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### Research Article

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# Mechanisms Underlying CO<sub>2</sub> 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 eu-capnea 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<sub>2</sub>O/liter per s) throughout inspiration and expiration while subjects breathed 100% O<sub>2</sub>. Application of loads of increasing severity caused progressive increases in PCO<sub>2</sub> in the patients, but the magnitude of the increase in PCO<sub>2</sub> varied substantially between subjects. On a resistance of 10 cm H<sub>2</sub>O/liter per s, the highest load that could be tolerated by all COPD patients, the increase in PCO<sub>2</sub> ranged from 1 to 11 mm Hg, while none of the normal subjects retained CO<sub>2</sub>. Based on the magnitude of the increase in PCO<sub>2</sub> the patients could be divided into two groups: seven subjects whose PCO<sub>2</sub> increased by  $\leq 3$  mm Hg (group I) and five subjects whose PCO<sub>2</sub> 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<sub>T</sub>). 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<sub>2</sub> retention during loading was inversely related to the magnitude of the change in V<sub>T</sub> ( $r = -0.91$ ) and inspiratory time (T<sub>i</sub>) ( $r = -0.87$ ) but only weakly related to the change in ventilation ( $r = -0.53$ ). The changes in PCO<sub>2</sub>, V<sub>T</sub>, and T<sub>i</sub> 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<sub>2</sub> retention during loaded breathing.

## INTRODUCTION

Recent studies suggest that in patients with chronic obstructive pulmonary disease (COPD)<sup>1</sup> there may be relationship between the pattern of breathing and the development of CO<sub>2</sub> retention (1-5). The size of the tidal volume appears to be crucial in this regard. Those patients who retain CO<sub>2</sub> 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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<sup>1</sup> Abbreviations used in this paper: COPD, chronic obstructive lung disease; FEV<sub>1</sub>, forced expiratory volume in seconds; FRC, functional residual capacity; MIP, maximal inspiratory pressure; Raw, airway resistance; SRaw, specific airway resistance; T<sub>e</sub>, expiratory time; T<sub>i</sub>, inspiratory time; VC, vital capacity; V<sub>T</sub>, tidal volume.

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  $\text{PCO}_2$ , 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  $\text{CO}_2$ , 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  $\text{PCO}_2$  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  $\text{PCO}_2$  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  $59 \pm 5.5$  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 ( $\text{FEV}_1$ ) 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  $\pm 100$  cm  $\text{H}_2\text{O}$ , 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  $\pm 2$  cm  $\text{H}_2\text{O}$ ). The duration of inspiration ( $T_i$ ) and expiration ( $T_e$ ) were measured from the mouth pressure sig-

nals 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  $\text{PCO}_2$  was recorded breath by breath by using a rapidly responding infrared  $\text{CO}_2$  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  $\text{H}_2\text{O}$ /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  $\text{CO}_2$  was assessed from the respiratory response to progressive hypercapnia, produced by rebreathing a gas mixture of 7%  $\text{CO}_2$  in oxygen after an initial 10-min period breathing 100% oxygen. In nine of the patients  $\text{CO}_2$  rebreathing was repeated with a resistance of 10 cm  $\text{H}_2\text{O}$ /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  $\text{PCO}_2$  (i.e.,  $\Delta V_E/\Delta \text{PCO}_2$  and  $\Delta P_{100}/\Delta \text{PCO}_2$ , respectively). The responses of two to three rebreathing trials were averaged.

In three normal subjects, aged 65–71 yr, the pattern of breathing and  $\text{PCO}_2$  were recorded in the unloaded state and while breathing on a combined inspiratory and expiratory resistance of 10 cm  $\text{H}_2\text{O}$ /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  $\text{FEV}_1/\text{FVC}$  ranged in the 12 patients from 28 to 63% and averaged  $46 \pm 13\%$  SD. FRC ranged from 157 to 265% of predicted and Raw ranged from 1.3 to 4.8 cm  $\text{H}_2\text{O}$ /liters per s (mean  $3.0 \pm 1.2$  SD). Maximal static inspiratory pressure, a reflection of the pressure generating ability of the inspiratory muscles, ranged from 42 to 95 cm  $\text{H}_2\text{O}$  (mean  $60.6 \pm 7.8$  cm  $\text{H}_2\text{O}$  SD). 11 of the patients were eucapnic ( $\text{PaCO}_2$  35–42 mm Hg).  $\text{PaCO}_2$  in the remaining patient was 52 mm Hg. The arterial  $\text{PO}_2$  was  $>60$  mm Hg in 11 of the 12 subjects and 47 mm Hg in the remaining subject ( $70.5 \pm 9$  mm Hg, mean  $\pm$  SD for the whole group).

