An analysis of the physiological strain of submaximal exercise in patients with chronic obstructive bronchitis

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An analysis of the physiological strain of submaximal exercise in patients with chronic obstructive bronchitis. An increasing work rate was performed by 40 patients with chronic obstructive bronchitis, split into two groups according to FEV₁ (group M, mean FEV₁ 1.45 l. and group S, mean FEV₁ 0.62 l.), and by 20 normal, non-athletic men of similar age to the patients. Values for cardiac frequency and ventilation were interpolated to standard oxygen uptakes of 0.75, 1.0, and, where possible, 1.5 l min⁻¹. The tidal volume at a ventilation of 20 and 30 l min⁻¹ was also determined.

The cardiac frequencies at oxygen uptakes of 0.75 and 1.0 l min⁻¹ were significantly higher in the patient groups than in the normal men, and were highest in patient group S. The cardiac output when related to the oxygen uptake was in the normal range in all three groups of subjects, so that the patients had smaller stroke volumes than the normal men. Ventilation at oxygen uptakes of 0.75 and 1.0 l min⁻¹ was significantly higher in both patient groups than in the normal subjects; there were no significant differences between the two patient groups. Values for dead space/tidal volume ratio, alveolar-arterial oxygen gradient, and the percent venous admixture measured during a constant work rate test were significantly greater than normal in the patient groups.

Possible factors limiting exercise tolerance in these patients were assessed by extending the increasing work rate test from submaximum to maximum exercise. Changes in blood gas tensions and blood lactate concentrations from resting levels were small, and probably did not limit exercise performance. Measurements at maximum exercise did not add appreciably to the analysis of the disturbed cardiopulmonary function. This study has shown that major disturbances in cardiopulmonary function can be demonstrated without the need for stressing a patient to the limit of his effort tolerance.

INTRODUCTION

Although the working capacity of patients with chronic obstructive bronchitis has been studied by many authors, no simple way of comparing the capacity of these patients with that of normal subjects has been developed. Working capacity in normal subjects is assessed by measuring maximum oxygen uptake (Vo₂ max) (Robinson, 1938, Astrand, 1952; Astrand, I, 1960) but this requires several exercise tests carried to exhaustion and is obviously impractical, and possibly hazardous, in clinical practice. A simpler and less exhausting method is to predict Vo₂ max from the relationship between cardiac frequency and oxygen consumption during progressive submaximal exercise by a linear ex-

trapolation of oxygen consumption to a theoretical maximum cardiac frequency (Shephard *et al.*, 1968). However, this prediction does not take into account the curvilinearity of the relation between cardiac frequency and oxygen consumption as maximum values are approached and tends to underestimate Vo₂ max (Davies, 1968). Furthermore, the working capacity of patients with chronic obstructive bronchitis usually is limited by their impaired ventilatory capacity so that their cardiac frequencies on exercise do not approach the expected maximum values for their age (Armstrong *et al.*, 1966; Gabriel, 1973). Recently, because of these difficulties in obtaining Vo₂ max, Cotes *et al.* (1969) have suggested comparing measurements obtained during submaximal

exercise at a standard oxygen uptake ($\dot{V}O_2$). In normal populations they have used a $\dot{V}O_2$ of 1.5 l min⁻¹. This $\dot{V}O_2$ is too high for older women and for many patients; furthermore, values at a single $\dot{V}O_2$ provide no information on the evolution of the exercise response or of the overall capacity for exercise. For these reasons we have suggested an alternative approach in which measurements are made throughout an increasing work rate test and the results expressed, not only at suitable levels of $\dot{V}O_2$ (0.75, 1.0, and, where possible, 1.5 l min⁻¹), but also in terms of the slope of the relationship of cardiac frequency (fH) and ventilation ($\dot{V}$) with $\dot{V}O_2$. From these slopes and a knowledge of the maximum ventilation and heart rate a measure of 'physiological strain' can be obtained, which can be applied to both normal populations and patients (Spiro *et al.*, 1974).

In this paper we describe the changes in cardiac frequency and in ventilation in 40 patients with chronic obstructive bronchitis and in 20 normal middle-aged men during a constant work rate exercise test. Some additional measurements of gas exchange and cardiac output were also made in all the subjects during a constant work rate test.

