each subject over a wide range of external loads. The relative contribution of alterations in respiratory drive and timing to load compensation were assessed by relating changes in P_{CO_2} and tidal volume to changes in occlusion pressure and duration of inspiration, respectively. The importance of chemosensitivity and respiratory mechanics were evaluated by relating the changes in P_{CO_2} and tidal volume observed during loaded breathing to the subject's ventilatory and occlusion pressure responses to hypercapnia and base-line lung function.

METHODS

Studies were performed in 12 patients with COPD who ranged in age from 50 to 70 yr (mean 59 + 5.5 SD yr). These patients had been followed in the pulmonary clinic for more than 2 yr. All had previously demonstrated pulmonary function tests consistent with COPD. All had chronic cough, expectoration, and exertional dyspnea for between 2 and 20 yr. At the time of the study, all of the patients were in a stable clinical state. Bronchodilators were withheld for 14 h before the study. Informed consent was obtained from each subject before the start of the experiments.

Pulmonary function was characterized in the control state by spirometry and plethysmography. Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured with a Collins 13.5-liter spirometer (Warren E. Collins, Inc., Braintree, MA). Functional residual capacity (FRC) and airway resistance (Raw) were measured in a pressure variable body plethysmograph, and the specific resistance (SRaw) was calculated. Maximal static inspiratory pressure (MIP) was measured at FRC with a pressure transducer (Validyne MP45-1±100 cm H_2O, Validyne Engineering Corp., Northridge, CA). Arterial blood samples taken with the patients at rest and breathing room air were analyzed for oxygen, carbon dioxide tension, and pH with a standard blood gas analyzer.

Patients were studied in the seated position while breathing 100% oxygen. Tidal volume (V_T) was recorded by electrical integration of the signal from a pneumotachograph (Fleisch pneumotachograph [O. E. M. Medical, Richmond, VA] 2, 8/1 7320) and a differential pressure transducer (Validyne±2 cm H_2O). The duration of inspiration (T_i) and expiration (T_e) were measured from the mouth pressure signals recorded with a pressure transducer. Occlusion pressure 100 ms after the onset of inspiration performed against closed airways at FRC (P_{100}) was measured as previously reported (8, 11, 12). End-tidal P_{CO_2} was recorded breath by breath by using a rapidly responding infrared CO_2 gas analyzer (Beckman LB-2, Beckman Instruments, Inc., Fullerton, CA).

External resistive loading throughout both inspiration and expiration was produced by introducing fine, wire-mesh screen disks in plexiglass cassettes into the breathing circuit. The number of screens was varied to produce resistances of 2.5, 5, 10, 15, 20, 25, and 30 cm H_2O/liter per s (R 2.5, 5, 10, etc.). The patients attempted to breathe against each resistive load for 10 min. The resistances were applied in rank order in six of the patients, and randomly in the others.

Sensitivity to CO_2 was assessed from the respiratory response to progressive hypercapnia, produced by rebreathing a gas mixture of 7% CO_2 in oxygen after an initial 10-min period breathing 100% oxygen. In nine of the patients CO_2 rebreathing was repeated with a resistance of 10 cm H_2O/liter per s applied during both inspiration and expiration. Responses were assessed by calculating the change in ventilation and occlusion pressure produced by a given change in P_{CO_2} (i.e., $\Delta\dot{V}_E/\Delta P_{CO_2}$ and $\Delta P_{100}/\Delta P_{CO_2}$, respectively). The responses of two to three rebreathing trials were averaged.

In three normal subjects, aged 65–71 yr, the pattern of breathing and P_{CO_2} were recorded in the unloaded state and while breathing on a combined inspiratory and expiratory resistance of 10 cm H_2O/liter per s.

Statistical significance of differences between group mean values was examined by the independent t test. Correlation coefficients for the relationship between variables were obtained by linear regression analysis.

