Results

Like previous workers (Westlake, Simpson, and Kaye, 1955; and Sieker and Hickam, 1956), we were unable to find a constant relation between the presence or absence of individual signs and the absolute mixed venous PCO_2 . For example, one patient who was in coma on admission had a mixed venous PCO_2 of 75 mm. Hg, while another patient, with the same mixed venous PCO_2 , had almost no signs of hypercapnia.

However, we were able, in retrospect, to find a better correlation between the presence or absence of individual signs and the amount by which the mixed venous PCO_2 was elevated above the usual level for each patient. The details are shown in diagrammatic form in the Chart.

It can be seen from this diagram that hot hands, a rapid bounding pulse, and small pupils were often found with even small elevations of the mixed venous PCO_2 (5 to 10 mm. Hg) above usual levels. Engorged fundal veins, confusion or drowsiness, and twitching were found when the mixed venous PCO_2 had risen by 15 mm. Hg or more above the usual level. Depressed tendon reflexes, extensor plantar responses, and coma occurred with any frequency only when the mixed venous PCO_2 was raised by 30 mm. Hg or more above the usual level. It was only with the highest elevations of the mixed venous PCO_2 (40 mm. Hg or more) above usual levels that papilloedema and headache (if the patient was not in coma) occurred.

Discussion

With this information it should usually be possible on clinical examination to arrive at an approximate assessment of the amount by which the PCO_2 has risen during the acute exacerbation, this being one index of the severity of respiratory failure. This assessment has a further value: we have discussed in a previous paper (Hamilton and Gross, 1963)

the protective effect which CO_2 retention may have on the cerebral oxygen supply. If the PCO_2 is to be controlled by respiratory stimulants this should be done with reference to the usual PCO_2 level for that patient, and not to the accepted normal level.

Furthermore, the appearance of hot hands, a rapid bounding pulse, and small pupils in a convalescent patient gives warning of increasing CO_2 retention before the neurological signs (which are usually taken as the warning signs) are manifest.

It is not possible to say from this study whether these signs are due to increases of PCO_2 or whether they are more closely related to the associated rise in the hydrogen-ion concentration, which seems more probable. A further study, estimating arterial pH, would be necessary to decide this.

Summary and Conclusions

It is suggested that there is a quantitative correlation between the appearance of individual signs of hypercapnia and the amount by which the PCO_2 has risen during the course of an acute exacerbation of respiratory failure.

Peripheral vasodilatation, a rapid bounding pulse, small pupils, engorged fundal veins, confusion or drowsiness, muscular twitching, depressed tendon reflexes, extensor plantar responses, coma, headache (if the patient is not in coma), and papilloedema, in approximately that order, are shown to occur with successive increases of the mixed venous PCO_2 above the patients' usual mixed venous PCO_2 levels.

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EFFECT OF BRONCHODILATOR AEROSOL ON VENTILATORY CAPACITY IN CHRONIC LUNG AND HEART DISEASES

BY

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During a review of the results of pulmonary function tests carried out in a diagnostic laboratory note was made of the effect on ventilatory capacity of a bronchodilator aerosol in three groups of patients: those with obstructive lung disease, those with diffuse interstitial pulmonary fibrosis, and those with mitral and aortic valve disease. The findings are here briefly recorded as they are of some therapeutic significance and interest.

Patients and Methods

The number of patients in each diagnostic group, with their age, sex, and ventilatory capacity, is set out in Table I.

Obstructive Lung Disease.—The series of 100 cases is a consecutive one from patients referred for investigation by clinicians from hospital and private practice, both in-patient and out-patient. The diagnosis is based on the clinical findings and the results of tests of ventilatory capacity. All the patients had asthma, bronchitis, or

emphysema: those with industrial pneumoconiosis were excluded.

Diffuse Interstitial Pulmonary Fibrosis.—The 22 patients were referred for investigation and consultation from many sources in Victoria, and all were examined clinically by

TABLE I.—Number of Patients, Age, Sex, and Ventilatory Capacity in the Diagnostic Groups

	Obstructive Lung Disease		Diffuse Fibrosis	Aortic Valve Disease	Mitral Valve Disease
	Moderate (F.E.V. ₁ /V.C. >0.5)	Severe (F.E.V. ₁ /V.C. <0.5)			
No. of patients	39	38	11	19	20
	Male 11	12	11	3	39
Age (years)	Mean 47.6	54.8	56.3	45.4	39.1
	Range 15-72	14-76	35-72	26-63	14-57
F.E.V. ₁ /V.C.	Mean 62.8	37.3	78.1	71.1	75.7
	Range 51.0-86.0	24.1-50.1	53.7-92.5	43.4-93.0	37.1-93.3
F.E.V. ₁ (litres)	Mean 2.20	0.98	1.97	2.73	2.31
	Range 1.06-4.88	0.15-2.56	0.79-3.20	1.39-4.35	0.95-4.34

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one of us (B. G.). The diagnosis was based on the usual clinical, radiological, and functional criteria, and confirmed by biopsy or necropsy study in half the cases.

