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Research Article

THE EFFECT OF OBSTRUCTION TO BREATHING ON THE VENTILATORY RESPONSE TO CO_2 [1]

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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 center, 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 in 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 nebulized 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 normal subjects, 5 males and 1 female, ranging in age between 20 and 35 and whose maximum breathing capacities ranged between 100 to 200 liters per 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 9 liter 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 per cent CO_2 and 93 per cent oxygen. The subjects were instructed to expire maximally before commencing, in an attempt to reduce the effect of delayed mixing. They rebreathed the mixture to the end of their tolerance, more than five minutes in all cases, and the ventilation during the last minute was taken as their maximal response to CO_2.

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 to 20) at rest, and after the inhalation of nebulized bronchodilator (Vaponefrin®) 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 inspiring and expiring through three to seven increasing grades of artificial airway obstruction composed of cylinders containing porous bronze discs.

It is recognized that there is a large subjective component in this procedure. Alveolar gas samples were therefore obtained by the Haldane-Priestly technique during the resting states and at the termination of the procedure, and were analyzed in a Scholander Micro Gas Analyzer. The final alveolar CO_2 tensions were within 5 mm. Hg of each other in any one normal subject, indicating that there was a similar stimulus to respiration (pCO_2) while breathing through all resistances. In all subjects the final alveolar pCO_2 was between 65 to 80 mm. Hg. Also, the alveolar oxygen tension at the end of CO_2 breathing was over 200 mm. Hg, indicating that anoxia played no part in the respiratory response.

Ventilatory response curves were determined while breathing 3 per cent, 5.5 per cent and 7.8 per cent 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, the dead space of the mouthpiece apparatus (50 cc.) and the dead space of the added resistance (50

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TABLE I

Ventilatory function in 24 male patients with pulmonary emphysema before and after bronchodilator

				Vital capacity (cc.)			Maximum breathing capacity (L./min.)		
					Observed			Observed	
Subj. No.	Age yrs.	Ht. cm.	Duration of dyspnea yrs.	Predicted	Before B.D.	After B.D.	Predicted	Before B.D.	After B.D.
1	59	174	10	3,800	1,390	1,700	98	17	23
2	57	172	8	3,670	1,475	2,150	92	16	22
3	64	164	2	3,220	3,300	3,140	82	62	69
4	49	179	13	3,980	3,300	3,140	109	61	78
5	41	178	11	4,090	4,150	4,100	116	85	98
6	27	177	1	4,300	4,650	4,610	129	79	90
7	31	177	1.5	4,200	1,640	2,780	124	76	97
8	71	167	15	3,250	1,360	1,690	79	20	20
9	26	169	2.5	4,000	4,200	5,000	123	102	138
10	59	178	4	3,890	4,140	4,560	101	103	134
11	52	174	16	3,710	4,160	4,540	101	67	84
12	74	181	13	3,640	3,600	4,000	86	86	109
13	35	189	10	4,550	5,630	6,100	130	86	130
14	71	177	2	3,580	2,500	4,360	86	32	69
15	55	184	12	4,050	2,410	1,600	107	46	59
16	71	162	2	3,050	1,860	2,110	75	40	54
17	39	171	3	3,900	1,400	1,430	113	39	42
18	62	160	10	3,100	865	1,250	81	10	16
19	59	178	12	3,800	2,460	2,380	99	26	34
20	40	175	11	4,000	4,690	4,710	114	131	169
21	57	171	8	3,550	1,900	2,950	94	20	32
22	74	167	10	3,150	2,815	3,370	75	26	37
23	71	177	2	3,500	2,500	4,400	86	31	69
24	71	161	2	3,000	1,800	2,110	75	40	54

cc.), assuming a dead space of 150 cc. in the normal subjects and 200 cc. in the emphysematous subjects. The range of anticipated error in the calculated alveolar ventilation ratio imposed by an error in estimated dead space volume of ± 50 cc. would be ± 0.15.