RESULTS

The FEV_1/FVC ranged in the 12 patients from 28 to 63% and averaged 46±13% SD. FRC ranged from 157 to 265% of predicted and Raw ranged from 1.3 to 4.8 cm H_2O/liters per s (mean 3.0±1.2 SD). Maximal static inspiratory pressure, a reflection of the pressure generating ability of the inspiratory muscles, ranged from 42 to 95 cm H_2O (mean 60.6 + 7.8 cm H_2O SD). 11 of the patients were eucapnic (P_{aCO_2} 35–42 mm Hg). P_{aCO_2} in the remaining patient was 52 mm Hg. The arterial P_{O_2} was >60 mm Hg in 11 of the 12 subjects and 47 mm Hg in the remaining subject (70.5 + 9 mm Hg, mean±SD for the whole group).

All 12 subjects were able to breathe on the resistance of 2.5, 5, and 10 cm H_2O/liters per s for 10 min; 11 of the 12 were able to tolerate R15; 8 the R20 load; 5 the R25 load; and only 2 patients were able to breathe on R30 for 10 min. The effect of resistive loading on P_{CO_2} in each patient is shown in Fig. 1. In each of the patients end-tidal P_{CO_2} rose progressively as the load was made more severe. However, the change in P_{CO_2} for a given change in resistance varied substantially between subjects. In seven patients (group I) P_{CO_2} rose modestly (ΔP_{CO_2} = 1.2 mm Hg/Δ 5 cm H_2O/liter per s resistance), while in the other five patients (group II) a much greater degree of CO_2 retention occurred

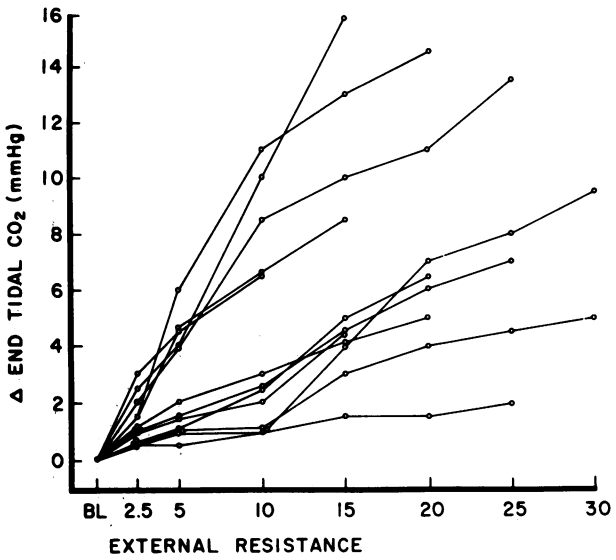

FIGURE 1 Effect of increasing external resistive loads (centimeters H_2O per liter per second) on end-tidal P_{CO_2} in each COPD subject. Data of a single subject are shown at each level of resistance and connected by a single line. BL, base line).

(ΔP_{CO_2} = 4.0 mm Hg/Δ5 cm H_2O/liter per s resistance).

The data obtained in R10, the highest level of load tolerated by all patients for the required 10 min, was analyzed in greater detail. In the seven patients in group I P_{CO_2} increased by 3 mm Hg or less on this load while in the remaining five patients (group II) P_{CO_2} increased from 6.5 to 11 mm Hg. As shown in Table I, base-line ventilation, pattern of breathing, and occlusion pressure were not significantly different in the two groups. However, the groups had a substantially different ventilatory response to R10, as shown in Table II.

Minute ventilation decreased during loading in all patients. However, group II patients who had the greater increase in end-tidal P_{CO_2} had the larger reduction in minute ventilation ($P < 0.05$). This difference was not due to the change in breathing frequency, as group I patients reduced frequency more than group II ($P < 0.05$), but solely to the direction and magnitude of the changes in V_T. All but one patient in group I increased tidal volume, while every patient in group II decreased V_T ($P < 0.01$). The difference in V_T in the two groups was caused by greater prolongation in inspiration in group I subjects since the changes in average inspiratory air flow (V_T/T_i) and P_{100} were similar in both groups. Inspiratory time increased on the average by 0.37 s in group I; but by only 0.11 s in group II patients ($P < 0.01$). The duration of expiration also tended to increase more in group I than in group II subjects. The increase in T_i was proportionally greater than the increase in T_e since the duty cycle of breathing, T_i/T_{tot}, tended to increase more in group I subjects. The difference in T_i/T_{tot} and T_e were not statistically significant, however.

