THE EFFECT OF OBSTRUCTION TO BREATHING ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE

A Thesis

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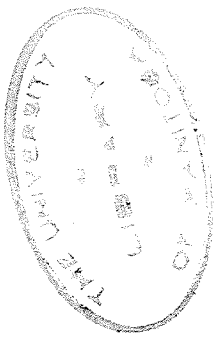

ABSTRACT

Emphysematous patients having an impaired pulmonary ventilation maintain an elevated arterial tension of carbon dioxide and respond to further increases in concentration much less than the normal does to a similar increase. Artificial airway obstruction in the normal is accompanied by a decrease in ventilation and an elevation in arterial carbon dioxide tension. In as much as there is an element of obstruction to breathing in the emphysematous patient, the present study was undertaken to determine whether artificial airway obstruction in the normal subject is accompanied by similar impaired response to carbon dioxide inhalation as that shown by the emphysematous patient.

The maximum ventilatory response to carbon dioxide and maximum breathing capacity were measured before and during various degrees of obstruction to breathing in twenty emphysematous patients and six normal subjects. The normals breathed through three to seven grades of increasing respiratory obstruction. The emphysematous patients were measured before and after their obstruction had been partially relieved by bronchodilator drugs.

There was a good correlation between the maximum breathing capacity and the ventilatory response to carbon dioxide during all states in the normal subjects. Patients with obstructive bronchiolar disease showed a similar correlation before and after procedures which reduced their respiratory obstruction.

A further study on two normals and four emphysematous patients was performed using increasing concentrations of carbon dioxide to obtain the effect of obstruction on carbon dioxide response curves. In the normals, decreased slopes of the response curves were obtained with obstruction, while in the emphysematous patients an increase was obtained in the slope after bronchodilator therapy.

The diminished ventilatory response to carbon dioxide in emphysema can therefore be attributed, at least in part, to the reduced ventilatory capacity due to bronchial obstruction.

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PART I

A REVIEW OF THE LITERATURE

INTRODUCTION

The individual with chronic pulmonary emphysema has a reduced ability to ventilate his lungs. This is reflected in a reduced maximum breathing capacity, a poor respiratory response to exercise and a reduced ventilatory response to the inhalation of carbon dioxide. The majority have an obstructive component to their ventilatory disability which can be improved to varying degrees by treatment.

The purpose of the present study was to determine the effect of respiratory obstruction on the ventilatory response to carbon dioxide inhalation in normals and in patients with pulmonary emphysema. Changes in airway obstruction were accomplished by inserting graded artificial resistances to the circuit of the normal and by the use of bronchodilation in the emphysematous subject.

Part I of this thesis considers previous investigation on this subject, and in addition some of the factors that might condition the investigation reported in Part II.

PATHOPHYSIOLOGY OF PULMONARY EMPHYSEMA.

Chronic pulmonary emphysema occurs in people who have had chronic bronchitis with cough and sputum for many years. It is also found in association with bronchial asthma, silicosis and other chronic pulmonary disease states. There are some cases where it has been said to occur without bronchiolar obstruction or disease.(2) The only characteristic complaint is of dyspnoea; but cough, sputum and wheezing usually accompany the dyspnoea. On physical examination they have fixed thoracic cages with an increase in their relative antero-posterior diameters. The lung fields are hyperresonant, the diaphragms are low and move little. They may be cyanotic and have clubbed fingers.

On pathologic examination the lungs are voluminous and do not collapse or retract when the chest cavity is opened. Bullae formation, chiefly apical in distribution, is usually present, and the lungs feel light and feathery. On microscopic examination the alveoli and terminal bronchioles are dilated and their walls are thinned. There is complete loss or fragmentation of elastic tissue. The stroma appears deficient and the vascularity is reduced. The bronchiolar walls may show atrophic changes, but are more characteristically the site of chronic infection with muscle hypertrophy.

In the functional changes are found the more important features of the disease.(1,2) The important physiologic alteration in the lung volume is a considerable increase in the residual capacity which encroaches

on and reduces the vital capacity. The total lung volume may show an actual increase. The increase in the residual capacity is no doubt related to the loss of elasticity. The chest cage assumes an inspiratory position and there is an accompanying loss in diaphragmatic breathing as the chest cage shifts upwards creating the increased antero-posterior diameter. Because of this fixation of the chest and loss of diaphragmatic breathing, the accessory muscles of respiration, mainly those of the neck, are used to an increasing degree as the disease progresses. Changes on the spirogram are those of incoordination of breathing, prolonged slowing of the expiratory phase, air trapping after deep inspiration and a decrease in the vital capacity and the maximal breathing capacity. Evidence of spasm or oedema of the bronchiolar airways is shown by improvement in the spirographic tracings after the inhalation of a nebulised bronchodilator drug. Related to the poor ventilation and obstruction there is poor intrapulmonary mixing and distribution of gases.(3) The maximum oxygen diffusing capacity(4) is less, but this is probably related to the secondary reduction in the size of the vascular bed. The combination of impaired alveolar ventilation and reduction of available vascular bed interfering with diffusion leads to arterial anoxia and carbon dioxide retention.(1)

