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REGIONAL PULMONARY FUNCTION STUDIED WITH XENON^{133} IN PATIENTS WITH BRONCHIAL ASTHMA *

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It has been known for some years that there may be impairment in the distribution of an inert gas in the lungs of patients with bronchial asthma at a time when the disease appears to be in remission (1, 2). Maximal ventilatory air flow may also be reduced in the absence of symptoms (2).

A recently described technique for the study of regional distribution of pulmonary ventilation and perfusion using xenon^{133} (3) appeared to be suitable for the study of zonal variations in function in these patients.

METHODS

Selection of patients. One of us (B.R.) selected twelve asthmatic patients in remission, eight men and four women, ranging in age from 17 to 46 years, with an average age of 31 years. All patients had been observed over the course of several years and gave an average 10-year history (3 to 26 years) of recurrent, typical attacks. Between attacks, all patients were free from cough and dyspnea, and this, together with the nature of the attacks of spasmodic asthma, clearly distinguished them from patients with chronic bronchitis and emphysema. Two patients were on no treatment at the time of the study, while the remainder were receiving vaccine injections at varying intervals, and small doses of steroids, or conventional bronchodilators, or both.

Routine pulmonary function tests in ten patients immediately followed the xenon^{133} study; in two subjects, the tests preceded the study by a variable interval, but airflow measurements at the time of the xenon study agreed with those recorded earlier, indicating that the clinical condition of the patients had not changed. The tests included the study of the total lung capacity and its subdivisions, maximal mid-expiratory flow rate, forced expiratory volume, mixing efficiency, and steady-state resting diffusing capacity of the lung for carbon monoxide (end-tidal sample). Details of these techniques and prediction tables have been reported elsewhere (4–7). For maximal mid-expiratory flow rates, the prediction formulas for men had to be used, owing to the lack of prediction data for women.

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Xenon^{133} technique. A technique using xenon^{133} to measure regional lung function has recently been reported from this laboratory (3). Six scintillation counters were placed over the chest posteriorly, in standard positions in relation to a 6-foot posteroanterior chest film. Pulses from each counter were fed through amplifying and discriminating circuits, recorded on a multichannel magnetic tape recorder, and displayed through counting-rate meters onto a 4-channel direct writer. The zonal distribution of ventilation was studied by recording the count-rate plateaus after the subject took a normal and a full inspiration from a spirometer containing xenon^{133} in air. The zonal distribution of pulmonary blood flow was determined by rapid intravenous injection of xenon^{133} dissolved in saline, followed immediately by a breathholding maneuver in full inspiration. Since approximately 95% of the injected xenon^{133} is discharged into the alveoli during its first passage through the lung (8), the regional concentration is directly proportional to regional perfusion. Likewise, the regional concentration of xenon^{133} after a single inspiration of a mixture of this gas in air is directly proportional to regional ventilation.

To obtain regional concentration from the regional count rate, the ratio between external count rate and concentration must be established for each counter in each subject. This was determined by equilibrating the gas in the lung with a xenon^{133}-in-air mixture in a closed spirometer circuit, in which the concentration is continuously monitored. At equilibrium, each lung zone has a concentration equal to the spirometer concentration, and the count rate from each counter was proportional to this. In order to permit direct comparison of data from different subjects, Ball, Stewart, Newsham, and Bates (3) expressed the zonal concentrations as distribution indexes. These expressed the actual concentration as a percentage of the concentration that would have existed if the distribution had been completely uniform. This ideal concentration is calculated from the amount of xenon inspired (or injected) and the functional residual capacity.

