Pulmonary function in status asthmaticus: effect of therapy

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In 11 patients with bronchial asthma, lung volumes, $FEV_{1.0}$, PaO_2 , and lung diffusing capacity (single breath CO method) were measured in status asthmaticus and after recovery.

Ventilatory capacity improved following therapy. The improvement was associated with a rise in vital capacity and a fall in residual volume, but the total lung capacity might either decrease, increase or remain unchanged.

A decreased value of PaO_2 was found in all patients in status asthmaticus. After treatment PaO_2 increased in all patients. In two of them PaO_2 increased despite the unchanged values of the other parameters of pulmonary function. The improvement of PaO_2 after treatment is considered to be the result of adjustment of perfusion to ventilation.

The lung diffusing capacity was below normal values in three patients before treatment. After treatment the diffusing capacity increased in six patients. The diffusion constant, although within the normal range in status asthmaticus, increased after treatment in one and decreased in three other patients. The decreased diffusing capacity in status asthmaticus is the consequence of a reduced effective alveolar volume due to uneven distribution of ventilation. The changes observed in the diffusion constant following corticotherapy are ascribed to a dependence of this constant on the different level of the alveolar volume at which the single breath test is performed.

In recent years much information has been published about the impairment of lung function in bronchial asthma. However, most of it was obtained at one stage in the evolution of the disease only, i.e., at a symptom-free period or during exacerbation of bronchial asthma. We consider that a better insight into pulmonary function impairment in bronchial asthma can be obtained by following the same patient from status asthmaticus to a symptom-free interval.

Although serial changes of lung volume in bronchial asthma have been reported already, less attention has been paid to serial changes of oxygen arterial tension (PaO_2) and lung diffusing capacity.

The purpose of this study was to assess the changes of lung volumes, ventilatory capacity, PaO_2 , and lung diffusing capacity in patients with bronchial asthma in status asthmaticus and after recovery.

MATERIAL AND METHODS

Eleven patients (six females) with bronchial asthma in status asthmaticus were studied after admission to

the Department of Allergy of the Institute of Internal Medicine in Bucharest. All had been previously followed in this department for several years. The diagnosis of bronchial asthma was based on clinical criteria (Ciba Guest Symposium, 1959). They had a history of paroxysmal dyspnoea and wheezing interspaced with symptom-free intervals. As some of them were corticoid-dependent, free intervals occurred during the last years only following treatment. Blood or sputum eosinophilia was found in all but one patient. In order to exclude coexisting chronic bronchitis and/or pulmonary emphysema patients with chronic purulent sputum and attenuation of peripheral vessels on the chest radiograph (Laws and Heard, 1962) were not included.

Vital capacity (VC), forced expiratory volume at 1 second ($FEV_{1.0}$), and minute ventilation were measured on a ventilated spirometer (Pulmotest, Godart). Residual volume (RV) was measured using the closed circuit helium dilution method. In order to maintain a constant volume of the spirometer, oxygen was continuously added during the test through a semi-automatic device. Rebreathing was continued until equilibration of the helium in the system was achieved, less than 0.002–0.003% decrease per minute (initial helium concentration 2%) for at least 20 minutes in all patients. Residual volume determina-

tions were carried out in each patient in duplicate, with a pause of about 40 minutes between the tests. Measurements were discarded whenever a difference greater than 10% in functional residual capacity (FRC) between two successive tests was found. Normal values for static lung volumes and $FEV_{1.0}$ in males were those of Jouasset (1960). For VC and $FEV_{1.0}$ in females we used the prediction equations of Berglund, Birath, Bjure, Grimby, Kjellmer, Sandquist, and Söderholm (1963). Normal values for residual volume and total lung capacity (TLC) in females were computed from the RV/TLC ratio of Jouasset (1960) and normal values for VC in females.

The oxygen tension in the arterialized blood (PaO_2) was measured with the Radiometer electrode (E 5046) calibrated with an oxygen free solution and ambient air. Arterialized capillary blood was obtained from the pulp of the finger after at least 10 minutes' warming in a water-bath at 45° C. Three to four blood samples were obtained and measured within five minutes. The results retained represented the means of measurements differing by less than 2 mm Hg.