THE CONTROL OF RESPIRATION

The rate and depth of respiration upon which is dependent the effective alveolar ventilation are influenced by a number of factors.(5) The most effective stimulus is that of muscular exercise. The mechanism for this response is not understood, but is perhaps related to lactic acid production.(6)

It is known that the respiratory centre is sensitive to small changes in the arterial tension of carbon dioxide and hydrogen ion concentration (C_{H+}). An increase in either one results in hyperventilation. A decrease in carbon dioxide tension results in hypoventilation, but there is less evidence that a decrease in hydrogen ion concentration gives a similar hypoventilation. Changes in the C_{H+} of arterial blood have a compensatory type of action in that an increase in C_{H+} increases ventilation which, by lowering the carbon dioxide tension, tends to decrease the C_{H+}. There is less evidence that a primary fall in C_{H+} leads to a decrease in ventilation resulting in hypercapnea. At one time it was suggested that the carbon dioxide tension exerted its effect through changes in hydrogen ion.(35) Recently Lenson(7) has shown by direct experiments on cerebral ventricles that if the C_{H+} is kept constant, changes in carbon dioxide tension affects respiration, while the reverse had no ventilatory effects within the small ranges employed.

Oxygen tension of arterial blood alters respiration only with high or low concentrations. Haldane(8,9) demonstrated that there was no stimulating action until an inspired oxygen percentage of thirteen was reached. The anoxic stimulus is known to act mainly through the chemoreceptor areas

in the aortic and carotid bodies. Very high concentrations of oxygen also have an excitatory effect.[10] This action is probably caused by a cerebral vasoconstricting action with resulting elevation of carbon dioxide tension in the respiratory centre.

The multiple factor theory of the control of respiration as proposed by Gray[5] best explains the varied mechanisms behind ventilation. Considering that there are many methods of altering the ventilation, he suggests that they do not act independently, but because the action of one may change the stimulus of the other they have an interdependence. The effective ventilation he defines as the algebraic sum of the partial effects of the separate agents.

THE EFFECTS OF ARTIFICIAL AIRWAY OBSTRUCTION

In 1917 Freedman and Jackson[11] noted an elevation in alveolar and arterial blood carbon dioxide in dogs submitted to airway obstruction. They attributed this to a pulmonary circulatory defect caused by the elevated intrabronchial pressure. In 1917 Davies, Haldane and Priestly[12] studied obstructed breathing in normal humans. They used partly closed taps and tins filled with cotton wool giving increasing obstructions over the range of four to twenty-five centimeters of water. With the lesser degrees of obstruction, they obtained a slowing and deepening of respiration. As the obstruction was increased, the ventilation became faster and more shallow with increasingly poor ventilation, increasing hypercapnea and anoxia. The administration of oxygen did not relieve the effect of increased obstruction, but anoxia given by the inhalation of ten per cent oxygen hastened the poorer ventilatory effect. They attributed this to fatigue of the respiratory centre, with anoxia a contributing factor.

Moore and Binger[13] and Baruch[14] studied the differing effects of obstruction in the expiratory and inspiratory phases of respiration in dogs. On expiratory obstruction the respiratory rate was slowed, minute ventilation was decreased and carbon dioxide retention occurred with some anoxia. On relief of the obstruction the respiratory patterns returned to normal. On inspiratory obstruction the respiratory rate went up, minute volume again fell, oxygen administration prevented the anoxia,

but carbon dioxide retention then increased further. When inspiratory obstruction was removed, the dogs did not return to normal, but maintained high ineffective rates and many died of pulmonary oedema. At post mortem the expiratory obstruction dogs showed early emphysema and the inspiratory obstructed dogs showed pulmonary congestion and oedema. They suggested that there was no evidence for fatigue of the respiratory centre, but that the reactions probably were related to hypercapnea. Cain and Otis[15] finding the same raised carbon dioxide tensions in obstructed breathing, suggest that the body tolerates the rise in carbon dioxide in preference to expending the energy required to ventilate off the excess.

No work has been done on the ventilation through obstruction in response to carbon dioxide inhalations.

THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN NORMAL SUBJECTS

Haldane[9] first showed the normal response curve to the inhalation of carbon dioxide. Using a rebreathing technique and measuring the concentration of carbon dioxide and oxygen of the inspired air, he clearly demonstrated that as the percentage of carbon dioxide rose, the amount of air moving in and out of the lungs increased proportionately. He found that there was no ventilatory effect from oxygen until it became less than thirteen per cent.

