have been shown to be associated with an unusual variety of osteoporosis (Grusin and Samuel, 1957 ; Seftel *et al.*, 1966 ; Lynch *et al.*, 1967a). This osteoporosis occurs in middle-aged manual labourers, and commonly presents with vertebral body collapse. Some affected individuals exhibit clinical scurvy, but in others the ascorbic acid deficiency has been manifested only by decreased leucocyte ascorbic acid concentrations. It has been suggested, though not proved, that the severe siderosis contributes to the development of the ascorbic acid deficiency, which in its turn leads to diminished bone formation. While this may prove not to be the correct explanation there is no doubt that a close clinical association exists in the Bantu between severe siderosis, ascorbic acid deficiency, and osteoporosis. In this context it may be noteworthy that osteoporosis has been found in white subjects with haemochromatosis (Delbarre, 1960). In addition, it is possible that the skeletal changes noted in thalassaemia (Caffey, 1957) may not be the result only of an expanded bone marrow. The subject is therefore one which warrants further study.

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Relation between Airways Obstruction and CO_2 Tension in Chronic Obstructive Airways Disease

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Summary: The relationship between the F.E.V.$_1$ as an index of airways obstruction and P_{CO_2} as an index of hypoventilation was investigated in 13 patients with chronic obstructive airways disease. Patients who had a normal P_{CO_2} despite severe airways obstruction retained relatively normal sensitivity to CO_2 as assessed by their "inspiratory mechanical work rate" response to CO_2. Others showed a raised P_{CO_2} in the presence of lesser degrees of airways obstruction and had reduced sensitivity to CO_2.

Introduction

While hypoventilation in obstructive airways disease is generally considered to be proportional to the degree of airways obstruction (Baldwin *et al.*, 1949) a number of exceptions have been reported. McNicol and Pride (1965) described four cases of "unexplained underventilation of the lungs" in the presence of only mild airways obstruction; the one-second forced expiratory volume (F.E.V.$_1$) in these subjects was 1.30–1.45 l., while the arterial carbon dioxide tension (P_{CO_2}) ranged from 55 to 83 mm. Hg. By contrast Tai and Read (1967) reported blood gas studies in acute bronchial asthma, where, despite severe airways obstruction—for example, F.E.V.$_1$ 0.5 l.—hypoventilation, as measured by a raised P_{CO_2}, was uncommon. This apparent discrepancy is not confined to these two situations ; even among patients with chronic airways obstruction associated with chronic bronchitis and emphysema the P_{CO_2} does not necessarily rise with increasingly severe airways obstruction. Those cases described by Fletcher *et al.* (1963) as "emphysematous" tend to have a lower P_{CO_2} than those described as "bronchitic" at similar values of F.E.V.$_1$. These differences between patients indicate that the level of P_{CO_2} is influenced by a factor or factors other than the degree of airways obstruction.

This report concerns a further examination of the relation between F.E.V.$_1$ and P_{CO_2} in a group of patients with chronic obstructive airways disease and follows up an earlier suggestion (Howell, 1966) of some correlation between the F.E.V.$_1$/P_{CO_2} relationship and CO_2 sensitivity.

Patients and Methods

The 13 patients included in this study were attending the outpatient department regularly for follow-up of chronic airways obstruction associated with chronic bronchitis, emphysema, or allergic airways disease (Howell and Altounyan, 1967). They were selected because sufficient measurements of F.E.V.$_1$ and P_{CO_2} had been made at different times to construct plots such as those shown in Fig. 2.

Spirometry was performed on a Godart Pulmonet, and resting P_{CO_2} was estimated by the rebreathing method of Campbell and Howell (1962). Dynamic response to CO_2 was measured during rebreathing from a 4-litre bag of 100% oxygen. End-tidal P_{CO_2} was measured with an infrared analyser (Infra Red Development Company, Model DVB). Minute-ventilation and tidal volumes were measured with a Godart pneumotachograph with integrator, and pressure recordings from an intraoesophageal balloon sited in the lower third of the oesophagus were made by means of an N.E.P. capacitance manometer. Simultaneous volume and pressure signals were fed into an XY recorder (Bryans Model 20171), where pressure/volume loops were traced out for individual breaths. The dynamic compliance line for the lungs and the compliance line for the chest wall (calculated from a previously determined total compliance) were drawn in. From this plot the area representing work done during inspiration against viscous and elastic resistances in the lungs was measured by planimetry. Figures for work done per breath were converted to a work rate ("inspiratory

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mechanical work rate," $\dot{W}_I$, kg.m./min.) and plotted against the end-tidal P_{CO_2} (see Fig. 3). The slope of the most linear part of each curve was measured and expressed in kg.m./min./mm. Hg P_{CO_2}. Response to CO_2 was also measured in five normal subjects.