Pulmonary diffusing capacity (D_L') and 'diffusion constant' (D_L'/V_A') were measured by the single breath method, using the 'effective' alveolar volume (V_A') obtained from helium dilution in the test breath (McGrath and Thomson, 1959) and breath-holding time according to Jones and Meade (1961). Pulmonary diffusing capacity (D_L) was also computed as recommended by Ogilvie, Forster, Blakemore, and Morton (1957) using the sum of RV (helium closed circuit) and inspired vital capacity. Whenever the alveolar sample after anatomical and instrumental dead space washout (minimum 700 ml.) was too reduced (less than 600 ml.) to permit analysis, the alveolar sample was diluted with air in a tonometer. Details of the method have been given elsewhere (Teculescu and Stănescu, in press). Normal values for D_L' and D_L'/V_A' ratio for males were obtained in this laboratory (Teculescu and Stănescu, in press). For females we used the prediction values of Billiet (1966) verified in our laboratory.

PROCEDURE Patients were investigated, while in status asthmaticus (American Thoracic Society, 1968), as soon as they were able to reach the laboratory and perform the tests. At this time they had corticotherapy for one to three days but were still severely short of breath. Bronchodilator drugs were withdrawn eight hours before testing. The sequence of pulmonary investigation was as follows: duplicate measurements of residual volume, determination of oxygen tension in arterialized blood and then duplicate measurements of diffusing capacity. Patients were retested in their best clinical condition 7 to 26 days after the initial investigation. Treatment consisted of corticotherapy, bronchodilators, adrenaline and theophylline derivatives.

The significance of differences in various functional parameters before and after corticotherapy was ascertained with Fisher's *t* test for paired variates.

RESULTS

After treatment all patients claimed that corticotherapy had improved their clinical condition. Some of them, however, were not symptom-free but a better result had not previously been achieved.

Physical data, lung volumes, and ventilatory capacities in all patients before and after treatment are shown in Table I. Vital capacity was reduced in all patients and rose significantly after treatment ($P<0.001$), reaching normal values in all but three patients. $FEV_{1.0}$ and the $FEV_{1.0}/VC$ ratio fell in all patients before treatment, with values as low as 415 ml. and 26.4% respectively. Following corticotherapy the mean values of $FEV_{1.0}$ rose significantly ($P<0.001$) although in two patients it did not change. However, the $FEV_{1.0}/VC$ ratio became normal in only two patients. Mean minute ventilation before treatment (12.7 l./min.) did not differ significantly from the value after treatment (9.23 l./min.). The respiratory rate was similar before (21.7/min.) and after (20.5/min.) treatment. Mean values of TLC after treatment did not differ significantly from those before treatment. However, TLC decreased after corticotherapy in one and increased in three other patients. The RV/TLC ratio was raised in all patients (up to 65%) and fell after treatment in all but two patients. As a group, the RV/TLC ratio decreased significantly ($P<0.001$) after treatment; but was still higher than normal in five patients. The V_A'/TLC ratio was lower than unity in all patients when symptomatic and increased afterwards in all but three patients, reaching unity or near unity.

The PaO_2 , diffusing capacity, and diffusion constant values before and after treatment are shown in Table II.

The arterialized oxygen tension was below normal values in all patients before treatment. Afterwards it increased in all patients ($P<0.001$), reaching normal or near normal values. It must be stressed that PaO_2 attained normal values despite the persistence of an obstructive ventilatory impairment in some patients.