Similar studies[16-31] using open circuit techniques have shown considerable individual variation, especially in the lower concentrations of inspired carbon dioxide, but they are all in general agreement with Haldane.

It has been noted, however, that the slope of the response curve could be modified by many agents, most of which appear to have a cerebral excitatory action.

Linhard[16] increased the response curve with the administration of strychnine as well as with anoxia. In acidotics with apparently normal ventilatory ability, Peabody[18] obtained an much higher curve than in his normals. However Alexander[30] found a normal response in two of his patients with metabolic acidosis.

Increased curves have been obtained with the anoxia and hyperventilation of altitude.[31] Similar responses have been obtained after twenty-four hours of passive hyperventilation in a body respirator.[25] These authors believed this to be a result of chronic hypocapnea resulting in

an increase in sensitivity of the respiratory centre to carbon dioxide. Shock and Soley, using gases containing carbon dioxide in air and oxygen obtained larger responses with the oxygen mixtures.

Subjects given high doses of salicylates over long periods appear to increase their response according to Tenney and Miller.(32) This they consider a direct sensitising action on the respiratory centre, probably related to the respiratory alkalosis seen in early salicylate poisoning.(33) With the resulting hypocapnea, it is possible that this increased response is similar to the response found in hyperventilation at altitude or in a body respirator.

Depressed responses have been obtained with morphine and chloral hydrate. A decrease was also found in two patients with chronic metabolic alkalosis (Cushing's Disease) for considerable periods after the defect had been remedied.(30)

THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN EMPHYSEMATOUS PATIENTS.

That emphysematous patients had a poor ventilatory response to carbon dioxide was first noted by Scott.[19] Compared to his normal stimulus response curves, his two patients showed the typical low flat curve that has been obtained by subsequent workers.[26-30] He found an increased carbon dioxide content with a normal hydrogen ion concentration in the arterial blood of both patients at rest. From this he reasoned they must have an increased buffering capacity and to this he attributed the poor response. Donald and Christie[26] found the alkali reserve to be within normal limits and suggested that the delayed intrapulmonary mixing, as noted by Darling et al,[34] may be a causative factor. Alexander et al[30] doing similar work related the change in C_{H+} and the increases in carbon dioxide tension to the increments in ventilation and found a similar poor relationship on the inhalation of carbon dioxide in patients with emphysema. As the response to one factor was as poor as the other, they report that there is no evidence for poor buffering power.

More recently, investigators have believed that the elevation in carbon dioxide tensions that occurs chronically or intermittently due to the poor ventilatory ability of subjects with emphysema, resulted in a decrease in sensitivity of the respiratory centre. Prince and Westlake[27] related the rise in tension of carbon dioxide to the rise in ventilation and found this grossly impaired in emphysematous patients compared to their

normals. In ascribing this to the above mentioned decrease in sensitivity, they are supported by Tenney.[28] Obtaining similar results he gave three patients a carbonic anhydrase inhibitor (Diamox). This lowered their carbon dioxide tension and they subsequently gave more normal response curves. This finding was not confirmed by Fishman[29] who believed the decrease in sensitivity to be irreversible. Further evidence has been obtained from the response curves of patients with metabolic alkalosis.[28-30] These patients having chronic carbon dioxide retention for long periods also had low response curves.

The later investigators all report a decrease in ventilatory ability as shown by a reduction in maximum breathing capacity. In considering the possibility that diminished response might be due to this defect, they have believed that the level of the maximum breathing capacity was sufficient to allow ventilation as predicted from the normal response to carbon dioxide.

To date, no attempt has been made to relate the reduction in maximum breathing capacity with the reduction in ventilatory response to carbon dioxide.

SUMMARY

Carbon dioxide is a strong stimulus to ventilation, and in health the body contrives to maintain a carbon dioxide level within fairly narrow limits. Artificial airway obstruction in the normal is accompanied by a decrease in ventilation and an elevation in arterial carbon dioxide tension. The emphysematous patients with an impaired ventilatory ability maintains an elevated arterial tension of carbon dioxide and responds to further increases in concentration of carbon dioxide much less than the normal does to a similar increase.

In as much as there is an element of obstruction to breathing in the emphysematous patient, the present study was undertaken in an attempt to determine whether artificial airway obstruction in the normal subject is accompanied by similar impaired response to carbon dioxide inhalation as that shown by the emphysematous patient.

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PART II

THE EFFECT OF OBSTRUCTION IN BREATHING ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE

INTRODUCTION

In patients with pulmonary emphysema the increase in minute ventilation in response to the inhalation of CO_2 is much less than in normal individuals (1-4). This has been attributed to a decrease in the sensitivity of the respiratory centre, perhaps the result of increased buffer base in chronic compensated respiratory acidosis. While the ventilatory response to CO_2 will obviously be limited by a restricted ventilatory capacity, most workers have felt that this defect could not account for the diminished response (1-5).