For detection of minor ventilatory abnormalities, the ventilation distribution indexes previously described (3) present certain limitations. *1)* The error due to the random nature of radioactive decay is inversely proportional to the counting rate and the duration of counting. With a deep inspiration, the counting rates are relatively high because of the large volume inspired, and the error due to the random nature of the decay is not more than 5%

(3). When the breath is held after a small tidal volume, however, relatively low counting rates are recorded, for a shorter time interval, and thus the error from this cause is higher. *2*) The distribution of a single breath measured during breathholding is an incomplete description of the dynamic distribution of ventilation during normal respiration. It may be shown that the distribution during a single breath and subsequent breathhold is primarily determined by the regional compliance and the initial pressure-volume conditions of the region. Airway resistance does not influence the distribution except indirectly by affecting the initial conditions created by previous respirations. Thus it is to be expected that if the abnormality in the lung is only of differing degrees of airway obstruction in different zones, such defects would be demonstrable by the study of dynamic distribution of ventilation during normal breathing, but might be obscured if the single-breath distribution only is measured.

In order to avoid these shortcomings, the resting ventilation, in addition to being appraised by the routine method, was also studied by measurement of the rate at which each lung zone equilibrated during breathing of a xenon^{133}-in-air mixture from a closed circuit. The quantitative analysis of the xenon "wash-in" curves so obtained would theoretically provide a better estimate of regional ventilation inequality than the static indexes for the following reasons. *1*) The xenon wash-in curve follows ventilation over several minutes, and the calculation uses a portion of the curve that has higher counting rates. *2*) Each zone can be assessed independently of other lung zones.

Dollery, Hugh-Jones, and Matthews (9) have recently suggested that the "wash-out" of xenon may be the best method of studying continuous ventilation. We have found, however, that it is preferable to study the wash-in phase, since the residual tissue xenon in the muscles of the chest wall and that returning to the lung produce serious distortion of the later part of the lung clearance curves.

To allow the recording of undistorted xenon^{133} wash-in curves, the original technique was slightly modified (Figure 1). After the initial breathholding maneuvers, the patient was disconnected from the xenon circuit and allowed to clear the xenon from his lungs. The equilibration procedure was then carried out with the patient instructed to breathe regularly and evenly while the respiratory excursions were recorded on the spirometer kymograph as well as electrically onto the tape. When no further increment of counting rate occurred over any lung zone, the xenon^{133} counting rate from the spirometer circuit had also reached an equilibrium value.

The observed time to reach 90% of the equilibrium counts over each lung zone was then compared with the predicted time (calculated from a suitable formula) and could thus be expressed as a percentage of the predicted time. The formula, derived by the same principle as that used to calculate mixing efficiency by closed-circuit helium wash-in (10), $n = -1/\log Q$, where n = number of breaths needed to reach 90% of the equilibrium value