D_L' was below normal values in three patients before treatment. A normal value for the D_L'/V_A' ratio was found in all patients. The mean values of D_L' increased significantly after treatment ($P<0.05$). A net increase in D_L' was found, however, in only six patients after treatment, including two of those with a low initial value. The D_L'/V_A' ratio increased in one and decreased in three patients after corticotherapy. Only a change of

TABLE I

PHYSICAL DATA, LUNG VOLUMES AND VENTILATORY CAPACITIES BEFORE AND AFTER CORTICOTHERAPY IN ASTHMATIC PATIENTS

Patient	Sex	Age	Height (cm.)	VC (ml. BTPS)	VC (% of predicted)	TLC (ml. BTPS)	TLC (% of predicted)	VA' (ml. BTPS)	VA'/TLC %	RV (ml. BTPS)	RV/TLC %	FEV _{1.0} (ml. BTPS)	FEV _{1.0} /VC %
1	M	43	168	2,700 4,470	57 95	4,600 6,130	73.6 98.0	4,250 5,530	0.92 0.90	1,900 1,660	41.5 27.0	1,180 3,240	43.8 72.5
2	M	45	164	3,020 4,350	69 99	6,830 6,900	118 119	3,820 6,120	0.56 0.88	3,780 2,550	55.5 37.0	790 1,910	26.4 44.0
3	F	31	155	1,380 2,920	43 91	3,900 5,290	93 126	2,990 5,250	0.77 0.59	2,530 2,370	65.0 45.0	410 1,070	30.0 36.6
4	M	53	159	2,880 2,850	74 74	5,180 4,430	97.7 83.5	4,100 4,500	0.79 1.00	2,300 1,580	44.5 36.0	1,470 1,680	51.0 59.0
5	F	29	153	3,160 4,250	99 133	5,320 5,340	131 132	4,300 5,350	0.81 1.00	2,160 1,090	40.0 20.5	1,610 2,750	63.2 64.8
6	F	54	155	2,070 3,110	76 114	5,470 5,380	147 144	3,510 4,790	0.64 0.89	3,400 2,270	62.0 42.0	650 1,550	31.3 49.8
7	F	40	168	3,200 4,230	90 119	6,200 6,100	132 130	5,110 5,340	0.83 0.89	3,000 1,870	48.5 31.0	1,280 2,360	40.5 56.0
8	F	34	160	1,750 3,950	52 118	4,600 6,000	106 139	3,980 5,390	0.86 0.90	2,850 2,040	62.0 34.0	560 2,350	27.8 59.5
9	M	52	168	1,750 1,750	38 38	4,620 4,530	74 72.5	3,800 3,820	0.82 0.82	2,870 2,780	62.0 61.5	780 680	41.8 39.0
10	M	47	165	3,150 3,300	71 74	6,130 6,240	103 105	5,320 5,450	0.85 0.87	2,970 2,840	48.5 47.0	1,200 1,470	36.4 44.5
11	F	30	155	2,240 3,450	69 106	4,000 4,190	96 100	3,330 3,900	0.83 0.93	1,760 740	44.0 17.5	1,280 2,540	48.5 74.0

TABLE II

LUNG DIFFUSING CAPACITY, DIFFUSION CONSTANT AND ARTERIALIZED OXYGEN TENSION BEFORE AND AFTER CORTICOTHERAPY IN ASTHMATIC PATIENTS

Patient	DL' (ml. CO min. ⁻¹ mm. Hg ⁻¹)	DL ¹ (% of predicted)	DL (ml. CO min. ⁻¹ mm. Hg ⁻¹)	DL'/VA' (ml. CO min. ⁻¹ l. ⁻¹)	D'/VA' ² (% of predicted)	PaO ₂ (mm. Hg)
1	25.0 34.9	81 114	25.3 36.1	6.64 7.12	104 112	58 93
2	18.7 32.9	64.5 113	31.8 39.1	5.35 6.56	85.5 105	66 85
3	17.3 21.8	68 85.5	22.7 22.0	7.05 5.04	114 81.5	59 74.5
4	22.5 25.7	90 103	29.3 25.3	6.87 6.92	118 119	71 87.5
5	25.5 24.9	100 98	31.6 25.8	7.21 5.85	100 80.6	70.5 81.5
6	17.6 18.0	80 82	27.4 20.3	6.07 4.58	95 71.5	67 78
7	25.5 24.7	95 93	30.5 28.7	5.95 5.71	86.5 83	66.5 88
8	20.9 24.7	80 94.5	24.0 27.2	6.32 5.49	89 77.5	64 79
9	18.0 18.0	64 64	22.0 21.4	5.77 5.72	98 98	66.5 78.5
10	26.3 28.1	90 96	31.4 32.8	6.20 6.35	101 103	61 86
11	22.1 23.8	86.5 93	25.3 23.4	7.65 6.74	106 93.5	68 91.5