The present report is an attempt to evaluate the relationship between the ventilatory capacity and the response to CO_2 on normal subjects and patients with pulmonary emphysema. In normal subjects the ventilatory capacity was reduced by artificial airway obstruction, while in the emphysematous patients the ventilatory capacity was increased by the administration of a nebulised bronchodilator. The effect of these alterations in ventilatory capacity on the maximum ventilatory response to CO_2 and on the CO_2 stimulus-response curves was then determined.

METHODS

Six normals, ranging in age between 20-35 and whose maximum breathing capacities ranged between 100-200 litres/min., and 24 emphysematous patients, served as subjects. The diagnosis of emphysema was made clinically and was supported by spirographic evidence of a reduction of maximum breathing capacity and obstruction to expiratory outflow. (Table I).

The vital capacity and maximum breathing capacity were measured on a Collins Respirometer with valves and CO_2 absorber removed. The maximum breathing capacity was performed for 12 seconds, and the maximum of several estimations was taken and corrected to body temperature.

The maximum responses to carbon dioxide were measured with the same spirometer which was initially filled with 7% CO_2 and 93% oxygen. The subjects were instructed to expire maximally before commencing, in an attempt to reduce the effect of delayed mixing. They rebreathed the mixture for as long as possible, five minutes or longer, and the ventilation during the last minute was taken as their maximal response to CO_2.

It is recognized that there is a large subjective component in this procedure. Alveolar gas samples were therefore obtained during the resting states and at the termination of the procedure, and were analysed in a Scholander Micro Gas Analyser. The final alveolar CO_2 tensions were within 5 mHg. of each other, indicating that there was a similar stimulus to respiration (pCO_2) in all cases. Also, the alveolar oxygen

tension at the end of CO_2 breathing was over 200 mmHg. indicating that anoxia played no part in the respiratory response.

Ventilatory response curves were determined while breathing 3%, 5.5%, and 7.8% CO_2 in air. Subjects breathed each gas for 13 minutes and the ventilation was measured by collecting the expired gas in a Tissot spirometer for the last three minutes. Ventilation was expressed as the alveolar ventilation ratio as described by Gray.(6) This is the ratio of the alveolar ventilation while breathing the various CO_2 mixtures, to the resting alveolar ventilation. Alveolar ventilation was calculated from the minute ventilation, respiratory rate and the dead space of the mouthpiece apparatus (50 cc.), assuming a dead space of 150 cc. in the normal subjects and 200 cc. in the emphysematous subjects.

All subjects were studied in the sitting position. The maximum breathing capacity and maximum ventilatory response to CO_2 were determined in emphysematous patients (Subjects 1-20) at rest, and after the inhalation of nebulised bronchodilator (Vaponefrin (R)) in 15 of these subjects. The maximum breathing capacity and maximum ventilatory response to CO_2 were determined on separate occasions in the normal subjects at rest and while breathing through three to seven increasing grades of artificial airway obstruction composed of cylinders containing porous bronze discs.

The CO_2 response curve was determined in four emphysematous patients (Subjects 21-24) before and after the inhalation of the nebulised bronchodilator. Similar measurements were made on two normal subjects at rest and while breathing through a single resistance.

Normal subjects breathed through each resistance for five minutes before any measurements were made.

TABLE I.

VENTILATORY FUNCTION IN 24 MALE PATIENTS WITH PULMONARY EMPHYSEMA

BEFORE AND AFTER BRONCHODILATOR

ject	Age (yrs)	Height (cm)	Duration of Dyspnea (yrs)	Vital Capacity (cc)			Maximum Breathing Capacity (L/Min.)		
				Predicted	Observed Before B.D.	Observed After B.D.	Predicted	Observed Before B.D.	Observed After B.D.
	59	174	10	3800	1390	1700	98	17	23
	57	172	8	3670	1475	2150	92	16	22
	64	164	2	3220	3300	3140	82	92	99
	49	179	13	3980	3300	3140	109	61	78
	41	178	11	4090	4150	4100	116	65	84
	27	177	1	4300	4650	4610	129	79	90
	31	177	1.5	4200	1640	2780	124	26	57
	71	167	15	3250	1360	1690	79	20	20
	26	169	2.5	4000	4200	5000	123	107	138
	59	178	4	3890	4140	4560	101	103	134
	52	174	16	3710	4160	4540	101	67	84
	74	181	13	3640	3600	4000	86	76	109
	35	189	10	4550	5630	6100	130	86	130
	71	177	2	3580	2500	4360	86	32	69
	55	184	12	4050	2410	1600	107	26	29
	71	162	2	3050	1860	2110	75	40	54
	39	171	3	3900	1400	1430	113	39	42
	62	160	10	3100	865	1250	81	10	16
	59	178	12	3800	2460	2380	99	26	34
	40	175	11	4000	4690	4710	114	141	169
	57	171	8	3550	1900	2950	94	20	32
	74	167	10	3150	2815	3370	75	26	37
	71	177	2	3500	2500	4400	86	31	69
	71	161	2	3000	1800	2110	75	40	54

RESULTS

MAXIMUM VENTILATORY RESPONSE TO CO_2.