Mitral and Aortic Valve Disease.—These patients, 59 with mitral and 22 with aortic lesions, all rheumatic, comprise nearly all the patients with these conditions referred to the cardiac clinic at the hospital during 1959 and part of 1960, and they form part of a larger series described elsewhere (Sloman and Gandevia, 1963). Patients with frank clinical evidence of bronchitis or asthma were excluded, but patients were included when evidence of airways obstruction was found only on functional studies.

Ventilatory capacity was assessed in the conventional manner, using a low-resistance recording spirometer. The forced expiratory volume at one second (F.E.V.₁) and the F.E.V.₁ expressed as a percentage of the vital capacity (F.E.V.₁% V.C.) are the only parameters relevant to this paper. The latter ratio is recorded merely as some index of the severity or otherwise of airways obstruction; it does not necessarily change when an effective bronchodilator drug is given (Thompson and Hugh-Jones, 1958). The highest value for F.E.V.₁ derived from three "satisfactory" spiograms (defined as spiograms free from artifacts or evidence of lack of co-operation and of consistent appearance as judged by eye) was accepted. The same procedure was repeated a minute or so after the inhalation of an aerosol of 1% solution of isoprenaline sulphate† from a Wright nebulizer or plastic "alevizer" using compressed air as the source of pressure. Four or five cardiac patients with clinical evidence of left ventricular failure were given "bronkephrin" 0.75 ml. subcutaneously in preference to isoprenaline, in which case the spiograms were repeated after 10 and 20 minutes.

Exercise tolerance was assessed in grades: grade 1, able to keep up with others of own age up hills and stairs; grade 2, able to keep up on flat only; grade 3, able to walk "indefinitely" (20 minutes or half a mile) on the flat but at own pace only; grade 4, able to walk on flat for shorter distance or period only.

Right heart catheterization was performed by Dr. G. Sloman on 30 of the patients with mitral valve disease, and data on the mean pulmonary artery and mean left atrial pressure are recorded in relation to ventilatory capacity changes.

Results

The results are summarized in Table II. The patients with obstructive lung disease are arbitrarily divided into two groups—those in whom the ratio F.E.V.₁/V.C. exceeded 0.5 (described as having "moderate" obstructive lung disease) and those in whom this ratio was less than 0.5 (described as having "severe" obstructive lung disease). In the former group a mean increase of 13% in F.E.V.₁ was observed, and in the latter a mean increase of 28%. In 28 of the moderate and 40 of the severe cases the increase exceeded 10% of the initial value (conventionally regarded as a "significant" increase, although in these patients a 5% change is probably outside the experimental error). Of the 32 patients in both groups recorded in Table II as showing either no significant change or a significant decrease in F.E.V.₁, only 9 showed either no change whatsoever or small decreases, the remainder (23%) having increases of less than 10%. The improvement after the bronchodilator drug occurred in all exercise-tolerance

grades. The mean actual increase in F.E.V.₁ was of the order of 250 ml. in both the moderate and the severe groups, but the range of increase was wide.

TABLE II.—Changes in F.E.V.₁ After a Bronchodilator Aerosol in Chronic Pulmonary and Cardiac Diseases

		Obstructive Lung Disease		Diffuse Fibrosis	Aortic Valve Disease	Mitral Valve Disease
		Moderate	Severe			
F.E.V. ₁ increase after aerosol (litres)	Mean... Range	0.29 -0.30 to +1.05	0.23 -0.06 to +0.87	0.06 -0.10 to +0.21	0.16 -0.32 to +0.41	0.14 -0.20 to +0.40
F.E.V. ₁ increase after aerosol (%)	Mean... Range	+13.2 -11.1 to +37.5	+28.3 -4.6 to +130.0	+4.7 -3.8 to +26.6	+6.8 -10.7 to +27.3	+7.2 -7.1 to +30.8
No. of significant increases in F.E.V. ₁ (>10%)		28	40	4	6	19
No significant change (-5% to +10%)		21	10	18	15	36
Significant decrease (>5%)		1	0	0	1	4

As might be anticipated, the 22 patients with diffuse interstitial pulmonary fibrosis showed little response to the aerosol, the average increase in F.E.V.₁ being about 60 ml., and the relative increase approximately 5%. However, there was an improvement of over 10% in four cases.

