Effects of Hypercapnia and Inspiratory Flow-Resistive Loading on Respiratory Activity in Chronic Airways Obstruction

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ABSTRACT The respiratory responses to hypercapnia alone and to hypercapnia and flow-resistive loading during inspiration were studied in normal individuals and in eucapnic and hypercapnic patients with chronic airways obstruction. Responses were assessed in terms of minute ventilation and occlusion pressure (mouth pressure during airway occlusion 100 ms after the onset of inspiration).

Ventilatory responses to CO_2 ($\Delta\dot{V}/\Delta PCO_2$) were distinctly subnormal in both groups of patients with airways obstruction. The two groups of patients, however, showed different occlusion pressure responses to CO_2 ($\Delta P_{100}/\Delta PCO_2$): $\Delta P_{100}/\Delta PCO_2$ was normal in the eucapnic patients but subnormal in the hypercapnic patients. Flow-resistive loading during inspiration reduced $\Delta\dot{V}/\Delta PCO_2$ both in normal subjects and in patients with airways obstruction. The occlusion pressure response to CO_2 increased in normal subjects during flow-resistive loading but remained unchanged in both groups of patients with chronic airways obstruction.

These results indicate that while chemosensitivity as determined by $\Delta P_{100}/\Delta PCO_2$ is impaired only in hypercapnic patients with chronic airways obstruction, an acute increase in flow resistance elicits a subnormal increase in respiratory efferent activity in both eucapnic and hypercapnic patients.

INTRODUCTION

The efferent activity of the respiratory neurons is regulated through an interplay between chemical and neuromechanical control systems which produce compensatory changes in breathing whenever the concentrations of inspired gases, metabolic rate, or the mechanical properties of the lung and chest wall are altered (1, 2). Conceivably, defects in either the chemical or the neuromechanical regulatory systems could contribute to the hypoventilation and hypercapnia of chronic airways obstruction.

Chemical control is conventionally evaluated by determining the respiratory response to hypercapnia or hypoxia (3–6). Although there is no standard method for assessing neuromechanical control, the response to a mechanical load imposed on the chest bellows has been used for this purpose. One device for loading has been the addition of an external resistance to airflow. The reactions of normal individuals to these loads have been reported previously (7–9), but the respiratory responses to ventilatory loading in patients with lung disease have not been evaluated. In the present study, both chemical and neuromechanical control mechanisms in normal individuals and in patients with chronic airways obstruction were assessed by determining the changes in respiratory efferent activity during hypercapnia and after increasing the resistance to airflow during hypercapnia.

When airway resistance is increased either experimentally or by disease, ventilation is no longer a satisfactory index of respiratory activity (10). The mouth pressure during airway occlusion 100 ms after the onset of inspiration (P_{100}) has been suggested as a more reliable measure of respiratory neuron efferent activity (11). Also, changes in occlusion pressure during hypercapnia correlate with changes in the electrical activity of the diaphragm and with ventilatory responses to CO_2 in normal individuals (9). Consequently, P_{100} was used in the present study as an index of respiratory neural efferent activity.

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METHODS

Studies were performed in 26 normal subjects who ranged in age from 28 to 79 yr (mean 46±16 yr SD). These individuals had no respiratory symptoms and no abnormalities on physical examination and on chest roentgenogram.

14 patients ranging in age from 49 to 73 yr (mean 59±8 yr SD) with chronic airways obstruction were also studied. The patients with airways obstruction all complained of exertional dyspnea and cough and expectoration on most days of the year for between 7 and 24 yr. All had roentgenographic findings of overinflation of the lung and all had previously demonstrated a reduction in the forced expiratory volume in 1 s ($FEV_{1.0}$). At the time of the study, all the patients were in a stable clinical and functional state. Informed consent was obtained from each subject before the start of the experiments.