The maximum ventilatory response to CO_2 in the 6 normal and 20 emphysematous subjects is shown in Fig. 1. It can be seen that the emphysematous patients did not achieve as high a ventilation in response to the inhalation of CO_2 as did the normal subjects.

In Fig. 2 the effects of increasing airway obstruction on the maximum breathing capacity and the maximum ventilatory response to CO_2 are shown in the six normal subjects. It can be seen that, as the maximum breathing capacity was reduced due to increasing airway resistance, the maximum ventilatory response to CO_2 was also reduced.

In Fig. 3 the relationship between the maximum breathing capacity and the maximum ventilation with CO_2 in the 20 emphysematous patients is shown. It can be seen that this relationship in the emphysematous subjects was similar to that found when normal subjects breathed through an obstruction.

The effect of nebulised bronchodilators on the relationship between maximum breathing capacity and ventilatory response to CO_2 is shown in 15 patients in Fig. 4. It can be seen that as the airway obstruction was reduced in each subject, as indicated by an increase in maximum breathing capacity, there was a concomitant increase in the maximum ventilation achieved with CO_2.

CO_2 STIMULUS-RESPONSE CURVES

The CO_2 stimulus-response curves in two normal and four emphysematous subjects are shown in Fig. 5. It can be seen that the slopes of the response curves are much lower than normal in the emphysematous subjects. It can also be seen that when normal subjects breathed through an obstruction, reducing the ventilatory capacity to the level of the emphysematous patients as indicated by the maximum breathing capacity, the slopes of the CO_2 response curves became similar to that of the emphysematous patients. In addition, it is noted that the slope of the response curve was increased in the four emphysematous subjects when the ventilatory capacity was increased by the inhalation of a nebulized bronchodilator.