Only 6 of the 22 patients with aortic valve disease, one or two from each exercise-tolerance grade (Table III), showed more than 10% improvement in F.E.V.₁; one showed a decrease of over 5%. By contrast, more than 10% improvement in F.E.V.₁ was found in 19—almost a third—of the patients with mitral valve disease; none of the patients with a normal exercise tolerance showed any

TABLE III.—Change in F.E.V.₁ According to Exercise-tolerance Grade in Patients with Aortic and Mitral Valve Disease

	No. of Cases	Change in F.E.V. ₁		
		Increase +10%	-5% to +10%	Decrease >5%
Mitral valve disease:				
Exercise tolerance:				
Grade 1	8	—	8	—
" 2	22	7	10	1
" 3	20	8	6	—
" 4	9	4	2	3
Aortic valve disease:				
Exercise tolerance:				
Grade 1	8	1	4	—
" 2	6	2	3	1
" 3	6	2	3	—
" 4	2	1	1	—

significant change (Table III), but 7 of 22 grade 2 patients, 8 of 20 grade 3 patients, and 4 of the 9 grade 4 patients improved significantly. The average increase in F.E.V.₁ was approximately 7% in both cardiac groups, although individual increases of up to 31% were observed; the mean absolute increase was of the order of 150 ml. In seven patients with mitral valve disease a decrease in F.E.V.₁ was observed, in four of whom (three in grade 4) the decrease exceeded 5%. This is a higher proportion of decreases after the aerosol than is found in the patients with obstructive lung disease, although the difference does not reach statistical significance. In several patients we have found these decreases after a bronchodilator aerosol to be reproducible and consistent.

The change in ventilatory capacity in 30 patients with mitral valve disease is shown in relation to resting mean pulmonary artery and mean left atrial pressures (Table IV). There is perhaps a tendency for the greater changes in ventilatory capacity to occur in those with the higher pressure levels, but this may imply no more than the correlation with the severity of disability suggested by the greater frequency of changes in patients with severely impaired exercise tolerance. No catheter studies were carried out during isoprenaline administration.

†We have used this drug by aerosol routinely because it is quick-acting and effective, but we do not wish to imply that this offers the ideal therapeutic approach.

TABLE IV.—Resting Mean Pulmonary Artery and Left Atrial Pressures in Relation to Change in F.E.V.₁ After a Bronchodilator Aerosol

Change in F.E.V. ₁	Mean Left Atrial Pressure (mm.Hg)			Mean Pulmonary Artery Pressure (mm.Hg)		
	0-9	10-20	21+	0-14	15-30	31+
Increase > 10% ..	0	4	5	0	4	5
Decrease > 5% ..	0	2	1	0	2	1
-5% to +10% ..	4	12	2	3	12	3

Discussion

In many patients with wheezing it is clinically obvious that bronchodilator therapy produces improvement. The present results indicate that a significant component of reversible airways obstruction is present at the time of testing in about 70% of a series of patients with clinically established obstructive lung disease of all grades of severity. Many of these patients had no audible wheeze, although a number of them gave a history of intermittent wheezing or of variability in exercise tolerance during the day or from day to day. The figure of 70% for those with clinically significant reversible bronchoconstriction may be an underestimate: 90%, representing all those showing some improvement, is probably a better estimate, as experience has shown that retesting may reveal a reversible component absent at the time of the first test. It is reasonable to conclude that all patients with symptoms due to established chronic obstructive lung disease, however apparently persistent and severe, should be given a therapeutic trial of intensive bronchodilator therapy.

In general, as regards the tendency for improvement in ventilatory capacity after a sympathomimetic drug, particularly in more severely disabled patients, and the comparative insensitivity of clinical assessment of reversible bronchoconstriction, the present results are in close agreement with those of Gilson and Hugh-Jones (1956) in patients with coalworkers' pneumoconiosis.