Pulmonary function tests were performed which included the determination of functional residual capacity (FRC)[1] with a body plethysmograph (Warren E. Collins, Inc., Braintree, Mass., P-2601), vital capacity, forced expiratory volume in 1 s ($FEV_{1.0}$), and maximum voluntary ventilation with a Collins 13.5-liter spirometer, and maximum inspiratory pressure with a mercury manometer. Arterial blood samples taken with the patients at rest and breathing room air were analyzed for oxygen tension (Pa_{O_2}), carbon dioxide tension (Pa_{CO_2}), and pH with appropriate electrodes (Radiometer Co., Copenhagen, Denmark). Based on Pa_{CO_2}, the patients with chronic airways obstruction were divided into two groups: (*a*) eucapnic—Pa_{CO_2} less than 44 torr, and (*b*) hypercapnic—Pa_{CO_2} greater than 49 torr.

With the subjects in a sitting position, progressive hypercapnia was produced by rebreathing a gas mixture of 7% CO_2 in oxygen after 5 min of 100% oxygen breathing. Thus, hyperoxia was assured throughout the entire 4- to 6-min period of rebreathing. End-tidal CO_2 concentrations were measured with an infrared analyzer (Godart Capnograph, Bilthoven, Holland). After analysis, the sampled gas was returned to the rebreathing bag. Tidal volumes were recorded by electrical integration of the signal from a pneumotachograph (Fleisch pneumotachograph 2, i/a 7320, and Statham differential pressure transducer, PM-5, Statham Instruments Div., Gould Inc., Oxnard, Calif.) which was connected to the rebreathing bag by a high-velocity one-way valve (Hans Rudolph, Inc., Kansas City, Mo., P-308). The resistance of the entire circuit was 1.5 cm H_2O/liter per s at a flow rate of 1.5 liter/s.

During rebreathing, the airway was periodically occluded during expiration by turning a stopcock placed in the inspiratory line. The mouth pressure 100 ms after the onset of the subsequent inspiratory effort (P_{100}) was recorded with a pressure transducer (Statham PM 131 TC). 8–10 occlusions were performed during each rebreathing trial. All tracings were displayed on an oscilloscopic apparatus and recorded on a photosensitive paper (Electronics for Medicine Inc., White Plains, N. Y., DR-8).

Flow-resistive loading during inspiration was achieved by placing fine wire-mesh screen disks in the inspiratory line. Two different loads were used; one had a resistance of 8 cm H_2O/liter per s at a flow rate of 1.5 liter/s (load 1); the other, of 18 cm H_2O/liter per s at a flow rate of 1.5 liter/s (load 2). The resistances of these loads changed less than 5% as the flow rate was increased from 1 liter/s to 2 liter/s.

Mechanical loading is accompanied by changes in ventilation that can, per se, change alveolar and arterial P_{CO_2}. Consequently, the effects of inspiratory flow-resistive loading were assessed during rebreathing so that respiratory responses under control conditions could be compared to those during mechanical loading at the same level of chemical drive.

Minute ventilation was calculated from the average values of the three breaths preceding each occlusion. Ventilatory and occlusion pressure responses to CO_2 were determined from the slope of regression lines calculated by the method of least squares.

For a given level of respiratory efferent neural activity, the occlusion pressure in patients with chronic airways obstruction may be affected by the decrease in the resting length of the inspiratory muscles brought about by the increase in FRC. To evaluate the effect of change in FRC on occlusion pressure, the P_{100} was also determined during rebreathing in five normal subjects after FRC was increased by the addition of an expiratory resistance of 8 cm H_2O/liter per s to the rebreathing circuit.

TABLE I

Pulmonary Function in Patients with Chronic Airways Obstruction

	Eucapnic	Hypercapnic
Number of patients	9	5
Age (*yr*)	60±3	57±3
Vital capacity (% predicted)	72±6	69±4
FRC (% predicted)	134±10	127±8
Forced expiratory volume in 1 s (% predicted)	38±5	42±9
Maximum voluntary ventilation (% predicted)	36±3	41±9
Maximum inspiratory pressure (% predicted)	89±6	80±5
P_aO_2 (*torr*)	74±3	52±1
P_aCO_2 (*torr*)	39±1	55±1

Values are means±SE.

RESULTS

Ventilatory and blood gas data from the eucapnic and hypercapnic groups of patients with chronic airways obstruction are compared in Table I. The ages of the patients in the two groups were not statistically different. In both groups, the vital capacity was abnormally low and the FRC was greater than normal. The forced expiratory volume in 1 s ($FEV_{1.0}$) and the maximum voluntary ventilation were also low. There was, however, no statistically significant difference between the results of these tests in the eucapnic and hypercapnic groups. In contrast, significant differences did exist between the two groups with respect to Pa_{O_2} ($P < 0.001$). Ventilatory and occlusion pressure responses to CO_2 in normal subjects and eucapnic and hypercapnic patients with chronic airways obstruction are shown in Table II.