All 12 subjects were able to breathe on the resistance of 2.5, 5, and 10 cm  $\text{H}_2\text{O}$ /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  $\text{PCO}_2$  in each patient is shown in Fig. 1. In each of the patients end-tidal  $\text{PCO}_2$  rose progressively as the load was made more severe. However, the change in  $\text{PCO}_2$  for a given change in resistance varied substantially between subjects. In seven patients (group I)  $\text{PCO}_2$  rose modestly ( $\Delta \text{PCO}_2 = 1.2$  mm Hg/ $\Delta 5$  cm  $\text{H}_2\text{O}$ /liter per s resistance), while in the other five patients (group II) a much greater degree of  $\text{CO}_2$  retention occurred

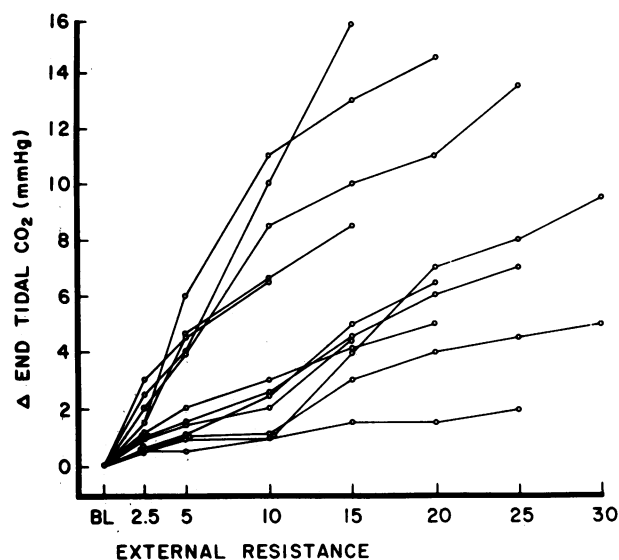


FIGURE 1 Effect of increasing external resistive loads (centimeters H<sub>2</sub>O per liter per second) on end-tidal PCO<sub>2</sub> in each COPD subject. Data of a single subject are shown at each level of resistance and connected by a single line. BL, base line).

( $\Delta$ PCO<sub>2</sub> = 4.0 mm Hg/ $\Delta$ 5 cm H<sub>2</sub>O/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 PCO<sub>2</sub> increased by 3 mm Hg or less on this load while in the remaining five patients (group II) PCO<sub>2</sub> 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 PCO<sub>2</sub> 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 PCO<sub>2</sub> 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 PCO<sub>2</sub> 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 PCO<sub>2</sub>. 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 $\pm$ SD	Group II mean $\pm$ SD	*P
Minute ventilation, liters/min	17.7 $\pm$ 4.1	17.9 $\pm$ 4.1	NS
Tidal volume, liters	0.92 $\pm$ 0.2	0.91 $\pm$ 0.2	NS
Breathing frequency, breaths/min	19.3 $\pm$ 2.8	19.5 $\pm$ 5.0	NS
Inspiratory time, s	1.09 $\pm$ 0.18	1.18 $\pm$ 0.25	NS
Expiratory time, s	2.02 $\pm$ 0.23	1.91 $\pm$ 0.49	NS
Duty cycle, $T_i/T_{tot}$	0.35 $\pm$ 0.03	0.39 $\pm$ 0.04	NS
$P_{100}$ , cm H <sub>2</sub> O	4.3 $\pm$ 1.0	3.2 $\pm$ 1.2	NS
Mean inspiratory flow, liters/s	0.85 $\pm$ 0.20	0.77 $\pm$ 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<sub>2</sub>O/liter per s) in Group I and II Patients