Results

The overall relation between the P_{CO_2}, as an index of hypoventilation, and the F.E.V.$_1$, as an index of airways obstruction, in patients with chronic obstructive airways disease is shown in Fig. 1. The measurements were made at routine outpatient visits or during hospital admission over the course of 15 months to five years and their variability was attributed to exacerbations of the disease or to the results of therapy. Relevant clinical data on the patients studied are given in the Table. In Fig. 2 the results of repeated observations on five individuals in whom it was possible to detect a distinct regression of P_{CO_2} on F.E.V.$_1$ are shown. Curves have been drawn free-hand through these points and the five curves are plotted together in the final graph of Fig. 2.

Sensitivity to CO_2 assessed in terms of the increase in "inspiratory mechanical work rate" per mm. Hg rise in P_{CO_2} is listed in the Table. The responses of the five patients depicted in Fig. 2 are plotted in Fig. 3 and compared with

Subject	Diagnosis	Sex and Age	Height (cm.)	Weight (kg.)	V.C. (l.)	F.E.V.$_1$ (l.)	P_{CO_2} (mm. Hg)	Slope $\dot{W}_I/P_{CO_2}$ Response (kg.m./min./mm.Hg)
				Normal Controls				
A		F 20	170	57	4·02	3·50	37	0·59
B		M 32	176	72	4·85	3·95	41	0·71
C		M 39	187	84	6·30	4·36	42	0·74
D		M 32	180	70	5·69	4·97	40	0·59
E		M 48	165	45	3·94	2·97	39	0·50
				Cases				
1	C.B.	M 64	174	67	1·61–3·15	0·42–0·94	43–71	0·07
2	A.+C.B.	M 47	170	68	2·15–3·56	0·45–1·03	38–73	0·24
3	Br.	M 64	163	45	1·50–1·90	0·40–0·89	49–79	0·04
4	A.	M 56	178	80	1·30–4·29	0·65–1·15	42–54	0·23
5	E.	M 64	184	70	3·40–4·45	0·52–0·84	35–44	0·40
6	C.B.	M 39	176	66	2·87–3·74	1·05–1·55	47–61	0·07
7	C.B.	M 47	178	74	1·39–2·75	0·43–1·56	57–87	0·16
8	C.B.+E.	M 60	180	63	2·01–3·25	0·42–0·80	44–61	0·10
9	C.B.+E.	M 54	180	69	2·75–4·80	0·30–0·94	45–70	0·14
10	C.B.+E.	F 45	147	35	1·32–2·42	0·29–0·55	44–68	0·07
11	C.B.	M 59	178	64	1·52–2·32	0·58–0·98	42–63	0·17
12	A.+C.B.	M 58	168	70	1·00–1·90	0·40–0·81	44–67	0·25
13	C.B.	M 59	175	86	0·98–3·60	0·40–1·55	45–73	0·04

C.B. = Chronic bronchitis. E. = Emphysema. A. = Allergic airways disease. Br. = Bronchiectasis.

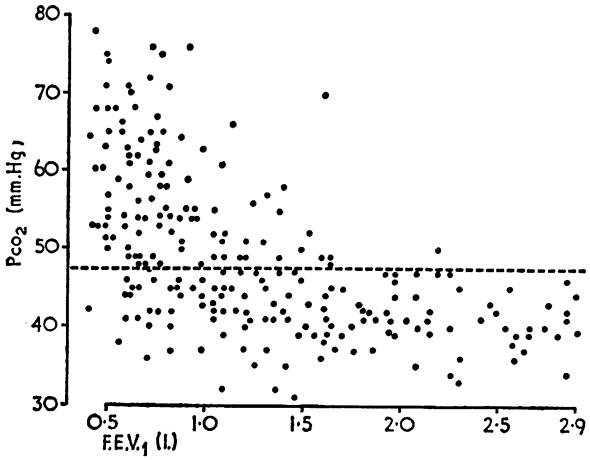

FIG. 1.—Overall relation between F.E.V.$_1$ and P_{CO_2} in 13 patients with chronic airways obstruction. The broken line represents the upper limit of normal for P_{CO_2} in our laboratory.