The mean ventilatory response to progressive hypercapnia ($\Delta\dot{V}/\Delta P_{CO_2}$) in the 26 subjects with normal

[1] *Abbreviation used in this paper*: FRC, functional residual capacity.

TABLE II
Ventilatory and Occlusion Pressure Responses to Hypercapnia

	Subjects			Patients with airways obstruction	
	All normal	Young normal	Old normal	Eucapnic	Hypercapnic
Number of individuals	26	17	9	9	5
Age (*yr*)	44±3	34±1	63±2	60±3	57±3
$\Delta\dot{V}/\Delta P_{CO_2}$ (*liter/min/torr*)	2.4±0.2	2.7±0.3	1.8±0.2	0.7±0.2	0.5±0.2
$\dot{V}$ at P_{CO_2} 60 torr (*liter/min*)	45.2±2.8	47.9±3.8	40.7±3.7	25.7±3.6	19.2±2.7
$\Delta P_{100}/\Delta P_{CO_2}$ (*cm H_2O/torr*)	0.6±0.1	0.7±0.1	0.5±0.1	0.6±0.1	0.2±0.03
P_{100} at P_{CO_2} 60 torr (*cm H_2O*)	9.3±0.8	9.6±1.3	8.8±1.0	13.8±1.3	5.2±0.9

Values are means±SE.

lung function was 2.4 liter/min per torr, and the absolute value for minute ventilation at P_{CO_2} 60 torr was 45.2 liter/min. As shown in the second and third columns of Table II, the normal subjects were divided into two groups on the basis of age. There were 17 young normal subjects ranging in age from 28 to 42 yr and 9 older normal subjects, ranging in age from 54 to 75 yr who comprised a population comparable in age to the patients with airways obstruction. The ventilatory response to CO_2 was decreased in the older normal subjects as compared to the young subjects ($P < 0.025$). Similarly, ventilation at P_{CO_2} 60 torr was decreased in the older normal subjects but this difference was not statistically significant.

In both eucapnic and hypercapnic patients with chronic airways obstruction, $\Delta\dot{V}/\Delta P_{CO_2}$ and ventilation at P_{CO_2} 60 torr were significantly reduced as compared to all normal subjects ($P < 0.005$) and to older normal subjects alone ($P < 0.01$). There were no significant differences between the two groups of patients with airways obstruction in these measures of ventilatory response.

There was a linear relationship between P_{100} and P_{CO_2} during progressive hypercapnia in normal subjects and in patients with chronic airways obstruction. The mean linear correlation coefficient in all rebreathing trials was 0.94±0.02 SE.

Change in occlusion pressure during hypercapnia ($\Delta P_{100}/\Delta P_{CO_2}$) and P_{100} at P_{CO_2} 60 torr were not statistically different in the two groups of normal subjects. Also, $\Delta P_{100}/\Delta P_{CO_2}$ in the eucapnic patients with airways obstruction did not differ from normal, but P_{100} at P_{CO_2} 60 torr was significantly greater in the eucapnic group of patients than in the normal subjects as a whole ($P < 0.01$) and in the older normal subjects alone ($P < 0.01$). Values for $\Delta P_{100}/\Delta P_{CO_2}$ and for P_{100} at P_{CO_2} 60 torr were significantly reduced in the hypercapnic group of patients with airways obstruction as

TABLE III
Effects of Inspiratory Flow-Resistive Loading on Ventilation and Occlusion Pressure during Hypercapnia

	Young normal subjects		Old normal subjects		Patients with airways obstruction			
					Eucapnic		Hypercapnia	
	Load 1	Load 2	Load 1	Load 2	Load 1	Load 2	Load 1	Load 2
Number of individuals	17		9		9		5	
$\Delta\dot{V}/\Delta P_{CO_2}$ (% control)	88±4	81±7	86±7	82±8	84±6	73±6	80±9	59±9
$\Delta P_{100}/\Delta P_{CO_2}$ (% control)	129±9	148±12	132±10	155±11	94±5	96±7	95±11	105±12
P_{100} at P_{CO_2} 60 torr (% control)	125±10	155±9	130±12	156±16	100±5	103±6	95±7	102±10

Values are means±SE.