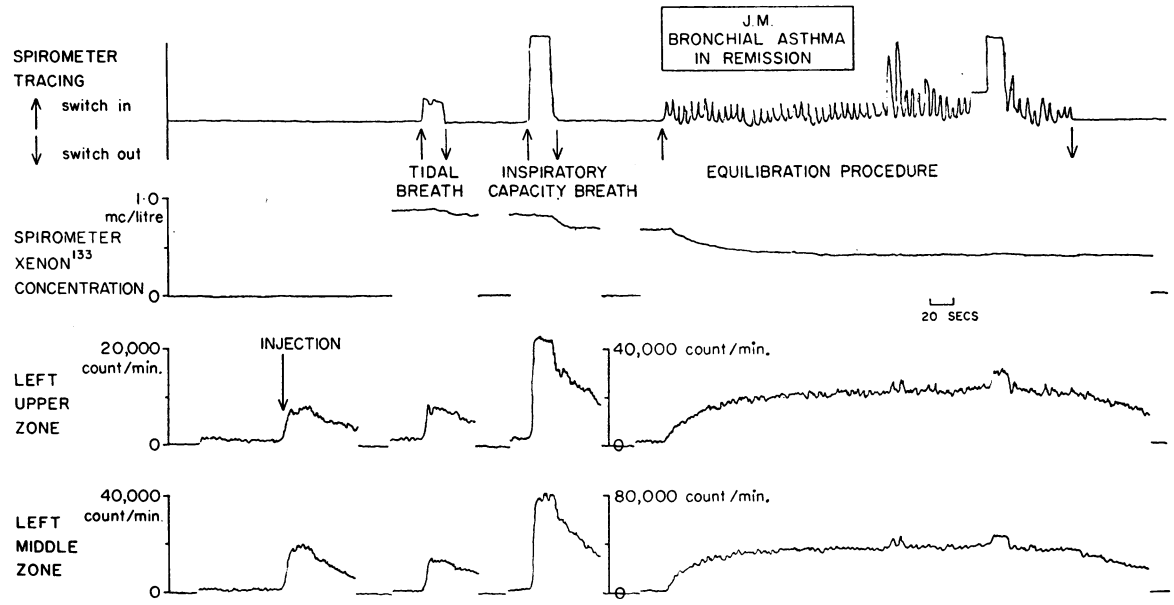

FIG. 1. REPRESENTATIVE TRACING TO ILLUSTRATE EXPERIMENTAL PROCEDURE. The tracing reads from left to right. The injection arrow indicates the time of intravenous injection of a xenon^{133} solution. Note that equilibrium during the rebreathing procedure was reached by both zones well before the end of the study. The time for each zone to reach 90% of the final equilibrium value was obtained by replotting the tracings on semilog paper. The signal of the spirometer xenon concentration returns to zero between the two individual breaths because the electrical signal has been discontinued at these times.

and $Q = F/(F+T) \times (V-T)/V$; F = functional residual capacity of the subject, T = alveolar tidal volume, and V = volume of the spirometer circuit. Since $n = t \times f$ (where f is the rate of breathing), the time necessary to reach 90% of the equilibrium value will be: $t = -1/(f \times \log Q)$. All terms of this formula are known.

The subject's functional residual capacity was obtained by a helium dilution technique before the xenon [133] study. The volume of the spirometer circuit was kept constant in all experiments at 6.72 L. The average tidal volume was obtained by measuring on the spirometer tracing the volume inspired during the initial 90% of the total drop of the spirometer xenon[133] concentration and dividing it by the corresponding number of breaths. The average alveolar tidal volume was obtained by subtracting from the tidal volume the instrumental dead space (15 ml) and the individual anatomical dead space, calculated from a suitable formula (11). The average rate of breathing was obtained by dividing the above number of breaths by the corresponding time in minutes. The fall of xenon[133] concentration in the spirometer was measured by a scintillation counter over the inspired air line (Figure 1).

TABLE I

*Mean zonal times (±SD) for 90% equilibrium expressed as percentage of predicted time in eleven normal subjects seated upright**

Upper zone		Middle zone		Lower zone	
Right	Left	Right	Left	Right	Left
%	%	%	%	%	%
168 ± 49	160 ± 48	121 ± 30	117 ± 29	95 ± 20	96 ± 22

* After calculation in each subject of the predicted time for his lungs to reach 90% of the equilibrium concentration of inhaled xenon[133], the observed times over each lung zone have been expressed as percentages of the theoretical value. Note the proportionate underventilation of the upper zones.

In order to test the possibility of an instrumental source of delay over the predicted values during xenon[133] wash-in, owing to incomplete mixing in the spirometer circuit at the end of expiration and to response time of the electrical circuitry, a model of 3,000-ml functional residual capacity and 184-ml dead space was ventilated at rates of 6, 10, 20, and 30 times per minute, with tidal volumes of 715, 715, 544, and 460 ml, respectively. The measured times to reach 90% of the equilibrium values