¹ Normal range 74–126% for males and 72–128% for females.² Normal range 73–127% for males and 75–125% for females.

more than 15% in the DL was taken into account. Previous investigations had shown a coefficient of variation of DL₁₀₀ measurements on separate days of between 4.0 and 7.8% (Smith and Hamilton, 1962; Englert, 1967; Billiet, 1966). After treatment DL' remained below normal in one patient; in another patient, DL'/VA' became normal.

DISCUSSION

LUNG VOLUMES A few studies have dealt with the serial changes of lung volumes in asthmatic patients (Engström, 1964; Woolcock and Read, 1966; Gold, Kaufman, and Nadel, 1967; Meisner and Hugh-Jones, 1968; Weng and Levi-son, 1969).

Lung volume in the above-mentioned studies was measured either as thoracic gas volume (TGV) by body plethysmograph or using dilution methods (helium closed circuit, TLC_{He}; or N₂ washout procedure, TLC_{N2}). As is known, when there is no communication between ambient air and some pulmonary regions, dilution methods underestimate the measurement of FRC compared with the plethysmographic method. No comparative determinations of TGV and TLC_{He} or TLC_{N2} from status asthmaticus to the symptom-free interval have been done, except by Meisner and

Hugh-Jones (1968). However, these authors made a further sub-estimation of the TLC_{He} , limiting the helium equilibration time to 7 minutes.

Our results are similar to those of other studies using the helium dilution method. After treatment TLC_{He} decreased, increased or remained unchanged. In all these circumstances FRC and RV either decreased or remained unchanged and VC increased or remained unchanged. The increased FRC and RV after treatment in some of the patients reported by Woolcock and Read (1966) is a surprising result, not confirmed by the present data or by other studies.

Any attempt to explain the mechanisms governing lung volume changes in bronchial asthma must take into account that only FRC is determined 'objectively', while RV and inspiratory capacity can be influenced by the fatigue and/or lack of co-operation of the subjects. RV is related in some way to airway obstruction and FRC is determined by the equilibrium between the opposite forces of the lung and thorax, but we know very little about the factors limiting maximal inspiratory volume in health and disease.

The results reported by Gold *et al.* (1967) with the plethysmographic method showed that TGV in status asthmaticus is increased or has the same value comparatively as after treatment. No decrease of TGV in status asthmaticus was reported. One can conclude that the decrease of TLC, as measured with the dilution methods, observed in exacerbations of asthma is probably due, as has been previously pointed out, to an underestimation of FRC due to closure and/or plugging with mucus of some airways resulting in regions in which helium does not dilute. The increase of TLC (observed with both dilution and plethysmographic methods) during symptomatic asthma has not as yet received a satisfactory explanation. Recently, Finucane and Colebatch (1969) suggested a reduction of tissue forces in overinflation of the lung in asthma. Their explanation is, however, not compatible with the rapid deflation of the lung following the use of bronchodilator drugs. It is puzzling that some patients 'respond' to airways obstruction with closure of airways, leading to a decrease of TLC_{He} , while in others there is apparently no airways closure but hyperinflation (an increase of both TLC_{He} and TGV). There is still another category in which both TLC_{He} and TGV remain unchanged and there is only a relative hyperinflation, i.e., the increase in RV is counterbalanced by an equal decrease of VC. The different behaviour of the TLC bears no relation to the degree of airway obstruction as measured

by $FEV_{1.0}$. It is of interest to point out that in both studies of lung volumes in asthmatic children no increase of TLC_{He} during asthmatic attacks was reported (Engström, 1964; Weng and Levison, 1969). The lack of increase in TLC in asthmatic exacerbations in children may be due to plugging of airways with mucus (smaller airways diameter) and/or an underestimation of inspiratory capacity due to exhaustion of respiratory muscles.