In the three normal subjects studied, end-tidal P_{CO_2} changed 1 mm Hg or less. Ventilation decreased by 0.8 liter/min. Tidal volume increased in all three subjects (mean 0.25 liter) as a result of prolongation in inspiratory time (mean 0.53 s); V_T/T_i decreased slightly (mean −0.03 liters/s).

The magnitude of the change in end-tidal P_{CO_2} on R10 observed in each subject was inversely related to the magnitude of the change in tidal volume as shown in Fig. 2, ($r = -0.91$; $P < 0.01$). Those subjects with the greatest decrease in V_T had the largest increase in P_{CO_2}. Tidal volume compensation during loading appeared in turn to depend on the changes in inspiratory time. As shown in Fig. 3, there was a linear relationship between the change in tidal volume on the load and the magnitude of the prolongation of T_i ($r = 0.89$; P

TABLE I
Base-line Breathing Parameters in Group I and II Patients

	Group I mean±SD	Group II mean±SD	*P
Minute ventilation, *liters/min*	17.7±4.1	17.9±4.1	NS
Tidal volume, *liters*	0.92±0.2	0.91±0.2	NS
Breathing frequency, *breaths/min*	19.3±2.8	19.5±5.0	NS
Inspiratory time, *s*	1.09±0.18	1.18±0.25	NS
Expiratory time, *s*	2.02±0.23	1.91±0.49	NS
Duty cycle, T_i/T_{tot}	0.35±0.03	0.39±0.04	NS
P_{100}, *cm* H_2O	4.3±1.0	3.2±1.2	NS
Mean inspiratory flow, *liters/s*	0.85±0.20	0.77±0.17	NS

* *P* for comparison between groups I and II.

TABLE II

Changes in Breathing Parameters Induced by External Resistive Loading (10 cm H_2O/liter per s) in Group I and II Patients

	Group I mean±SD	Group II mean±SD	P
*ΔEnd-tidal P_{CO_2}, *mm Hg*	2.0±1.0	8.5±2.0	—
ΔMinute ventilation, *liters/min*	−1.76±1.1	−4.0±1.7	<0.05
ΔTidal volume, *liters*	0.12±0.1	−0.14±0.08	<0.01
ΔBreathing frequency, *breaths/min*	−3.7±1.4	−0.09±2.1	<0.05
ΔInspiratory time, *s*	0.37±0.09	0.11±0.09	<0.01
ΔExpiratory time, *s*	0.35±0.25	0.09±0.18	NS
ΔDuty cycle, T_i/T_{tot}	0.05±0.05	0.02±0.02	NS
ΔP_{100}, *cm* H_2O	2.1±1.5	2.3±1.4	NS
ΔMean inspiratory flow, *liters/s*	−0.19±0.08	−0.14±0.07	NS

* Change from base-line value.

< 0.01). Only those subjects who increased inspiratory time by >0.2 s increased tidal volume.

To assess further the factors that might have contributed to the varying tidal volume and inspiratory time responses to the resistive load, the relationship, of the changes in tidal volume and T_i to the subjects' pulmonary function were examined. As shown in Table III, pulmonary function on the average tended to be more abnormal in group II than in group I patients but with the exception of maximum inspiratory pressure and FRC, which were greater in group I, respiratory mechanics were not significantly different in the two groups. As shown in Fig. 4, the magnitude of the change in tidal volume and inspiratory time on R10 were directly related to the subject's base-line MIP. The greater the maximum pressure the greater the increase in inspiratory time and tidal volume. All the patients who decreased V_T on the load had a maximum inspiratory pressure <55 cm H_2O. Apparently, below some critical level, the pressure generating ability of the respiratory muscles seems to be important for load compensation.