SUBJECTS AND METHODS

Forty men (aged 47 to 72 years) attending the Bronchitis Clinic at Hammersmith Hospital agreed to take part in the study. The criteria of chronic obstructive bronchitis were the same as those of Jones, Jones, and Edwards (1971). All the men had been cigarette smokers and 25 were still smoking at the time of the study. None gave a history of asthma or showed more than a 20% increase in the forced expiratory volume in 1 second (FEV₁) after bronchodilator. For analysis the patients were divided into two groups according to their FEV₁—a group M, with moderate airways obstruction, mean FEV₁ 1.45 l. (range 1.0–2.2 l.), and a group S with severe airways obstruction, mean FEV₁ 0.62 l. (range 0.2–0.9 l.). Bronchodilator therapy was omitted on the day of the study. All the subjects were in sinus rhythm and none was taking digoxin; two had a previous history of oedema and four had electrocardiographic evidence of right ventricular hypertrophy.

Twenty normal, sedentary, middle-aged men volunteered to take part in the study. A detailed medical history was taken on the day of the study. No subject had a history of abnormal exertional dyspnoea, angina or any other systemic illness. Dyspnoea grade was assessed as set out by the Medical Research Council (1965).

Height and weight were measured, and the lean

body mass (LBM) calculated with the formulae of Durnin and Rahaman (1967) from the sum of four skinfold thicknesses measured over the triceps and biceps muscles and in the subscapular and supriliac regions. A resting venous blood sample was taken from each subject for haemoglobin estimation. Vital capacity (VC) and FEV₁ were measured with a waterless bellows spirometer (McDermott, McDermott, and Collins, 1968). Three attempts were made and the highest value was recorded. Lung volumes and specific airways conductance were measured in the patients using a body plethysmograph (DuBois *et al.*, 1956; DuBois, Botelho, and Comroe, 1956). The transfer factor for carbon monoxide (CO) was also measured in the patients using the single breath technique (Ogilvie *et al.*, 1957), and expressed as the ratio of CO transfer per litre alveolar lung volume STPD (K_{co}). The personal details of the subjects are summarized in Table I.

The subjects exercised while seated on an electrically braked cycle ergometer (ELEMA). They first performed an increasing work rate test. After reaching a steady resting state, as judged by the continuous tracings of fH, $\dot{V}$, and mixed expired gas concentrations, exercise was begun at a power output of 100 kpm min⁻¹ (16.7 watts) and increased by 100 kpm min⁻¹ each minute. The patients were encouraged to continue for as long as possible, and in every case exercise was stopped because of dyspnoea. The normal subjects were asked to stop, for safety reasons, when the cardiac frequency reached 85% of the maximum predicted for their age (Astrand, 1960). When it appeared that the patients were approaching their maximum exercise capacity, blood samples were taken from a vasodilated ear lobe (Godfrey, *et al.*, 1971) for measurement of oxygen tension (P_{O₂}) and carbon dioxide tension (P_{CO₂}) during the last minute of exercise. In preliminary experiments we found no significant differences in blood gas tensions in simultaneous samples taken from the brachial artery and ear lobe in 12 patients, so we have taken the blood gas tensions of capillary blood from the ear as equivalent to the tensions in arterial blood (P_{aO₂}, P_{aCO₂}). Measurement of blood gas tensions in 34 duplicate samples of ear lobe blood gave a coefficient of variation of 2.7% for P_{aO₂} and 3.8% for P_{aCO₂}.

A further sample for blood lactate concentration was taken from the ear lobe 5 minutes after the end of exercise. Blood lactate concentration was measured from five drops of blood collected into a tube containing a weighed amount (0.5 ml) of 0.86 mol l⁻¹ perchlorate solution. The tubes were shaken and stored before being analysed by an enzymatic

TABLE I
PERSONAL DETAILS OF SUBJECTS (MEAN $\pm$ SEM SHOWN)

