

The "within-patient" variance for P.I.F.R. was greater than that for P.E.F.R. over most ranges, but was not excessive.

Change in P.E.F.R. was significantly correlated with change in F.E.V.₁, but not with change in F.V.C. Change in P.I.F.R. was significantly correlated with change in F.V.C., but not with change in F.E.V.₁.

In a group of patients without radiological emphysema P.E.F.R., F.E.V.₁, P.I.F.R., and F.V.C. increased significantly after isoprenaline. In a group of patients with radiological emphysema P.I.F.R. and F.V.C. increased significantly but P.E.F.R. and F.E.V.₁ did not. It is suggested that in the second group expiratory airways collapse may mask the relief of peripheral bronchial spasm by isoprenaline.

Lack of response to isoprenaline when tests of forced expiration are used alone should not be regarded as evidence that bronchodilator drugs are of no benefit to the patient. Measurements of inspiratory flow may prove a more sensitive index of bronchodilator response.

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Hypoxia in Bronchial Asthma

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The increased resistance to air flow, bronchial closure, and uneven distribution of ventilation which occurs in bronchial asthma has been extensively described, but relatively little attention has been paid to the effects on the gas exchange and on the arterial blood gas tensions during actual paroxysms of asthma.

The purpose of this paper is to present the results of blood gas studies during and after recovery from acute attacks of asthma severe enough to require steroid therapy; also before and after inhalation of isoprenaline.

Methods

The patients studied all gave a history of paroxysmal expiratory distress associated with objective evidence of airways obstruction but without conclusive radiological signs of emphysema, nor a history of regular daily sputum production. None of the patients was in cardiac failure; in many the attacks of dyspnoea appeared to be related to episodes of emotional stress or to the pollen season; they all obtained considerable subjective benefit from bronchodilator drugs, and most had less than grade II dyspnoea during remissions.

The patients were studied initially when in hospital; the measurements were made in a reclining position. Follow-up measurements were made when the patients appeared to be clinically improved, usually one to three weeks after the first measurements. After an acclimatization period expired air was collected in a Douglas bag for five minutes while three heparin-

ized arterial blood samples were slowly withdrawn. The arterial blood oxygen tension (Pao₂) was measured with a Clark Bishop oxygen electrode which was calibrated with two samples of water equilibrated with known gas mixtures (8% oxygen and 13.3% oxygen or air). The electrode was also checked against tonometered blood; the mean ratio of Po₂ determined in blood to that in water was 1.06, a figure which agrees closely with that of other laboratories. The arterial carbon dioxide tension (Paco₂) was measured with the Astrup micro pH electrode and microequilibration apparatus. Expired air was analysed with a Haldane apparatus.

The physiological dead space (VD) was calculated from the Bohr formula:

$$VD = \frac{VT \times (Paco_2 - PECO_2)}{Paco_2} - \text{apparatus dead space.}$$

where VT = Tidal volume.

PECO₂ = Tension of carbon dioxide in expired air.

The "ideal" alveolar oxygen tension (PAO₂) was calculated from the alveolar air equation:

$$PAO_2 = P_I O_2 - Paco_2 \left(F_I O_2 + \frac{1 - F_I O_2}{R} \right)$$

where P_IO₂ = Inspired air oxygen tension.

F_IO₂ = Fraction of oxygen in inspired air.

R = Respiratory exchange ratio.

Isoprenaline was administered by Medihaler, and the measurements were repeated immediately without an acclimatiza-

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tion period. Results were also obtained on nine subjects who were thought to have no disturbance of respiratory function. Five of these subjects were healthy non-hospitalized volunteers and four were inpatients.

Results

In the Table the age, sex, PAO₂, Pao₂, P_aCO₂, and P.E.F.R. are shown for each patient during an attack of asthma.