To determine whether altered chemosensitivity also contributed to the differing response to the loads in the two groups, occlusion pressure and ventilatory responses to CO_2 in the unloaded state were compared as shown in Table III. Although the ventilatory ($\Delta\dot{V}E/\Delta P_{CO_2}$), tidal volume ($\Delta V_T/\Delta P_{CO_2}$) and occlusion

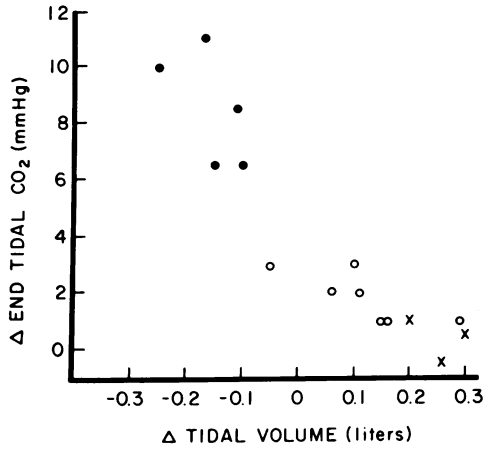

FIGURE 2 Relationship between the change in end-tidal P_{CO_2} and tidal volume on an external resistance of 10 cm H_2O/liter per s (R10). Each symbol represents data from a single subject. O and ● indicate data from group I and group II subjects, respectively. Values obtained in normal subjects are shown by ×. r by least squares regression = −0.91; (P < 0.01).

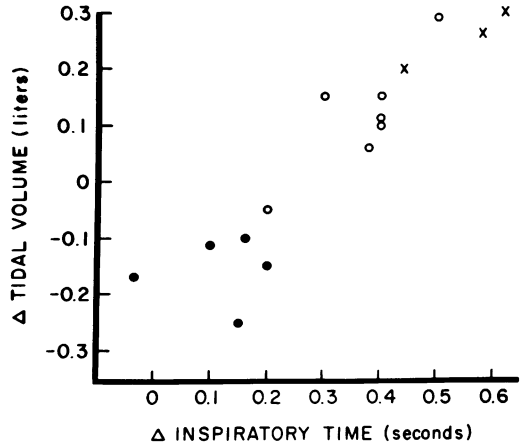

FIGURE 3 Relationship between the change in tidal volume and the change in the duration of inspiration on an external resistance of 10 cm H_2O/liter per s (R10). Symbols as in Fig. 2. r for the relation = 0.89; (P < 0.01).

TABLE III
Comparison of Respiratory Function, Blood Gas Tensions, and Sensitivity to CO_2 in Group I and Group II Patients

	Group I mean±SD	Group II mean±SD	P
Age	58±4.7	60±6.8	NS
FEV_1 % *predicted*	54.4±14.5	42.8±12.8	NS
FEV_1/FVC, %	50.4±11.3	39.2±11.6	NS
Raw, *cm/H_2O per liter per s*	3.3±1.0	2.7±1.1	NS
FRC, % *predicted*	190±24.8	228±28.4	<0.05
MIP, *cm H_2O*	69±16.9	49±4.5	<0.05
PaO_2, *mm Hg*	74±3.3	65.4±12.3	NS
$PaCo_2$, *mm Hg*	38±2.3	41±7.4	NS
$\Delta P_{100}/\Delta PCO_2$, *cm H_2O/mm Hg*	0.61±0.30	0.41±0.23	NS
$\Delta \dot{V}E/\Delta PCO_2$, *liters/min per mm Hg*	1.77±0.63	1.3±0.73	NS
$\Delta VT/\Delta PCO_2$, *ml/mm Hg*	46±13	38±32	NS

pressure ($\Delta P_{100}/\Delta PCO_2$) responses to hypercapnia were greater in group I than in group II, there was considerable overlap between groups so that the differences in the means were not significant. In addition, there was no correlation between these responses and the observed changes in tidal volume with loading. Also the correlation between the change in tidal volume (or PCO_2) induced by loading and maximum inspiratory pressure was not improved by including any of the measurements of hypercapnic sensitivity in a multiregression analysis.