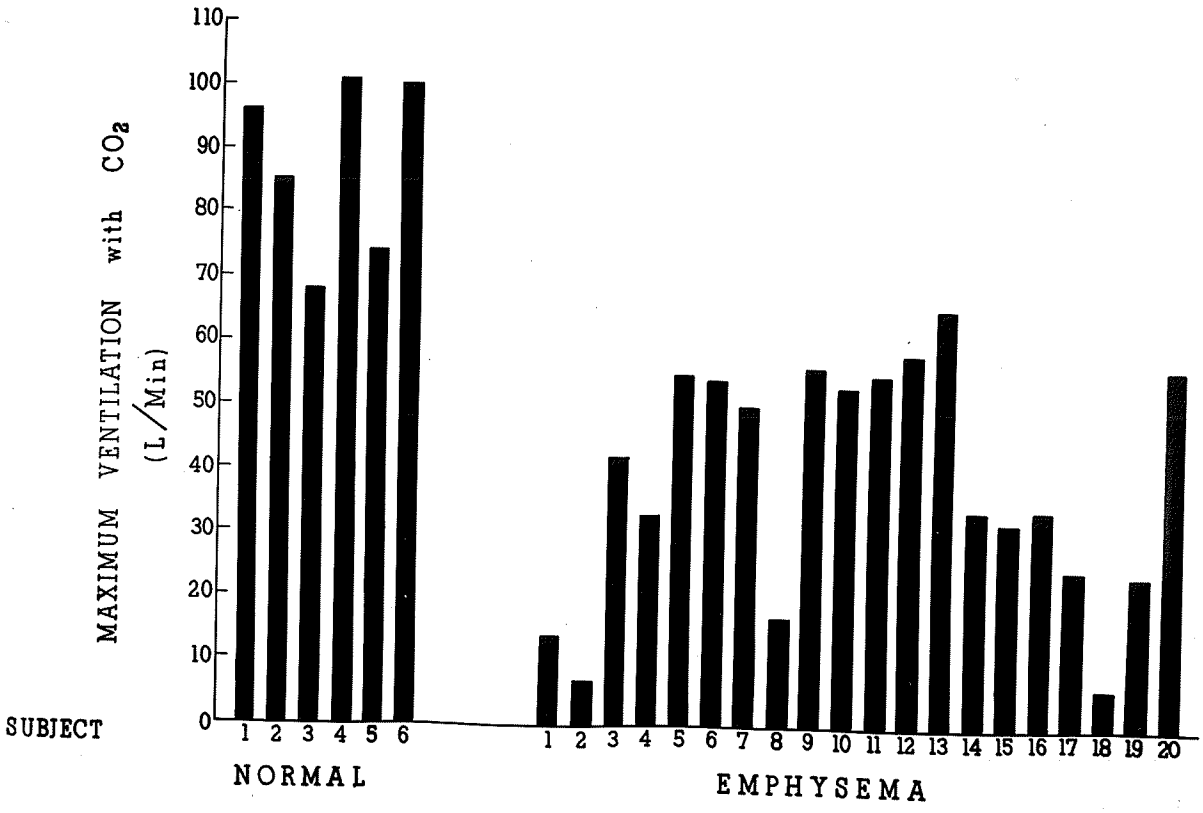

Figure 1. The maximum ventilatory response to carbon dioxide in 6 normal subjects and 20 patients with pulmonary emphysema.

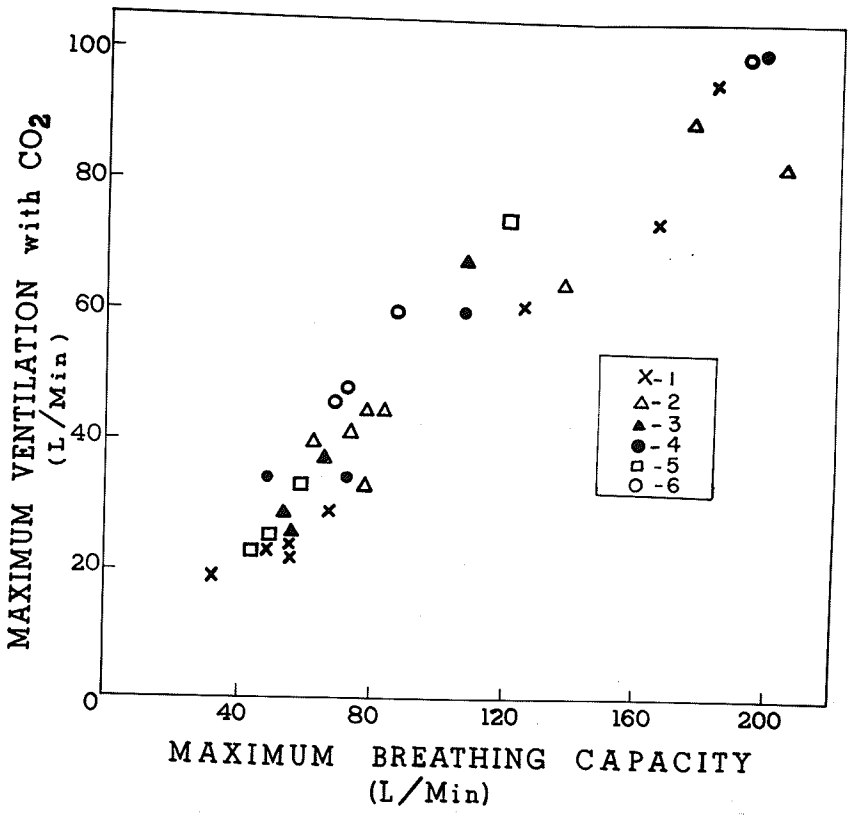

Figure 2. The effect of increasing grades of artificial airway obstruction on the ventilatory capacity and maximum ventilatory response to carbon dioxide in 6 normal individuals.