TABLE II

Comparison of data in twelve patients with bronchial asthma in remission

	Xenon[133] distribution				Significance of difference
	Normal*		Abnormal†		
No. of subjects	6		6		
Average age ± SD	34	± 8.0	28	± 6.3	<0.01
Vital capacity, *L*					
Predicted	4.03		5.26		
Observed	3.71		4.04		
% Predicted ± SD	89	± 39.5	77	± 16.5	<0.2
Functional residual capacity, *L*					
Predicted	3.17		3.87		
Observed	3.14		3.48		
% Predicted ± SD	97	± 20.9	90	± 27.6	<0.4
Mixing efficiency, %					
Predicted	61		65		
Observed	53		40		
% Predicted ± SD	85	± 18.8	63	± 9.9	<0.001
Forced expiratory volume$_{0.75sec}$ × 40 *L/min*					
Predicted	107		145		
Observed	99		86.5		
% Predicted ± SD	92	± 19.7	60	± 12.9	<0.001
Maximal mid-expiratory flow rate, *L/sec*					
Predicted	3.66		4.43		
Observed	2.4		1.65		
% Predicted ± SD	67	± 22.7	37	± 16.1	<0.001
D_{LCO},‡ *ml/min/mm Hg*					
Predicted	19.2		23.1		
Observed	26.5		23.5		
% Predicted ± SD	141	± 31.3	102	± 31.3	<0.001

* See Figure 2A.
† See Figure 2B.
‡ Steady-state resting diffusing capacity of the lung for carbon monoxide.

were in every case within 5% of the predicted times. It was concluded that the delay introduced by the spirometer and electrical circuits did not result in an appreciable error in the calculation of wash-in time.

The prediction formula assumes uniform lung ventilation. In such a situation, all lung zones of a normal subject would reach 90% of the equilibrium counts in 100% of the predicted time. Previous studies have demonstrated, however, that even in normal subjects the pulmonary ventilation per unit of lung volume is uneven, and that the upper zones are less ventilated than the lower (3, 12, 13). Therefore, in order to establish the range of normality for each lung zone, the analysis of wash-in curves was carried out in a series of eleven normal subjects of comparable age. The average percentage of predicted time to reach 90% of the equilibrium value over each lung zone, and their standard deviations, are shown in Table I.

Of 66 zonal observations in the eleven normal subjects, 62 fell within 2 SD of the mean value. The normal domains are represented by rectangular areas in Figure 2. From the reciprocals of the mean percentages of predicted wash-in times in Table II, the ventilation ratio between upper and lower zones was found to be 1 to 1.71, close to the ratio of 1 to 1.55 obtained with the static xenon ventilation indexes (3). The percentages of predicted times found in the asthmatic patients over each lung zone were checked against the normal values, and all observations falling more than 2 SD above the normal mean were taken to indicate a significant impairment of ventilation.

RESULTS

At the time of the study, ten patients were completely asymptomatic, whereas two complained of