FEV ₁ (range, l.) n	Normal Subjects	Patients	
		Group M	Group S
	2.8-4.7 20	1.0-2.2 20	0.2-0.9 20
Age (years)	54.1 $\pm$ 1.1	60.0 $\pm$ 1.0	62.0 $\pm$ 1.7
Height (cm)	173.4 $\pm$ 1.5	172.8 $\pm$ 1.4	166.4 $\pm$ 1.3
Weight (kg)	76.2 $\pm$ 2.3	72.9 $\pm$ 2.8	68.6 $\pm$ 2.9
Lean body mass (kg)	62.3 $\pm$ 1.6	60.2 $\pm$ 1.8	56.6 $\pm$ 2.0
FEV ₁ (l.)	3.44 $\pm$ 0.1	1.45 $\pm$ 0.1	0.62 $\pm$ 0.1
VC (l.)	4.48 $\pm$ 0.1	2.92 $\pm$ 0.1	2.01 $\pm$ 0.1
FEV ₁ % normal ¹	115.0 $\pm$ 2.8	49.2 $\pm$ 2.9	24.0 $\pm$ 1.7
Resting P $\bar{V}$ CO ₂ (mmHg)		46.2 $\pm$ 1.1	56.6 $\pm$ 1.6
Dyspnoea grade ²		2.2 $\pm$ 0.2	3.0 $\pm$ 0.2
Total lung capacity (l.)		7.58 $\pm$ 0.2	7.72 $\pm$ 0.4
Total lung capacity % normal ¹		123 $\pm$ 5.8	130 $\pm$ 2.7
Residual volume (l.)		4.3 $\pm$ 0.2	5.2 $\pm$ 0.3
K _{co} (ml min ⁻¹ mmHg ⁻¹ l ⁻¹)		3.71 $\pm$ 0.3	3.37 $\pm$ 0.3
SGaw (sec ⁻¹ cmH ₂ O ⁻¹)		0.071 $\pm$ 0.007	0.043 $\pm$ 0.006

K_{co} = transfer factor for carbon monoxide per unit of alveolar volume (STPD).

SGaw = specific airways conductance.

¹Normal value predicted from age and height according to Cotes (1968).

²MRC instructions for the use of the questionnaire on respiratory symptoms, Medical Research Council (1965).

method (Hohorst, 1957). The coefficient of variation for 40 analyses of duplicate samples was 8.6% over the range of 0.5-4 mmol l⁻¹ (mean 1.4 mmol l⁻¹).

Following a rest of at least 30 minutes the subjects performed a constant work rate test for 6 minutes. The power output selected for the patients was approximately 50% of the final work rate achieved during the progressive exercise test, and for the normal subjects was approximately 60% of their final work rate. Duplicate resting ear lobe blood samples were taken for measurement of PaO₂, Paco₂, and blood lactate. Constant work rate exercise then began and during the sixth minute a further ear lobe sample was taken for blood gas tensions and lactate concentration. The mixed venous CO₂ tension (P $\bar{V}$ CO₂) was measured at rest and at the end of the sixth minute of exercise by the rebreathing method of Jones *et al.* (1967). Cardiac frequency, ventilation, and oxygen uptake were calculated from the Mingograf recordings in the resting period and at the end of each minute of exercise. The apparatus used, together with details of its accuracy, and the measurements made for the calculation of gas exchange have been described previously (Spiro *et al.*, 1974).

The slope of the relationship of cardiac frequency and oxygen uptake (SfH) was measured from a 'least squares' regression line (fH against $\dot{V}$ O₂) automatically calculated and drawn by an Elliott 4100 digital computer. The slope for ventilation and oxygen uptake (SV) was drawn by eye through the linear (submaximal) range and did not include the inflexion that is often seen in normal subjects at high power outputs (Cotes, 1968). The slopes (SfH, SV) were expressed as the increases in fH or in $\dot{V}$ required for an increase in $\dot{V}$ O₂ of 1 l min⁻¹. The range over

which fH or $\dot{V}$ could potentially be increased during exercise (that is, the difference between resting and maximum values) was taken as the 'adaptation capacity' (ACfH, AC $\dot{V}$). Resting values for calculating ACfH and AC $\dot{V}$ were obtained from measurements made with the subject seated at rest on the cycle ergometer. In the normal subjects maximum ventilation was taken as the FEV₁ $\times$ 35 (Gandevia and Hugh-Jones, 1957). In the patients, because of the relatively poor accuracy of existing predictions, the actual ventilation reached at the end of the exercise test was used. In all subjects the maximum heart rate was predicted from their age using the formula of Astrand (1960). By relating the absolute increase in ventilation or cardiac frequency (SV, SfH) for a standard stress (an increase in $\dot{V}$ O₂ of 1 l min⁻¹) to an estimate of the individual's capacity to increase fH or $\dot{V}$ (ACfH, AC $\dot{V}$), the 'physiological strain' for ventilation or heart rate can be obtained (Spiro *et al.*, 1974).

The pattern of breathing for each group was assessed by plotting ventilation against tidal volume after the method of Hey *et al.* (1966). The submaximal tidal volumes at a ventilation of 20 and 30 l min⁻¹ were interpolated from the individual plots.