Results During an Attack of Asthma

Case No.	Sex	Age in Years	PAO ₂ (mm. Hg)	Pao ₂ (mm. Hg)	P _a CO ₂ (mm. Hg)	P.E.F.R. (l./min.)
1	M	12	114	71	35	60
2	M	24	110	57	46	60
3	M	26	86	68	61	75
4	F	28	98	61	37	75
5	F	28	117	72	38	235
6	M	30	85	39	43	130
7	F	31	90	36	45	50
8	M	49	99	75	45	30
9	F	51	104	69	33	60
10	F	53	117	71	39	150
11	M	53	107	55	44	125
12	F	56	105	72	33	135
13	F	56	105	49	40	120
14	F	64	86	51	51	60
15	F	72	112	67	34	60

The other results are shown in Figs. 1-3. The PAO₂, alveolar-arterial oxygen difference (A-aDO₂) and the V_D/V_T ratio are each plotted against age. For clarity the results are separated into those obtained before and after recovery (A) and before and after isoprenaline (B). The predicted normal means are shown by the solid regression lines and two standard deviations by the broken lines (Raine and Bishop, 1963).

It will be seen from Fig. 1 A that in all the patients there was arterial hypoxia during the attacks of asthma, and that the Pao₂ consistently improved on recovery. The improvement in Pao₂ was less consistent and invariably less in degree after the inhalation of isoprenaline (Fig. 1 B). In two patients (Cases 8 and 9) the hypoxia became worse after isoprenaline.

Fig. 2 A shows that the A-aDO₂ was abnormally high in all the patients during their attacks of asthma and returned to more normal levels on recovery, except in one patient (Case 4). After the second A-aDO₂ estimation had been made in this patient further clinical recovery took place, and if the estimation had been made a third time some improvement might have been expected. It will be seen from Fig. 2 B that isoprenaline failed to produce a consistent improvement in the A-aDO₂, and in one patient (Case 8) it was actually made worse.

Fig. 3 A shows that improvement in the ratio of physiological dead space to tidal volume (V_D/V_T%) during recovery

occurred consistently only in patients aged under 35 years. It will be seen from Fig. 3 B that isoprenaline did not produce any significant improvement in any of the patients, and in one patient (Case 8) it was made considerably worse.

Discussion

Little attention has been paid to the blood gas changes during actual attacks of bronchial asthma until recent years. It has generally been assumed that the P_aCO₂ is usually normal or low, due to hyperventilation, until the terminal stages of status asthmaticus, when respiratory failure supervenes and the P_aCO₂ rapidly rises (Marchand and van Hasselt, 1966).

Previous studies of the blood gas changes in bronchial asthma have not suggested that arterial oxygen desaturation is common, at least in ordinary attacks of bronchial asthma not severe enough to be described as terminal status asthmaticus.

Herschfus *et al.* (1953) studied 15 patients during attacks of bronchial asthma, and found that in only two patients was there arterial oxygen desaturation. Similarly, Williams and Zohman (1960) found slight desaturation (average 89%) in 11 out of 15 patients studied during paroxysms of bronchial asthma. In none of these patients were blood carbon dioxide levels raised, suggesting that alveolar hypoventilation was not the cause of the hypoxaemia.

In our studies the normal P_aCO₂ in all but two patients (Cases 3 and 14) and the normal calculated PAO₂ in all but three patients (Cases 3, 6, and 14) suggests that alveolar hypoventilation was rarely a contributing factor to the arterial hypoxaemia. On the other hand, the increased A-aDO₂ and physiological dead space suggests that the hypoxaemia was largely caused by uneven ventilation perfusion (V/Q) ratios. This is not surprising, since ventilation is uneven in attacks of asthma because of the very nature of the disease (Herschfus *et al.*, 1953), and it is unlikely that local alterations in perfusion could compensate for all this unevenness of ventilation.