	Group I mean±SD	Group II mean±SD	P
*ΔEnd-tidal PCO <sub>2</sub> , 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 <sub>i</sub> /T <sub>tot</sub>	0.05±0.05	0.02±0.02	NS
ΔP <sub>100</sub> , cm H <sub>2</sub> O	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<sub>i</sub> 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<sub>T</sub> on the load had a maximum inspiratory pressure <55 cm H<sub>2</sub>O. 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<sub>2</sub> in the unloaded state were compared as shown in Table III. Although the ventilatory (ΔV<sub>E</sub>/ΔPCO<sub>2</sub>), tidal volume (ΔV<sub>T</sub>/ΔPCO<sub>2</sub>) and occlusion

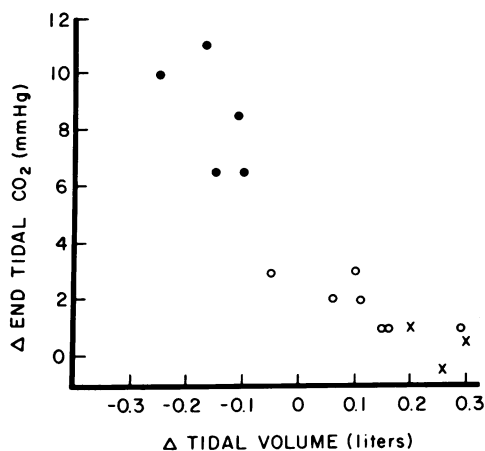


FIGURE 2 Relationship between the change in end-tidal PCO<sub>2</sub> and tidal volume on an external resistance of 10 cm H<sub>2</sub>O/liter per s (R10). Each symbol represents data from a single subject. ○ and ● indicate data from group I and group II subjects, respectively. Values obtained in normal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

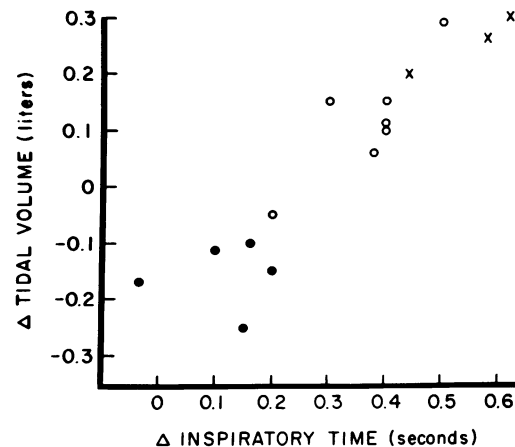


FIGURE 3 Relationship between the change in tidal volume and the change in the duration of inspiration on an external resistance of 10 cm H<sub>2</sub>O/liter per s (R10). Symbols as in Fig. 2. *r* for the relation = 0.89; (*P* < 0.01).

TABLE III  
Comparison of Respiratory Function, Blood Gas Tensions, and Sensitivity to CO<sub>2</sub> 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 <sub>1</sub> % predicted	54.4±14.5	42.8±12.8	NS
FEV <sub>1</sub> /FVC, %	50.4±11.3	39.2±11.6	NS
Raw, cm/H <sub>2</sub> O 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 <sub>2</sub> O	69±16.9	49±4.5	<0.05
PaO <sub>2</sub> , mm Hg	74±3.3	65.4±12.3	NS
PaCO <sub>2</sub> , mm Hg	38±2.3	41±7.4	NS
ΔP <sub>100</sub> /ΔPCO <sub>2</sub> , cm H <sub>2</sub> O/mm Hg	0.61±0.30	0.41±0.23	NS
ΔVE/ΔPCO <sub>2</sub> , liters/min per mm Hg	1.77±0.63	1.3±0.73	NS
ΔVT/ΔPCO <sub>2</sub> , ml/mm Hg	46±13	38±32	NS

pressure (ΔP<sub>100</sub>/ΔPCO<sub>2</sub>) 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<sub>2</sub>) induced by loading and maximum inspiratory pressure was not improved by including any of the measurements of hypercapnic sensitivity in a multiregression analysis.

Finally, in order to evaluate the breathing response to resistive loads independent of changes in chemical stimuli, loads (R10) were applied during CO<sub>2</sub> rebreathing. The effect of R10 on ventilatory and occlusion pressure responses to CO<sub>2</sub> rebreathing are shown in Table IV. Loading altered both the ventilatory and the P<sub>100</sub> responses to hypercapnea by a similar magnitude in both groups. Moreover, when compared at the same PCO<sub>2</sub> (55 mm Hg), ventilation decreased and P<sub>100</sub> 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<sub>2</sub> 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*<sub>i</sub> 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*<sub>i</sub> and maintain *V*<sub>T</sub>.