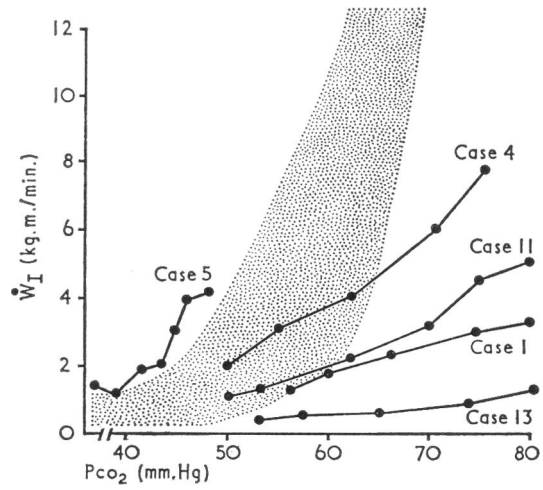

FIG. 3.—CO_2 response curves measured in terms of inspiratory mechanical work rate (kg.m./min. $-\dot{W}_I$) in the same five subjects as in Fig. 2. The shaded area represents the range of response in the normal subjects.

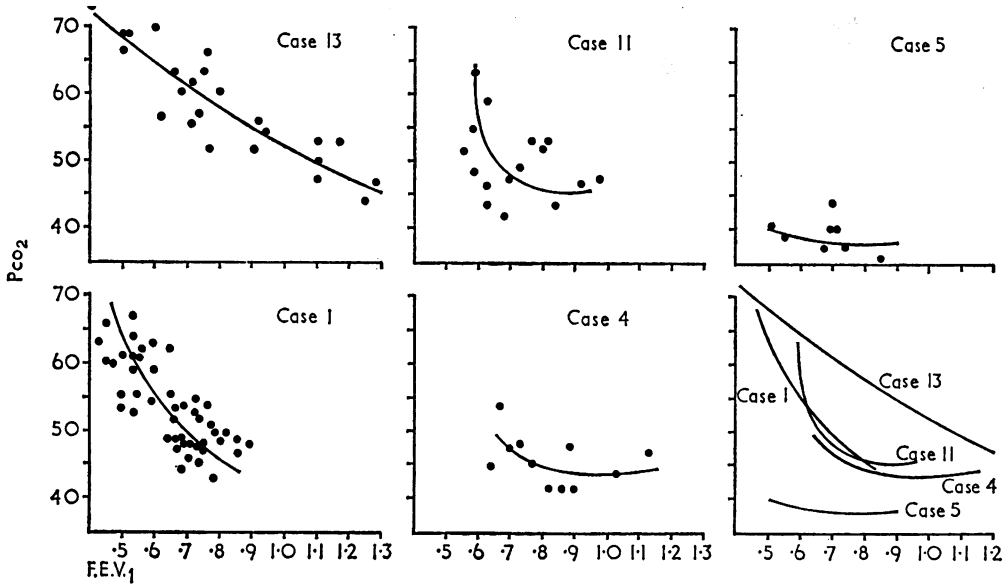

FIG. 2.—Results of repeated observations of F.E.V.$_1$ and P_{CO_2} in five individual subjects. The freehand curves drawn through the data are plotted together in the final graph.

results obtained in the normal subjects (shaded area). CO_2 sensitivity was found to be normal in the patient (Case 5), showing no rise in P_{CO_2} even when the F.E.V.$_1$ was reduced to 0.5 l., but greatly diminished in the patient (Case 13) having a raised P_{CO_2} when the F.E.V.$_1$ was as high as 1.2 l. The other three patients (Cases 1, 4, and 11) were intermediate in sensitivity and in position on the F.E.V.$_1$/P_{CO_2} plot (Fig. 2).

Discussion

Though the correlation between F.E.V.$_1$ and airways resistance measured by the body plethysmograph is not high ($r=0.72$; Payne *et al.*, 1967), it is generally accepted in this country as the best clinical index of airways obstruction (Fairbairn *et al.*, 1962). Likewise the level of arterial P_{CO_2} would seem to be the best clinical index of the adequacy of alveolar ventilation. The relation between these measurements has been examined on several occasions (Smart *et al.*, 1961; Burrows *et al.*, 1965; McNicol and Pride, 1965; Segall and Butterworth, 1966). A general trend of rising P_{CO_2} with falling F.E.V.$_1$ has been noted. No one previously seems to have reported the alterations in these two measurements in individual patients over a period of time.