Single cases of asthma with V/Q disturbances have been reported by Donald *et al.* (1952) and by West *et al.* (1957). Bentivoglio *et al.* (1963), studying asthmatic patients during remission with radioactive xenon, found zonal abnormalities of V/Q ratios but thought that their method was relatively insensitive. An abnormally high percentage of the cardiac output perfused poorly ventilated compartments in the lungs of asthmatic children studied by Ledbetter *et al.* (1964). This would have the effect of increasing venous admixture.

Disturbances of V/Q ratio do, of course, occur in chronic bronchitis and emphysema, but we do not think that this was

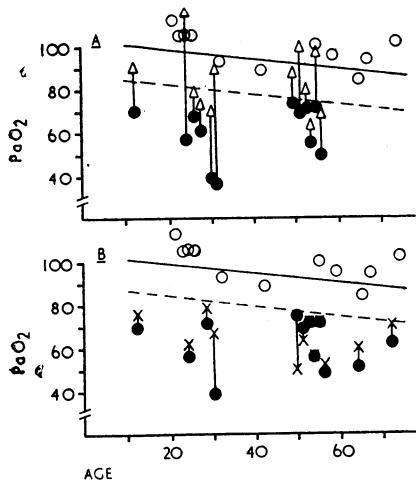


FIG. 1.—Pao₂ (mm. Hg) in asthmatics measured: A, before (●) and after (△) recovery. B, before (●) and after (×) isoprenaline. Open circles (○) indicate normal controls.

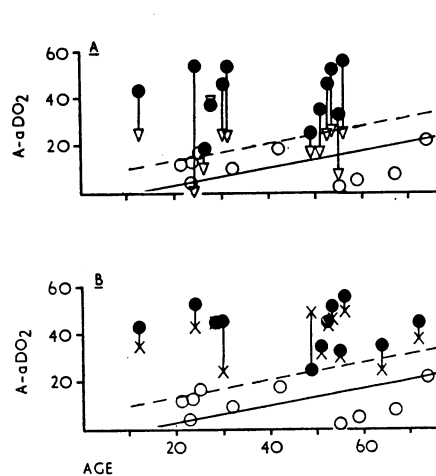


FIG. 2.—A-aDO₂ (mm. Hg) in asthmatics measured: A, before (●) and after (▽) recovery. B, before (●) and after (×) isoprenaline. Open circles (○) indicate normal controls.

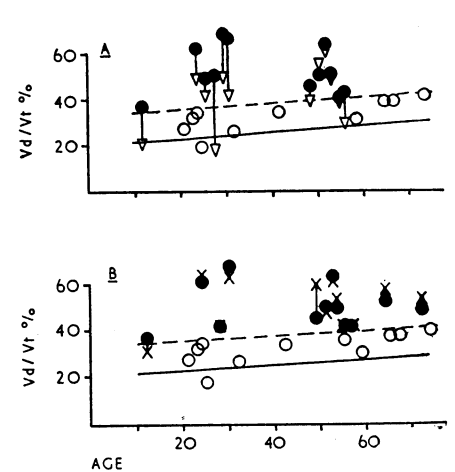


FIG. 3.—V_D/V_T% in asthmatics measured: A, before (●) and after (▽) recovery. B, before (●) and after (×) isoprenaline. Open circles (○) indicate normal controls.

the cause of the disturbances in our patients. None showed radiological evidence of emphysema, and because emphysema was less likely to be present in younger patients the results in the under 35-year-old patients were considered separately. In these younger patients the $A-aDO_2$ and V_D/V_T ratios were disturbed just as severely during their attacks of asthma as in those patients who were more than 35 years old. Furthermore, the return of the Pao_2 measurements to more normal levels on recovery helps to differentiate "variable" or "reversible" airways obstruction due to asthma from irreversible obstruction due to chronic bronchitis and emphysema.

Our results indicate that the $Paco_2$ alone is not an adequate estimate of respiratory failure in bronchial asthma. The respiratory defect in asthma, at least before the terminal stage is reached, is predominantly one of V/Q disturbance rather than alveolar hypoventilation, and consequently the $Paco_2$ is nearly always normal.