The CO_2 response curve was determined in four emphysematous patients (subjects 21 to 24) before and after the inhalation of the nebulized 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.

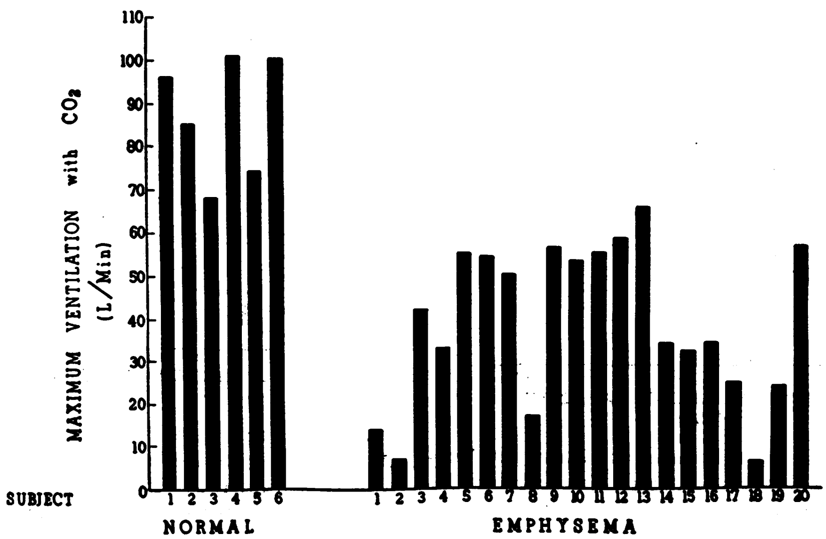

FIG. 1. THE MAXIMUM VENTILATORY RESPONSE TO CARBON DIOXIDE IN 6 NORMAL SUBJECTS AND 20 PATIENTS WITH PULMONARY EMPHYSEMA

RESULTS

Maximum ventilatory response to CO_2

The maximum ventilatory response to CO_2 in the six normal and 20 emphysematous subjects is shown in Figure 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 Figure 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 Figure 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 nebulized bronchodilators on the relationship between maximum breathing capacity and ventilatory response to CO_2 is shown in 15 patients in Figure 4. It can be seen that as the

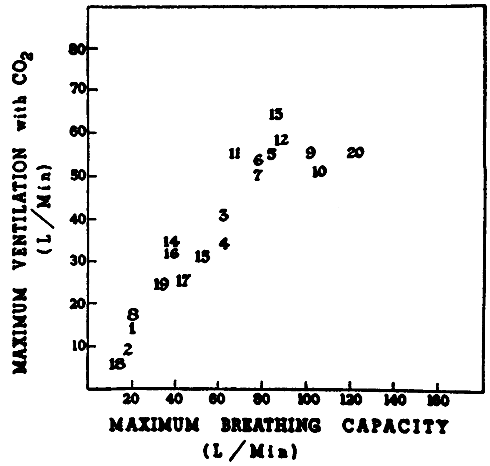

FIG. 3. THE RELATIONSHIP BETWEEN THE MAXIMUM VENTILATORY RESPONSE TO CARBON DIOXIDE AND THE VENTILATORY CAPACITY IN 20 PATIENTS WITH PULMONARY EMPHYSEMA

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 Figure 5. It can be seen that the mean slopes of the response curves are much lower than normal

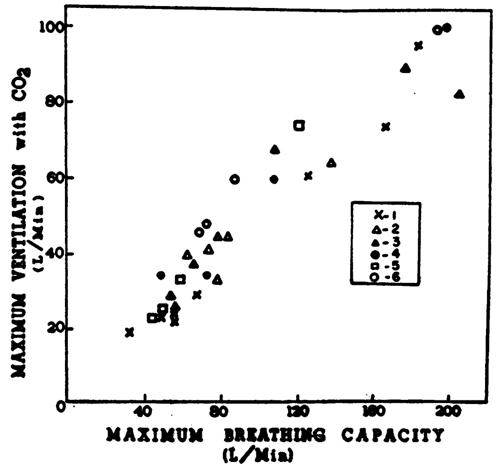

FIG. 2. THE EFFECT OF INCREASING GRADES OF ARTIFICIAL AIRWAY OBSTRUCTION ON THE VENTILATORY CAPACITY AND MAXIMUM VENTILATORY RESPONSE TO CARBON DIOXIDE IN 6 NORMAL INDIVIDUALS

Symbols are individuals and different points represent different resistances.