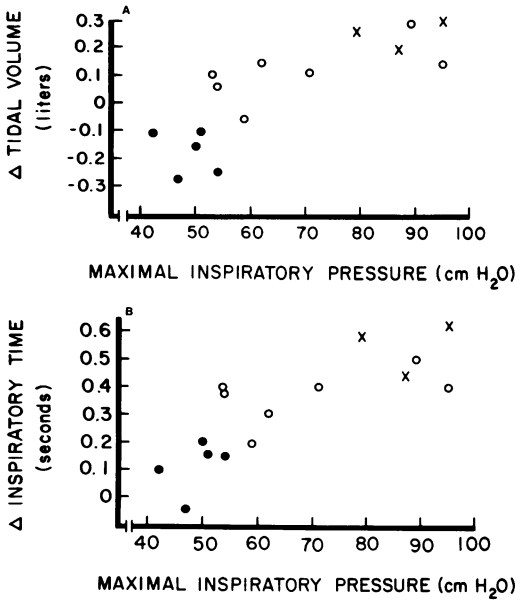

FIGURE 4 Relationship between MIP and the change in tidal volume (A) and T_i (B) in each subject on the R10 load. O and ● indicate group I and group II patients, respectively. Values obtained in normal subjects are shown by ×. *r* for the relationship between tidal volume and inspiratory duration and MIP were 0.79 and 0.70, respectively ($P < 0.05$ for both).

Finally, in order to evaluate the breathing response to resistive loads independent of changes in chemical stimuli, loads (R10) were applied during CO_2 rebreathing. The effect of R10 on ventilatory and occlusion pressure responses to CO_2 rebreathing are shown in Table IV. Loading altered both the ventilatory and the P_{100} responses to hypercapnea by a similar magnitude in both groups. Moreover, when compared at the same PCO_2 (55 mm Hg), ventilation decreased and P_{100} increased by the same amount in groups I and II. However, the effect of the load on the pattern of breathing was different in the two groups. At PCO_2 55 mm Hg tidal volume increased in group I subjects during loading by 0.20 liter but decreased in group II subjects by −0.23 ($P < 0.05$). In group I subjects T_i increased by a significantly greater magnitude than in group II subjects ($P < 0.05$). These results suggest that nonchemical mechanisms activated during loading underlie the greater ability of group I subjects to prolong T_i and maintain V_T.

DISCUSSION

The results of this study indicate that mechanisms that increase tidal volume are critical in maintaining PCO_2 during breathing on external resistive loads and that these compensatory mechanisms are impaired in patients with chronic obstructive pulmonary disease.

In all patients studied, end-tidal PCO_2 could be made to increase with sufficiently large loads and the increase in PCO_2 was linearly related to the load. However, there were large individual variations in the de-

TABLE IV
*Effect of Loading (R10) on Ventilatory Parameters during CO_2 Rebreathing**

	Group I mean±SD	Group II mean±SD	‡P
$\Delta\dot{V}E/\Delta P_{CO_2}$, *liters/min per mm Hg*	−0.63±0.32	−0.71±0.14	NS
$\Delta P_{100}/\Delta P_{CO_2}$, *cm H_2O/mm Hg*	−0.08±0.23	+0.02±0.12	NS
$\dot{V}E$ at P_{CO_2} 55, *liters/min*	−7.3±7.4	−7.7±6.8	NS
P_{100} at P_{CO_2} 55, *cm H_2O*	3.2±6.9	2.1±1.0	NS
V_T at P_{CO_2} 55, *liters*	0.20±0.21	−0.23±0.14	<0.05
T_i at P_{CO_2} 55, *s*	0.43±0.11	0.17±0.06	<0.05

* Data represent the difference between the loaded and control responses.
‡ P for comparison of changes induced by loading between group I and II.

gree to which P_{CO_2} increased. The variability allowed us to study the relative contribution of various factors previously postulated to be important in the development of CO_2 retention in patients with chronic obstructive pulmonary disease.

In this study, there was no correlation between conventional indices of airway obstruction (FEV_1, FEV_1/VC, Raw, SRaw) and the change in tidal volume and P_{CO_2} during loading. Neither was the sensitivity to CO_2, measured as $\Delta P_{100}/\Delta P_{CO_2}$, $\Delta V_E/\Delta P_{CO_2}$ or $\Delta V_T/\Delta P_{CO_2}$ correlated with the change in tidal volume and P_{CO_2} on the load. The apparent absence of an influence of CO_2 chemosensitivity on the magnitude of the increase in P_{CO_2} during loading may be due in part to the small number of subjects studied and/or the limited range of their CO_2 response.

On the other hand, there was an inverse relationship between increases in inspiratory time and tidal volume during loading and the magnitude of CO_2 retention. Both changes in V_T and T_i in turn appeared to depend on the ability to generate a large maximal inspiratory pressure. Failure of group II subjects to increase tidal volume on the load was not due to an absolute limitation in V_T. When loading was performed during CO_2 rebreathing, group II subjects increased V_T with rising P_{CO_2} indicating an ability to increase V_T with appropriate drive.