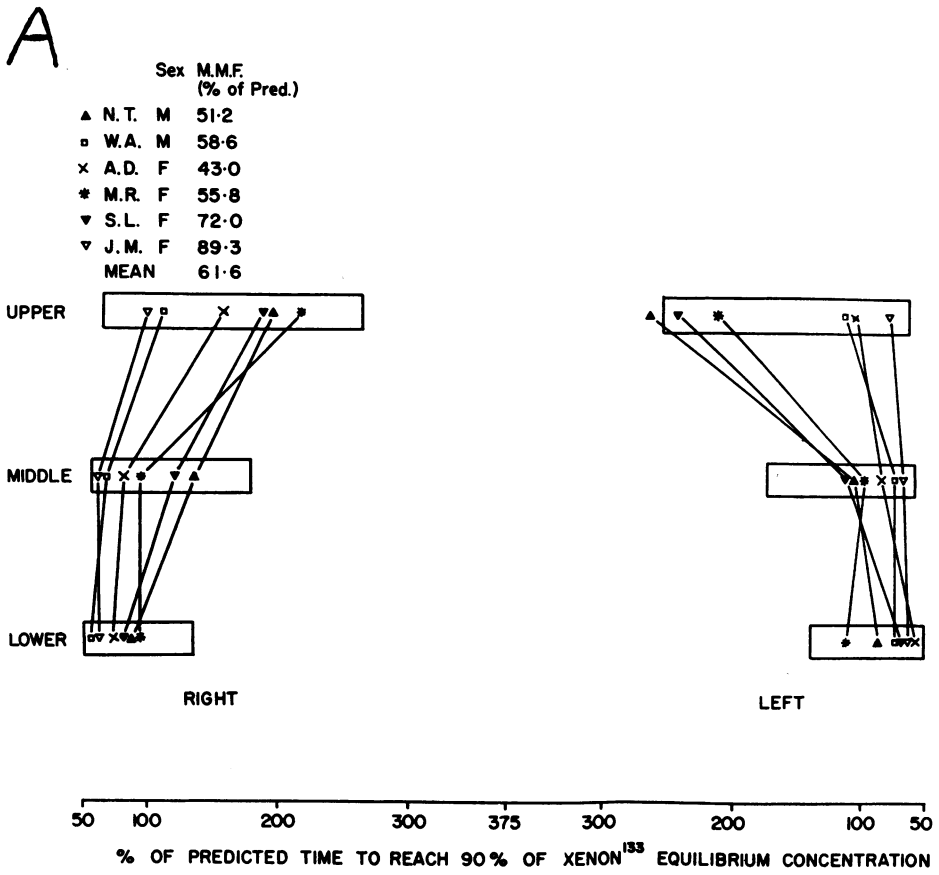

FIG. 2. PERCENTAGE OF PREDICTED TIME TO REACH 90% OF THE XENON^{133} EQUILIBRIUM CONCENTRATION OVER UPPER, MIDDLE, AND LOWER ZONES BILATERALLY IN 12 PATIENTS WITH BRONCHIAL ASTHMA IN REMISSION. Rectangles denote limits of values found in normal subjects (see Table I). A. Results in six patients with no zonal impairment of ventilation. In all but one, the maximal mid-expiratory flow rate was above 50% of predicted. B. Six patients with zonal impairment of ventilation. Maximal mid-expiratory flow rate is significantly lower than in the previous group ($p < 0.05$). Note marked zonal variations in P.T., G.W., and A.G.

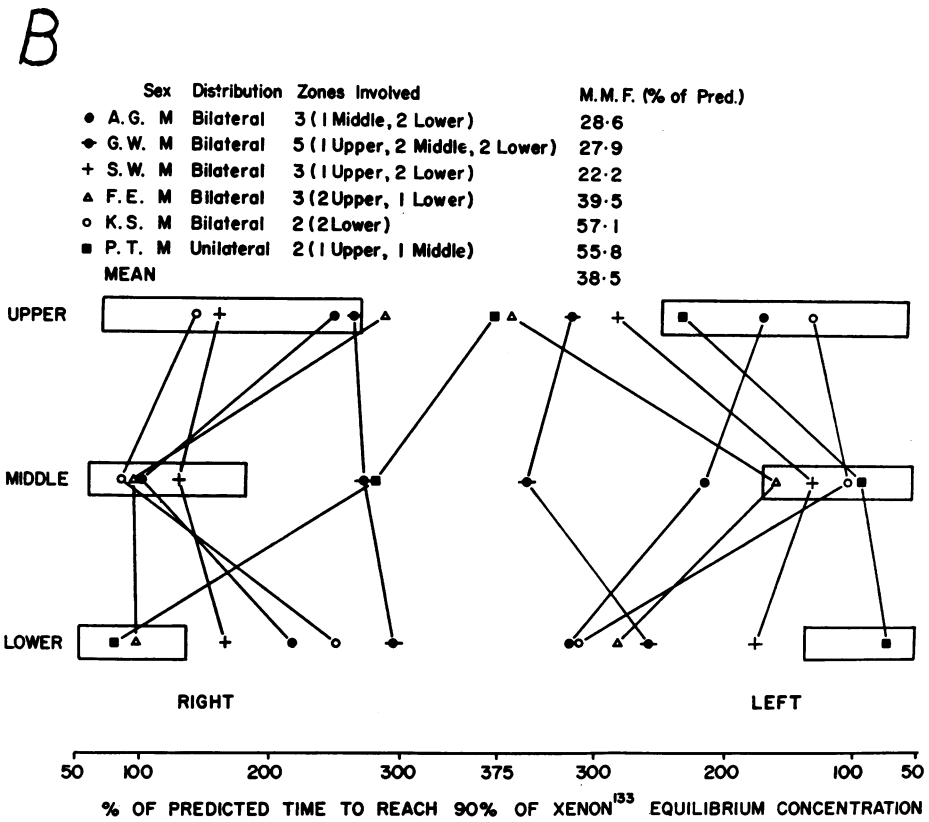

FIG. 2.