Our results reveal a considerable variability in the relation of F.E.V.$_1$ to P_{CO_2} from subject to subject and show that one important determinant of this relationship is CO_2 sensitivity as assessed by responsiveness to increased concentrations of inspired CO_2. It is customary to measure this response in terms of ventilation, and an impaired ventilatory response to CO_2 in emphysema was noted as early as 1912 by Reinhardt. Normal subjects, however, show a diminished CO_2 response in terms of ventilation when studied with added external viscous resistances (Cherniack and Snidal, 1956). Since the addition of an external resistance can hardly be expected to alter central sensitivity to CO_2, it is clear that CO_2 sensitivity in obstructive airways disease cannot be assessed adequately in terms of a ventilatory response curve (Richards *et al.*, 1958). As an alternative CO_2 response may be measured in terms of the oxygen consumption of the respiratory muscles or the mechanical work done by them. Brodovsky *et al.* (1960) measured both and concluded that the response expressed in terms of derived total mechanical work was the more reliable index of central CO_2 sensitivity though it ignored the factor of efficiency.

Milic-Emili and Tyler (1963), studying CO_2 responsiveness in normal subjects, showed that the work done by expiratory muscles was not related to the level of CO_2 and recommended assessment in terms of the work done by inspiratory muscles on viscous and elastic resistances in the lungs. These workers also showed that in normal subjects the CO_2 response measured in these terms was independent of an added external viscous resistance. It can be used, therefore, as a more reliable index of CO_2 sensitivity than the ventilatory response to CO_2 in patients with obstructive airways disease. Using this index we have shown that patients who retain a normal P_{CO_2} even when severely obstructed have a normal CO_2 sensitivity, whereas patients who have a raised P_{CO_2} at relatively lower grades of obstruction have a diminished CO_2 sensitivity.

In the present study it was possible to describe with confidence a curvilinear relation between F.E.V.$_1$ and P_{CO_2} in 7 of the 13 patients. In the remaining six the scatter of points was wide. This is attributed to the influence of factors other than CO_2 sensitivity on ventilation and thus on the level of P_{CO_2}. Such factors include hypoxia, acidaemia, and neurogenic stimuli. Furthermore, the degree of reproducibility of the F.E.V.$_1$ is ± 0.08 l. (Simonsson, 1963) and that of the P_{CO_2} measured by the rebreathing method of Campbell and Howell (1962) is ± 2 mm. Hg. Such technical considerations influence the relationship described. Nevertheless the results indicate that if the P_{CO_2} remains within normal limits at an F.E.V.$_1$ of less than 0.5 l. then CO_2 sensitivity is likely to be intact. If, on the other hand, the P_{CO_2} is raised at a level of F.E.V.$_1$ around 1 l. then CO_2 sensitivity is almost certainly severely depressed.

The relation of these findings to clinical features is complex (Lane and Howell, to be published). However, it was noted that the two extremes of clinical presentation correlated with the extremes of CO_2 sensitivity. Case 5, with no rise in P_{CO_2} despite an F.E.V.$_1$ of 0.5 l. and with normal CO_2 sensitivity, presented the "pink and puffing" (Scadding, 1963) or "emphysematous" (Fletcher *et al.*, 1963) pattern, whereas Case 13, with a raised P_{CO_2} even at an F.E.V.$_1$ of 1.2 l. and with much-reduced CO_2 sensitivity, showed the "blue and bloated" or "bronchitic" pattern.

The three patients (Cases 2, 4, and 12) who had a significant element of bronchial allergy as judged by the presence of sputum eosinophilia (Howell and Altounyan, 1967) had CO_2 sensitivities which, while depressed, all fell above the mean for the group. In a fourth patient (Case 7) sputum eosinophils were found on one occasion only, and though this was associated with increasing airways obstruction (F.E.V.$_1$ 0.83→0.51 l.) there was a reduction in arterial P_{CO_2} from 66 to 60 mm. Hg. These observations suggest the possibility that changes associated with bronchial allergy may provide an additional ventilatory drive.

In this series the patient (Case 5) with the most marked radiological evidence of emphysema (Laws and Heard, 1962) also had the most normal CO_2 sensitivity. However, two other subjects (Cases 8 and 9) with significant radiological emphysema had much-reduced sensitivities, and it is not possible from this small series to draw any conclusions about the relation between CO_2 sensitivity and radiological evidence of emphysema.

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