The dead space/tidal volume ratio (V_D/V_T%) was calculated using the Bohr equation, from which the dead space (V_D) was derived, allowing 60 ml for the valve box dead space. Alveolar Po₂ was derived with the alveolar air equation, and the measured Pao₂ subtracted to obtain the alveolar-arterial Po₂ gradient (PA-aO₂). The cardiac output ($\dot{Q}$) was calculated by the indirect Fick equation for CO₂, incorporating the 'downstream' correction (Jones *et al.*, 1967). The percent venous admixture ($\dot{Q}_s/\dot{Q}_T$ %)

was estimated by use of the classical 'shunt' equation. Calculations were performed with the Elliott 4100 digital computer, using a programme based on the manipulation of the indirect Fick principle (Godfrey, 1970).

In the text and tables all gas volumes, except the K_{CO} , are given corrected to BTPS, and values for $\dot{V}O_2$ are corrected to STPD.

RESULTS

The two patient groups were on average 6 to 8 years older than the normal subjects. The patients in group M were smaller and lighter and had a lower lean body mass than the normal men (Table I); these anthropometric differences were only significant between group S and the normal men ($t=2.05$; $0.025 > P > 0.01$). The dyspnoea grade (MRC, 1965) was significantly greater in patient group S than in patient group M ($t=2.63$; $0.025 > P > 0.01$). The mean total lung capacity was above the predicted value in both patient groups but there was no significant difference between the two groups. The residual volume was significantly greater in patient group S than in group M ($t=2.92$; $0.01 > P > 0.005$). The transfer factor for CO related to alveolar volume (K_{CO}) was considerably lower in the patient groups, than for normal middle-aged men (van Ganse Ferris, and Cotes, 1972). Specific airways conductance was significantly lower in patient group S than in patient group M ($t=3.13$; $0.005 > P > 0.001$). These pulmonary function tests were not carried out on the normal men, but measurements of these variables in other normal subjects studied in this laboratory agree with published values (Cotes, 1968).

The interpolated responses of cardiac frequency at the submaximal levels of exercise ($fH_{0.75}$, $fH_{1.0}$, $fH_{1.5}$) are summarized in Table II and in Figure 1. Only two of the group S patients achieved an oxygen

uptake of 1.5 l min^{-1} and these data have not been included. As half of the group M subjects exceeded $1.5 \text{ l } \dot{V}O_2 \text{ min}^{-1}$, the mean value for this submaximal index was included. Only six subjects in group S failed to reach an oxygen uptake of 1.0 l min^{-1} . The submaximal values for cardiac frequency were significantly higher in both the patient groups than the normal men at 0.75 and $1.01 \text{ min}^{-1} \dot{V}O_2$ ($t=3.18$; $P < 0.001$). The differences between the two patient groups did not reach statistical significance. The slope (SfH) was similar for all three groups of subjects, but the $ACfH$ was smaller in both the patient groups than in the normal men, as the patients were older and also had higher resting cardiac frequencies (Table II). However, the physiological strain index showed no significant difference between the three groups studied.

Ventilation at 0.75 , 1.0 , and $1.5 \text{ l min}^{-1} \dot{V}O_2$ was higher in the patients than in the normal men ($t=2.77$; $0.01 > P > 0.005$), but there were no significant differences in ventilation between group M and group S patients (Table III and Fig. 1). The slope of ventilation on oxygen uptake was slightly increased (compared to the normal subjects) in the group M patients ($t=2.03$; $0.05 > P > 0.025$) but there was no significant change in the severely obstructed patients.

The $AC\dot{V}$ was significantly smaller in patient group M than in the normal subjects ($t=9.1$; $P < 0.001$) and smaller still in patient group S than in patient group M ($t=4.9$; $P < 0.001$). The physiological strain index for ventilation was much greater in both the patient groups than in the normal men and was significantly larger in patient group S than in group M ($t=2.82$; $0.01 > P > 0.005$). The influence of differences of somatic muscle mass was corrected for by multiplying the physiological strain index by the LBM. This did not cause any significant change in physiological strain for $\dot{V}O_2$ or fH between any of the groups.