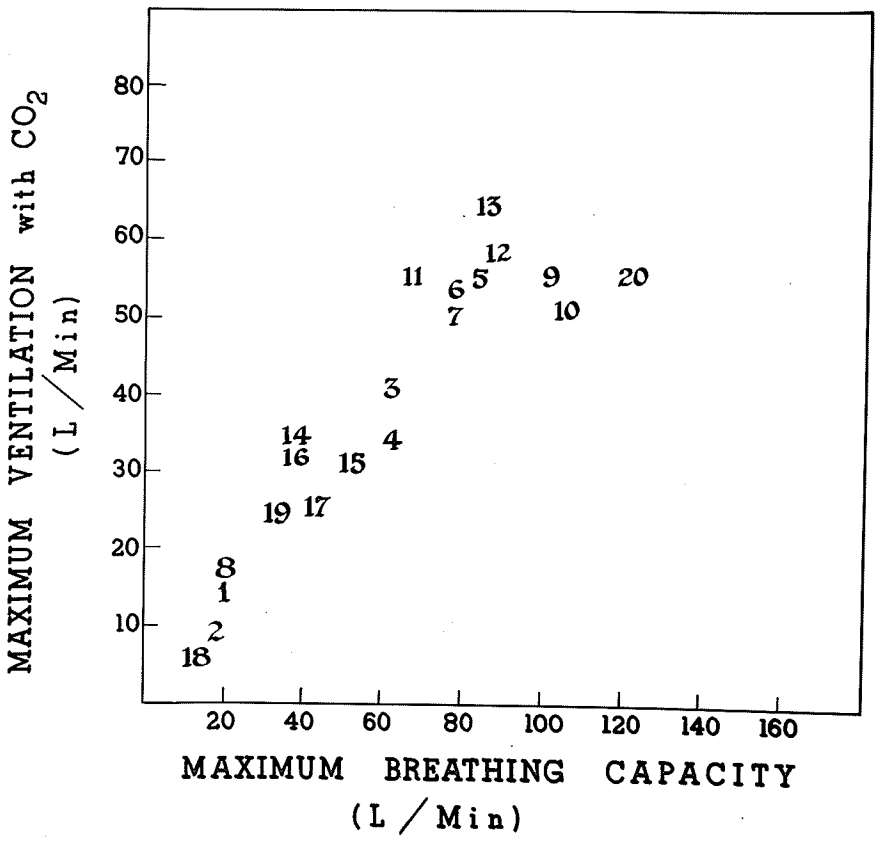

Figure 3. The relationship between the maximum ventilatory response to carbon dioxide and the ventilatory capacity in 20 patients with pulmonary emphysema.

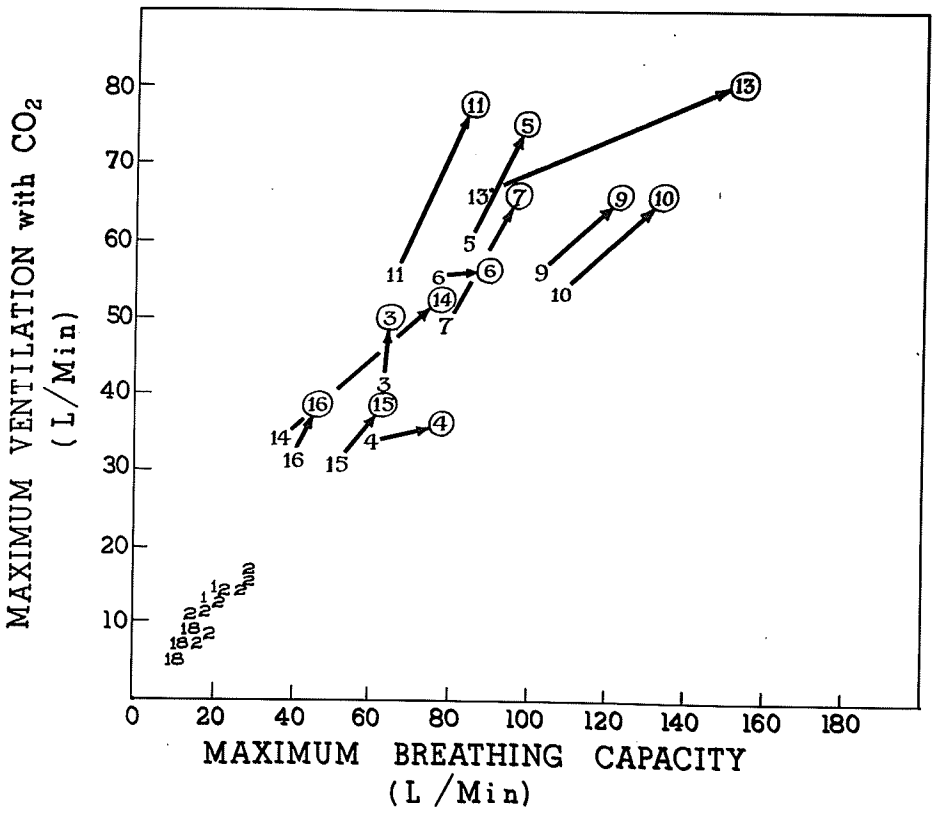

Figure 4. The effect of partial alleviation of airway obstruction on the ventilatory capacity and the maximum ventilatory response to carbon dioxide in 15 patients with pulmonary emphysema.