The frequent failure of the $A-aDO_2$ and V_D/V_T to improve after isoprenaline inhalation may at first seem surprising. However, it can be readily explained if ventilation is preferentially increased to already overventilated alveoli and if perfusion is preferentially increased to already overperfused alveoli and thereby fails to diminish venous admixture. Halmagyi and Cotes (1959) and Daly and Howard (1965) similarly found that bronchodilators failed to improve arterial desaturation in patients with airways obstruction.

All our patients felt considerable subjective improvement during recovery, but in four there was no improvement in the P.E.F.R. and in the others the P.E.F.R. failed to return to normal levels; this failure of changes in objective tests of airways obstruction to match subjective improvement is a common clinical observation. On the other hand, subjective improvement was invariably associated with an improvement in the Pao_2 and in the $A-aDO_2$. These observations in the recovery phase could be accounted for by an increase in ventilation or decrease in perfusion of alveoli with a low V/Q ratio—that is, a decrease in venous admixture. It is possible that this is the mode of action of corticosteroid drugs, in contrast to that of sympathomimetic drugs such as isoprenaline. The latter do not appear to cause a consistent reduction in the $A-aDO_2$ and in venous admixture.

It is clear, therefore, that tests of airways resistance and uneven ventilation are not alone adequate for the full assessment

of the severity of bronchial asthma, and particularly the response to therapeutic agents. For many years practically all assessments of drugs in the treatment of bronchial asthma have been made on the basis of the relief of bronchospasm measured by tests of airways resistance. There are now good reasons for a search for drugs which will also improve the disturbance of V/Q ratios. For routine clinical purposes, however, measurement of Pao_2 and calculation of the $A-aDO_2$ and V_D/V_T are not necessary, because the hypoxaemia, whatever the type and degree, is readily correctable by the administration of oxygen.

Summary

The arterial oxygen tension, alveolar arterial oxygen difference, and physiological dead space have been measured in 11 controls and in 15 patients during and after acute attacks of asthma, severe enough to require steroid therapy. The results were consistently abnormal during an attack of asthma but returned to more normal levels on recovery. It is concluded that uneven ventilation-perfusion ratios occur during attacks of asthma and give rise to arterial hypoxia more often than is appreciated on clinical evidence.

Isoprenaline produced inconsistent changes in the ventilation-perfusion abnormalities, and it is concluded that these factors are important in the assessment of drugs for the treatment of bronchial asthma, and that tests of airways resistance are not alone adequate for the assessment of response to treatment.

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Summer and Death from Neuroblastoma

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It has been shown that the peak incidence of acute leukaemia is in the summer (Lee, 1962) and that peak mortality is also in the summer (Lee, 1967). Its age distribution and naturally occurring remissions and relapses distinguish acute leukaemia from other forms of neoplastic disease. It is therefore important to determine whether this unexpected seasonal distribution is limited to acute leukaemia.

Most solid tumours affect middle-aged or elderly people. Their mortality (Allan, 1966) and the incidence of the first symptom of new cases (Lee and Gardner, 1965) are highest in the winter months; this seasonal pattern can reasonably be related to coincidental respiratory infections. Now such infections are likely to be of less consequence in children.

Furthermore, neoplastic diseases in children generally run a more rapid course than in adults, so that opportunities are fewer for infections to occur and for determining the clinical course. I have therefore made a study of neoplastic disease in children. The date of onset of disease, however defined, is always open to question. Did the patients notice their symptoms just then? and why? Why were they admitted on that day? To avoid this type of difficulty a study was made of the seasonal distribution of deaths from neoplastic disease in children.

Deaths from Neoplastic Disease in Children

The various types of neoplastic disease in children aged 0-14 in England and Wales during the years 1958-64 caused the

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