TABLE II
SUBMAXIMAL INDICES AND ESTIMATION OF ADAPTATION CAPACITY AND RELATED 'PHYSIOLOGICAL STRAIN'
FOR CARDIAC FREQUENCY (MEAN $\pm$ SEM SHOWN)

	Normal Subjects	Patients	
		Group M	Group S
FEV_1 (l.) n	2.8-4.7 20	1.0-2.2 20	0.2-0.9 20
fH rest (beats min^{-1})	81.4 $\pm$ 3.5	85.9 $\pm$ 2.9	85.0 $\pm$ 2.6
$fH_{0.75}$ (beats min^{-1})	95.0 $\pm$ 3.1	102.9 $\pm$ 3.5	109.5 $\pm$ 2.9
$fH_{1.0}$ (beats min^{-1})	105.6 $\pm$ 3.1	113.2 $\pm$ 3.5	120.1 $\pm$ 3.8
$fH_{1.5}$ (beats min^{-1})	126.9 $\pm$ 3.4	127.6 $\pm$ 5.9 ¹	
Predicted fH max (beats min^{-1})	175.1 $\pm$ 0.8	171.0 $\pm$ 0.7	169.8 $\pm$ 1.1
Adaptation capacity for fH ($ACfH$; beats min^{-1})	93.6 $\pm$ 3.5	85.2 $\pm$ 3.3	84.9 $\pm$ 2.6
'Slope' for fH (SfH ; beats $1 \text{ } \dot{V}O_2^{-1}$)	42.5 $\pm$ 1.9	40.9 $\pm$ 2.1	43.3 $\pm$ 4.9
'Physiological strain' for fH $\frac{SfH \times 100}{ACfH}$ (%)	46.3 $\pm$ 2.1	49.1 $\pm$ 2.9	52.1 $\pm$ 6.9

¹14 patients.

²10 patients.

TABLE III

SUBMAXIMAL INDICES AND ESTIMATIONS OF ADAPTATION CAPACITY AND RELATED 'PHYSIOLOGICAL STRAIN' FOR VENTILATION (MEAN $\pm$ SEM SHOWN)

FEV ₁ (l.) n	Normal Subjects	Patients	
		Group M	Group S
	2.8-4.7 20	1.0-2.2 20	0.2-0.9 20
$\dot{V}_{\text{rest}}$ (l min ⁻¹)	13.9 $\pm$ 1.3	13.8 $\pm$ 1.0	11.4 $\pm$ 0.5
$\dot{V}_{0.75}$ (l min ⁻¹)	18.7 $\pm$ 1.0	24.4 $\pm$ 1.1	23.0 $\pm$ 0.9
$\dot{V}_{1.0}$ (l min ⁻¹)	25.0 $\pm$ 1.0	32.0 $\pm$ 1.4	29.5 $\pm$ 1.2 ¹
$\dot{V}_{1.5}$ (l min ⁻¹)	36.6 $\pm$ 1.5	43.3 $\pm$ 2.4 ²	
FEV ₁ $\times$ 35 (l min ⁻¹)	121.1 $\pm$ 3.9	50.8 $\pm$ 2.9	21.9 $\pm$ 1.6
Max observed ventilation (l min ⁻¹)	49.4 $\pm$ 2.4	48.6 $\pm$ 2.1	30.0 $\pm$ 2.1
Adaptation capacity for $\dot{V}$ (ACV; l min ⁻¹)	108.0 $\pm$ 4.1	34.8 $\pm$ 2.6 ²	19.0 $\pm$ 1.9 ²
Slope for $\dot{V}$ (SV)	23.8 $\pm$ 1.4	31.5 $\pm$ 1.8	25.6 $\pm$ 1.4
'Physiological strain' for $\dot{V}$ $\frac{\dot{SV} \times 100}{\text{ACV}}$ (%)	22.5 $\pm$ 1.4	97.2 $\pm$ 7.50 ²	152.7 $\pm$ 18.7 ²

¹14 patients.²10 patients.³Adaptation capacity and physiological strain in patient groups calculated from the maximum observed ventilation.

FIG. 1. Mean values for cardiac frequency and ventilation at rest and at the submaximal levels of $\dot{V}\text{O}_2$ (0.75, 1.0, and 1.5 l min⁻¹) for all three groups of subjects (open symbols). The values during the last minute of constant work rate exercise (closed symbols) are also shown. The submaximal indices for cardiac frequency are higher in the patient groups than in the normal subjects and are higher in patient group S than group M. There is no increase in the submaximal ventilatory indices in group S from group M.

Plots of V_T against $\dot{V}$ (Hey *et al.*, 1966) for 24 of the patients and for half of the normal men who were selected at random are summarized in Figure 2a. Of the other 16 patients, four showed no increase in V_T but only in frequency during exercise, and 12 were unable to achieve a ventilation of 30 l min⁻¹.