Comparative determinations of the multibreath (TLC_{He}) and single breath helium technique (V_A') showed a lower than unity (V_A'/TLC_{He}) ratio in all our patients during status asthmaticus, confirming previous experience that the helium single breath method underestimates TLC compared with the closed circuit method in patients with obstructive airways (Morton and Ostensoe, 1965; Teculescu and Stănescu, 1969). Improvement in the clinical condition resulted in a marked increase of V_A' irrespective of the divergent changes of TLC_{He} , leading to a rise in the V_A'/TLC_{He} ratio, which reached unity in most of the subjects. We agree that this phenomenon occurred although the $FEV_{1.0}$ and RV/TLC ratio did not reach normal values. We might think that below a certain level of obstruction an apnoea of 10 seconds allows helium to reach by diffusion the terminal air spaces, i.e., the series component of the distribution impairment is cancelled. If this is the correct explanation, we can assume that no major parallel distribution component is present at this time.

ARTERIAL OXYGEN TENSION A decreased value of PaO_2 was found in all patients in status asthmaticus. PaO_2 increased significantly ($P < 0.001$) after treatment. Similar results have been reported by several authors (McFadden and Lyons, 1968; Meisner and Hugh-Jones, 1968; Palmer and Diamant, 1969; Simpson, Forfar, and Grubb, 1968; Tai and Read, 1967; Valabhji, 1968). A ventilation-perfusion imbalance seems to be the cause of hypoxaemia in acute attacks of asthma, and we think the increase of PaO_2 values after clinical improvement is associated with a more even distribution of ventilation and perfusion. In several patients PaO_2 reached normal or near normal values; though $FEV_{1.0}$ increased and the RV/TLC ratio decreased, a spirographic defect and hyperinflation were still present. A similar observation was made recently by Valabhji (1968) in 6 out of 12 patients with bronchial asthma. In these 6 patients clinical recovery was associated with a normal level for the alveolo-arterial gradient despite persisting airways obstruction. These results

suggest the intervention of a protective homeostatic mechanism matching the perfusion to ventilation, as an uneven distribution of ventilation was previously found in asymptomatic patients (Stănescu, Teculescu, Păcuraru, and Popa, 1968).

In patients 9 and 10, PaO_2 values increased significantly after corticotherapy although the airway obstruction remained unchanged. Recently, Fuleihan, Feisal, and Malouf (1967) also reported a significant increase of PaO_2 after corticotherapy in patients with chronic bronchitis, without any change in the clinical condition or spirographic performance. They thought that a more uniform distribution of ventilation in relation to perfusion was responsible for this improvement in PaO_2 values, and probably the same mechanism operated in our two patients.

LUNG DIFFUSING CAPACITY Previous studies have shown that the diffusing capacity of the lung is normal in bronchial asthma (Burrows, Kasik, Niden, and Barclay, 1961; Kanagami, Katsura, Shiroishi, Baba, and Ebina, 1961; Bedell and Ostiguy, 1967; Pecora, Bernstein, and Feldman, 1966), and so this test has been considered useful to differentiate bronchial asthma from pulmonary emphysema. However, the clinical condition of the patients investigated in these studies has not been mentioned. A significant fall of D_L was reported by Palmer and Diamant (1969) in a group of asthmatic patients with severe obstructive ventilatory impairment compared with a group with mild obstruction. No influence of the ventilatory obstruction on D_L was found by McFadden and Lyons (1968) when comparing asthmatics with severe and mild to moderate obstruction. The above-mentioned studies presented the results of D_L as mean values, so that individual trends could be overlooked: these investigations were carried out only at one moment in time. In our present survey only the studies dealing with the single breath method were mentioned. The other methods for measuring $D_{L\infty}$ are too sensitive to the distribution of ventilation and perfusion to be useful in patients with bronchial asthma.