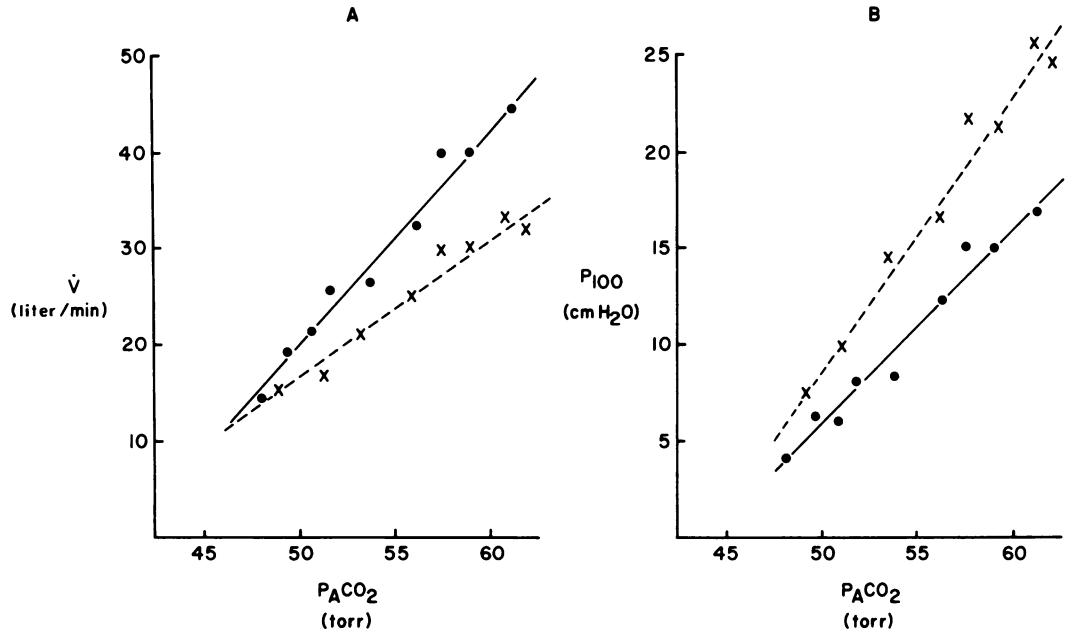

FIGURE 1 The effect of inspiratory flow-resistive loading on (A) the ventilatory response to hypercapnia and (B) the occlusion pressure response to hypercapnia in a normal subject. Closed circles represent control values and X's represent values during inspiratory flow-resistive loading. Flow-resistive loading during inspiration reduced the ventilatory response to hypercapnia but increased the occlusion pressure response to hypercapnia.

compared to normal subjects ($P < 0.05$) and eucapnic patients ($P < 0.01$).

The effects of flow-resistive loading during inspiration are summarized in Table III. Inspiratory flow-resistive loading reduced $\Delta\dot{V}/\Delta PCO_2$ in young and old normal subjects and in both groups of patients with chronic airways obstruction. In normal subjects, inspiratory loading increased P_{100} at PCO_2 60 torr and $\Delta P_{100}/\Delta PCO_2$. The responses of old and young normal subjects were qualitatively the same. A typical response to load 2 in a normal subject is shown in Fig. 1. Increases in P_{100} at PCO_2 60 torr and $\Delta P_{100}/\Delta PCO_2$ did not occur during mechanical loading in patients with airways obstruction. Responses to inspiratory flow-resistive loading (load 2) in a eucapnic patient with airways obstruction is shown in Fig. 2.

Table III also shows that graded inspiratory loads resulted in a progressive fall in $\Delta\dot{V}/\Delta PCO_2$ in all groups. In both young and old normal subjects, but not in patients with chronic airways obstruction, there was a progressive increase in P_{100} at PCO_2 60 torr and $\Delta P_{100}/\Delta PCO_2$ with flow-resistive loads of increasing severity.