The mean values of V_{T20} and V_{T30} were significantly smaller in both the patient groups than in the normal men ($t=3.5$; $P<0.001$) as were the maximum tidal volumes recorded ($V_{T\text{max}}$) ($t=4.4$; $P<0.001$). When the tidal volumes were expressed as a percentage of the VC, the submaximal and maximal tidal volume

FIG. 2(a). Mean relationships of exercise tidal volume and ventilation illustrating the patterns in the two patient groups and the normal subjects. The maximum tidal volumes reached are indicated by the inflexions.

(b). Mean relationships between the tidal volume as percentage of the vital capacity, and ventilation.

TABLE IV

MEASUREMENTS DURING LAST MINUTE OF INCREASING WORK RATE TEST (MEAN $\pm$ SEM SHOWN)

	Normal Subjects	Patients	
		Group M	Group S
FEV ₁ (l.)	2.8-4.7	1.0-2.2	0.2-0.9
n	20	20	20
Power output (kpm min ⁻¹)	900 $\pm$ 54.7	595 $\pm$ 32.8	385 $\pm$ 33.5
Maximum $\dot{V}O_2$ (ml min ⁻¹)	2012 $\pm$ 104	1511 $\pm$ 83	1034 $\pm$ 85
Maximum cardiac frequency (beats min ⁻¹)	152.4 $\pm$ 2.6	140.0 $\pm$ 4.2	120.9 $\pm$ 3.6
Maximum cardiac frequency as % predicted max fH (%)	86.7 $\pm$ 1.9	82.0 $\pm$ 2.4	71.0 $\pm$ 1.9
Maximum ventilation (l min ⁻¹)	54.4 $\pm$ 2.6	48.6 $\pm$ 2.1	30.0 $\pm$ 2.1
Maximum ventilation as % predicted MVV (%)	45.5 $\pm$ 2.1	99.0 $\pm$ 4.7	146.0 $\pm$ 10.6
Lactate rest (mmol l ⁻¹)	—	0.80 $\pm$ 0.1	0.82 $\pm$ 0.1
Lactate maximum (mmol l ⁻¹)	—	3.63 $\pm$ 0.3	2.56 $\pm$ 0.2
Pao ₂ (rest) mmHg	91.5 $\pm$ 1.7	76.3 $\pm$ 2.1	69.7 $\pm$ 1.4
Pao ₂ (last min of exercise) mmHg	—	76.2 $\pm$ 3.0	60.9 $\pm$ 2.3
Paco ₂ (rest) mmHg	37.6 $\pm$ 1.1	36.5 $\pm$ 0.8	44.6 $\pm$ 1.5
Paco ₂ (last min of exercise) mmHg	—	41.0 $\pm$ 1.3	49.0 $\pm$ 1.8

measurements became similar in all three groups (Fig. 2b). Complete details of the mean and individual data are available elsewhere (Spiro, 1975).

The slope (m) of each Hey plot was similar in group M and the normal subjects but was significantly steeper in group S ($t=2.15$; $0.05 > P > 0.025$). The intercept (k) was similar in all three groups.

Data relating to the last minute of the increasing work rate test are summarized in Table IV. The blood lactate concentration after exercise was significantly higher in group M than in group S ($t=2.71$; $P < 0.01$). The resting Pao₂ was significantly lower in patient group M than in the normal subjects ($t=7.1$; $P < 0.001$) and was significantly lower in group S than in group M ($t=2.28$; $0.05 > P > 0.025$). The resting Paco₂ was significantly raised in group S from that in the normal subjects ($t=4.24$;

$P < 0.001$). In the last minute of exercise, a significant fall in Pao₂ had occurred only in patient group S ($t=2.97$; $0.005 > P > 0.001$). The Paco₂ showed a slight increase in both patient groups which was not significant.

The resting Pao₂ was found to correlate well with the FEV₁ ($r=0.78$; $P < 0.001$; Fig. 3). The maximum ventilation reached during the last minute of exercise was significantly correlated with the measured $\dot{V}O_2$ max ($r=0.85$; $P < 0.001$) and there was also a significant relationship between FEV₁ and the measured $\dot{V}O_2$ max in the patients ($r=0.70$; $P < 0.001$; Fig. 4).

Data obtained in the constant work rate test are summarized in Table V. All subjects exercised in approximately the middle of their working capacity. The V_D/V_T %, V_D , A-a PO₂ gradient, and $\dot{Q}_S/\dot{Q}_T$ %.

FIG. 3. Relationship between the resting PaO_2 and the FEV_1 for the two patient groups and the normal subjects.

were all significantly larger in both the patient groups than in the normal men ($t=4.0$; $P<0.001$). The alveolar-arterial PO_2 gradient was greater in group S than in group M, and the increase in $V_D/V_T\%$ and $Q_S/Q_T\%$ in group S reached statistical significance over group M ($t=2.9$; $0.01>P>0.005$).