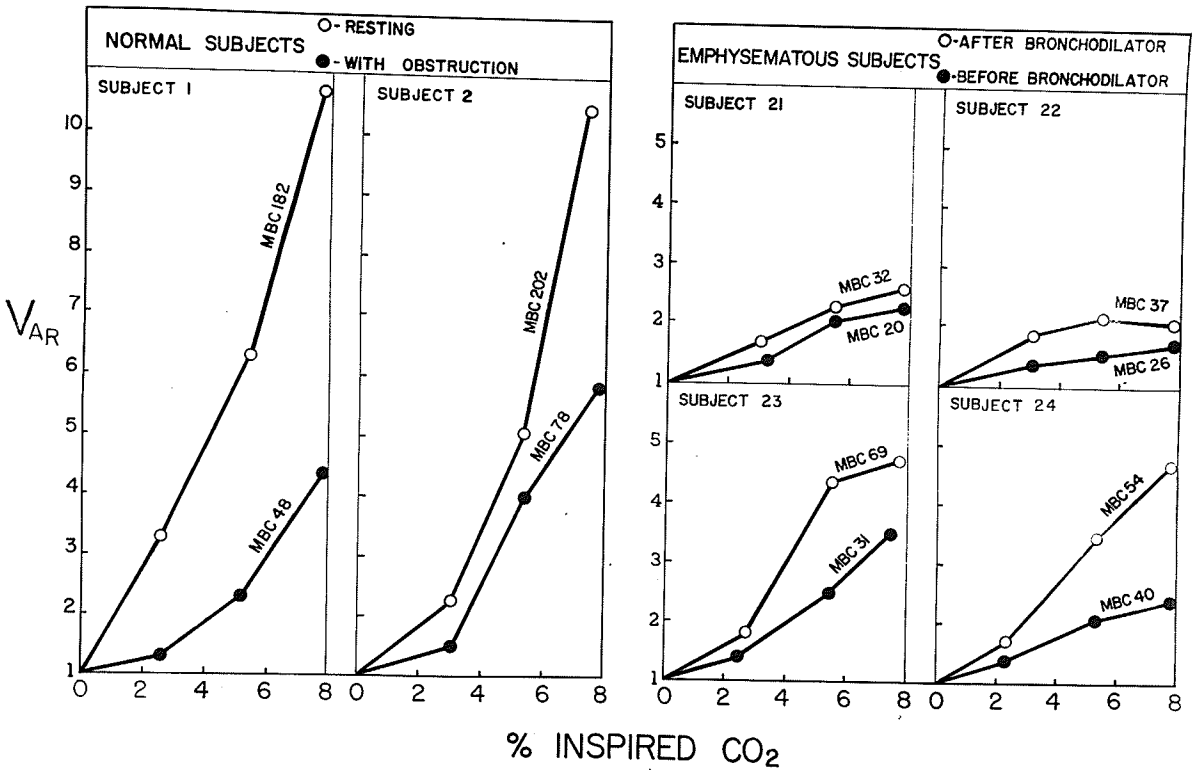

Figure 5. The carbon dioxide response curves in 2 normal subjects and 4 patients with pulmonary emphysema. Note the effect of increased airway obstruction in normal subjects and decreased airway obstruction in the abnormal subjects.

DISCUSSION

The data reported in this study show that the introduction of an airway obstruction in normal subjects resulted in a fall in the maximum breathing capacity and a concomitant decrease in the maximum ventilatory response to CO_2. In the emphysematous subjects a reduction in the airway obstruction resulted in an increased maximum breathing capacity and a concomitant increase in the maximum ventilatory response to CO_2. This indicates that the reduced ventilatory capacity in itself may play a large part in the diminished ventilatory response to CO_2 in patients with pulmonary emphysema.

This conclusion is further substantiated by the results reported in regard to the CO_2 stimulus-response curves. These show that the slope of the response curve was markedly affected by the ventilatory capacity. When the ventilatory capacity of normal subjects was artificially lowered to the level of the emphysematous subjects, the stimulus-response curves obtained were similar to those of the emphysematous patients.

Tenney[5] and Alexander[1] have also demonstrated a reduced CO_2 stimulus-response curve in patients with pulmonary emphysema and have attributed this to a diminished sensitivity of the medullary respiratory centre. Tenney felt supported in this view because the administration of Diamox(R) increased the slope of the CO_2 response curve; but it is possible that the action of Diamox was due to a reduction of pulmonary congestion.

It is concluded that emphysematous subjects show a diminished

ventilatory response to CO_2 due in large part to a reduced ventilatory capacity. This is presumably related to the increased work of breathing required to overcome bronchial obstruction (7). While the restricted ventilatory capacity may explain the diminished ventilatory response to CO_2, these results do not necessarily clarify the altered role of oxygen and carbon dioxide in the control of respiration in patients with pulmonary emphysema.

SUMMARY

1. The maximum ventilatory response to CO_2 was lower in 20 emphysematous subjects than in six normal subjects, while the CO_2 response curve was lower in four emphysematous patients than in two normal subjects.

2. In normal subjects artificial obstruction to respiration resulted in a fall in maximum breathing capacity, in the ventilatory response to CO_2 and in a diminished CO_2 response curve.

3. In emphysematous patients alleviation of airway obstruction resulted in an increase in maximum breathing capacity, in the ventilatory response to CO_2 and in the slope of the CO_2 response curve.

4. No difference in the response to inhaled CO_2 was found between patients with obstructive disease and normals with artificial airway obstruction.

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