The addition of an expiratory resistance to the breathing circuit increased the end-expiratory volume by 322 ±36 ml SE. The added expiratory resistance reduced breathing frequency by prolonging the duration of expiration and lowered $\Delta\dot{V}/\Delta PCO_2$. The expiratory resistance did not affect $\Delta P_{100}/\Delta PCO_2$. Inspiratory flow-resistive loading reduced $\Delta\dot{V}/\Delta PCO_2$ and increased $\Delta P_{100}/\Delta PCO_2$ even during elevations in the end-expiratory position. The effects of changes in FRC on ventilatory and occlusion pressure responses and on the responses to inspiratory flow-resistive loading are shown in Table IV.

DISCUSSION

The present study demonstrates that although ventilatory responses to hypercapnia may be reduced in both eucapnic and hypercapnic individuals with chronic airways obstruction, changes in occlusion pressure with CO_2 are abnormally low only in hypercapnic subjects.

Lourenço and Miranda (12) have previously shown that the increase in diaphragmatic electrical activity during hypercapnia is greater in eucapnic patients with chronic airways obstruction than in hypercapnic patients. The results of the present study with occlusion pressure as an index of respiratory activity are in accord with their findings.

Occlusion pressure. When inspiration is performed against a closed airway, the inspiratory muscles contract nearly isometrically. The resulting occlusion pressure is proportional to respiratory neural efferent activity but the relationship between respiratory activity and occlusion pressure depends on the end-expiratory lung volume and the initial length of the inspiratory

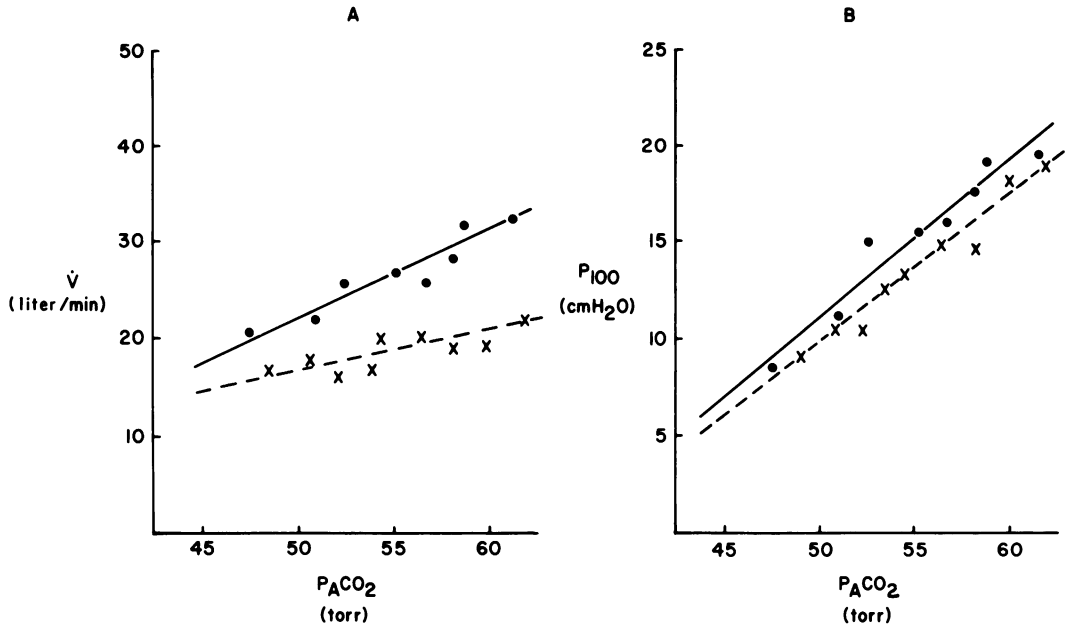

FIGURE 2 The effects of inspiratory flow-resistive loading on (A) the ventilatory response to hypercapnia and (B) the occlusion pressure response to hypercapnia in a patient with chronic airways obstruction and a normal resting arterial P_{CO_2}. Closed circles represent control values and X's represent values during inspiratory flow-resistive loading. Flow-resistive loading reduced the ventilatory response to hypercapnia but did not increase the occlusion pressure response to hypercapnia.