Although the improvement obtained may be small in absolute units, it may be large relative to the patient's initial ventilatory state: there are few chronic diseases in which it is possible to produce 25% improvement in one or two minutes. Furthermore, it is likely that the forced expiratory manœuvre underestimates the benefit gained during quiet breathing (Gandevia and Prime, 1957). By contrast, bronchodilator therapy will not necessarily improve arterial oxygen saturation when this is abnormal (Halmagyi and Cotes, 1959).

In diffuse interstitial pulmonary fibrosis, where the ventilatory defect is predominantly restrictive rather than obstructive, there is little change in ventilatory capacity after a bronchodilator aerosol. However, there are occasional exceptions, and in none of these cases was it possible to predict this on clinical grounds. It may be desirable to test the response to a bronchodilator drug in these patients on one or two occasions to see whether bronchodilator therapy may have some subsidiary therapeutic part to play.

Patients severely disabled by mitral valve disease, and to a lesser extent by aortic valve disease, often develop an obstructive as well as a restrictive ventilatory defect (Sloman and Gandevia, 1963); in the present series the mean ratio of F.E.V.₁ to V.C. fell from 0.84 in those with a normal exercise tolerance to 0.73 for the patients of grade 4. In some instances considerable improvement followed a bronchodilator aerosol, although no close correlation between this improvement and the value for

the ratio could be demonstrated. The presence of reversible bronchoconstriction, clinically undetected, may simply reflect the known clinical tendency for these patients to develop "bronchitis."

The significant decreases, which are reproducible, following isoprenaline in a majority of the patients with mitral disease are unexplained, but indicate that, if possible, deliberate tests, perhaps of more than one bronchodilator drug, should precede treatment. This phenomenon is rare in obstructive lung disease; in the past five years we have observed it only twice in patients showing a significant response to other bronchodilator drugs.

Summary

The effect of a bronchodilator aerosol on the forced expiratory volume at one second (F.E.V.₁) is described in patients with obstructive lung disease, in patients with diffuse pulmonary fibrosis, and in patients with rheumatic heart disease.

In most patients with obstructive lung disease the F.E.V.₁ increased significantly after use of the aerosol, suggesting that a trial of intensive bronchodilator therapy is always worth while. Few of those with diffuse fibrosis showed any increase. In about a third of the patients with mitral valve disease an increase in ventilatory capacity followed the use of the aerosol; bronchodilator therapy may therefore be useful in some patients with cardiac disease, but occasionally the use of isoprenaline by aerosol has consistently been followed by a decrease in ventilatory capacity.

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The London Council of Social Service has compiled a list of Christmas cards for good causes. Copies of this list may be obtained from "Christmas Cards," L.C.S.S., 4 Gower Street, London W.C.1, by enclosing a stamped addressed envelope. A display of sample cards is on view until December 7 at the Y.W.C.A. Central Club, Great Russell Street, London W.C.1. Among the charities of medical interest who are offering cards are: African Medical and Research Foundation, 12 Crane Court, Fleet Street, E.C.4; British Diabetic Association, 152 Harley Street, W.1; British Empire Cancer Campaign, 11 Grosvenor Crescent, Hyde Park Corner, S.W.1; British Epilepsy Association, 27 Nassau Street, W.1; British Polio Fellowship, Polio Employment Centre, 1 Lindisfarne Road, Jesmond, Newcastle on Tyne 2; British Rheumatism and Arthritis Association, 11 Beaumont Street, W.1; Elderly Invalids' Fund, 34 King Street, E.C.2; Empire Rheumatism Council, Faraday House, 8-10 Charing Cross Road, W.C.2; Friends of the Centre for Spastic Children, 63 Cheyne Walk, Chelsea, S.W.3; Greater London Fund for the Blind (Dept. Y), 2 Wyndham Place, W.1; Grenfell Association of Great Britain and Ireland, Hope House, 45 Great Peter Street, S.W.1; Invalid Children's Aid Association, 4 Palace Gate, Kensington, W.8; Multiple Sclerosis Society, 10 Stratford Road, W.8; Muscular Dystrophy Group of Great Britain, 26 Borough High Street, London Bridge, S.E.1; National Association for Mental Health, 39 Queen Anne Street, W.1; National Deaf Children's Society, 31 Gloucester Place, W.1; National Society for Mentally Handicapped Children, Christmas Card Dept., 5 Bulstrode Street, W.1; Royal Association in Aid of the Deaf and Dumb, 7-11 Armstrong Road, Acton, W.3.