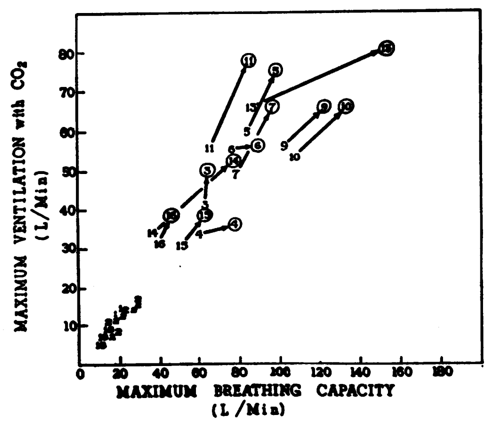

FIG. 4. THE EFFECT OF PARTIAL ALLEVIATION OF AIRWAY OBSTRUCTION ON THE VENTILATORY CAPACITY AND THE MAXIMUM VENTILATORY RESPONSE TO CARBON DIOXIDE IN 15 PATIENTS WITH PULMONARY EMPHYSEMA

Daily measurements were made on subjects 2 and 18 during intensive therapy directed at increasing the ventilatory capacity.

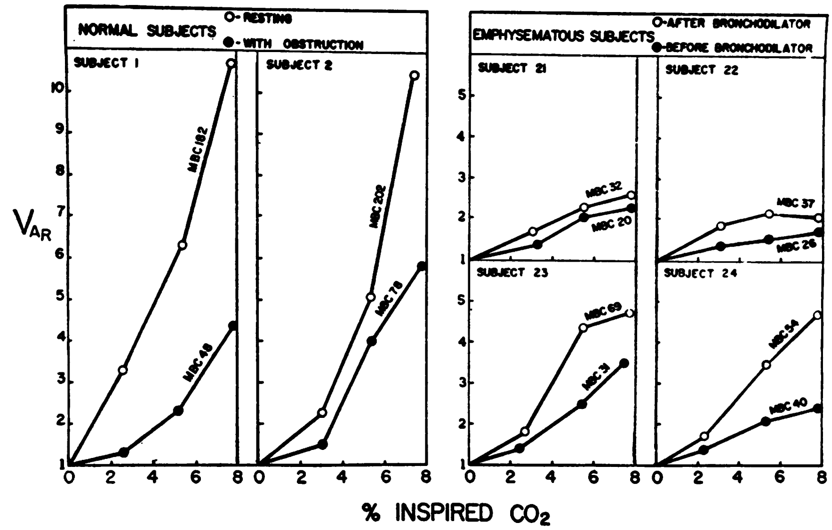

FIG. 5. THE CARBON DIOXIDE RESPONSE CURVES IN 2 NORMAL SUBJECTS AND 4 PATIENTS WITH PULMONARY EMPHYSEMA

Note the effect of increased airway obstruction in normal subjects and decreased airway obstruction in the abnormal subjects.

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 mean slopes of the CO_2 response curves approached that of the emphysematous patients. In addition, it is noted that the mean 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.

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 mean 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 approached those of the emphysematous patients.

Tenney (5) and Alexander, West, Wood, and Richards (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 center. Tenney felt supported in this view because the administration of Diamox® 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 and work of breathing.

It is concluded that emphysematous subjects show a diminished ventilatory response to CO_2 which may be 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 help to 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. Little if any difference in the response to inhaled CO_2 was found between patients with obstructive disease and normal subjects with artificial airway obstruction.

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