The relationship of cardiac output ($\dot{Q}$) to $\dot{V}O_2$ for all three groups fell within the ranges previously reported for normal middle-aged subjects (Reeves *et al.*, 1961; Granath, Jonsson and Strandell, 1964; Becklake *et al.*, 1965; Higgs *et al.*, 1967). The stroke volume (SV) was greatest in the normal men, but this differed significantly only from patient group S ($t=3.29$; $0.005>P>0.001$).

DISCUSSION

These results confirm previous studies in showing that the major limitation to exercise was the impaired ventilatory capacity; as a result both maximum O_2 uptake and the maximum cardiac frequency achieved on exercise were often greatly reduced. Hence it is not possible to use comparative data obtained in normal populations at a $\dot{V}O_2$ of $1.5\ l\ min^{-1}$

$\min^{-1}$ (Davies, 1972) and even comparisons at a standard heart rate of $130\ bt\ min^{-1}$ (Gabriel, 1973) may be impossible in more severely affected patients. Detailed submaximal indices at lower levels of $\dot{V}O_2$ are therefore essential in order to allow direct comparison between patient and normal populations.

CIRCULATORY RESPONSE TO EXERCISE Cardiac output was normal, but the heart rate was abnormally high on exercise in both patient groups S and M. Heart rate in group S was higher than in group M; those patients in group M who achieved a $\dot{V}O_2$ in excess of $1.5\ l\ min^{-1}$ had a normal response. The similar

FIG. 4. Relationship between the maximum oxygen uptake measured during the last minute of the increasing work rate test in the two patient groups and the maximum exercise ventilation achieved (above) and the FEV_1 (below).

TABLE V
MEASUREMENTS DURING SIXTH MINUTE OF CONSTANT WORK RATE EXERCISE (MEAN $\pm$ SEM SHOWN)

	Normal Subjects	Patients	
		Group M	Group S
FEV_1 (l.) n	$2.8-4.7$ 20	$1.0-2.2$ 20	$0.2-0.9$ 20
Oxygen uptake ($ml\ min^{-1}$)	1502 ± 41	1172 ± 59	864 ± 60
Cardiac frequency ($bt\ min^{-1}$)	123.2 ± 3.0	117.6 ± 3.5	109.0 ± 3.2
Cardiac output ($l\ min^{-1}$)	14.9 ± 0.7	12.4 ± 0.7	9.8 ± 0.7
Stroke volume (ml)	122.4 ± 7.1	105.9 ± 6.5	94.2 ± 4.8
A- aPO_2 gradient (mmHg)	19.8 ± 2.3	28.8 ± 2.4	34.4 ± 1.4
Ventilation ($l\ min^{-1}$)	39.1 ± 1.9	33.6 ± 2.2	25.3 ± 1.5
V_D/V_T (%)	16.1 ± 1.4	31.6 ± 2.1	42.5 ± 2.3
V_D (ml)	264 ± 20	409 ± 34	319 ± 16
Venous admixture (%)	2.8 ± 0.4	7.2 ± 1.9	14.5 ± 1.6

slope (SfH) in all three groups indicated that the patients, despite a high resting cardiac frequency, had their greatest increase at the start of exercise (Fig. 1). While normal subjects commencing seated exercise increase their stroke volume by approximately 30% (Astrand and Rodahl, 1970), Gabriel (1973) measured only an 8% increase in SV in a group of subjects with chronic obstructive bronchitis and a mean FEV₁ similar to that of patient group M. Marcus *et al.* (1970) also found a low SV with no change on exercise and a normal cardiac output in patients with chronic airways obstruction. Whether the impaired SV response is due to raised pulmonary artery pressure (Gabriel, 1973) or to features of left ventricular dysfunction (Baum *et al.*, 1971) is uncertain.