muscles. Rodarte and Hyatt (13) found that CO_2 breathing reduced pulmonary conductance presumably as a result of an increase in laryngeal resistance. This change would be expected to increase the end-expiratory position and, in fact, Garfinkel and Fitzgerald (14) have shown that hypercapnia does increase the resting lung volume of seated subjects. In contrast, Derenne et al. (15) reported that seated men tended to decrease their end-expiratory lung volume during CO_2 rebreathing, and this finding could account for the exponential relationship between P_{CO_2} and P_{100} described by Whitelaw et al. (11) and Kryger et al. (8). We and others (16,17), however, have found linear relationship between P_{CO_2} and P_{100}, and we have been unable to demonstrate any consistent change in FRC in normal subjects during progressive hypercapnia (9). That P_{CO_2} and P_{100} were also linearly related in patients with chronic airways obstruction suggests that significant changes in end-expiratory lung volume probably did not occur in these individuals during progressive hypercapnia. The responses of normal individuals in the present study, after the addition of an expiratory resistance, further indicate that small changes in FRC would have little effect on occlusion pressure.

TABLE IV
Effects of Changes in FRC on Ventilatory and Occlusion Pressure Responses

	$\Delta\dot{V}/\Delta P_{CO_2}$		$\Delta P_{100}/\Delta P_{CO_2}$	
	Normal FRC	Elevated FRC	Normal FRC	Elevated FRC
	liter/min/torr		*cm H_2O/torr*	
Control	3.1±0.6	2.0±0.5	0.5±0.1	0.5±0.1
Inspiratory load	2.4±0.3	1.5±0.3	0.6±0.2	0.7±0.2

Values are means±SE.

The occlusion pressure can be regarded as an index of the force exerted by the inspiratory muscles to produce ventilation. Consequently, in adults with normal lung function, occlusion pressure responses and ventilatory responses to CO_2 tend to correlate (9). This correlation need not exist, for example, if there are large interindividual variations in airway resistance or lung compliance. Although occlusion pressure responses to CO_2 are virtually the same in infants and adults, the ventilatory responses of adults are considerably greater because of their lower airway resistance and higher lung compliance (17). Whereas occlusion pressure reflects only the rate of inspiratory activity, ventilation is affected by both inspiratory events and the duration of expiration. Occlusion pressure and ventilatory responses will not correspond if

the usual relationship between inspiratory and expiratory duration is disturbed. Also, when thoracic impedence is high, ventilatory response will be relatively uninfluenced by variations in occlusion pressure response. It is not surprising, therefore, that despite the larger occlusion pressure responses in the eucapnic patients with airways obstruction as compared to the hypercapnic patients, ventilatory responses differ only slightly.

Effects of age on the responses to hypercapnia. The present study has demonstrated that ventilatory responses to hypercapnia in normal individuals fall with age. These observations are in accord with the findings of Kronenberg and Drage (18). Additionally, the occlusion pressure responses to hypercapnia were lower in older individuals than in young subjects although the differences were not statistically significant. The approximately parallel changes in ventilatory and occlusion pressure responses support the contention that chemoreceptor function may become attenuated with age.

Responses to mechanical loading. Unlike normal individuals, both eucapnic and hypercapnic patients with chronic airways obstruction do not increase respiratory efferent activity when a resistive load is added during inspiration. This impaired response to an artificial increase in flow resistance may indicate that the patient also fails to respond to intrinsic increases in airway resistance. The failure to heighten respiratory drive during acute increases in resistance to airflow would contribute to the development of alveolar hypoventilation during acute bronchospasm or respiratory infection in these patients. The finding that occlusion pressure at P_{CO_2} 60 torr during free rebreathing was greater in eucapnic patients with chronic airways obstruction than in normal subjects may reflect the ability of these patients to respond to more chronic, long-term changes in airway resistance.

An increase in occlusion pressure during mechanical loading has previously been described in normal awake individuals (7–9) and has been demonstrated in unanesthetized goats (19). The observation that changes in occlusion pressure during mechanical loading are abolished in the goat by light anesthesia suggests that the augmented respiratory activity is mediated through supraspinal mechanisms and that awareness of the added resistance is necessary for load compensation (19).