Our results show that in status asthmaticus the D_L'/V_A' ratio was normal in all patients and D_L' was below normal in 3 out of 11 patients. After treatment the D_L'/V_A' ratio became abnormal in one patient while D_L' reached normal levels in all. D_L' increased in five patients and the D_L'/V_A' ratio increased in one and decreased in three others. This variable pattern of response of the D_L' and D_L'/V_A' ratio was present despite a definite increase of $\text{FEV}_{1.0}$ in 10 and PaO_2 in all

patients. An increase of D_L and a decrease of the D_L/V_A ratio was reported in three asthmatic patients when the ventilatory obstruction improved (Meisner and Hugh-Jones, 1968).

The decrease of D_L' observed in our patients in status asthmaticus is due to the reduced value of the effective alveolar volume. Although the D_L single breath method is reputed to be less sensitive to functional unevenness than other methods, in extreme cases an impaired distribution of inspired air, regional variations of V/Q and the D_L/Q ratio can decrease $D_{L\infty}$ (Piiper and Sikand, 1966). A decrease of D_L' was previously found by us in asthmatic patients following an induced attack of asthma (Stănescu and Teculescu, 1969). Whenever a ventilation unevenness is present Piiper and Sikand (1966) proposed to calculate the true D_L by multiplying D_L' by the V_A/V_A' ratio, i.e., using D_L instead of D_L' . It is evident that as TLC is greater than V_A' , D_L would be greater than D_L' (see Table II). At present there is no agreement concerning the use of V_A' or TLC to compute D_L' . In recent years, however, several investigations have used V_A' as this is the actual volume involved in the uptake of CO during the single breath test. To use D_L instead of D_L' is merely to ascribe to the total lung capacity the diffusion characteristics measured in a smaller lung volume.

In normal subjects it has been shown that D_L increases and the D_L/V_A ratio decreases with the increase of alveolar volume (McGrath and Thomson, 1959; Cadigan, Marks, Ellicott, Jones, and Gaensler, 1961). The rate of change of $D_{L\infty}$ and D_L/V_A with the alveolar volume is variable from one subject to another. This relationship is not linear over the whole alveolar volume. One can observe an increase in D_L with a concomitant decrease or little change in D_L/V_A , or a decrease in D_L/V_A with little change in D_L (Billiet, 1965). It may be questioned whether this relationship is valid in the nonhomogeneous lung. Apart from the six patients with chronic bronchitis and emphysema of McGrath and Thomson (1961) studied over a limited range of alveolar volume, there are no other studies in patients with obstructed airways. We believe that in our patients one can ascribe the changes of D_L' and D_L'/V_A' ratio to the increase in effective alveolar volume. This explanation is compatible with the results of all but one patient, in whom an increase of V_A' was accompanied by an increase in both D_L' and D_L'/V_A' ratio. We think that in status asthmaticus the low V_A' is well ventilated and perfused. As the clinical condition improved new lung territories were included with a smaller blood to gas ratio,

leading to a reduced uptake of CO.

We believe that the decrease of D_L' in status asthmaticus is 'apparent', i.e., does not represent a true impairment of diffusing capacity of the lung. The decrease of PaO_2 in status asthmaticus is not considered to be the result of diffusion limitation, as an uneven ventilation-perfusion ratio and an increased venous admixture, both documented findings, fully explain hypoxaemia. Moreover, if D_L' bears any relationship to PaO_2 , it is difficult to explain the increase of PaO_2 observed in several of our patients without an increase in D_L' and in the D_L'/V_A' ratio.

Irrespective of the hypothesis advanced for the alterations of D_{Lco} , the abnormal values of this parameter in some of our patients in status asthmaticus may limit the value of the D_{Lco} method to differentiate asthmatics from emphysematous patients, though the return to normal values of D_{Lco} after treatment may help in this separation.

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