slight wheezing and dyspnea on exertion. The physical examination was essentially negative except for the presence of scattered rhonchi on forced expiration in a number of patients. The two subjects with dyspnea on exertion also had rhonchi present on quiet breathing. One of the two had a generalized, exudative, allergic dermatitis. The chest roentgenograms were not remarkable except for the suggestion of some degree of overinflation in a number of patients.

The results of the routine pulmonary function tests are reported in Table II. The twelve asthmatic subjects have been divided into two groups, for comparison of the resting function test results with the abnormalities found in xenon distribution. This table shows that the six asthmatic subjects with xenon impairment had a greater degree of abnormality of vital capacity, helium mixing efficiency, and ventilation than did those with a normal xenon distribution. The maximal mid-expiratory flow rate was only 67% of predicted values in subjects with a normal xenon distribution, but the predicted values in women for this measurement are uncertain, and this factor may have influenced the low percentage predicted. Neither group showed overinflation of the lung as judged by the functional residual capacity. The demonstration of impaired gas distribution and ventilatory defect even in patients who appear to be in clinical remission accords satisfactorily with other data (1, 2). In both groups, the resting diffusing capacity (measured by an end-tidal technique) was normal. Possibly, the high value in subjects with a normal xenon distribution was related to their anxiety about the test, but this explanation is not certain.

Comparative values of mean static ventilation and perfusion indexes between 21 normal subjects and the patients in the present series are shown in Table III. The general similarity of these results is evident. Greater variation occurred, however, and the ventilation indexes for a tidal breath, instead of showing a gradual increase from upper to lower zones, were slightly reduced

TABLE III

Comparison of mean static distribution indexes ± standard deviations in 21 normal and 12 asthmatic subjects in remission

Zone	Tidal breath		Deep inspiration		Perfusion	
	Right	Left	Right	Left	Right	Left
Normal subjects						
Upper	58 ± 11	57 ± 9	71 ± 8	71 ± 7	38 ± 12	42 ± 14
Middle	70 ± 11	70 ± 10	81 ± 8	85* ± 8	70 ± 17	67 ± 20
Lower	87 ± 16	91 ± 16	95 ± 9	104* ± 10	137* ± 20	129 ± 19
Asthmatic subjects						
Upper	65 ± 21	63 ± 20	74 ± 15	77 ± 12	57 ± 20	57 ± 23
Middle	79 ± 23	78 ± 24	87 ± 14	89 ± 12	98 ± 27	102 ± 35
Lower	84 ± 23	83 ± 27	99 ± 12	105* ± 12	150 ± 41	143 ± 47

* Significantly greater than the corresponding index on the opposite side.

over the lower zones as compared with the middle zones on the right side in three patients, and on the left side in five. In one additional patient (K.S.), the reduction over both lower zones was marked, and the measured value over the left lower zone after a tidal breath was more than 2 SD below the predicted value. His static indexes for a maximal inspiration and for perfusion, however, were quite normal. With regard to the perfusion indexes, all but two subjects showed normal values. Of these two, one showed a higher perfusion index in the right middle zone than in the lower zone, and the other showed the same abnormality on the left side. Both of these patients had normal ventilation indexes for a tidal breath and deep inspiration.