## DISCUSSION

The results of this study indicate that mechanisms that increase tidal volume are critical in maintaining PCO<sub>2</sub> 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<sub>2</sub> could be made to increase with sufficiently large loads and the increase in PCO<sub>2</sub> was linearly related to the load. However, there were large individual variations in the de-

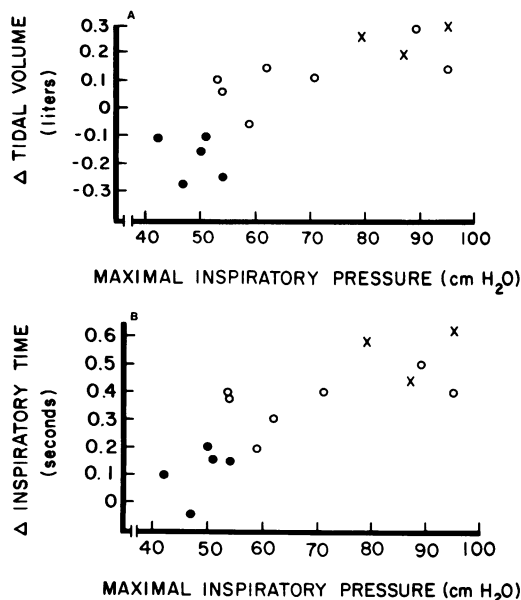


FIGURE 4 Relationship between MIP and the change in tidal volume (A) and *T*<sub>i</sub> (B) in each subject on the R10 load. ○ and ● indicate group I and group II patients, respectively. Values obtained in normal subjects are shown by X. *r* for the relationship between tidal volume and inspiratory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

TABLE IV  
Effect of Loading (R10) on Ventilatory Parameters during CO<sub>2</sub> 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 <sub>2</sub> O/mm Hg	-0.08±0.23	+0.02±0.12	NS
$\dot{V}_E$ at PCO <sub>2</sub> 55, liters/min	-7.3±7.4	-7.7±6.8	NS
P <sub>100</sub> at PCO <sub>2</sub> 55, cm H <sub>2</sub> O	3.2±6.9	2.1±1.0	NS
V <sub>T</sub> at PCO <sub>2</sub> 55, liters	0.20±0.21	-0.23±0.14	<0.05
T <sub>i</sub> at PCO <sub>2</sub> 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 PCO<sub>2</sub> increased. The variability allowed us to study the relative contribution of various factors previously postulated to be important in the development of CO<sub>2</sub> retention in patients with chronic obstructive pulmonary disease.

In this study, there was no correlation between conventional indices of airway obstruction (FEV<sub>1</sub>, FEV<sub>1</sub>/VC, Raw, SRaw) and the change in tidal volume and PCO<sub>2</sub> during loading. Neither was the sensitivity to CO<sub>2</sub>, measured as  $\Delta P_{100}/\Delta P_{CO_2}$ ,  $\Delta\dot{V}_E/\Delta P_{CO_2}$  or  $\Delta V_T/\Delta P_{CO_2}$  correlated with the change in tidal volume and PCO<sub>2</sub> on the load. The apparent absence of an influence of CO<sub>2</sub> chemosensitivity on the magnitude of the increase in PCO<sub>2</sub> during loading may be due in part to the small number of subjects studied and/or the limited range of their CO<sub>2</sub> 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<sub>2</sub> retention. Both changes in V<sub>T</sub> and T<sub>i</sub> 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<sub>T</sub>. When loading was performed during CO<sub>2</sub> rebreathing, group II subjects increased V<sub>T</sub> with rising PCO<sub>2</sub> indicating an ability to increase V<sub>T</sub> with appropriate drive.

Previous studies suggest that patients with COPD may lack the normal P<sub>100</sub> 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<sub>100</sub> 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<sub>i</sub> of hypercapnic patients. Chronically in-

creased airway receptor discharge in patients with chronic bronchitis could shorten T<sub>i</sub> (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<sub>i</sub>. 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<sub>2</sub> retention and the patients' maximum inspiratory pressure, it is possible that the large increases in PCO<sub>2</sub> 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<sub>2</sub> 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 PCO<sub>2</sub> 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  $\text{CO}_2$  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  $\text{CO}_2$  retention in patients with COPD.

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