Previous studies suggest that patients with COPD may lack the normal P_{100} response to inspiratory resistive loads (11). It is unknown whether this decreased pressure production represents an inadequate neural drive or an impairment in inspiratory muscle function in response to normal neural output. In the present study there was no difference in the magnitude of the increase in P_{100} during loading in the two groups despite the differences in the subject's ability to generate pressure.

Increase vagal afferent activity may explain the shorter T_i of hypercapnic patients. Chronically increased airway receptor discharge in patients with chronic bronchitis could shorten T_i (2, 5, 13). However, differences in activity of vagal mechanoreceptors do not seem to explain the differing responses observed in the two groups of the present study. There was no difference in the incidence of bronchitis in group I and group II patients, and no difference in base-line T_i. In addition, at any given flow rate, external increases in resistance to airflow should not alter the magnitude of the pressure drop across the intrathoracic airways or lung and so should not affect irritant or J receptor activity.

Considering the relationship between the magnitude of CO_2 retention and the patients' maximum inspiratory pressure, it is possible that the large increases in P_{CO_2} with loading in group II patients might be related to impaired respiratory muscle performance. The lower maximum inspiratory pressure of group II patients was probably the result of their higher FRC. However, poor nutrition, which has been shown to impair respiratory muscle function and is a common problem in patients with COPD, could also have decreased inspiratory muscle strength (14–16). Decreases in inspiratory muscle strength increase susceptibility to fatigue, which could have occurred while breathing on the resistive loads (17). However, muscle fatigue seems an unlikely explanation for the decrease in tidal volume and greater CO_2 retention in group II patients. At each level of load, the pattern of breathing adopted in the first 1–2 min, was maintained for the remainder of the trial. In none of the patients was a gradual increase in P_{CO_2} observed during the run as might be expected if fatigue had developed. In addition, maximum static inspiratory pressure performed at the end of the period on the load in three subjects was unchanged in two of the subjects and decreased by 10% in the third. On the other hand, since muscle fatigue occurs more readily when the proportion of the respiratory cycle spent in inspiration is increased (18,

19), the smaller T_i increase in group II patients might have occurred in an attempt to prevent fatigue.

The reduced ability to produce inspiratory pressure and the change in the position of the inspiratory muscles as a result of hyperinflation of the thorax may have altered the activity of mechanoreceptors in chest wall structures whose reflex responses affect the duration of the inspiratory neural output. Animal studies have shown that mechanical or electrical stimulation of intercostal muscle spindles in the mid-thoracic segments shortens T_i and decreases phrenic nerve activity (20, 21). Similar effects have been demonstrated recently in man in response to chest wall vibration that selectively increases muscle spindle afferent activity (22). In conscious man, however, load compensation depends to a large extent on higher central nervous system structures, active only during consciousness; the importance of reflex responses in the compensation for external loads appears to be rather slight (7, 23–25).

It has been suggested that minimization of respiratory muscle force during breathing is important in the selection of respiratory frequency (26). Changes in the pattern of breathing on the load may have been based on the need to maintain adequate ventilation while reducing subjective discomfort associated with the effort of breathing. The intensity of the sensations elicited during loaded breathing, therefore, may be of major importance in determining the pattern of breathing when the mechanics of breathing are altered. Respiratory muscle weakness produced by partial curarization has been shown to increase the subjective estimate of the perceived magnitude of any given external load, while diminishing the subject's ability to estimate changes in load (27). An increased sensation of effort on any given load as a result of muscle weakness may explain why our patients tolerated much lower loads than normal subjects (10). Recent studies demonstrate that increasing the duration of inspiration further heightens the intensity of the sensations elicited by external flow loads (28). An attempt to minimize the "sense of effort" (29) may, therefore, explain why patients with COPD with reduced maximum inspiration pressure did not adequately prolong T_i during loading even when CO_2 retention occurred. The above suggests that consciously perceived respiratory sensations elicited during loaded breathing may affect respiratory timing, and, in turn, the pattern of breathing and CO_2 retention in patients with COPD.

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