As shown in Figure 2A, the xenon dynamic wash-in curves were normal in six patients, all with normal static ventilation indexes. In Figure 2B, abnormal results are recorded in the remaining six; among these, the zonal pattern of ventilatory abnormality, the number of zones involved, and the degree of involvement apparently differed. Thus, P.T. showed a unilateral type of derangement affecting only the right middle and upper zones; in K.S., A.G., and S.W., the ventilatory defect was limited to or predominant in both lower zones; F.E. had involvement of both upper zones and the left lower zone; and finally, G.W. was normal only over the right upper zone. There was general correspondence between the degree of reduction of maximal mid-expiratory flow rate and the extent and degree of abnormality of wash-in curves.

DISCUSSION

The results of the routine pulmonary function tests in this series agree in general with previous reports concerning the same type of patients (1, 2, 14–18). One noticeable exception is represented by the functional residual capacity, which was normal in our group, but was increased in most previous reports. The cause of this discrepancy is not readily apparent. In accord with previous findings (2), the presence of slight abnormality of air flow in our patients indicates the persistence of impaired function even in the complete absence of symptoms.

The xenon^{133} static distribution indexes for ventilation and perfusion in bronchial asthma in remission, in spite of wider scatter about the mean values, did not differ significantly in our series from the findings in normal subjects. In contrast, the quantitative analysis of the rates of wash-in of inhaled xenon^{133} revealed significant abnormalities of ventilation in six patients, and these abnormalities were regional rather than diffuse. This regional impairment of ventilation bore a general relation to the degree of reduction of maximal mid-expiratory flow rate and was presumably responsible for the residual abnormality of air flow in these subjects. These findings indicate that minor regional differences in ventilation are better demonstrated by analysis of wash-in curves of inhaled xenon than by the static ventilation distribution indexes. Apart from the technical superiority of the ventilation distribution measurement during continuous breathing compared to single-breath distribution indexes, this phenome-

non is probably explained by the sensitivity of the dynamic wash-in distribution to airway resistance.

It seems likely that persistent bronchospasm or patchy atelectasis on a lobar or sublobar basis was responsible for the zonal ventilatory abnormalities. Arborelius and coauthors in a recent article on experimental acute unilateral bronchial asthma (19) demonstrated the absence of nervous bronchoconstrictor reflexes between the two lungs. The results reported in the present paper would appear to indicate the presence of autonomy even among the various segments of the same lung. In this series, there was no evidence of a reduction of perfusion to the poorly ventilated regions of the lung, which therefore implies a regional reduction of the ventilation perfusion ratio with consequent changes in regional gas exchange. With the present xenon^{133} technique, however, ventilation and perfusion are summed over relatively large lung volumes, and it is possible that some reduction of perfusion to compensate for the reduced ventilation might occur within smaller units that are essentially beyond the range of detection. The present findings suggest, however, that a study of the total V/Q distribution pattern in patients with bronchial asthma in remission might reveal significant continued perfusion of areas with a reduced ventilation.

SUMMARY

1. Twelve patients with bronchial asthma in spontaneous or medically maintained remission have been studied by routine pulmonary function tests and the xenon^{133} technique.

2. In spite of a somewhat wider scatter of data, the xenon^{133} static distribution indexes for ventilation and perfusion in asthmatic subjects showed, in general, close agreement with the previously reported findings in normal subjects. In some cases, slight zonal abnormalities of the ventilation indexes after a single tidal breath indicated minor local reductions of ventilation. The perfusion distribution appeared to be normal.

3. A development of the xenon^{133} technique is described whereby the time course of gas distribution during equilibration with a closed circuit can be followed over six lung zones simultaneously. In six of the twelve patients studied, the residual impairment of gas distribution was found to follow a zonal rather than a diffuse uniform pattern. The patients showing this defect had a significantly greater degree of impairment of forced expiratory volume, maximal mid-expiratory flow rate, and helium mixing efficiency than did those not showing this abnormality.

4. These findings indicate that the residual ventilatory impairment in patients with bronchial asthma in remission must be seen as a zonal or possibly lobar phenomenon. Such regional ventilatory impairment does not seem to be accompanied by a corresponding reduction in perfusion.

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