VENTILATORY RESPONSE TO EXERCISE Ventilation at a given oxygen uptake was greater in both patient groups than in the normal subjects. This enabled the less severely affected patients (group M) to maintain an arterial Pao₂ within normal limits despite the increased dead space. However, there was no tendency for the more severely affected patients (group S) to show larger increases in ventilation than group M patients even though they had more severe abnormalities in V_D/V_T% and in other indices of pulmonary gas exchange such as A-a_o gradient, venous admixture (Table V), and K_{co}. We presume that patients with airflow obstruction initially try to keep Pao₂ normal during exercise by augmenting their ventilation on exercise but that as obstruction progresses this compensation becomes uneconomic and Pao₂ rises. Nevertheless the deterioration in blood gases during exercise was still remarkably small considering the severity of the airways obstruction. The patients tended to have smaller tidal volumes during exercise, but, when related to VC, their maximum tidal volume incorporated approximately 50% of the VC. The overall pattern became similar to that of the normal men and to normal subjects performing voluntary hyperventilation (Freedman, 1970) and breathing CO₂ (Hey *et al.*, 1966). The intercept 'k' was considered to be 'related to the respiratory dead space' by Hey *et al.* (1966). There was, however, no significant difference between any of the patient groups and the normal subjects for 'k', although dead spaces and V_D/V_T ratios were higher in both patient groups. Thus the possible significance of 'k' remains obscure.

It was the purpose of this study to introduce new indices for assessing the cardiorespiratory responses to submaximal exercise. Indices at submaximal oxygen uptakes, well within the range of capability of patients, can readily be compared with those

reported for normal subjects (Spiro *et al.*, 1974). The slopes (SfH, SV) indicate how much these variables will increase in the course of everyday activities requiring an increase in energy expenditure equivalent to 1 l min⁻¹ V_O₂. The physiological strain, however, depends on the overall physical capacity of the individual to exercise, and in turn requires accurate knowledge of maximum values of fH and V. fH max can be estimated from the age according to the well established formula of Astrand (1960)—for details see Spiro *et al.* (1974).

The prediction of maximum exercise ventilation is difficult, especially in patients with severe airway obstruction. Clark *et al.* (1969) showed that although the ventilatory capacity could be predicted from the FEV₁, this was subject to considerable variation. In the present study the opportunity was taken to re-examine the relation of FEV₁ and exercise ventilatory capacity. The relationship obtained in this part of the study agreed with that taken from the data of Raimondi *et al.* (1970) and Jones *et al.* (1971). By combining all three studies (performed in the same laboratory), it has been possible to have a more confident assessment of maximum exercise ventilation from the FEV₁ (Fig. 5). It should be noted that the prediction of maximum exercise ventilation as FEV₁ × 35, though adequate in normal subjects, considerably underestimates the exercise ventilation achieved by patients with a FEV₁ < 1.0 l.

CHANGES SEEN AT MAXIMUM EXERCISE The resting Pao₂ in the middle-aged normal subjects was similar to those of other studies (Mellemegaard, 1966; Harrison *et al.*, 1974). The resting Pao₂ was lower in our patients than in patients with milder bronchitis studied elsewhere (Levine *et al.*, 1970) but, when matched for FEV₁, the values for group M lay close to values reported in other studies (Simonsson, Malmberg, and Berglund, 1969; Gabriel, 1973). There was a significant drop in Pao₂ from rest to maximal exercise only in patient group S (Table IV), and this was similar to that found by Gabriel (1973) in his patients with chronic obstructive bronchitis. It seems unlikely that this fall in Pao₂ was large enough to influence the end point of the exercise test. There was no correlation between the size of the fall in Pao₂ on exercise and the pulmonary transfer factor for CO (K_{co}).

The peak rise in blood lactate concentration measured 5 to 10 minutes after maximal exercise (Astrand, 1960), was much smaller than that found in normal subjects (Robinson, 1938; Astrand, 1958; Strandell, 1964). None of the patients showed the disproportionate increase in ventilation as maximum

FIG. 5. Summary of different predictors of maximum exercise ventilation in patients with chronic obstructive bronchitis, and the FEV₁. The solid lines are based on actual values, while the FEV₁ × 35 (dashed line) considerably underestimates the exercise ventilation in subjects with FEV₁ < 1 l.

exercise levels were approached which is associated with a rising blood lactate concentration (Cotes, 1968), and it appears unlikely that the peak blood lactate concentrations were high enough to influence their exercise tolerance. Hence we found no evidence that factors other than the maximum exercise ventilation were playing an important rôle in limiting exercise. The only useful information obtained during the final minute of exercise was the level of maximum ventilation, which we have used to calculate an equation for predicting maximum ventilation from the resting FEV₁. We conclude that abnormalities in the cardiac and ventilatory response to exercise in these patients can be detected readily at low levels of O₂ uptake. For most purposes the stress of maximum exercise in patients with chronic obstructive bronchitis appears to be unnecessary since the essential information can be obtained by sub-maximal testing.

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Full details of the individual data are available from S. G. Spiro.

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