Why patients with chronic airways obstruction fail to increase respiratory neural efferent activity when flow resistance is increased is obscure. Flow-resistive loads of a much smaller magnitude than those used in the present study are readily detected by normal individuals (20). However, the ability to detect added inspiratory resistances may be impaired as a result of the long-standing derangements in lung mechanics in chronic airways obstruction. According to the Weber-Fechner law, the larger the initial level of a stimulus, the greater the change in stimulus level needed to produce a change in sensation (21, 22). The magnitudes of the added inspiratory loads were the same in normal individuals and patients with chronic airways obstruction so that the relative increase in airway resistance was less in the patients with airways obstruction. Although no increase in efferent activity was seen even with the greatest load, an increase in occlusion pressure might have occurred in patients with airways obstruction with an even greater increase in airway resistance.

The failure of P_{100} to increase during mechanical loading in chronic airways obstruction could also be caused by abnormalities in length, configuration, or action of the respiratory muscles. In both normal subjects and patients with airways obstruction, the mouth pressures during airway occlusion even at the highest levels of hypercapnia were considerably less than the maximum static inspiratory pressures. Although maximum inspiratory pressure was slightly reduced in patients with airways obstruction, it seems unlikely that weakness of the inspiratory muscles could account for the failure of P_{100} to increase during mechanical loading.

Hyperinflation of the thorax in chronic airways obstruction and the resulting decrease in resting inspiratory muscle length place the inspiratory muscles at a mechanical disadvantage so that for a given rate of phrenic nerve activity, the transdiaphragmatic pressure developed is less at large lung volumes than at smaller volumes (23). Also, because of the increased radius of curvature of the flattened diaphragm, there is a reduction in the pressure which can be developed by a unit of muscle tension according to the LaPlace law (24, 25). The paradoxical inward movement of the base of the chest during inspiration attributed to the action of the flattened diaphragm may also reduce the change in the transdiaphragmatic pressure for a given change in respiratory neural activity. However, the acute increase in the end-expiratory level, produced in the present study by an expiratory resistance, failed to influence the response to mechanical loading in normal individuals. Nonetheless, elevation in resting lung volume in normal subjects may not be strictly comparable to the alterations in FRC and thoracic cage configuration in chronic airways obstruction, and changes in the length-tension relationship of the inspiratory muscle may still be responsible for the failure of the occlusion pressure to increase during mechanical loading in patients with airway obstruction.

Responses to hypercapnia. The abnormally low response to CO_2 in hypercapnic patients with chronic airways obstruction cannot be attributed solely to mechanical derangements of the ventilatory apparatus

because the hypercapnic patients did not differ from the eucapnic patients with respect to lung volumes, expiratory flow rates, and maximum inspiratory pressures.

Elevations in cerebrospinal fluid bicarbonate concentration found in chronic hypercapnia have been suggested as a cause of reduced CO_2 responsiveness since the hydrogen ion concentration change in the cerebrospinal fluid during acute hypercapnia will be less as a result of a greater degree of buffering (26). However, the increased buffering is unable to prevent considerable rise in hydrogen ion concentration on acute exposure to CO_2 (27).

The poor occlusion pressure response to CO_2 in the hypercapnic patients may simply be caused by an intrinsically blunted response to hypercapnia which existed before the development of the lung disease. In normal individuals there is a wide variation in ventilatory responses to CO_2 but when lung function is normal, arterial P_{CO_2} is maintained in the normal range despite low chemosensitivity (28). Intrinsically low CO_2 responsiveness, operating in conjunction with the mechanical derangements of chronic airways obstruction may, however, produce hypercapnia (29–31).

Occlusion pressure responses to hypercapnia in the eucapnic patients with chronic airways obstruction did not differ from those of normal subjects. One reasonable interpretation of this finding is that CO_2 responsiveness is normal in patients with airways obstruction as long as resting arterial P_{CO_2} is also normal. This conclusion may not be justified because occlusion pressure responses in the patients with airways obstruction depend not only on chemosensitivity, per se, but may also be affected by the shorter resting inspiratory muscle length and the greater airway resistance.

In the past, efforts have been made to separate the respiratory effects of chemical stimulation from those of mechanical loading (12, 32–34). However, it may not be possible to make this distinction in patients with chronic airways obstruction because of the interplay of chemical and nonchemical stimuli on respiratory efferent activity.

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